ENANTIOSELECTIVE TERPENE SYNTHESIS

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

By
N. KRISHNAMURTHY

SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD-500 134
INDIA

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DEDICATED

TO

MY PARENTS

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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 invesitgators.

N. KRISHNAMURTHY

CERTIFICATE

Certified that the work contained in this thesis entitled: "ENANTIOSELECTIVE TERPENE SYNTHESIS" has been carried out by N. Krishnamurthy, under my supervision and the same has not been submitted elsewhere for a Degree.

G. Mehta

GOVERDHAN MEHTA

(THESIS SUPERVISOR)

R Jagannathan.

DEAN

SCHOOL OF CHEMISTRY

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ABBREVIATIONS

Ac	acetyl
Bu	butyl
DMF	dimethylformamide
Et	ethyl
LAH	lithium aluminium hydride
LHMDS	lithium hexamethyldisilazide
MCPBA	meta-chloroperbenzoic acid
Me	methyl
MeOH	methanol
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Py	pyridine
THF	tetrahydrofuran
TIPSCl	triisopropylsilylchloride
TMSCl	trimethylsilylchloride
$h\nu$	photo-irradiation
Δ	thermolysis

PREFACE

Nature's expertise and virtuosity in creating a phenomenal array of carbocyclic frameworks finds its full expression in the terpenoid group of natural products. Indeed, the number and type of carbocyclic skeleta among terpenes continues to grow unabated as more and more natural products are being isolated from plant, marine, microbial and insect sources. An interesting development in the past few years is the structure elucidation of terpenoids bearing uncommon assembly of rings. Thus, multi-carbocyclic ring systems bearing 5-5-5, 5-5-5-5, 5-6-5, 5-7-6, 5-7-5, 5-8-5, 5-11, fused assemblies have been encountered. This vast and diverse repository of interesting carbocyclic compounds of natural origin provides the synthetic chemists with tempting and challenging targets for total synthesis. The synthetic endeavours in the pursuit of these novel systems call for the development of new methods of ring construction and annulation. It is only in the past few years that due attention has been given to the synthesis of these interesting molecules bearing uncommon carbocyclic frameworks. The present investigation is an attempt in the area and aimed at the development of new and general methodologies towards the construction of sesqui-, di- and sesterterpenes bearing 5-7-6, 5-11 and 5-8-5 fused carbocyclic skeleta.

The thesis entitled "ENANTIOSELECTIVE TERPENE SYNTHESIS" is divided into four Chapters. I. A new hydroazulene synthesis. Application to the total synthesis of marine diterpenes (+)-isoamijiol and (+)-dolasta-1(15),7,9-trien-14-ol; II. Total syntheses of daucane sesquiterpene (-)-daucene and isodaucane sesquiterpenes Aphanamol-I and 2-oxo-isodauc-5-en-

12-al; III. An oxy-Cope rearrangement route to 5,11-fused bicyclic dolabellane diterpenes. IV. Model studies towards fusicoccane diterpenes: Construction of the 5,8,5-fused tricarbocyclic ring system.

The first chapter describes a new and useful methodology for the construction of several functionalised hydroazulenones from commercially available R-(+)-limonene. Acid catalysed enone-olefin cyclisation and Lewis acid catalysed ene-reactions have been employed as the key steps in the construction of hydroazulenone framework. One of the hydroazulenones, 8-isopropyl-1S-methylbicyclo[5.3.0]dec-7-en-3-one is a versatile precursor for the synthesis of diverse sesqui- and diterpenes. The successful elaboration of 8-isopropyl-1S-methylbicyclo[5.3.0]dec-7-en-3-one to the novel 5,7,6-fused tricarbocyclic marine diterpenes (+)-isoamijiol and (+)-dolasta-1(15),7,9-trien-14-ol has been achieved. This is the first enantioselective synthetic accomplishment of dolastane diterpenes.

The second chapter describes the enantioselective total syntheses of daucane and isodaucane sesquiterpenes. (-)-Daucene, the simplest member of the carotane family has been synthesised from R-(+)-limonene. Novel restructuring of readily available 8-isopropyl-1S-methylbicyclo[5.3.0]dec-7-en-3-one has been effectively employed for the stereo- and enantioselective syntheses of isodaucane sesquiterpenes aphanamol I and 2-oxo-isodauc-5-en-12-al. The enantioselective syntheses of these natural products establishes their absolute configurations.

In the third chapter, successful evolution of the 8-isopropyl-1S-methylbicyclo[5.3.0]dec-7-en-3-one to the 5,11-fused bicyclic dolabellane

skeleton, *via* an oxy-Cope rearrangement is described. This is the first preparation of the complete C_{20}-dolabellane skeleton of considerable biogenetic importance. Attempts to transfer the C_{20}-dolabellane skeleton to one of the simplest known dolabellane natural products, δ-araneosene are outlined.

The last chapter of the thesis is concerned with the synthesis of 5,8,5-fused tricarbocyclic skeleton present in diterpenes like fusicoccanes and sesterterpenes like ophiobolines. The main strategy in our approach to the 5,8,5-system is the recognition of the bicyclo[3.3.0]oct-1(8)-ene as a cyclooctane equivalent. Thus, a 5,5,5,5-fused tetraquinene has been synthesised and transferred to the 5,8,5-dione *via* oxidative cleavage. In the next phase of this work, a substituted tetraquinene was synthesised from (+)-limonene and further transformed to (+)-3-methyl-6-isopropyl-*cis*,*anti*,*cis*-tricyclo[9.3.0.$0^{3,7}$]tetradeca-2,9-dione having close structural resemblance to the fusicoccane diterpenes.

Chapter I

A New Hydroazulene Synthesis.

Application to the Total Synthesis of Marine diterpenes (+)-Isoamijiol and (+)-dolasta-1(15),7,9-trien-14-ol

I.1. ABSTRACT

A new, general, enantioselective approach for the construction of 5-7-6 fused tricyclic dolastane-type diterpenes has been developed from (+)-limonene 45. For the construction of the 5-7-6 tricarbocyclic framework, properly functionalised bicarbocyclic hydroazulenones (-)-30, (+)-43 and (-)-44 were identified as advanced precursors. Synthetic routes to these hydroazulenones were first developed from 5S-isopropyl-2-methylcyclopent-1-ene-1-carboxaldehyde 48, a chiral building block readily available from (+)-limonene 45, Scheme I. 8.

The enal 48 was first quaternised and homologated *via* a diastereoselective Claisen rearrangement to furnish enantiomerically pure (-)-51, Scheme 1.9. Three different strategies were employed for the 2C-homologation of the aldehyde functionality in 51 and subsequent seven membered ring closure to furnish hydroazulenones 30, 43 and 44. In the first set of reactions, Wadsworth-Emmons modification of the Wittig reaction on (-)-51 and reduction of the resulting unsaturated ester 55, with Li-liq.ammonia led to the C_{14}-alcohol 56, Scheme I.11. Oxidation of the alcohol 56 to aldehyde 57 with PDC and Lewis acid catalysed intramolecular ene reaction afforded hydroazulenol 58, which was readily oxidised to the hydroazulenone 43. In the second set of reactions, Reformatsky reaction on aldehyde using ethyl bromoacetate gave the hydroxy ester 59 in which the hydroxyl group was protected as THP derivative 60. The protected ester 60 was reduced to

aldehyde 61 with DIBAL-H and cyclised in the presence of $SnCl_4$ to give the bicyclic diol 62 *via* intramolecular ene reaction. The diol 62 on oxidation furnished the hydroazulene-dione 44, Scheme I.13. The same diol 62 was converted to hydroxyketone 63 by controlled oxidation with PCC. Reductive elimination of hydroxyl functionality in 63 was achieved through mesylation, LAH reduction and oxidation, to afford the key hydroazulenone 30, Scheme I.14.

An alternate, shorter and practical approach to the hydroazulenone (-)-30 consisted of addition of the vinylmagnesium bromide and oxidation to furnish the enone 68. An efficient acid catalysed olefin-enone cyclisation on 68 led to the hydroazulenone 30, Scheme I.15. Stereoselective, sequential alkylations on 30 with TIPS protected 5-iodo-1-pentyne and methyl iodide afforded 79, which on deprotection followed by ketone-acetylene cyclisation employing sodium naphthalenide furnished the 5-7-6 dolastane framework 71, with concomitant generation of the bridgehead hydroxy and exocyclic methylene functionalities, Scheme I.18. Allylic oxidation of 71 with cat.SeO_2-Bu^tOOH afforded the natural products (+)-isoamijiol 28 and (+)-dolasta-1(15),7,9-trien-14-ol 29, Scheme I.20. Thus, enantioselective syntheses of (+)-isoamijiol 28 and (+)-dolasta-1(15),7,9-trien-14-ol 29 were accomplished in 16 steps from R-(+)-limonene 45.

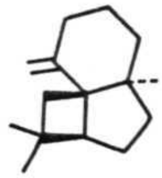
I.2. OBJECTIVE AND BACKGROUND

The construction of diverse molecular architecture, conceived and created by Nature, continues to be the most exciting challenge to the practicing synthetic chemists. The isolation and structure elucidation of complex natural products from newer and `exotic' sources, aided by the refinement of isolation techniques and advances in spectroscopic methods, continues to provide the organic chemist with increasing number of exciting objectives. The recent advances in the field of natural product syntheses testifies to the organic chemists' endeavours to meet these challenges.[1]

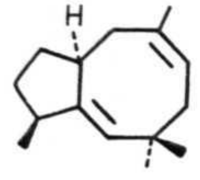
Among the various classes of natural products, terpenes are notable for the diversity of carbocyclic arrays present in them. Indeed, in a bewildering display of synthetic ingenuity, Nature creates a phenomenal number of carbocyclic networks made of different combination of ring sizes 3 - 14. A few examples from mono-, sesqui-, di-, sester- and triterpenes are displayed in Chart I.1. These and related terpene structures virtually provide a feast of target molecules for the synthetic chemists.

The bicarbocyclic structures composed of 5-7 ring fusion have been known among terpenoid natural products for a long time. Many of these hydroazulenic natural products, exemplified here by dehydrocostuslactone <u>13</u>[14], damsin <u>14</u>[15] and carotol <u>15</u> (Chart I.2) possess biological activity and have received a great deal of attention from the synthetic chemists.

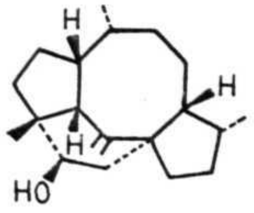
CHART I.1



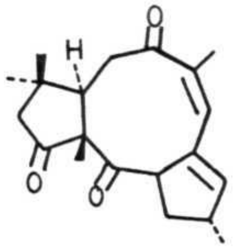
1. β-Panasinsene[2]



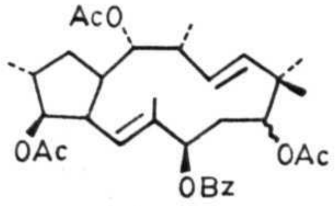
2. Precapnelladiene[3]



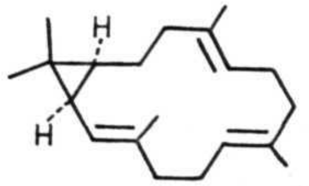
3. Longipenol[4]



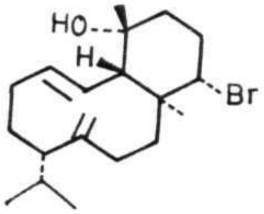
4. Jatrophatrione[5]



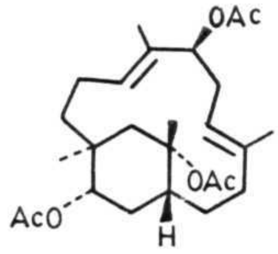
5. Euphorium[6]



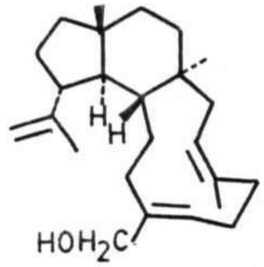
6. Casbene[7]



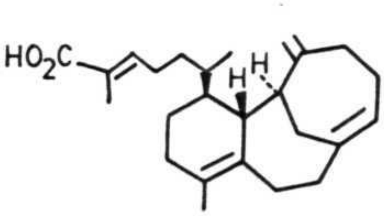
7. Bromocorodienol[8]



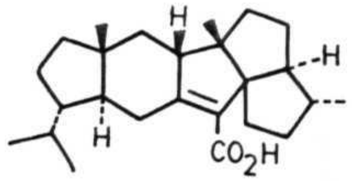
8. Triacetoxyseco-trinervitane[9]



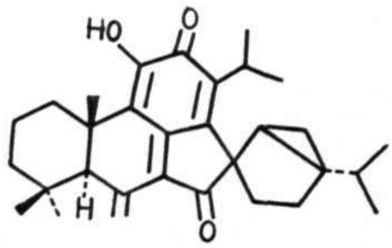
9. Flocerol[10]



10. Cerorubenic acid[11]

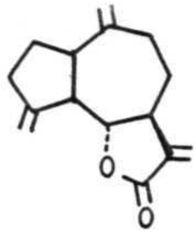


11. Retigeranic acid[12]

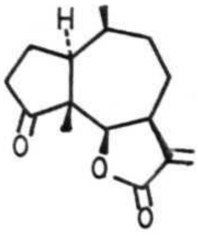


12. Chamaecydin[13]

CHART I.2



13



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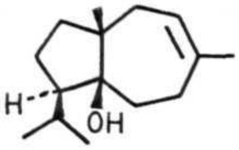
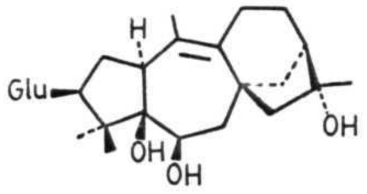


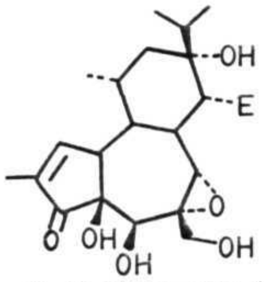
15

More recently, tri- and tetracarbocyclic skeleta in which a six-membered ring is fused to the hydroazulenic framework have been isolated. These include the grayanotoxin 16[16], daphnane 17[17] and phorbol 18[18] class of biologically important diterpenes, Chart I.3. The latest to join this group of tricarbocyclic diterpenes are the dolastanes bearing the basic carbocyclic skeleton 19.

CHART I.3

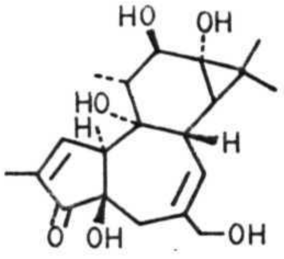


16

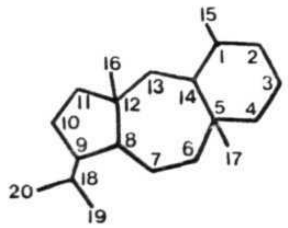


$E = O_2C[CH{=}CH]_2(CH_2)_4CH_3$

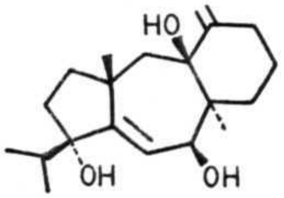
17



18



19



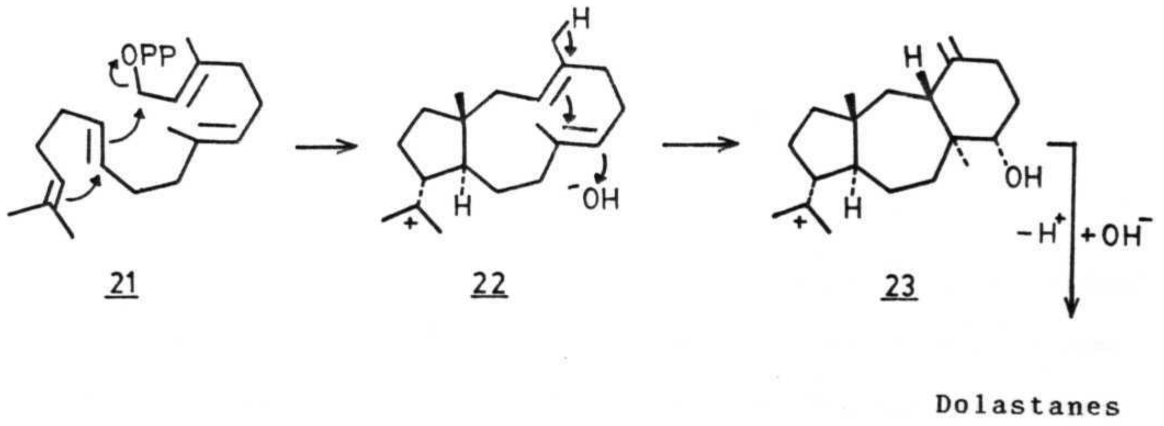
20

The first dolastane-type diterpene embodying the 5-7-6 fused tricarbocyclic framework, to be discovered in Nature in 1976 from a poisonous Indian Ocean sea-hare (*Dolabella aricularia*) was dolatriol 20.[19] In addition to having an intricate network of oxygen functionalities and unsaturation, 20 was also shown to be strikingly cytotoxic. Since then, dolastanes have frequently surfaced among sea weeds and presently about thirty of them with varying degrees of unsaturation and oxygen functionalisation are known (see, appendix of this chapter).

Stereostructures of dolastanes have been generally determined through a combination of X-ray crystallography, spectral data (^{1}H and ^{13}C-NMR) and chemical interconversions. The absolute configuration of these natural products have been determined through the application of Nakanishi's CD-allylic benzoate method,[20a] modified Horeau's method and intra-group chemical correlations.[20b]

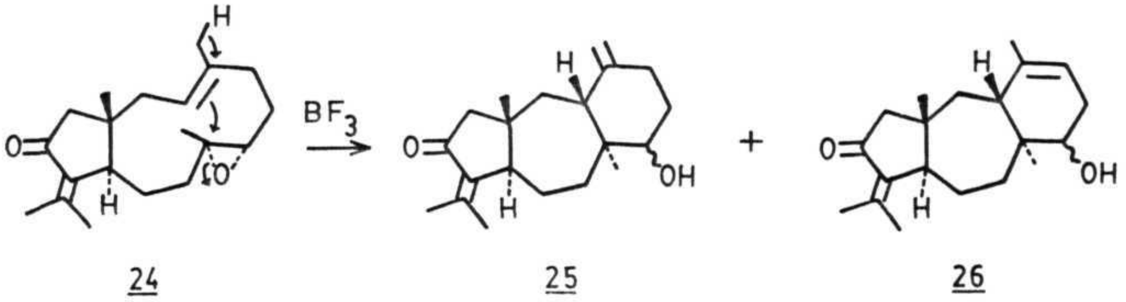
Biogenetically, dolastane diterpenes can be considered as arising through the 5-11 fused dolabellane cation 22, which in turn is formed from E,E,E-geranylgeraneol pyrophosphate 21 as shown in Scheme I.1.

SCHEME I.1



Support for this biogenetic pathway has been obtained through cationic cyclisation of a bicyclic dolabellane natural product 24 to the tricyclic dolastane derivatives 25 and 26, Scheme I.2.[21]

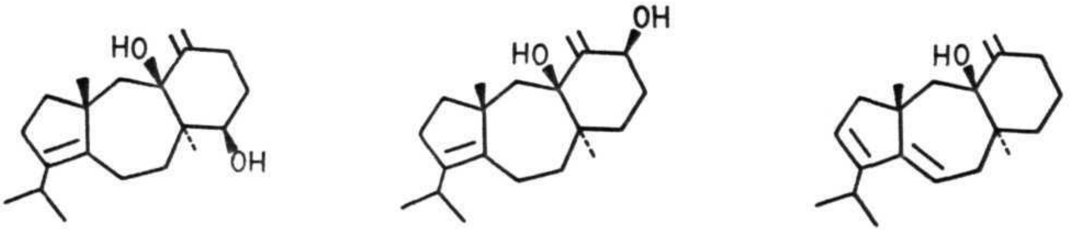
SCHEME I.2



The dolastane group of diterpenes hold considerable synthetic appeal. It emanates from the presence of a unique 5-7-6 fused carbocyclic assembly, embellished with quaternary carbon centres. The more complex dolastanes (see a ppendix) have a network of oxygen functionalisation and unsaturation and contain upto seven stereogenic centres. Their creation is a daunting task requiring generation and management of multiple functionalities with high degree of stereochemical control. In particular, the ubiquitous presence of the bis-allylic alcohol moiety in dolastanes requires deployment of specifically tailored synthetic protocols to handle this sensitive functionality.

Among the various dolastanes, we were attracted by the doubly unsaturated diols, (-)-amijiol 27 and (-)-isoamijiol 28 isolated from the brown seaweed Dictyota linearis by Ochi and co-workers[22] and triply unsaturated alcohol dolasta-1(15),7,9-trien-14-ol 29 isolated from the same species by Crews and co-workers[23] (Chart I.4). These dolastane derivatives have been shown to exhibit antimicrobial activity against Bacillus subtilus and Pencillus crustosum. Both, 28 and 29 are prototypes of the dolastane family and we selected them as our synthetic objectives.

CHART I.4



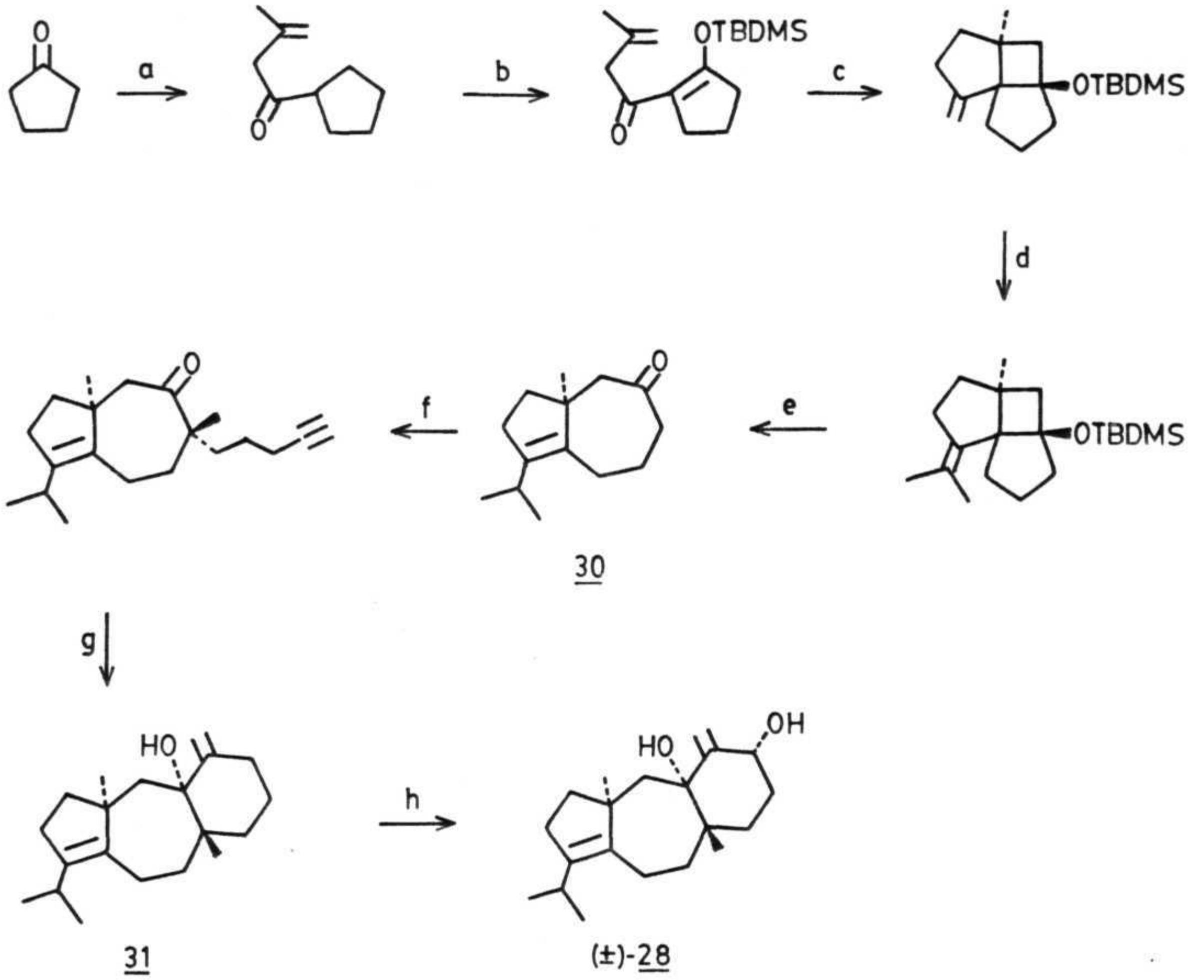
27 28 29

The tricyclic dolastane diterpenes have also attracted the attention of other synthetic chemists and since the inception of our efforts in the area in 1985, several synthetic studies towards dolastanes have appeared in the literature. Before describing our own results,[#] a quick, schematic review of these efforts is considered appropriate.

Pattenden in 1986, described the first synthesis of a dolastane diterpene and employed the deMayo reaction (2+2-cycloaddition-fragmentation) as the key step for the construction of the appropriately functionalised bicyclo[5.3.0]decanone (hydroazulenone) precursor 30, Scheme I.3.[24] The tricyclic framework was generated through the regioselective annulation of a six membered ring, utilising the radical mediated alkyne-carbonyl reductive coupling. The resulting dolastane derivative 31 was elaborated to (±)-isoamijiol 28 through stereo- and regioselective allylic oxidation.

[#] Preliminary account of our results in this area was published in 1987.[29]

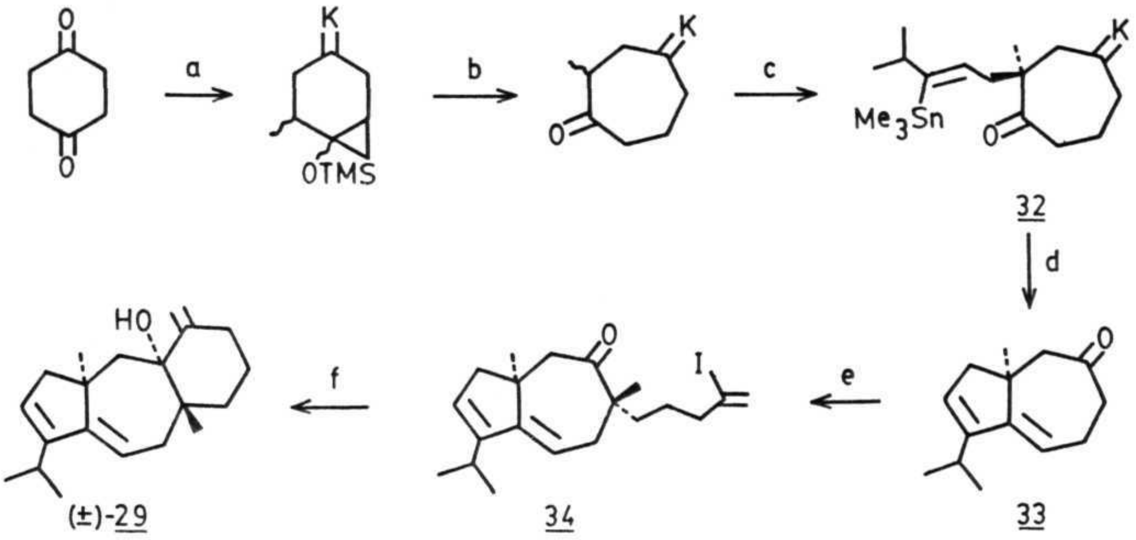
SCHEME I.3



Reagents & Conditions: a) i. Morpholine, PTS; ii. 4-Methylpent-4-enyl chloride, benzene, Δ ; iii. dil.HCl; b) Et_3N, TBDMSCl; c) hν, hexane, pyrex; d) Acetone, $TiCl_3$, Li, DME; e) aq.THF; f) i. LHMDS, HMPA, THF, $I(CH_2)_3C{=}C$-TIPS, $-15^{o}C$; ii. NaH, DME, MeI; g) $C_{10}H_8^{-}Na$, THF; h) SeO_2, $Bu^{t}OOH$, DCM.

Piers achieved the synthesis of a triply unsaturated dolastane natural product (±)-29 in 1987, Scheme I.4.[25a] The key steps involved in this

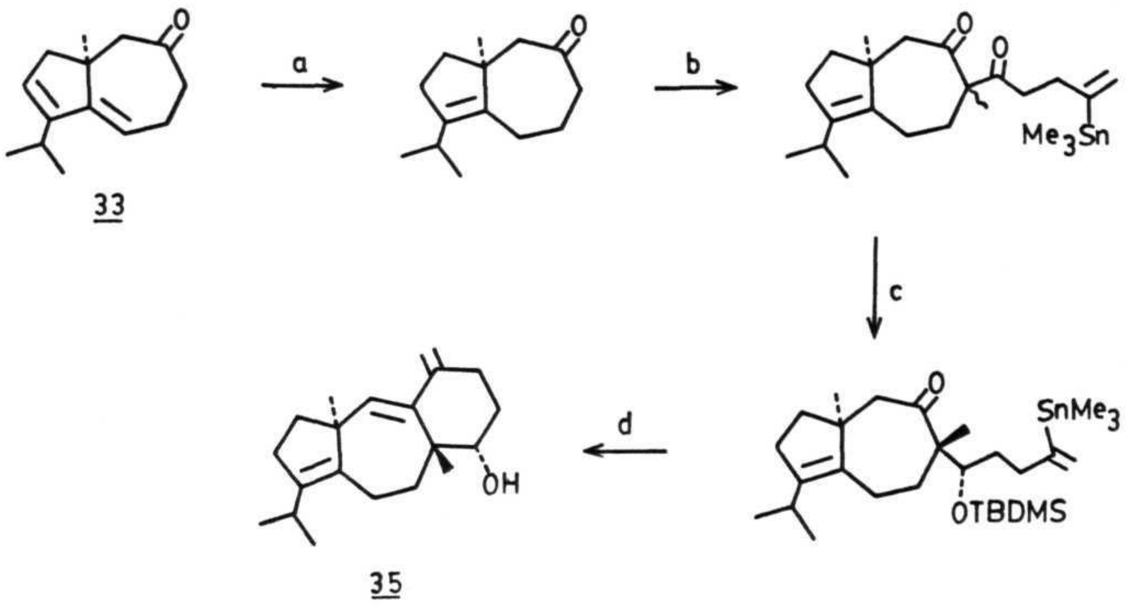
SCHEME I.4



Reagents & Conditions: a) i. H_2NNMe_2, benzene, Δ ; ii. LDA, THF, $-78^{o}C$, MeI; iii. $NaIO_4$, THF, pH 7-phosphate buffer; b) i. LDA, THF, TMSCl, Et_3N; ii. CH_2I_2, Et_2Zn, toluene, $55^{o}C$; c) i. $FeCl_3$, DMF, pyridine, $0^{o}C$; ii. NaOAc, MeOH, Δ ; iii) H_2, Pd/C, hexane; $K^{+}Bu^{t}O^{-}$, $Bu^{t}OH$, DME, RT, $(CH_3)_2CHC(Sn(CH_3)_3)=CH-CH_2Br$; d) i. LDA, THF, HMPA, $PhN(SO_2CF_3)_2$, RT: ii. cat. $(PPh_3)_4Pd$, RT; iii. 1N HCl, acetone, RT; e) H_2NNMe_2, MeOH, Δ ; ii. LDA, THF, $H_2C=C(Sn(CH_3)_3-(CH_2)_3-I$; iii. $NaIO_4$, THF, pH 7-phosphate buffer; iv. $K^{+}Bu^{t}O^{-}$, THF-HMPA, $60^{o}C$, MeI, v. I_2, DCM, RT; f) Mg, THF, Δ .

approach were Pd(0) catalysed annulation (32 → 33) on the enol triflate of 32 and intramolecular Grignard reaction (34 → 29). More recently, a similar Pd(0) catalysed annulation strategy has been applied to the synthesis of racemic natural product amijitrienol 35.[25b] In both these syntheses, the hydroazulenic dienone 33 served as an important advanced intermediate, Scheme I.5.

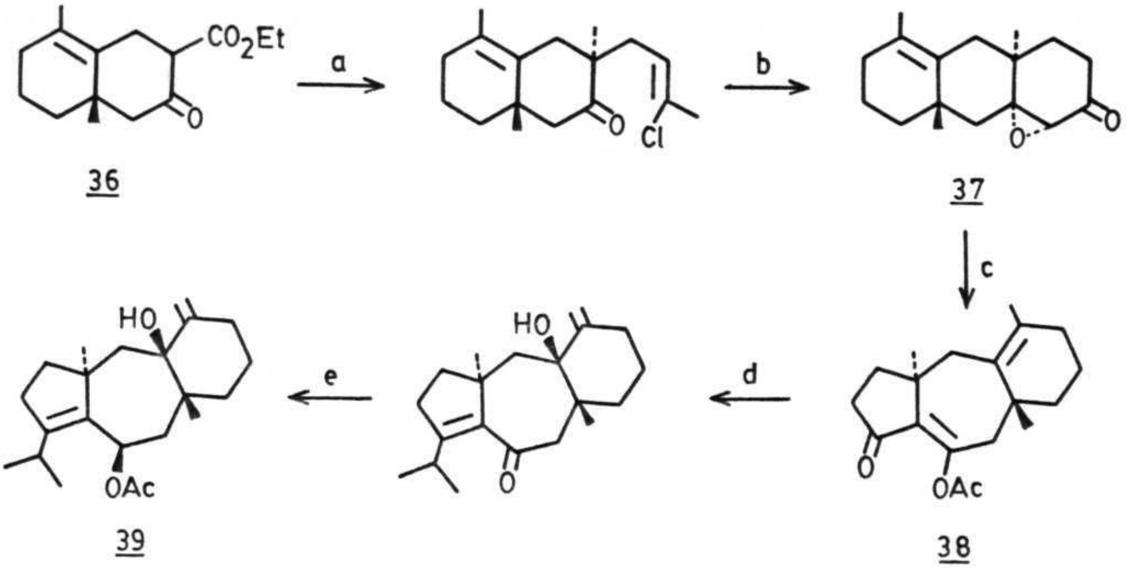
SCHEME I.5



Reagents & Conditions: a) i. $HOCH_2\ C(CH_3)_2CH_2OH$, PTS; ii. Li, liq.NH_3, THF, $-48^{o}C$; iii. HCl, H_2O, acetone; b) i. LDA, THF, 4-trimethylstannylpent-4-enal; ii. $(COCl_2)_2$, DMSO, DCM, Et_3N, $-78^{o}C$ - RT; iii. K_2CO_3, acetone, Δ ; c) i. DIBAL-H, LiCl(excess), THF, $-78^{o}C$; iii. $t\text{-}BuMe_2SiOSO_2CF_3$, DMAP, Et_3N, DCM, RT; d) i. KHMDS, THF, $PhN(SO_2CF_3)_2$; ii. $(Ph_3P)_4Pd$, Et_3N, CH_3CN, Δ ; iii. $n\text{-}Bu_4N^+\ F^-$, THF, Δ .

Paquette has succeeded in synthesising a dolastane derivative 39 in a very lengthy sequence but could not elaborate it into a natural product, of this family.[26] The key transformation in his approach was the excited-state rearrangement of the α,β-epoxyketone 37 to dolastane skeleton 38. The tricyclic precursor 37 was in turn assembled from the previously known bicyclic ketoester 36. Further functional group manipulations led to (±)-4 ,10 -doladiol acetate 39, Scheme I.6.

SCHEME I.6

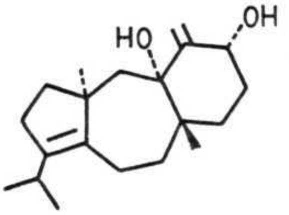


Reagents & Conditions: a) i. NaH, $ClCH=CClCH_3$; ii. $Ba(OH)_2$, H_2O, C_2H_5OH, iii. NaHMDS, THF, 25^oC, MeI; b) i. $Hg(OAc)_2$, HOAc; ii. $BF_3.Et_2O$; iii. K_2CO_3, MeOH, Δ ; iv. 30% H_2O_2; 4N NaOH, MeOH, 0^oC; c) i. hν (3000 A^o); ii. Ac_2O. pyridine, DMAP, DCM; d) i. n-BuSH, HOAc, HCl; ii. i-PrMgBr, CuCN, Et_2O, -20^oC; iii. $^1O_2$, MeOH, DCM, 0^oC, iv. $P(OC_2H_5)_3$; e) i. DIBAL-H; ii. Ac_2O, pyridine, DMAP, DCM.

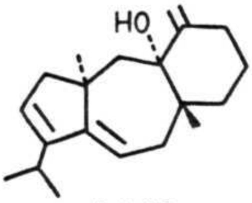
In addition to the efforts described above, Seto et al.,[27] and Rigby et al.,[28] have reported some preliminary investigations targeted towards the synthesis of dolastane skeleton.

In this chapter of the thesis, we delineate the first enantioselective approach to dolastanes, culminating in the total synthesis of (+)-isoamijiol 28 and (+)-dolasta-1(15),7,9-trien-14-ol 29 (Chart I.5), starting from (+)-limonene[#]. On way to 28 and 29, synthesis of several interesting hydroazulenones of intrinsic value in some related natural product syntheses, has also been achieved.[29]

CHART I.5



(+)-28



(+)-29

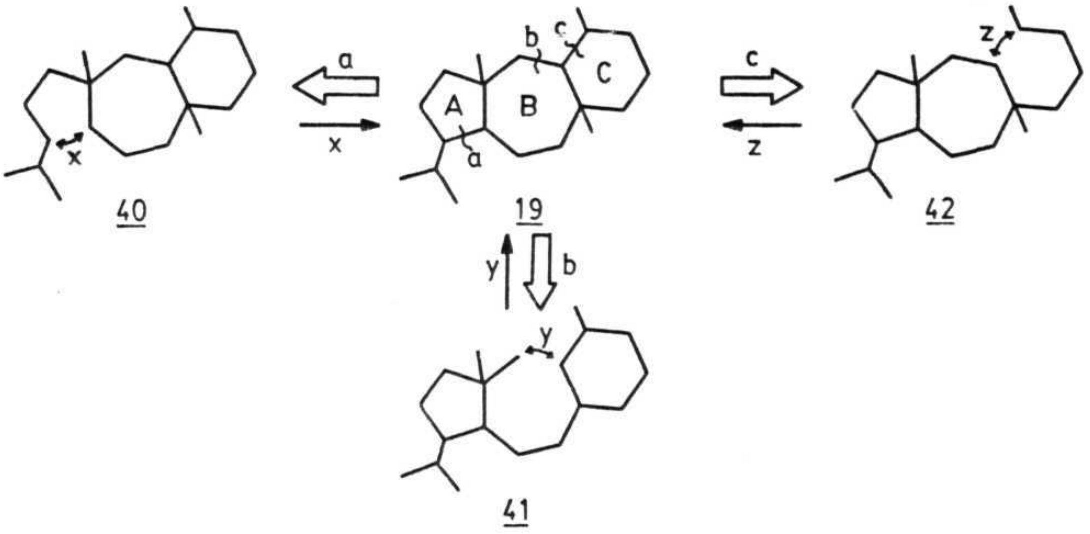
I.3. STRATEGY AND SYNTHESIS OF HYDROAZULENIC PRECURSORS

As already indicated, the primary synthetic challenge of dolastane natural products resides in the efficient and rapid construction of the 5-7-6 fused tricarbocyclic framework. Added to this, is the task of controlling the stereochemistry at four or more stereogenic centres and generation of requisite sites of unsaturation and oxygenation. In our quest for dolastane natural products (+)-28 and (+)-29, we first addressed ourselves to the question of carbocyclic ring construction, keeping in mind the ultimate objective and the requirement of building-up the functionalities.

[#] Dolastane structures prior to 28 in this chapter correspond to the naturally occurring enantiomers. The subsequent structures are of ent-series derived from (+)-limonene.

Conceptually, several broad strategies for the construction of the dolastane framework were indicated through straight-forward retrosynthetic analysis, involving strategic bond disconnections as shown in Scheme I.7. Thus, tricyclic dolastane framework 19 could be assembled from precursors

SCHEME I.7

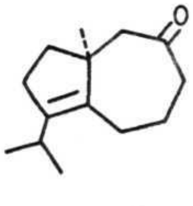


of the types 40 (path ˋx') or 41 (path ˋy') or 42 (path ˋz'), which required eventual closure of a 5- (40 → 19) or 7- (41 → 19) or 6- (42 → 19) membered ring, respectively. Among these strategic options, we preferred ring closure ˋz' (42 → 19) for several reasons. Firstly, there were discouraging literature precedences for following pathways ˋx' and ˋy'. Methodologies for the construction of the precursor 6,7-fused system (40 → 19, path ˋx') are rather limited and the approach involving closure of a medium ring last (41 → 19, path ˋy'), is fraught with uncertainties. Secondly, many accessible routes to hydroazulenes (bicyclo[5.3.0]decanes) are known and can be adapted for constructing a precursor like 42.

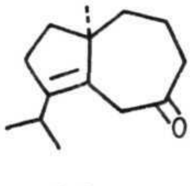
Furthermore, the hydroazulenic precursor 42 can find further applications in synthesis, as this structural moiety is present in many natural products. Finally, in the pathway `z', installation of sensitive functionality (bis-allylic alcohol) present in ring `C' can either be accommodated as part of the annulation process or its generation can be postponed till the very end.

Having identified path `z' as the strategy for constructing the dolastane framework 19, the immediate task was to identify and synthesise the hydroazulenic precursor(s) that could be elaborated to 19. Keeping in view, the AB-ring functionalisation pattern present in naturally occurring dolastane natural products and in particular in our target molecules, (+)-isoamijiol 28 and (+)-dolasta-1(15),7,9-trien-14-ol 29, hydroazulenones 30, 43 and 44 were considered as versatile and most serviceable precursors (Chart I.6). It was also our intent to prepare 30, 43 and 44 in enantiomerically pure form. Successful acquisition of (-)-30, (+)-43 and (-)-44 was achieved from readily and abundantly available chiron (+)-limonene 45, as detailed below.

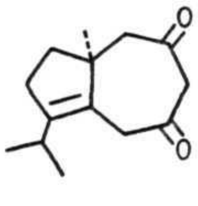
CHART I.6



(–)-30



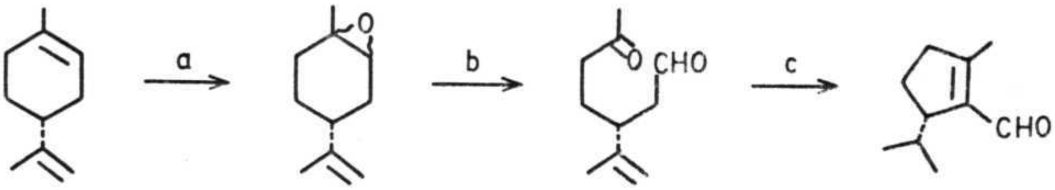
(+)-43



(–)-44

The α,β-unsaturated aldehyde 48, reported[30] previously from (+)-limonene 45 was chosen as our building block for the hydroazulenones 30, 43 and 44, as it had properly positioned methyl and isopropyl groups and adequate functionality to append the seven membered ring. As synthon 48 was required in large quantities, some tactical modifications of the literature procedure[30] were carried out, to suit our needs and inputs, Scheme I.8. For example, we started with (+)-limonene 45 and reduced the isopropenyl double bond at the stage of 47 rather than employ (+)-dihydrolimonene as the starting material.[30b] Complete details of preparation of 48 from (+)-limonene are provided in the experimental section and no further discussion is warranted here.

SCHEME I.8

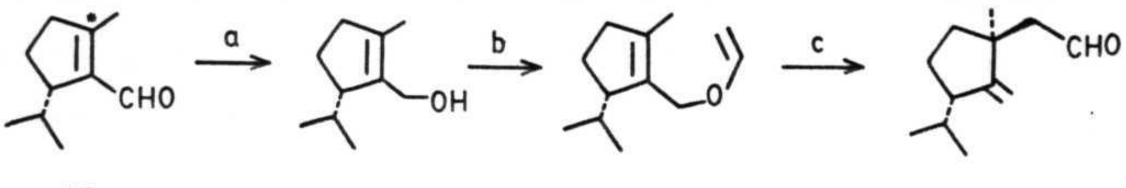


45 46 47 48

Reagents, Conditions & Yields: a) m-CPBA, $CHCl_3$, $0^{o}C$, 10h, 80%; b) i. 1%H_2SO_4, THF, RT, 1h; ii. $NaIO_4$, THF, H_2O, RT, 3h, 75% from 46; c) i. H_2-PtO_2, EtOAc, 20 psi, 1 h, 90%; ii. piperidine, HOAc, benzene, Δ, 1h, 70%.

Elaboration of 48 to the desired hydroazulenic systems 30, 43 and 44 required quaternisation of the methyl bearing carbon atom (*) in a stereo- and enantioselective manner with proper functionalities for further annulation of the seven membered ring. This was accomplished as shown in Scheme I.9, employing a diastereoselective [3s.3s]-shift (Claisen rearrangement) as the pivotal operation.

SCHEME I.9

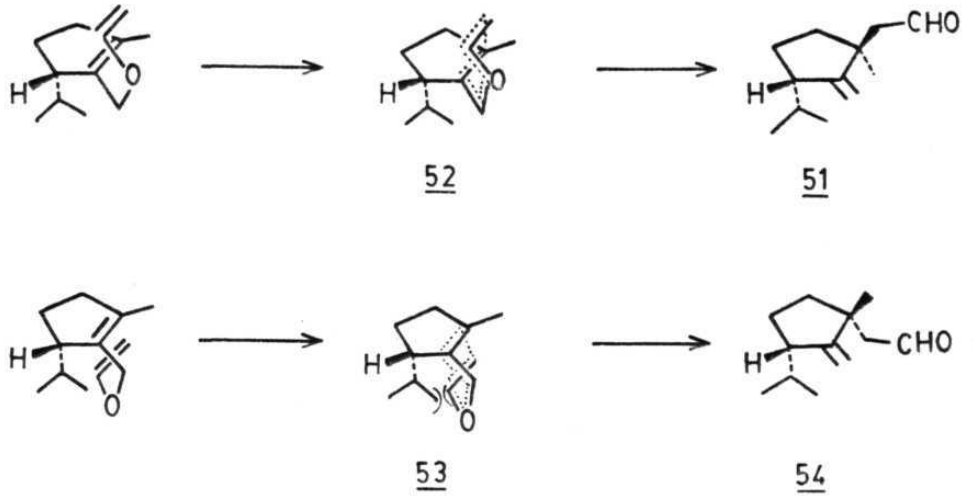


48 49 50 51

Reagents, Conditions & Yields: a) NaBH$_4$, CeCl$_3$.6H$_2$O, MeOH, 0^o, 0.5h, quantitative; b) Ethyl vinyl ether, Hg(OAc)$_2$, RT, 20h, 80%; c) sealed tube, 200^{o}C, 1h, 90%.

Chemoselective 1,2-reduction of α,β-unsaturated enal 48 with sodium borohydride in the presence of CeCl$_3$.6H$_2$O[31] furnished the allylic alcohol 49[30c] in near quantitative yield. The allylic alcohol 49 on Hg^{2+} catalysed transetherification[32] with ethyl vinyl ether furnished 50 in 80% yield, and its ^{1}H and ^{13}C-NMR spectral data (vide experimental) were in full agreement with its formulation. The stage was now set for the crucial quaternisation protocol through the Claisen rearrangement.[33] Heating 50 in a sealed tube at 200^{o}C for 1h, a common claisen rearangement regimen, led to a clean reaction and exclusive formation of unsaturated aldehyde (-)-51 was realised in 90% yield. Structure of 51 rests secured on its spectral data, particularly the methyl singlet at δ1.09 in the ^{1}H-NMR spectrum (Fig.I.1) and the quaternary sp^3 carbon signal at δ44.0 in the ^{13}C-NMR spectrum (Fig.I.2). The diastereofacial selectivity in the Claisen rearrangement (50 → 51), with the reaction taking place on the face opposite to the isopropyl group, was a most welcome outcome.[#] The observed stereochemistry can be readily rationalised in terms of preference for the transition state 52 over 53, Scheme I.10. No trace of 54 could be detected by us in the rearrangement of 50.

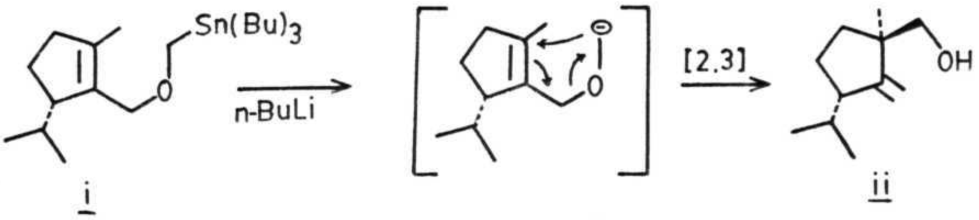
SCHEME I.10



Having acquired EPC (-)51 with secured stereogenicity at the quaternary centre, attention was turned towards the annulation of the seven membered ring, utilising the existing aldehyde and olefinic

---

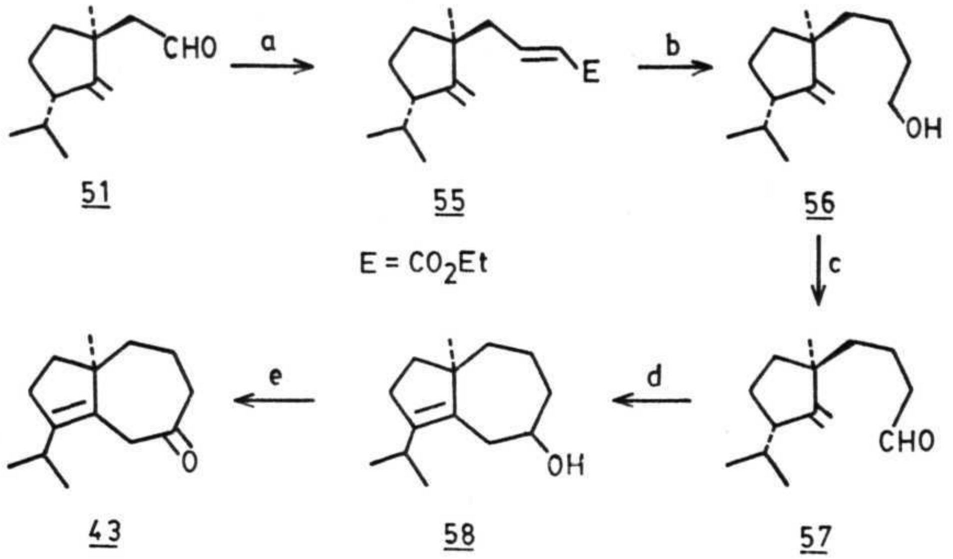
[#] After the completion of our work, Paquette[34] has reported a diastereoselective [2.3]-sigmatropic rearrangement i → ii in connection with his synthesis of retigeranic acid. Here also, the reaction takes place exclusively on the face opposite to the isopropyl group.



functionalities in 51. This required a `2C' homologation on 51 prior to an appropriate ring forming reaction. The desired elaboration of 51 to the hydroazulenic system was accomplished in several different ways. The choice of a particular methodology was dictated by the requirement of functionality on the hydroazulenic framework, eg., 30 or 43 or 44.

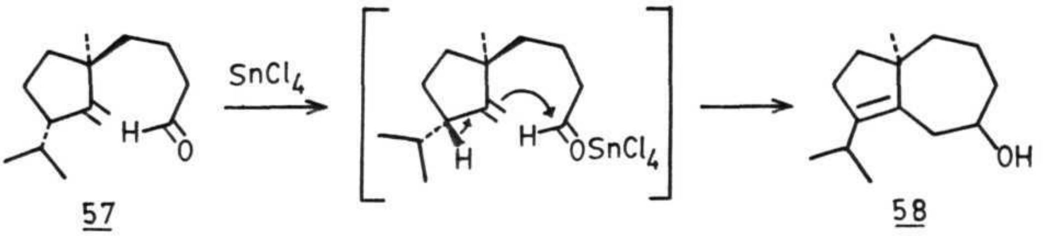
In the first set of reactions, aldehyde 51 was homologated through Wadsworth-Emmons[35] modification of the Wittig reaction using triethyl phosphonoacetate to furnish α, β-unsaturated ester 55 in 70% yield. Li-liq.NH_3 reduction[36] of 55 yielded the primary alcohol 56 in 50% yield. PDC oxidation[37] of 56 gave the labile aldehyde 57 (IR: 2740, 1715 cm^{-1}), which was directly employed for the crucial seven membered ring formation through an intramolecular Lewis acid catalysed ene reaction (Prins reaction)[38], Scheme I.11 & I.12. Exposure of unsaturated aldehyde 57 to $SnCl_4$ in dichloromethane at $0^{o}C$ resulted in the contemplated cyclisation and bicyclic alcohol 58 was obtained as a single stereoisomer, as revealed by its ^{1}H and ^{13}C-NMR spectra. No attempt was made to assign the stereochemistry to the hydroxyl group in 58 and it was further oxidised to the hydroazulenone 43 with PCC in dichloromethane. The structure of 43, $[\alpha]_D$+60(c 0.4, $CHCl_3$), was in full agreement with its IR (ν_{max} 1700 cm^{-1}), ^{1}H-NMR (Fig.I.3) and ^{13}C-NMR (Fig.I.4) spectral data. The ^{13}C-NMR showed the presence of three characteristic sp^2 carbon resonances at δ 211.0, 145.7 and 131.4. With the aquisition of 43, the first of the three targeted hydroazulenic ketones, effort was directed towards its more oxygenated derivative 44.

SCHEME I.11



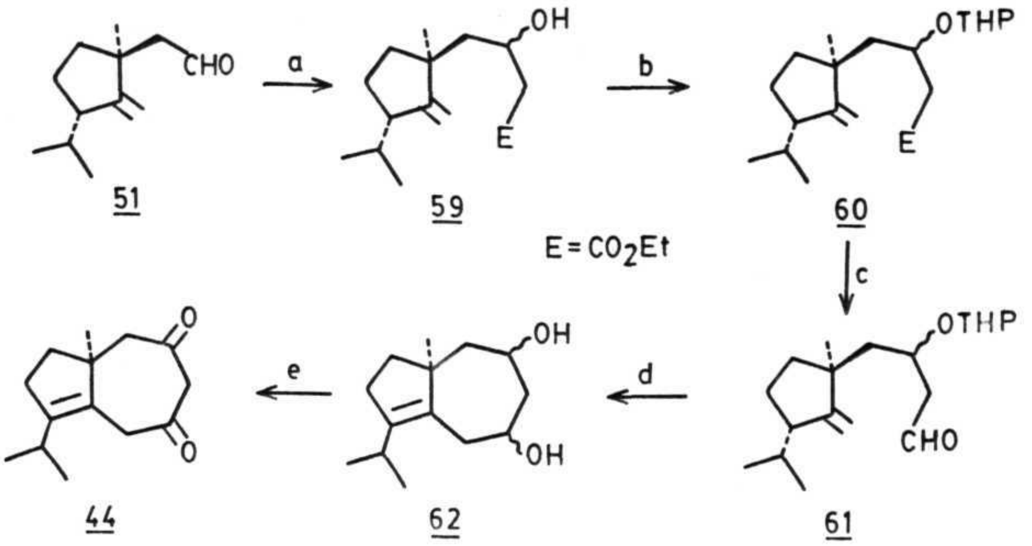
Reagents, Conditions & Yields: a) $(EtO)_3P^+OCH_2COOEtBr^-$, NaH, THF, RT, 1h, 70%; b) Li, liq.NH_3, THF, 50%; c) PDC, DCM, RT, 2h, 50%; d) $SnCl_4$, DCM, 25^{o}C, 65%; e) PCC, DCM, 4 A^o molecular sieves, 75%.

SCHEME I.12



Reformatsky reaction[39] of 51 with ethyl bromoactate furnished the homologated β-hydroxyester 59 as a mixture of diastereomers in 72% yield, Scheme I.13. The reactive β-hydroxy functionality in 59 was protected as a tetrahydropyranyl ether 60, to avoid proclivity towards elimination. The protected ester 60 was reduced to the aldehyde 61 through controlled reduction with DIBAL-H at -78^{o}C.[40] The crude, labile aldehyde 61 (ν_{max} : 2740, 1720 cm^{-1}) was used as such for the next step without further purification. Exposure of 61 to $SnCl_4$ in dichloromethane resulted in the

SCHEME I.13



Reagents, Conditions & Yields: a) Zn, $BrCH_2COOEt$, dioxane, RT, 1h, 72%; b) DHP, PPTS, DCM, RT, 6h, quantitative; c) DIBAL-H, DCM, $-78^{0}C$, 0.5h, 65%; d) $SnCl_4$, DCM, RT, 1h, 20%; e) PCC, DCM, 4 A^{0} molecular sieves, 0.5h, 60%.

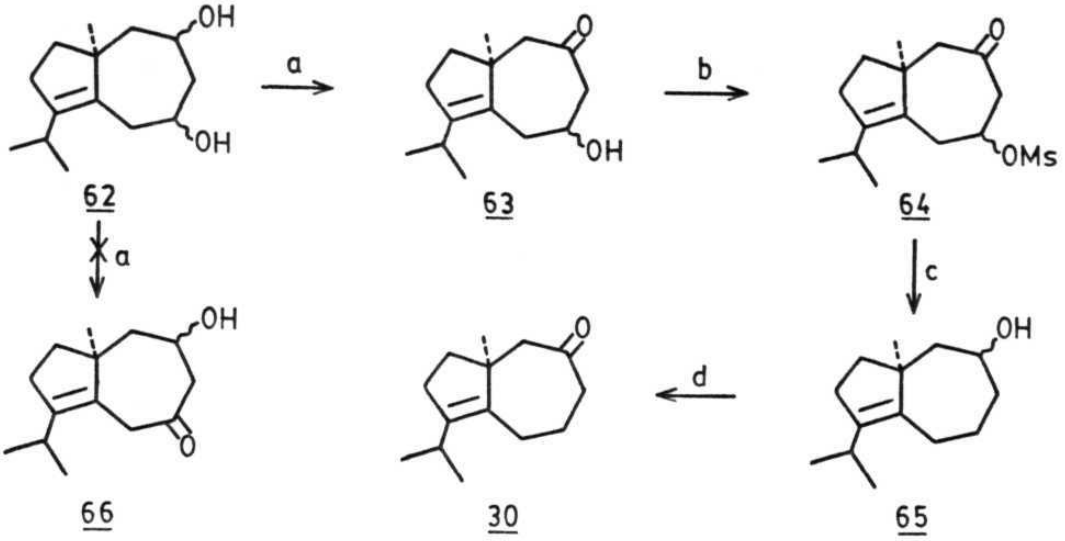
expected intramolecular ene cyclisation as well as removal of the tetrahydropyranyl protective group to yield 62, as a mixture of diastereomers, in a poor 20% yield. Changes in reaction conditions as well as Lewis acids (eg., BF_3-etherate) did not improve the yields of 62 significantly. At this stage 62 was subjected to PCC oxidation to furnish dione 44 in 60% yield. The hydroazulenic-1,3-dione 44, $[\alpha]_D$-34.2(c 1.0, $CHCl_3$), exhibited expected IR (ν_{max} 1700 cm^{-1}), ^{1}H-NMR (Fig.I.5) and ^{13}C-NMR (Fig.I.6) spectral values. In particular, the ^{13}C-NMR spectrum had signals at δ 203.0, 202.8, 148.8, 130.0 due to two carbonyl groups and tetrasubstituted olefinic sp^2 carbons.

Attention was now turned on the hydroazulenone 30. Regioselective and controlled oxidation of the diol 62 with PCC at $0^{o}C$ furnished the hydroxyketone 63 in 50% yield, Scheme I.14. The isomeric hydroxyketone 66 was not detected. The next requirement was the reductive removal of the β -hydroxy group. For this purpose, the β-hydroxy ketone 63 was converted to the keto-mesylate 64 and subjected to LAH reduction to furnish the hydroxy compound 65 in 50% yield from 64. The diastereomeric mixture 65 was oxidised with PCC to yield the required ketone 30. The structure of the hydroazulenone 30, $[\alpha]_D$ -13(c 1.0, $CHCl_3$), was fully secured on the basis of the IR, ^{1}H-NMR (Fig.I.7) and ^{13}C-NMR (Fig.I.8) spectral data.[#]

Although we successfully developed a methodology for constructing (-)-30 in enantiomerically pure form, Scheme I.14, the reaction sequence from aldehyde 51 to 30 was rather long and not quite amenable to scaling-up. Thus, an alternate, shorter and efficient way to 30 from aldehyde 51 was sought and developed.

[#] In the mean time, synthesis of (±)-30 by Pattenden et al., following an entirely different strategy (vide supra) appeared in literature.[24a] A direct spectral comparison established the identity of our (-)-30 with their compound. We thank Professor G. Pattenden for the IR and ^{1}H-NMR spectra of (±)-30.

SCHEME I.14

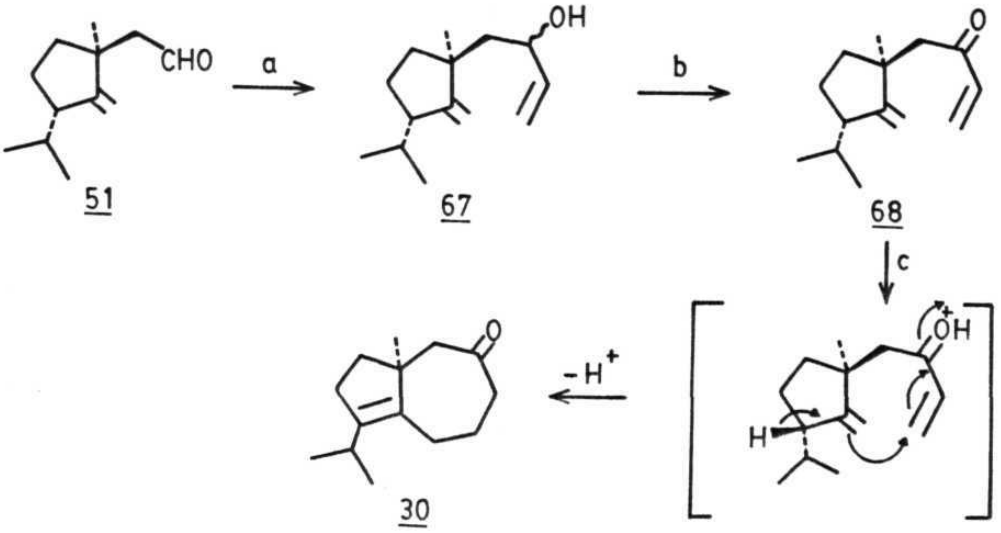


Reagents, Conditions & Yields: a) PCC, DCM, 0°C, 0.5h, 50%; b) MsCl, pyridine, 0°C, 4h, 74%, c) LAH, ether, RT, 0.5h; d) PCC, DCM, RT, 4 A° molecular sieves, 50% from 64.

Addition of vinylmagnesium bromide[41] to the aldehyde 51 readily furnished the allylic alcohol 67 as a mixture of diastereomers in 75% yield, Scheme I.15. This mixture was directly subjected to PCC oxidation to furnish the α,β-unsaturated enone 68 as a single compound, in 65% yield. The enone structure of 68 was consonant with the ^{13}C-NMR spectrum which showed the presence of five sp^{2} carbon resonances at δ 188.6, 162.5, 137.7, 127.4 and 107.8.

Acid catalysed enone-olefin cyclisation stratagem was now employed to construct the seven-membered ring in 30, Scheme I.15. Treatment of 68 with catalytic amount of 70% perchloric acid in ethyl acetate - acetic

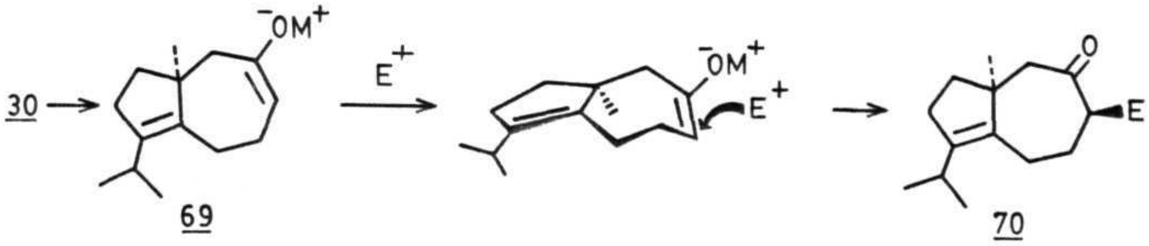
SCHEME I.15



Reagents, Conditions & Yields: a) Vinyl bromide(THF), Mg, THF, RT, 0.5h, 75%; b) PCC, DCM, $4 A^{0}$ molecular sieves, RT, 1h, 65%; c)EtOAc-Ac_2O, Cat.$HClO_4$, RT, 25 min, 65%.

anhydride[42] furnished the bicyclic ketone 30 as a clean, single product of the reaction, in 65% yield. This route to the hydroazulenone 30 enabled its ready preparation in multi-gram quantities. This was a very satisfying outcome as EPC(-)-30, had the potential to serve as a very efficacious building block for a variety of natural products, as described in this as well as later chapters of the thesis.

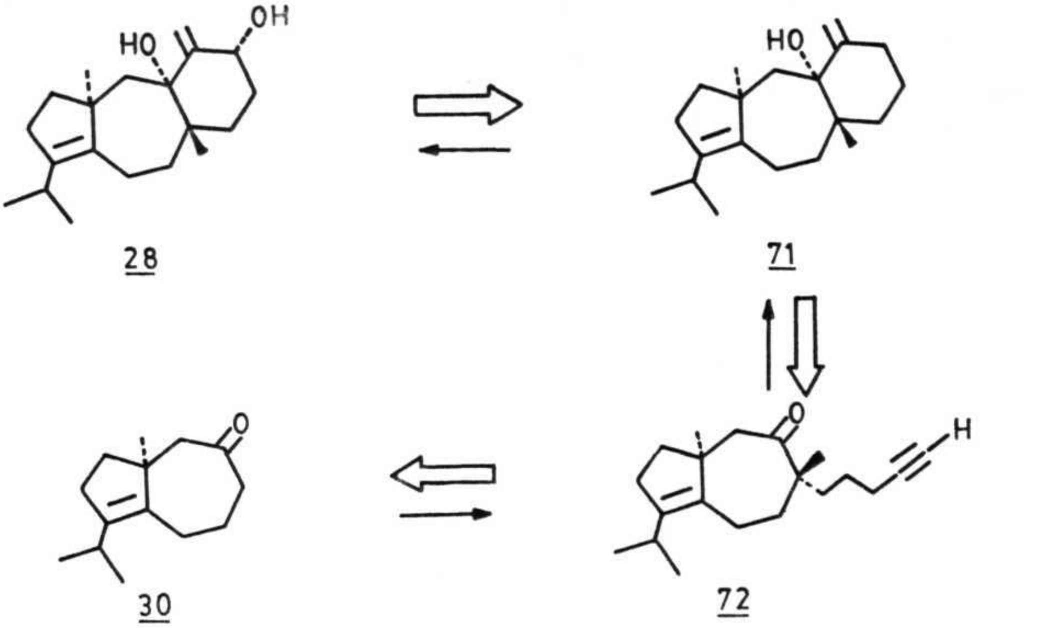
The stage was now set for further elaboration of hydroazulenones 30, 43 and 44 to the dolastane framework. Among 30, 43 and 44, we preferred 30 for further effort on account of its ready accessibility in quantity. More importantly, the conformation of 30 indicated that it was likely to exhibit pronounced regio- and stereoselectivity in its reactions. Thus, the enolate 69 derived from 30 was predicted to accept electrophiles from the β-face opposite to the angular methyl group to give 70. Efforts were now directed towards the synthesis of (+)-isoamijiol 28 and (+)-dolasta-1(15),7,9-trien-14-ol 29 from the hydroazulenone 30.



I.4. TOTAL SYNTHESIS OF (+)-ISOAMIJIOL 28 AND (+)-DOLASTA-1(15),7,9-TRIEN-14-OL 29

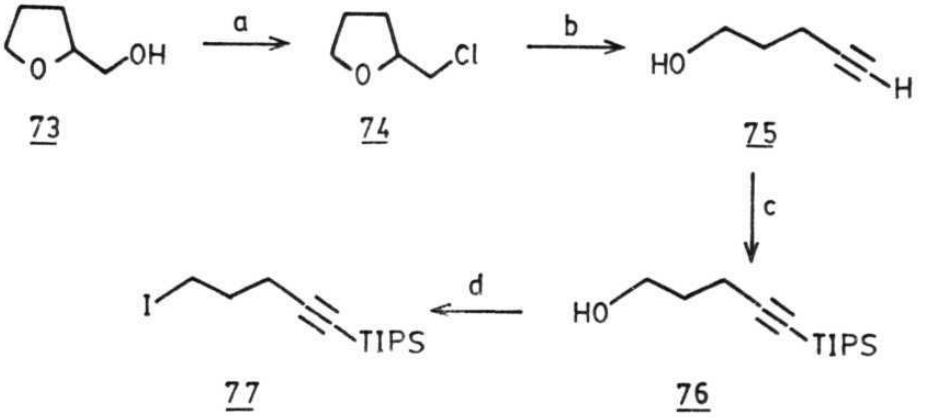
A retrosynthetic analysis on (+)-isoamijiol 28 led to the identification of hydroazulenone 30 as the advanced precursor and also delineated the methodology for its elaboration to the natural product, Scheme I.16. Three main synthetic operations emerged for the conversion of 30 to (+)-isomijiol 28. These were : (i) sequential, regio- and stereoselective alkylations of 30 with 5-iodo-1-pentyne and methyl iodide (30 → 72) (ii) radical induced terminal alkyne-ketone cyclisation to annulate the six membered ring with concomitant generation of the bridgehead hydroxy and terminal methylene functionalities (72 → 71) and (iii) regio- and stereoselctive allylic oxidation (71 → 28). Practical realisation of these steps depicted in Scheme I.16 was achieved as follows.

SCHEME I.16



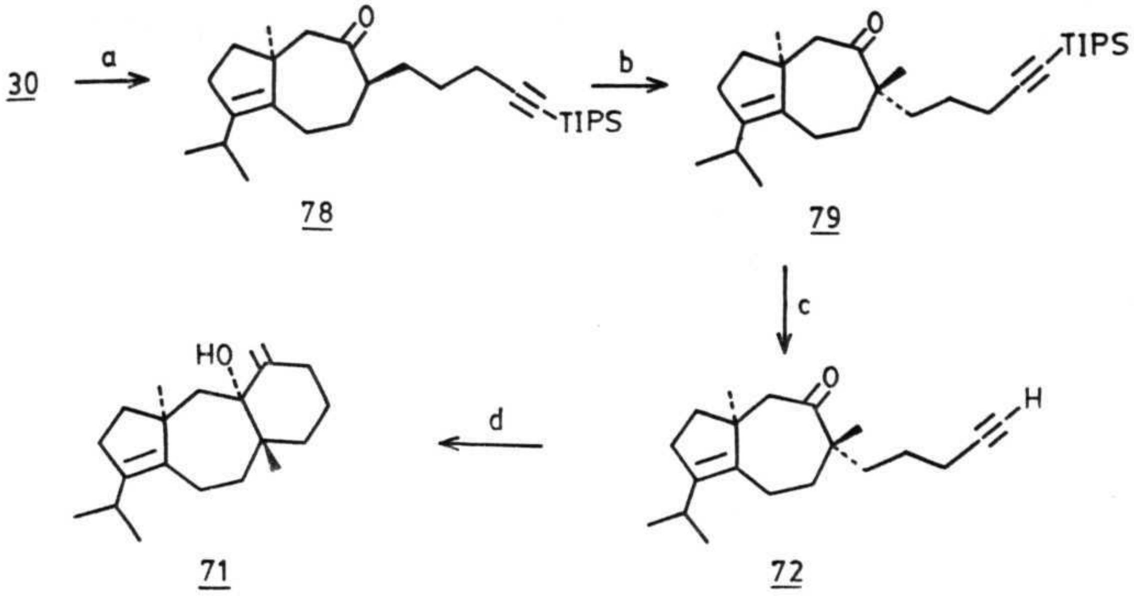
Deprotonation of 30 with LHMDS in the presence of HMPA and quenching of the lithium enolate with triisopropylsilyl (TIPS) protected 5-iodo-1-pentyne 77 (prepared from tetrahydrofurfuryl alcohol 73 as shown in Scheme I.17)[43] furnished 78 as a single stereoisomer in 80% yield, Scheme I.18.

SCHEME I.17



Reagents, Conditions & yields: a) $SOCl_2$, pyridine, RT, 4h, 75%; b) $NaNH_2$, liq.NH_3, 60%; c) EtMgBr, THF, TIPSCl, RT, 12h, quantitative; d) triphenoxyphosphonium iodide, 80°C, 60%.

SCHEME I.18

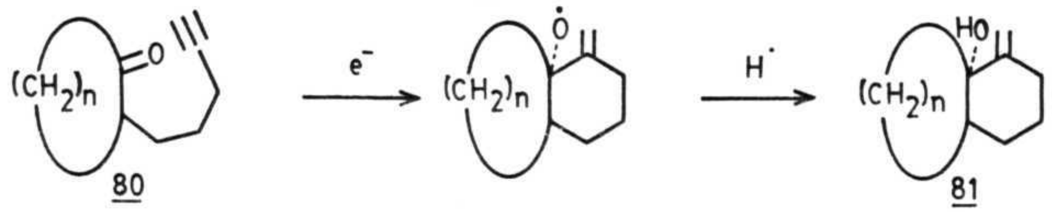


Reagents, Conditions & Yields: a) LHMDS, THF-HMPA, $I(CH_2)_3C{=}C$-$Si(CH(CH_3)_2)_3$, $-10^{o}C$, 1h, 80%; b) NaH, DME, MeI, RT, 24h, 65%; c) n-$Bu_4N^+F^-$, THF, RT, 5 min. quantitative; d) $C_{10}H_8^-Na$, THF, RT, 40%.

To introduce the second quaternary methyl group, the thermodynamic enolate generated from 78 with sodium hydride was quenched with methyl iodide to give 79 in 65% yield. The stereoselective placement of the methyl group was a consequence of the topological bias engendered by the pre-existing C(1) quaternary methyl group (see, 69 → 70). While 79 could be readily characterised, better spectra were obtained after deprotection of the TIPS protective group to eliminate the towering presence of the signal at δ 1.01 due to the three isopropyl groups. Treatment of 79 with tetra-n-butylammonium fluoride led to the bicyclic keto-alkyne 72 in quantitative yield. The ^1H-NMR (Fig.I.9) and ^{13}C-NMR (Fig.I.10) spectra of 72 fully supported its formulation.

For the alkyne-ketone cyclisation to furnish the bridgehead hydroxymethylene derivative (80 → 81), Scheme I.19, several reagents have been successfully employed. These include, sodium naphthalenide[44], metal-liq.NH_3[45], samarium iodide (SmI_2)[46], Zn-$(CH_3)_3SiCl$[47], electrochemical[48] and photochemical methods[49] etc. For the cyclisation of 72, we chose to employ the sodium naphthalenide based radical cyclisation procedure developed by the group of S.K. Pradhan, a fellow countryman.[44].

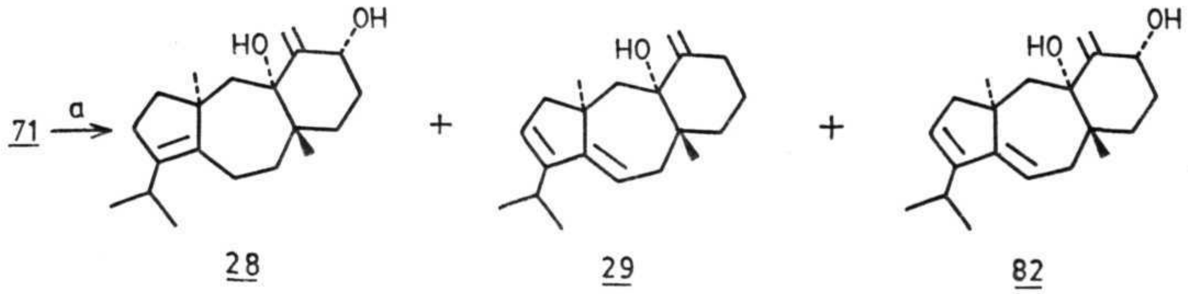
SCHEME I.19



When a THF solution of 72 was titrated with the dark-green solution of sodium naphthalenide, cyclised allylic alcohol 71 was obtained in 40% yield after careful column chromatography. Formation of 71 heralded the completion of the dolastane framework. The trans-stereoselectivity of the newly appended ring in 71 follows from the fact that its C(12) and C(5) angular methyl group resonances at δ 1.34 and 0.78 (Fig. I.11) are very similar to the corresponding resonances in the natural product isoamijiol 28 (δ 1.34 and δ 0.77).

The final step in the synthesis of (+)-isoamijiol 28 was the introduction of the second allylic hydroxy group at C(2). For this purpose, 71 was reacted with catalytic amount of selenium dioxide in the presence of t-butyl hydroperoxide[50], Scheme I.20. The reaction proved to be very sensitive to the reaction conditions and furnished a complex mixture of products. However, the overall outcome was quite fortuitous and after careful and repeated chromatography three products, (+)-isoamijiol 28, (+)-dolasta-1(15),7,9-trien-14-ol 29 and (+)-dolasta-1(15),7,9-trien-2,14-diol 82 were isolated in a ratio of ~ 2:3:1.

SCHEME I.20



Reagents, Conditions & Yields: a) SeO_2, t-BuOOH, DCM, -4° - 0°C, 60%.

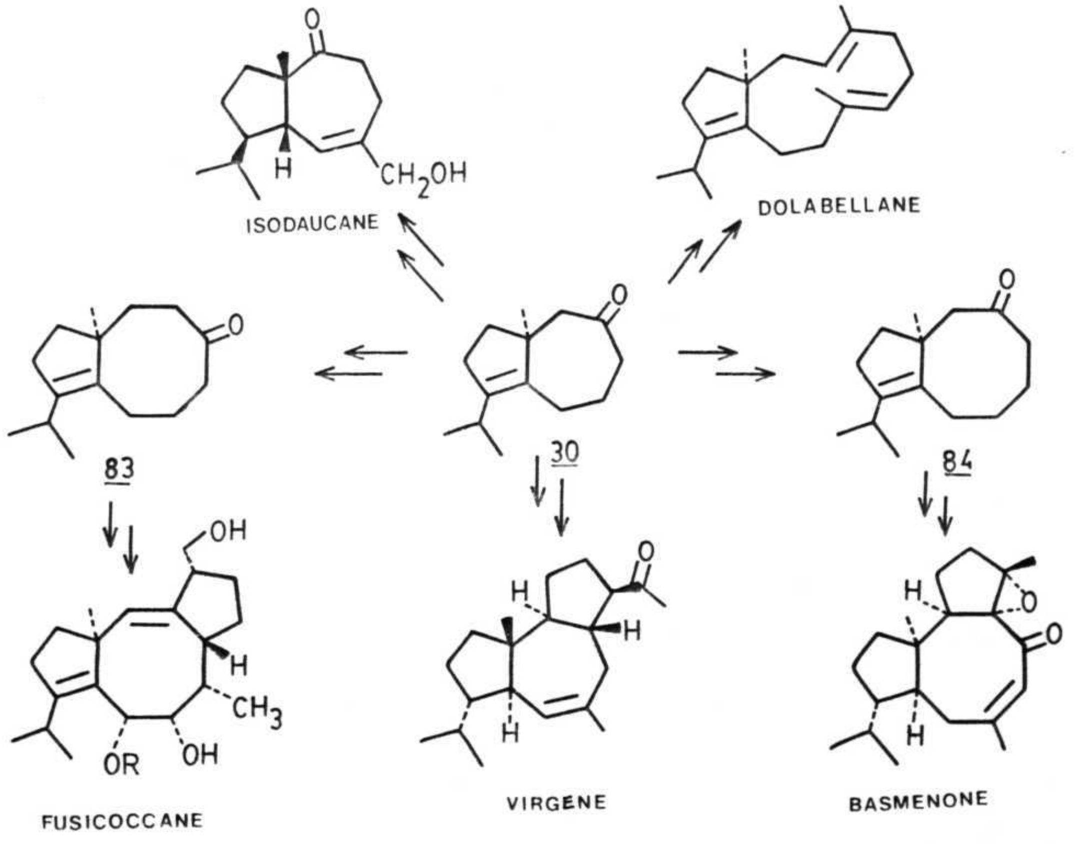
Identity of isoamijiol 28, $[\alpha]_D$+45 (c 0.1, $CHCl_3$), $[\alpha]_D$ (lit -45)[22], and (+)-dolasta-1(15),7,9-trien-14-ol- 29, $[\alpha]_D$+200 (c 0.2, $CHCl_3$; lit. rotation not reported)[23] were established through spectral comparison with the natural products.[#] Structure to 82 was tentatively assigned on the basis of its spectral characteristics summarised in the experimental section. Thus, the first-enantioselective syntheses of (+)-isoamijiol 28 and (+)-dolasta-1(15),7,9-trien-14-ol 29 were successfully achieved from R(+)-limonene 45 in 16 steps.

[#] We thank Professors Ochi and Piers for the comparison spectra of 28 and 29, respectively.

I.5. SUMMARY AND OUTLOOK

We have delineated new and practical approaches to several enantiomerically pure hydroazulenones (-)-30, (+)-43 and (-)-44 from (+)-limonene 45. One of them, the hydroazulenone 30 has served as the key advanced intermediate in the enantioselective synthesis of (+)-isoamijiol 28 and (+)-dolasta-1(15),7,9-trien-14-ol 29.

All the hydroazulenones reported here are potentially serviceable for the synthesis of other highly oxygenated dolastanes as well as many other related terpene natural products. For example, ring expansion of the hydroazulenones 30 and 44 provides advanced building blocks 83 and 84 for the fusicoccane and basmenone type diterpenes, respectively. These hydroazulenones can also serve as precursors for the novel tobacco diterpene virgene as well as isodaucane sesquiterpenes and dolabellane diterpenes. Some of these possiblities have been practically realised and are reported in the later chapters of this thesis.



I.6. EXPERIMENTAL

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

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

Ultraviolet spectra : Ultraviolet spectra were recorded on a Shimadzu 200S spectrophotometer.

Infrared spectra : Infrared spectra were recorded on Perkin-Elmer Model 1310 or 297 spectrophotometers. 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 (100 MHz) were recorded on JEOL MH-100 spectrometer or JEOL FX-100 spectrometer and carbon-13 magnetic resonance spectra (25 MHz) were recorded on JEOL FX-100 spectrometer. ^{1}H and ^{13}C-NMR samples were made in chloroform-d solvent and chemical shifts are reported in scale using tetramethylsilane (Me_4Si) as the internal standard. The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet and multiplet, respectively. ^{13}C-NMR assignments differing by only 2-3 ppm can in some cases be interchanged.

Optical rotation : Optical rotations were measured on AUTOPOL II polarimeter in chloroform solutions.

Elemental analysis : Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyser.

Chromatography : Analytical thin-layer chromatographies (tlc) were performed on (10 x 5 cm) glass plates coated (250 m) with Acme's Silica gel G or GF_{254} (containing 13% of calcium sulphate as binder). Visualisation 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 column was usually eluted with ethyl acetate - pet ether. Some of separations were done on LKB 2211 (Super rac) MPLC using dichloromethane as eluent.

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. Dichloromethane was distilled over P_2O_5. Benzene was distilled over sodium and stored over pressed sodium wire. Dry ether and dry THF were made by distilling them from sodium-benzophenone ketyl.

Hydrogenations were carried out on a Parr hydrogenation apparatus in 250 ml pressure bottles. 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.

Starting Materials : All the starting materials were either acquired commercially or prepared according to standard literature procedures. R-(+)-limonene 45 ([ ]$_D$ +112) and (+)-limonene oxide 46 ([ ]$_D$+69) which was used in later part of the thesis, were purchased from Aldrich chemical company, Inc. Triisopropylsilyl chloride and tetrahydrofurfuryl alcohol 73 were obtained from Fluka and Seisco chemical companies, respectively. All the commercial chemicals were distilled prior to use.

Epoxidation of (R)-(+)-limonene (45):[30]

Into a 1 l three necked RB flask fitted with dry N_2 inlet and mercury seal was placed (+)-limonene 45 (100 g, 0.7 mol) in dry chloroform (500 ml). To this reaction mixture was added m-chloroperbenzoic acid (130 g, 0.75 mol) in small portions over a period of 1 h. After addition was complete the reaction mixture was left at room temperature for 10 h with stirring. The reaction mixture was quenched by addition of saturated Na_2CO_3 solution and the organic layer separated. The aqueous layer was extracted with chloroform (250 ml x 3). The combined organic extract was washed and dried. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish limonene oxide 46 (83 g) in 80% yield as diastereomeric mixture.

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

^{1}H-NMR : δ4.73 (4H, $-C=C\underline{H}_2$), 3.02 (2H, m), 2.0 - 1.4 (20H, m), 1.31 and 1.33 (6H, s, $-C-C\underline{H}_3$)

5S-Isopropyl-2-methyl cyclopent-1-ene-1-carboxaldehyde (48):[30]

Into a 1 l RB flask limonene oxide 46 (80 g) was placed in 50% aq. THF (100 ml) and to this 1% H_2SO_4 (100 ml) was added slowly at 0°C and the reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was extracted with ether (500 ml x 3) and the ethereal extract was washed with saturated $NaHCO_3$ solution, water and dried. The crude product obtained after removal of the solvent was used as such for the next step.

Into a 500 ml RB flask the above diol (50 g, 0.3 mol) was placed in 50% aq. THF (150 ml) and cooled in an ice-bath. To this mixture, sodium metaperiodate (64 g, 0.3 mol) was added in small portions and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was extracted with ether (500 ml x 3) and the ethereal extract was washed and dried. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish the keto-aldehyde 47 (35 g) in 75% yield.

A solution of the above keto-aldehyde 47 (10.0 g, 60 mmol) in dry ethyl acetate (20 ml) was hydrogenated (25 psi, pressure) over PtO_2 (20 mg) for 1 h. The catalyst was filtered-off and the solvent was removed and distilled at 110^oC at 0.1 mm to furnish the saturated keto-aldehyde (9.0 g) in 90% yield.

Into a 500 ml RB flask fitted with a Dean-Stark water separator and reflux condenser, the above saturated keto-aldehyde (25 g, 150 mmol) was placed in dry benzene (250 ml). To this reaction mixture glacial acetic acid (3 ml) and piperidine (3 ml) were added and the contents refluxed for 1 h with periodic removal of water. The reaction mixture was diluted with water (100 ml) and the benzene layer was separated. The aqueous layer was extracted with ether (100 ml x 3). The combined organic extract was washed and dried. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish the aldehyde 48 (17 g) in 70% yield.

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

bp. : 65^oC/4.0 mm

IR : 2720, 1670 cm^{-1}

^1H-NMR : δ9.99 (1H, s, O=C$\underline{H}$), 2.6 - 1.6 (9H, m), 0.88 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.65 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

(5S-Isopropyl-2-methyl cyclopent-1-ene)-1- methanol (49):^{30c}

Into a 250 ml RB flask aldehyde 48 (10.0 g, 65.8 mmol) was placed and dry methanol (100 ml) was added followed by $CeCl_3.6H_2O$ (2.5 g). The reaction mixture was cooled to 0^oC in an ice-salt bath and to it sodium borohydride (2.65 g, 70.0 mmol) was added slowly in small portions. After the addition was over, the reaction mixture was stirred for 0.5 h and methanol was removed under reduced pressure. The residue was diluted with water (50 ml) and extracted with ether (150 ml x 3). The ethereal extract was washed with dilute HCl, saturated $NaHCO_3$ and dried. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish the allylic alcohol <u>49</u> (9.6 g) in near quantitative yield.

$[\alpha]_D$: +43 (c 1.0, $CHCl_3$)

bp. : 75°C/1.3 mm

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

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

<u>(5S-Isopropyl-2-methyl cyclopent-1-ene)-1-methyl vinyl ether</u> (<u>50</u>):

Into a 500 ml RB flask, allylic alcohol <u>49</u> (9.5 g, 61.6 mmol) was placed and freshly distilled ethyl vinyl ether (300 ml) was added. To this mixture mercuric acetate (1.0 g) was added and the reaction mixture was stirred at room temperature for 20 h. The excess ethyl vinyl ether was recovered by distillation and the residue was filtered through a basic alumina (50 g) column using pet ether to remove the insoluble mercuric acetate impurities. The pure vinyl ether <u>50</u> (8.9 g) was obtained in 80% yield after removal of the solvent.

$[\alpha]_D$: -53 (c 1.0, $CHCl_3$)

bp. : 100°C/0.5 mm

IR : 3050, 2950, 1630, 1600, 1460, 1190, 800 cm^{-1}

^{1}H-NMR : δ6.6 - 6.2 (1H, m, -O-C$\underline{H}$=CH$_2$), 4.4 - 3.8(4H, m, -C$\underline{H}_2$-O-CH=C$\underline{H}_2$), 3.0 - 1.8 (6H, series of m), 1.7 (3H, br s, -C=C-C$\underline{H}_3$), 0.9 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.7 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

^{13}C-NMR : δ151.8, 138.0, 132.7, 86.3, 63.1, 53.1, 38.0, 28.7, 21.9, 21.4, 16.0, 15.1

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

<u>3S-Isopropyl-1R-methyl-2-methylenecyclopentane-1R-acetaldehyde</u> (<u>51</u>):

Vinyl ether <u>50</u> (5.0 g, 27.8 mmol) was taken (neat) in to a corning glass tube and sealed under N_2 atmosphere. The sealed tube was heated at 200^{o}C for 1 h. After cooling it to room temperature the crude product was charged on a silica gel (50 g) column. Elution with pet ether resulted in the removal of less polar impurities and further elution with 5% ethyl acetate - pet ether furnished the aldehyde <u>51</u> (4.5 g) in 90% yield.

$[\alpha]_D$: -70 (c 1.0, $CHCl_3$)

bp. : 100^{o}C/0.5 mm

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

^{1}H-NMR (fig. I.1) : δ9.7 (1H, t, J = 4Hz, O=C-$\underline{H}$), 4.89 (1H, d, J = 4Hz, -C=C$\underline{H}_2$), 4.85 (1H, d. J = 4 Hz, -C=C$\underline{H}_2$), 2.44 (2H, m, -C$\underline{H}_2$-CHO), 2.25 - 1.3 (6H, m), 1.09 (3H, s, -C-C$\underline{H}_3$), 0.97 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.79(3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

^{13}C-NMR (fig. I.2) : δ202.9, 161.0, 104.9, 54.4, 50.7, 44.0, 37.3, 28.8, 27.6, 23.0, 21.7, 16.4

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

Found: C, 79.83 ; H, 11.14

<u>3S-Isopropyl-1R-methyl-2-methylene-1R-(ethylbutyrate-2'-ene-4'-yl)cyclopentane</u> (<u>55</u>):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, reflux condenser and mercury seal, sodium hydride (400 mg, 8.0 mmol, 50% dispersion in oil) was placed and washed with dry benzene (2 ml) to remove the oil. Dry THF (5 ml) was introduced followed by triethyl phosphonoacetate (1.24 g, 10 mmol) in dry THF (5 ml). After stirring for 20 min at room temperature, aldehyde <u>51</u> (1.0 g, 5.2 mmol) in dry THF (5 ml) was added at 5-10^{o}C and stirring was continued for 1 h. The reaction mixture was quenched by careful addition of water (25 ml) and extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried and concentrated to give the crude product which was charged on a silica gel (15 g) column. Elution with 10% ethyl acetate - pet ether furnished the unsaturated ester <u>55</u> (900 mg) in 70% yield.

$[\alpha]_D$: -35 (c 0.2, $CHCl_3$)

bp. : 160^{o}C/0.1 mm

IR : 3050, 1725, 1650, 1460, 1270, 1180, 1040, 890 cm^{-1}

^{1}H-NMR : δ6.9 (1H, dt, J_1 = 14 Hz, J_2 = 7Hz, $-C\underline{H}{=}CH-CO_2C_2H_5$), 5.8 (1H, br d, J = 14 Hz, $-CH{=}C\underline{H}-CO_2C_2H_5$), 4.8 (2H, m, $-C{=}C\underline{H}_2$), 4.15 (2H, q, J = 8Hz, $-OC\underline{H}_2CH_3$), 2.5 - 1.3 (8H, series of m), 1.25 (3H, t, J = 7Hz, $OCH_2C\underline{H}_3$), 1.0 (3H, s, $-C-C\underline{H}_3$), 0.95 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.8 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ166.7, 161.5, 146.7, 123.3, 104.3, 60.0, 50.9, 45.9, 44.6, 37.0, 29.0, 27.3, 23.1, 21.8, 16.6, 14,3

Analysis : $C_{16}H_{26}O_2$ Calcd: C, 76.75 ; H, 10.47
Found: C, 76.95 ; H, 10.42

3S-Isopropyl-1R-methyl-2-methylene-1R-(1'-hydroxybut-4'-yl)cyclopentane (56):

Into a two necked 100 ml RB flask fitted with a guard tube and septum was placed freshly distilled liq.NH_3 (50 ml). To this freshly cut sodium metal (90 mg, 4.0 mmol) was added piece by piece. The resulting blue solution was stirred for 15 min and the ester 55 (500 mg, 2.0 mmol) in dry ether (5 ml) was slowly added to it. After stirring for 1 h the reaction mixture was quenched by addition of solid NH_4Cl. Ammonia was allowed to escape and the residue was dissolved in water (25 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was charged on a silica gel (10 g) column. Elution with 15% ethyl acetate - pet ether furnished the primary alcohol 56 (180 mg) in 50% yield.

$[\alpha]_D$: -18.6 (c 0.7, $CHCl_3$)

bp. : $150^{o}C/0.1$ mm

IR : 3300, 3050, 2950, 1450, 1040, 890 cm^{-1}

^{1}H-NMR : δ4.75 (2H, m, $-C{=}C\underline{H}_2$), 3.6 (2H, t, J = 6Hz, $-C\underline{H}_2-OH$), 2.6 - 1.2 (12H, series of m), 1.02 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.98 (3H, s, $-C-C\underline{H}_3$), 0.75 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ162.8, 103.1, 62.9, 51.3, 45.9, 41.8, 36.9, 33.6, 28.9, 27.3, 23.2, 22.0, 21.0, 16.6

Analysis : $C_{14}H_{26}O$ Calcd: C, 79.93 ; H, 12.46

Found: C, 80.11 ; H, 12.48

3S-Isopropyl-1R-methyl-2-methylene-1R-(but-1'-al-4'-yl)cyclopentane (57):

Into a 50 ml RB flask pyridinium dichromate (430 mg, 2.0 mmol) in dry dichloromethane (10 ml) was placed and to this mixture was added hydroxy olefin 56 (200 mg, 0.95 mmol) in dry dichloromethane (10 ml) at 0°C. The reaction mixture was brought to room temperature and stirred for 1 h. Then the reaction mixture was diluted with dry ether (50 ml) and the resulting mixture was passed through a small florisil pad (3 g). The crude product obtained after removal of the solvent was charged on a silica gel (10 g) column. Elution with 10% ethyl acetate - pet ether furnished the labile aldehyde 57 (100 mg) in 50% yield.

bp. : 145°C/0.1 mm

IR : 3050, 2950, 2740, 1715 cm^{-1}

^{1}H-NMR : δ9.75 (1H, br s, O=C-H), 4.78 (2H, m, $-C=CH_2$), 2.5 -2.2 (4H, m), 1.8 - 1.2 (8H, series of m), 1.05 - 0.75 (9H, series of s and d)

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

Found: C, 80.79 ; H, 11.71

8-Isopropyl-1S-methyl bicyclo[5.3.0]dec-7-en-5-ol (58):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal was placed aldehyde 57 (100 mg, 0.5 mmol) in dry dichloromethane (10 ml). To this mixture, stannic chloride (0.1 ml, catalytic amount) was added at 0°C. The reaction mixture was slowly brought to room temperature and stirred for 30 min. Then the reaction was quenched by careful addition of $NaHCO_3$ solution. The resulting reaction mixture was extracted with dichloromethane (50 ml x 3). The combined extract was washed, dried and concentrated. The crude product thus obtained was chromatographed on a silica gel (10 g) column. Elution with 5% ethyl acetate - pet ether removed the less polar impurities and further elution with 10% ethyl acetate - pet ether furnished the bicyclic alcohol 58 (65 mg) in 65% yield.

$[\alpha]_D$: +24 (c 0.8, $CHCl_3$)

bp. : 150°C/0.06 mm

IR : 3450, 2950, 1450, 1040 cm^{-1}

^1H-NMR : δ3.9(1H, m. $-C\underline{H}-OH$), 3.2 - 1.2 (13H, series of m), 1.05 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.88 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.85 (3H, s, $-C-C\underline{H}_3$)

^{13}C-NMR : δ140.3, 137.0, 66.7, 50.0, 40.5, 39.7, 36.7, 30.9, 27.1, 27.0, 25.3, 21.6, 17.55

Analysis : $C_{14}H_{24}O$ Calcd: C, 80.71 ; H, 11.61
Found: C, 80.32 ; H, 11.64

8-Isopropyl-1S-methyl bicyclo[5.3.0]dec-7-en-5-one (43):

To a suspension of pyridinium chlorochromate (65 mg, 0.3 mmol) in dry dichloromethane (10 ml) containing 1.0 g of activated molecular sieves (4 A°) was added alcohol 58 (40 mg, 0.2 mmol) in dry dichloromethane (5 ml) at 0°C. The reaction mixture was brought to room temperature, stirred for an additional 1 h, diluted with dry ether (20 ml) and filtered through a small florisil (5 g) pad and repeatedly washed with dry ether. Removal of the solvent gave an oily liquid which was charged on a silica gel (10 g) column. Elution with 5% ethyl acetate - pet ether furnished the ketone (30 mg) in 75% yield.

$[\alpha]_D$: +60 (c 0.4, $CHCl_3$)

bp. : $140^{o}C/0.1$ mm

IR : 2950, 1700, 1450 cm^{-1}

^{1}H-NMR (fig. I.3) : δ3.24 (1H, d, J = 16 Hz), 2.9 (1H, br d, J = 16 Hz), 2.8 - 2.1 (5H, m), 1.8 - 1.4 (6H, m), 1.01 (3H, s, $-C-C\underline{H}_3$), 0.98 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.96 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR (fig. I.4) : δ211.0, 145.7, 131.4, 49.2, 43.9, 40.6, 38.5, 27.4, 27.0, 23.5, 20.8, 20.5

Analysis : $C_{14}H_{22}O$ Calcd: C, 81.50 ; H, 10.75
Found: C, 81.41 ; H, 10.76

3S-Isopropyl-1R-methyl-2-methylene-1R-(3'-hydroxyethylbutyrate-4'-yl)cyclopentane (59):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal, were placed zinc (1.0 g, 15 mmol), iodine (100 mg), ethyl bromoacetate (1.8 ml, 16 mmol) and dry dioxane (10 ml). To this mixture was added the aldehyde 51 (2.0 g, 11.11 mmol) in dry dioxane (10 ml). The resulting reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of water and then extracted with dichloromethane (100 ml x 3). The crude product obtained after removal of the solvent was filtered through a silica gel (20 g) column. Elution with 20%

ethyl acetate - pet ether furnished the hydroxy ester <u>59</u> (2.15 g) in 72% yield as a mixture of diastereomers.

bp. : $140^{0}C/0.1$ mm

IR : 3500, 3050, 2950, 1720, 1640, 1180, 1030, 890 cm^{-1}

^{1}H-NMR : δ5.0 - 4.8(4H, m, $-C=C\underline{H}_2$), 4.15 (6H, q, J = 7Hz, $O-C\underline{H}_2-CH_3$ and $-C\underline{H}-OH$), 3.1 - 2.9 (2H, m), 2.6 - 1.3 (20H, series of m), 1.3 (6H, t, J = 7Hz, $O-CH_2-C\underline{H}_3$), 1.08 and 1.04 (6H, s, $-C-C\underline{H}_3$), 1.0 (6H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.8 (6H, d, J = 7Hz, $-CH-C\underline{H}_3$)

Analysis : $C_{16}H_{28}O_3$ Calcd: C, 71.60 : H, 10.52

Found: C, 71.91 : H, 10.75

<u>3S-Isopropyl-1R-methyl-2-methylene-1R-(3′-O-tetrahydropyranylethylbutyrate-4′-yl)cyclopentane</u> (<u>60</u>):

Into a 25 ml RB flask hydroxy ester <u>59</u> (2.0 g, 7.7 mmol) was taken in dry dichloromethane (15 ml). 3,4-Dihydro-2H-pyran (2 ml, excess) and catalytic amount of PPTS were added to the reaction mixture and stirred for 6 h at room temperature. The reaction was quenched by addition of water and extracted with dichloromethane (25 ml x 3). The combined organic extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (5 g) column with 10% ethyl acetate - pet ether to furnish the ester <u>60</u> in quantitative yield as a diastereomeric mixture.

IR : 3050, 2950, 1725, 1640, 1160, 1010, 880 cm^{-1}

^{1}H-NMR : δ4.9 - 4.5 (6H, m), 4.2 - 3.3 (10H, m), 3.0 - 1.2 (32H, series of m), 1.2 (6H, t, J = 7Hz, $-O-CH_2-C\underline{H}_3$), 1.0 and 0.98 (3H, s, $-C-C\underline{H}_3$), 0.95 (6H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.85 (6H, d, J = 7Hz, $-CH-C\underline{H}_3$)

3S-Isopropyl-1R-methyl-2-methylene-1R-(3'-O-tetrahydropyranylbuten-1-al-4'-yl)cyclopentane (61):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal was placed the ester 60 (1.0 g, 2.84 mmol) in 20 ml of dry dichloromethane and cooled to -78^{0}C. To this mixture DIBAL-H (2.5 ml, 20% solution in dichloromethane, 3.0 mmol) was added carefully drop by drop through a syringe with vigorous stirring over a period of 0.5 h. The reaction was quenched by slow and careful addition of methanol followed b water. The reaction mixture was extracted with dichloromethane (50 ml x 3) and concentrated to give an oily crude product (1.5 g) which was filtered through a small silica gel (15 g) column to get rid of the polar and insoluble impurities. Elution with 15% ethyl acetate - pet ether furnished the labile aldehyde 61 (570 mg) in 65% yield.

IR : 3050, 2950, 2740, 1720, 1120, 1070, 1020, 810 cm^{-1}

^{1}H-NMR : δ9.77 (2H, m, O=C-$\underline{H}$), 5.0 - 1.3 (44H, series of m), 1.2 - 0.7 (18H, series of s and d)

8-isopropyl-1S-methyl bicyclo[5.3.0]dec-7-ene-3,5-diol (62):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal was introduced the labile aldehyde 61 (1.0 g, 3.25 mmol) in dry dichloromethane (20 ml). To this mixture stannic chloride (0.2 ml, catalytic amount) was added at 0°C. The reaction mixture was stirred for 1 h and then quenched by careful addition of $NaHCO_3$ solution. The resulting reaction mixture was washed, dried and concentrated. The crude product (1.0 g) thus obtained was chromatographed on a silica gel (20 g) column. Elution with 50% ethyl acetate - pet ether resulted in removal of the less polar impurities and further elution with ethyl acetate afforded the cyclised diol 62 (145 mg) in 20% yield.

bp. : 170°C/0.03 mm
IR : 3450, 2950, 1060 cm^{-1}
^1H-NMR : δ 4.2 - 3.8 (2H, m, -C$\underline{H}$-OH), 3.2 - 1.4 (11H, series of m), 1.1 - 0.75 (9H, series of s and m)
Analysis : $C_{14}H_{24}O_2$ Calcd: C, 74.95 ; H, 10.78
Found: C, 74.63 ; H, 10.88

8-Isopropyl-1S-methyl bicyclo[5.3.0]dec-7-ene-3,5-dione (44):

Into a 25 ml RB flask, diol 62 (100 mg, 0.48 mmol) in dry dichloromethane was taken and activated molecular sieves 4 A° (1.0 g) were added. To this mixture was added pyridinium chlorochromate (430 mg, 2.0 mmol) in small amounts at 0°C. The reaction mixture was stirred at 0°C for 30 min and then diluted with dry ether (25 ml). The resulting ethereal solution was filtered through a small florisil (5 g) column. Removal of the solvent gave an oily liquid which was charged on a silica gel (10 g) column. Elution with 5% ethyl acetate - pet ether resulted in removal of the less polar impurities and further elution with 5% ethyl acetate - pet ether furnished the pure dione 44 (60 mg) in 60% yield.

[α] : -34.2 (c 1.0, $CHCl_3$)

bp. : $150^oC/0.1$ mm

IR : 2950, 1700 cm^{-1}

^1H-NMR (fig. I.5) : δ2.43 (2H, dd, J_{gem} = 15 Hz), 2.24 (2H, dd, J_{gem} = 16 Hz), 2.8 - 1.6 (7H, m), 1.1 (3H, s, $-C-C\underline{H}_3$), 0.98 (6H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR (fig. I.6) : δ203.0, 202.8, 148.8, 130.0, 59.2, 55.3, 49.1, 40.4, 36.7, 27.7, 27.1, 24.4, 21.0, 20.8

Analysis : $C_{14}H_{20}O_2$ Calcd: C, 76.32 ; H, 9.15
Found: C, 76.98 ; H, 9.62

8-Isopropyl-1S-methyl bicyclo[5.3.0]dec-7-en-5-ol-3-one (63):

Into a 25 ml RB flask diol 62 (100 mg, 0.48 mmol) in dry dichloromethane was taken and activated molecular sieves 4 A^o (1.0 g) were placed. To this mixture was added pyridinium chlorochromate (100 mg, 0.5 mmol) in small amounts at 0^oC. The reaction mixture was stirred at 0^oC for 30 min and then diluted with dry ether (25 ml). The resulting ethereal solution was filtered through a small florisil (5 g) column. Removal of the solvent gave an oily liquid which was charged on a silica gel (10 g) column. Elution with 5% ethyl acetate - pet ether resulted in removal of the less polar impurities and further elution with 15% ethyl acetate - pet ether furnished the hydroxy ketone 63 (50 mg) in 50% yield as a mixture of diastereomers.

bp. : $170^oC/0.1$ mm

IR : 3400, 2950, 1700, 1040 cm^{-1}

^{1}H-NMR : δ4.25 - 4.0 (2H, m, -C$\underline{H}$-OH), 3.0 - 2.4 (22H, series of m), 1.02 (6H, s, -C-C$\underline{H}_3$), 0.95 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.92 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$)

Analysis : $C_{14}H_{22}O_2$ Calcd: C, 75.63 ; H, 9.97
Found: C, 75.74 ; H, 9.88

<u>8-Isopropyl-1S-methyl-5-O-mesyl bicyclo[5.3.0]dec-7-en-3-one</u> (<u>64</u>):

Into a 10 ml RB flask hydroxy ketone <u>63</u> (50 mg, 0.22 mmol) and dry pyridine (2 ml) were placed. To this mixture mesyl chloride (0.15 ml, 2.0 mmol) was added at 0^{o}C. The reaction mixture was brought to room temperature and stirred for 4 h. Then the reaction was quenched with water and extracted with ether (25 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product (100 mg) which was filtered through a small silica gel (5 g) column with 5% ethyl acetate - pet ether to obtain the keto-mesylate <u>64</u> (50 mg) in 74% yield.

IR : 2950, 1700, 1340, 1160, 900 cm^{-1}

^{1}H-NMR : δ5.21 - 5.0 (1H, m, -C$\underline{H}$-OSO$_2$CH$_3$), 3.0 (3H, s, -SO$_2$C$\underline{H}_3$), 2.8 - 1.4 (11H, series of m), 1.05 (3H, s, -C-C$\underline{H}_3$), 0.99 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.92 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

<u>8-Isopropyl-1S-methyl bicyclo[5.3.0]dec-7-en-3-one</u> (<u>30</u>):

Into a 25 ml RB flask keto-mesylate <u>64</u> (50 mg, 0.16 mmol) in dry ether (10 ml) was placed. This flask was cooled to 0^{o}C and excess lithium aluminium hydride (50 mg) was added. The reaction mixture was stirred at room temperature for 30 min and then excess lithium aluminium hydride was distroyed by careful addition of ethyl acetate followed by water. The aqueous layer was extracted with ethyl acetate (25 ml x 3) and the combined organic extract was washed and dried. The crude alcohol 65 obtained after removal of the solvent was directly used for the next step.

To a suspension of pyridinium chlorochromate (110 mg, 0.6 mmol) in dry dichloromethane (5 ml) containing activated molecular sieves 4 A^{o} (200 mg) was added the above crude alcohol 65 in dry dichloromethane (5 ml) at 0^{o}C. The reaction mixture was brought to room temperature and stirred for 1 h. Dilution with ether (25 ml) and passage through a small florisil (5 g) column removed chromium impurities. Removal of the solvent gave a crude product (75 mg) which was charged on a silica gel (10 g) column. Elution with 5% ethyl acetate - pet ether resulted in removal of the less polar impurities and further elution with 10% ethyl acetate - pet ether afforded the ketone 30 (18 mg) in 50% yield.

$[\alpha]_D$: -13 (c 1.0, CHCl$_3$)

bp. : 120^{o}C/0.1 mm

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

^{1}H-NMR (fig. I.7) : δ2.8 - 2.5 (13H, series of m), 1.0 (3H, s, -C-C$\underline{H}_3$), 0.97 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.94 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

^{13}C-NMR (fig. I.8) : δ213.0, 141.9, 138.7, 54.8, 47.59, 43.7, 38.0, 27.2, 26.5, 24.7, 24.1, 23.8, 21.3, 20.9

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

Found: C, 81.91 ; H, 10.91

Generation of vinyl bromide gas:[41b]

Into a 100 ml three necked RB flask fitted with a pressure equalizing addition funnel, septum and a tube connecting another three necked 50 ml RB flask containing dry THF (20 ml) and kept at -40^{o}C, were placed ethylene glycol (10 ml), water (8 ml) and potassium hydroxide (10 g). To this mixture 1,2-dibromoethane (5 ml) was added dropwise while heating the reaction mixture at 80^{o} - 85^{o}C. The vinyl bromide gas thus generated was passed through calcium chloride guard tube and bubbled in to dry THF (20 ml) at -40^{o}C. After bubbling for 2 h, the resulting vinyl bromide-THF solution was used for the preparation of the Grignard reagent.

3S-Isopropyl-1S-methyl-2-methylene-1R-(3`-hydroxy-1`-buten-4`-yl)cyclopentane (67):

Into a 50 ml three necked RB flask, fitted with a dry N_2 inlet, pressure equalizing addition funnel and mercury seal, magnesium turnings (730 mg, 30 mmol) were placed and dry THF (5 ml) was introduced. To this mixture vinyl bromide-THF solution was slowly added. Catalytic amount of 1,2-dibromoethane was also added and the mixture heated to reflux to initiate the reaction. After all the magnesium had reacted, the RB flask was cooled in an ice-bath and the aldehyde 51 (5.0 g, 27.8 mmol) in dry THF (10 ml) was slowly added. The reaction mixture was brought to room temperature, stirred for 1h and then quenched by pouring it into ice water. The resulting aqueous layer was extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried and concentrated to give an oily liquid which was filtered through a silica gel (50 g) column.

Elution with 10% ethyl acetate - pet ether furnished the allylic alcohol 67 (4.3 g) in 75% yield as a mixture of diastereomers.

bp. : 120°C/0.1 mm

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

^{1}H-NMR : δ6.0 - 5.6 (2H, m, -C$\underline{H}$=CH$_2$), 5.3 - 4.7 (8H, m, C=C$\underline{H}_2$), 4.4 - 4.0(2H, m, -C$\underline{H}$-OH), 2.6 - 1.3 (16H, series of m), 1.06 and 1.01 (6H, s, -C-C$\underline{H}_3$), 0.98 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.77 and 0.75 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$)

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

Found: C, 80.76 ; H, 11.58

3S-Isopropyl-1S-methyl-2-methylene-1R-(1\`-buten-4\`-yl-3\`-one)methylene cyclopentane (68):

To a suspension of pyridinium chlorochromate (6.5 g, 30 mmol) in dry dichloromethane (50 ml) containing 5.0 g of activated molecular sieves (4 A°) was added allylic alcohol 67 (4.0 g, 22.5 mmol) in dry dichloromethane (10 ml) at 0°C. The reaction mixture was brought to room temperature, stirred for an additional 1 h, diluted with dry ether (50 ml) and filtered through a small florisil (10 g) column and repeatedly washed with dry ether. Removal of the solvent gave an oily liquid which was charged on a silica gel (40 g) column. Elution with 5% ethyl acetate - pet ether furnished the pure enone 68 (2.6 g) in 65% yield.

bp. : 120°C/0.1 mm

$[\alpha]_D$: -62.2 (c 2.0, CHCl$_3$)

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

^1H-NMR : δ6.5 - 6.0 (2H, m, $-CH=C\underline{H}_2$), 5.7 (1H, dd, J_1 = 9Hz, J_2 = 3Hz, $-C\underline{H}=CH_2$), 4.78(1H, d, J=4Hz, $-C=C\underline{H}_2$), 4.72 (1H, d, J = 4Hz, $-C=C\underline{H}_2$), 2.7 - 1.2 (8H, series of m), 1.08 (3H, s, $-C-C\underline{H}_3$), 0.97 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.77 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ188.6, 162.5, 137.7, 127.4, 107.8, 50.8, 50.5, 37.1, 28.6, 27.2, 23.0, 21.7, 21.2, 16.3

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

8-Isopropyl-1S-methyl bicyclo[5.3.0]dec-7-en-3-one (30):

To a solution of enone 68 (2.5 g, 12.1 mmol) in dry ethyl acetate (50 ml) was added acetic anhydride (2 ml) and 70% perchloric acid (0.2 ml).[42] The reactants were stirred at room temperature for 25 min. The reaction mixture was then quenched with saturated $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was once again extracted with ethyl acetate (50 ml x 2) and the combined organic extract was washed, dried and concentrated to give an oily liquid which was chromatographed on a silica gel (25 g) column. Elution with 4% ethyl acetate - pet ether removed the less polar impurities and further elution with 10% ethyl acetate - pet ether furnished the cyclised ketone 30 (1.6 g) in 65% yield.

Tetrahydrofurfuryl chloride (74):[51]

Into a 500 ml three necked RB flask fitted with an addition funnel and septum are placed freshly distilled tetrahydrofurfuryl alcohol 73 (4.0 g, 40.0 mmol) and dry pyridine (3.5 g, 44.0 mmol). To the rapidly stirred mixture, which is cooled in an ice-bath, freshly distilled thionyl chloride (5.0 g, 42.0 mmol) was added dropwise from an addition funnel. The temperature of the reaction mixture was not allowed to rise above 60°C. As more of thionyl chloride was added a dark brown liquid results. After the addition was complete, the bath was removed and the mixture stirred for 3 h. The reaction mixture was carefully diluted with ice cold water and extracted with ether (100 ml x 3). The ethereal extract was washed, dried, concentrated and distilled at reduced pressure to afford tetrahydrofurfuryl chloride 74 (3.5 g) in 75% yield.

bp.	:	60°C/10mm
IR	:	2950, 1120, 860 cm^{-1}

1-Pentyn-5-ol (75):[52]

Into a 500 ml three necked RB flask fitted with a guard tube, freshly distilled liq. ammonia (100 ml) was placed and hydrated ferric nitrate (500 mg) was added followed by freshly cut sodium (2.30 g, 100 mmol). After all the sodium had converted into sodium amide, tetrahydrofurfuryl chloride 74 (3 g, 25 mmol) was added slowly through an addition funnel over a period of 0.5 h. The reaction mixture was stirred for an additional 1 h and solid ammonium chloride (2 g) was added in small portions. After all the ammonia had evaporated, the residue was dissolved in water (25 ml) and extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried, concentrated and the crude product thus obtained was distilled at reduced pressure to afford the acetylenic alcohol 75 (1.26 g) in 60 % yield.

bp. : $70^{o}C/10mm$

IR : 3500, 3300, 1120 cm^{-1}

^{1}H-NMR : δ3.70 (2H, t, J = 7Hz, $-C\underline{H}_2-OH$), 2.30 (2H, t, J = 7Hz), 1.70 (4H, m)

<u>1-(Triisopropyl silyl)pent-1-yn-5-ol</u> (<u>76</u>):

Into a 50 ml three necked RB flask, fitted with a dry N_2 inlet, pressure equalizing addition funnel and mercury seal, magnesium turnings (340 mg, 14.0 mmol) were placed and dry THF (10 ml) was introduced. To this ethyl bromide (2.7 g, 14.0 mmol) in THF (5 ml) was added slowly and the reactants were stirred until all the magnesium had reacted. Then the alcohol <u>75</u> (500 mg, 6.0 mmol) in dry THF (5 ml) was slowly added and stirring was continued for 2 h at room temperature. Triisopropylsilyl chloride (2.7 g, 14.0 mmol) in dry THF (5 ml) was added and the reaction mixture left aside at room temperature for 15 h. Reaction was quenched by pouring the contents into ice water. The resulting aqueous layer was extracted with ether (100 ml x 3) and the combined ethereal extract was washed, dried and concentrated to give an oily liquid which was filtered through a silica gel (5 g) column. Elution with 10% ethyl acetate - pet ether furnished the pure alcohol <u>76</u> (1.5 g) in quantitative yield.

IR : 3400, 2200 cm^{-1}

^{1}H-NMR : δ3.72(2H, t, J = 6Hz, $-C\underline{H}_2OH$), 2.32(2H, t, J = 7Hz), 1.70(6H, m), 0.92(21H, s, $Si(C\underline{H}(C\underline{H}_3)_2)_3$)

5-Iodo-1-(triisopropylsilyl)pent-1-yne (77):[43]

Into a 25 ml RB flask triphenoxyphosphonium iodide[53] (3.22 g, 10 mmol) was placed and to it alcohol 76 (2.0 g, 1.0 mmol) was added (neat) and the resulting reaction mixture was stirred at 50°C for 1 h. The reaction mixture was extracted with pentane (100 ml x 3). The combined pentane extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (10 g) column in pentane to furnish 77 (2.0 g) in 60% yield.

IR : 2200, 880 cm^{-1}

^{1}H-NMR : δ3.37(2H, t, J = 7Hz, $-C\underline{H}_2I$), 2.44(2H, t, J = 6Hz), 2.02(2H, dt, J = 7Hz), 1.08(21H, s, $Si(C\underline{H}(C\underline{H}_3)_2)_3$)

1S-Methyl-8-isopropyl-4S-(1`-triisopropylsilylpent-1`-yn-5'-yl)bicyclo-[5.3.0]dec-7-en-3-one (78):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal was introduced n-butyllithium (2.5 ml, 2.5 mmol in hexane) and cooled to -78°C. Hexamethyldisilazane (0.63 ml, 3.0 mmol) was carefully added and the resulting slurry was stirred for 20 min and then the slurry was dissolved by adding dry THF (2 ml). A solution of ketone 30 (500 mg, 2.4 mmol) in dry THF (2 ml) was then slowly added through a syringe. The resulting solution was brought to -10°C and stirred for 0.5 h. The enolate thus obtained was quenched by the addition of excess alkyl iodide (1.5 g) in HMPA (4 ml) at -10°C. After further stirring at -10°C for 45 min the reaction mixture was quenched by the addition of water and extracted with ether (50 ml x 3). The ethereal extract was washed, dried and the solvent was removed to give crude product (2 g), which was charged on a silica gel column. Elution with 5% ethyl acetate - pet ether first removed the excess alkyl iodide and other less polar impurities. Further elution with 10% ethyl acetate - pet ether furnished the alkylated ketone 78 (1.1 g) in 80% yield.

$[\alpha]_D$: -53.3^{o}(c 1.0, $CHCl_3$)

IR : 2950, 2200, 1710 cm^{-1}

^{1}H-NMR : δ2.8 - 1.2 (18H, series of m), 1.05 (21H, s, -Si($C\underline{H}$-($C\underline{H}_3)_2)_3$), 0.97 (s, 3H, -C-$C\underline{H}_3$), 0.96 (3H, d, J = 7Hz, -CH-$C\underline{H}_3$), 0.91 (3H, d, J = 7Hz, -CH-$C\underline{H}_3$)

^{13}C-NMR : δ213.7, 141.5, 139.6, 108.8, 80.5, 54.0, 53.5, 47.4, 37.5, 32.6, 31.4, 27.4, 26.7, 26.5, 24.8, 23.3, 21.5, 21.1, 19.8, 18.64(6C), 11.3(3C)

Analytical data could not be obtained because of its high boiling point.

1S,4S-Dimethyl-8-isopropyl-4S-(1`-triisopropylsilylpent-1`-yn-5'-yl)bicyclo[5.3.0]dec-7-en-3-one (79):

Into a three necked 50 ml RB flask fitted with a dry N_2 inlet, mercury seal and septum was placed sodium hydride (72 mg, 50% dispersion in oil, 1.5 mmol) and washed with dry benzene (2 ml) to remove the oil. The washed sodium hydride was covered with dry dimethoxyethane (3 ml) and to it was added ketone 78 (500 mg, 1.25 mmol) in dry dimethoxyethane (5 ml) and stirred for 2 h at room temperature. The resulting pale yellow coloured enolate solution was quenched with excess methyl iodide and stirring was continued for further 10 h at room temperature. The reaction mixture was quenched by addition of water and then extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product (600 mg) which was charged on a silica gel (10 g) column. Elution with 3% ethyl acetate - pet ether removed less polar oil impurities and further elution with 5% ethyl acetate - pet ether furnished the methylated product <u>79</u> (325 mg) in 65% yield.

$[\alpha]_D$: -42 (c 1.0, $CHCl_3$)

IR : 2950, 2200, 1695 cm^{-1}

^1H-NMR : δ2.8 - 1.2 (17H, series of m), 1.08 (24H, s, $-C-C\underline{H}_3$ and $Si(C\underline{H}(C\underline{H}_3)_2)_3$), 0.95 (3H, s, $-C-C\underline{H}_3$), 0.94 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.89 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ215.3, 142.7, 137.0, 108.7, 80.5, 51.3, 49.7, 48.1, 38.2, 37.5, 27.7, 26.8, 26.5, 25.4, 23.35, 21.17, 20.7, 20.4, 18.64(6C), 11.2(3C)

Analytical data could not be obtained because of its high boiling point.

<u>1S,4S-Dimethyl-8-isopropyl-4S-(pent-1`-yn-5'-yl)bicyclo[5.3.0]dec-7-en-3-one (72):</u>

Into a 25 ml RB flask bicyclic ketone <u>79</u> (300 mg, 0.725 mmol) was placed in dry THF (5 ml). To this solution tetra-n-butylammonium fluoride (260 mg, 1.0 mmol) was added and stirred for 2 min at room temperature. Then THF was removed at reduced pressure and the residue was diluted with water (5 ml) and extracted with ether (25 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (5 g) column to get the keto-acetylene <u>72</u> (195 mg) in quantitative yield.

$[\alpha]_D$: -21 (c 1.0, $CHCl_3$)

bp. : $190^oC/0.1mm$

IR : 3250, 2950, 1695, 1450, 1060 cm^{-1}

^1H-NMR (fig. I.9) : δ2.8 - 1.2 (18H, series of m), 1.02 (3H, s, $-C-C\underline{H}_3$), 0.93 (3H, s), 0.92 (3H, d, J=7Hz), 0.88 (3H, d, J=7Hz)

^{13}C-NMR (fig. I.10) : δ215.1, 142.5, 136.9, 114.4, 84.0, 68.6, 51.4, 49.7, 48.1, 38.1, 37.5, 35.4, 27.6, 26.7, 25.3, 23.0, 21.23, 21.0, 20.7, 18.9

Analysis : $C_{20}H_{30}O$ Calcd: C, 83.85 ; H, 10.55
Found: C, 83.42 ; H, 10.50

<u>Preparation of sodium naphthalenide reagent:</u>[44]

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal freshly sublimed naphthalene (1.0 g, 7.8 mmol) was placed. Dry THF (10 ml) was added to it followed by freshly cut sodium metal (17 mg, 7.5 mmol) in small pieces and the reaction mixture was stirred at room temperature for 1 h until all the sodium metal had reacted resulting in dark green coloured solution. This was preserved under nitrogen atmosphere.

Dolasta-1(15),7-dien-14-ol (71):

Into a 25 ml three necked RB flask fitted with a dry N_2 gas inlet, mercury seal and septum keto-acetylene 72 (100 mg, 0.35 mmol) was placed in dry THF (5 ml). The above prepared sodium naphthalenide solution was added slowly with stirring until the pale green colour persisted. Then THF was removed under reduced pressure, the residue was diluted with water (5 ml) and extracted with ether (25 ml x 3). The ethereal extract was washed, dried and concentrated to a crude product (150 mg) which was charged on a silica gel (3 g) column. Elution with pet ether removed the less polar naphthalene impurities and further elution with 5% ethyl acetate - pet ether furnished the cyclized product 71 (40 mg) in 40% yield, which was recrystallised from hexane - dichloromethane mixture.

$[\alpha]_D$: -12 (c 0.1, $CHCl_3$)

mp. : 105°C

IR : 3450, 2950, 1450, 1110, 890 cm^{-1}

^1H-NMR (fig. I.11) : δ4.81 (1H, t, J=1.5 Hz), 4.76 (1H, br s), 2.6 - 1.4 (17H, series of m), 1.34 (3H, s), 0.94 (3H, d, J=7Hz), 0.92 (3H, d, J=7Hz), 0.78 (3H, s)

Analysis : $C_{20}H_{32}O$ Calcd: C, 83.27 ; H, 11.18

Found: C, 83.62 ; H, 11.21

(+)-Isoamijiol (28), (+)-dolasta-1(15),7,9-trien-14-ol 29 and (+)-dolasta-1(15),7,9-trien-2,4-diol (82):

Into a 10 ml RB flask hydroxy compound 71 (10 mg, 0.035 mmol) was taken and dichloromethane (2 ml) was added. Selenium dioxide (0.1 mg) and t-butyl hydroperoxide (0.011 ml, 0.035 mmol) were added at $0^{o}C$ and the reaction mixture was kept in freezer for 8 h. Then the reaction mixture was diluted with dichloromethane (25 ml) and washed with 5% KOH solution followed by water and dried. The crude product obtained after removal of the solvent was charged on a silica gel (2 g) column. Elution with 3% ethyl acetate - pet ether gave (+)-dolasta-1(15),7,9-trien-14-ol 29 (2 mg) in 20% yield, which was recrystallised from hexane-benzene mixture.

$[\alpha]_D$: -200 (c0.25, $CHCl_3$) (lit. not reported)^{23}

mp. : $103\text{-}105^{o}C$ (lit. $105^{o}C$)^{23}

IR : 3400, 1000, 890 cm^{-1}

^{1}H-NMR (fig. I.12) : δ5.54 (1H, br s, -C$\underline{H}$=C-), 5.46 (1H, dd, J_1 = 9.5Hz, J_2 = 4.5Hz, -C=C$\underline{H}$-4.80 (1H, br s, -C=C$\underline{H}_2$), 4.65 (1H, br s, -C=C$\underline{H}_2$), 3.2 - 1.4 (13H, series of m), 1.37 (3H, s, -C-C$\underline{H}_3$), 1.14 (3H, d, J = 7 Hz, -CH-C$\underline{H}_3$), 1.11 (3H, d, J - 7 Hz, -CH-C$\underline{H}_3$), 0.88 (3H, s, -C-C$\underline{H}_3$)

^{13}C-NMR : δ154.2, 154.0, 149.5, 124.8, 114.5, 108.6, 79.5, 50.8, 45.4, 43.3, 41.4, 37.1, 35.0, 32.0, 27.4, 25.5, 23.1, 22.2, 22.1, 19.8

The spectral data of this product was found to be identical with those reported in literature. A direct comparison was also made with the authentic spectra provided by Professor Piers.

Further elution with 10% ethyl acetate - pet ether furnished (+)-isoamijiol 28 (3 mg) in 30% yield, which was recrystallised from hexane-dichloromethane.

$[\alpha]_D$: +45 (c 0.1, $CHCl_3$) (lit. -45)^{22}

mp. : 128°C (lit. 128°C)^{22}

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

^1H-NMR(200 MHz) : δ5.08(1H, m, -C=C$\underline{H}_2$), 5.01(1H, m, -C=C$\underline{H}_2$), 4.29(1H, t, J = 3Hz), 2.68 - 1.5(17H, m), 1.34(3H, s, -C-C$\underline{H}_3$), 0.94(3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.92(3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.77(3H, s, -C-C$\underline{H}_3$)

Direct comparison of our spectra with those supplied by Professor Ochi established the identity of our synthetic material with the natural product.

Further elution afforded 82 (1 mg) in 10% yield.

$[\alpha]_D$: +75 (c 0.05, $CHCl_3$)

mp. : 109°C

IR : 3400, 2950, 1020, 890 cm^{-1}

^1H-NMR (fig. I.13) : δ5.55 (1H, br s, -C$\underline{H}$=C), 5.4 (1H, dd, J_1 = 9Hz, J_2 = 5Hz, -C=C$\underline{H}$-), 5.04(1H, s, -C=C$\underline{H}_2$), 4.9(1H, s, -C=C$\underline{H}_2$), 4.3(1H, m, -C$\underline{H}$OH), 3.2 - 1.4(11H, series of m), 1.28(1H, s, -C-C$\underline{H}_3$), 1.05(3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 1.01(3H,d, J = 7Hz, -CH-C$\underline{H}_3$), 0.8(3H, s, -C-C$\underline{H}_3$)

Due to paucity of material combustion data could not be obtained.

I.7. SPECTRA

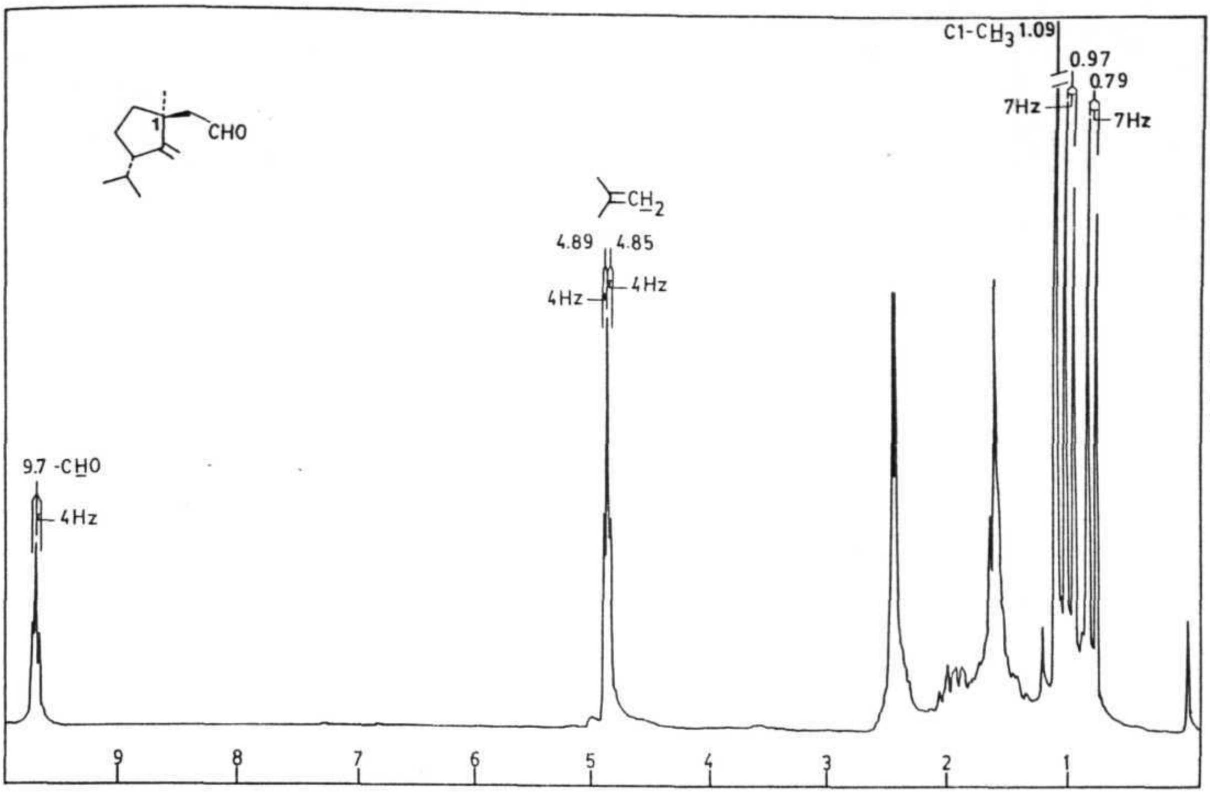


Fig. I.1 ^{1}H-NMR spectrum (100 MHz) of <u>51</u>

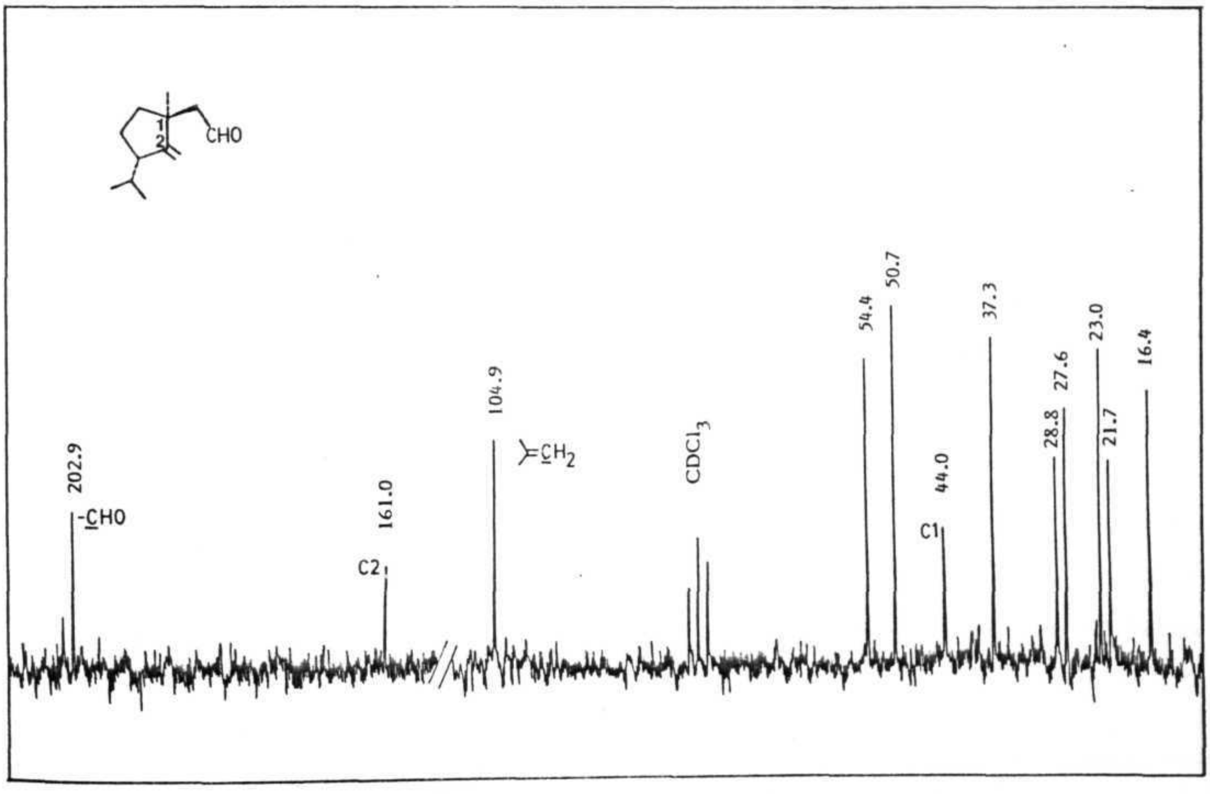


Fig. I.2 ^{13}C-NMR spectrum (25 MHz) of <u>51</u>

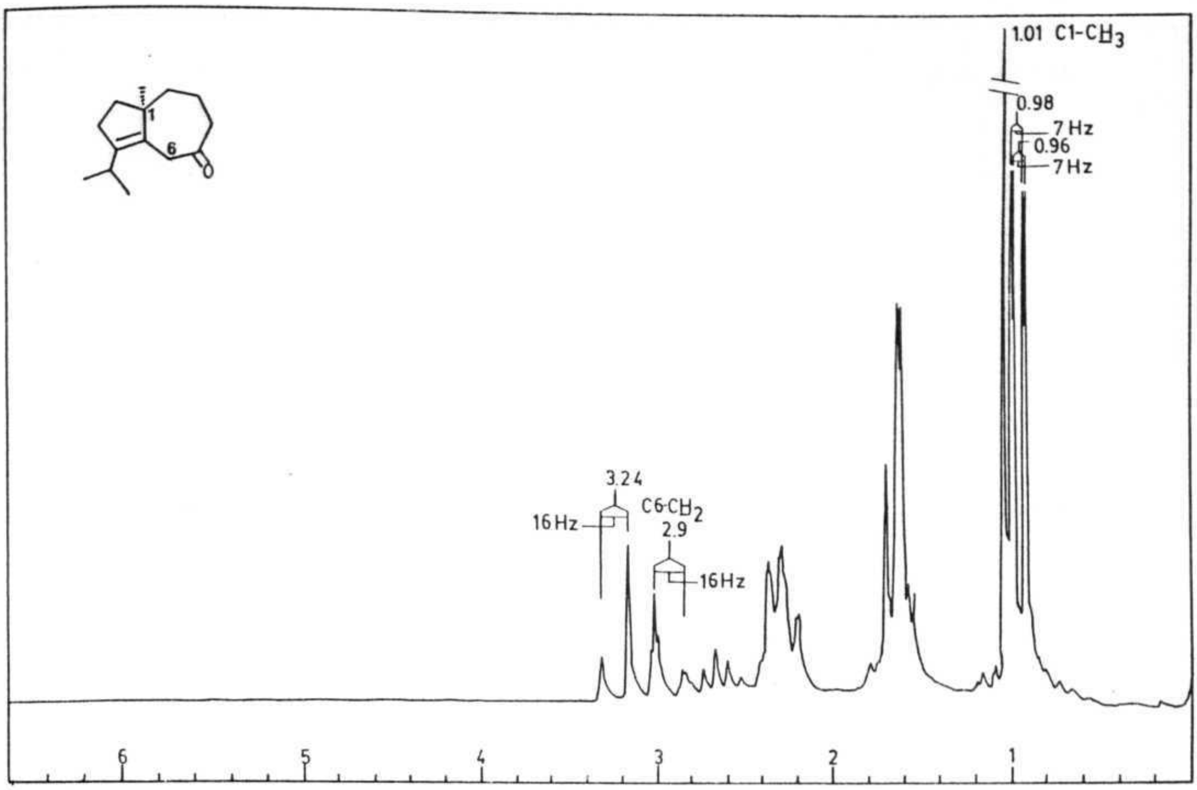


Fig. I.3 ^{1}H-NMR spectrum (100 MHz) of <u>43</u>

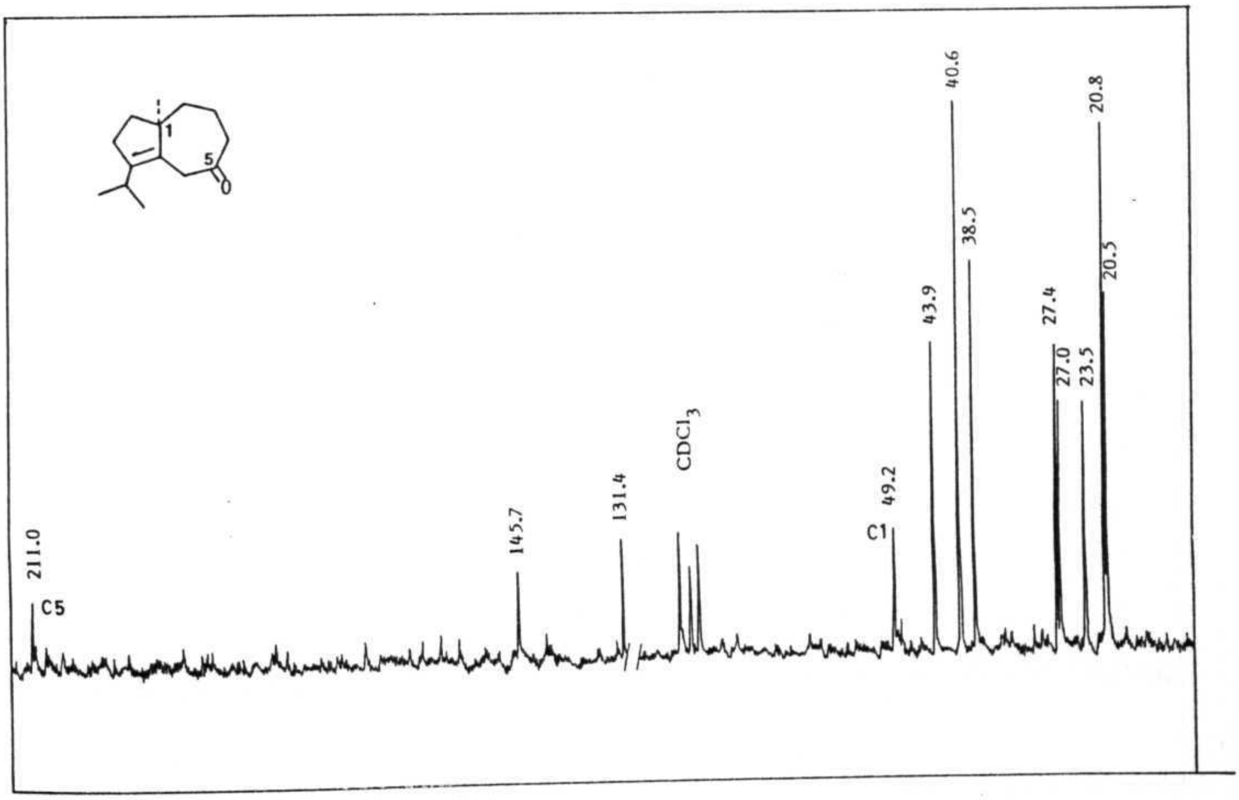


Fig. I.4 ^{13}C-NMR spectrum (25 MHz) of <u>43</u>

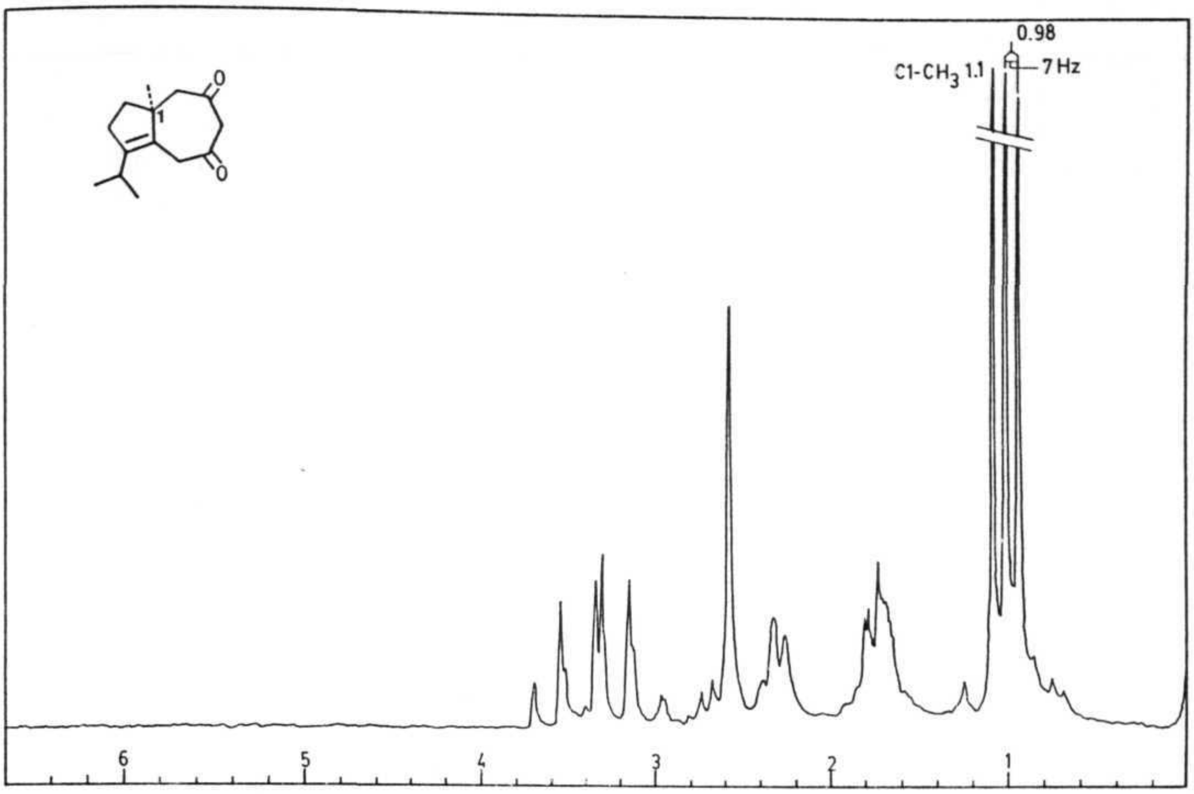


Fig. I.5 ^{1}H-NMR spectrum (100 MHz) of <u>44</u>

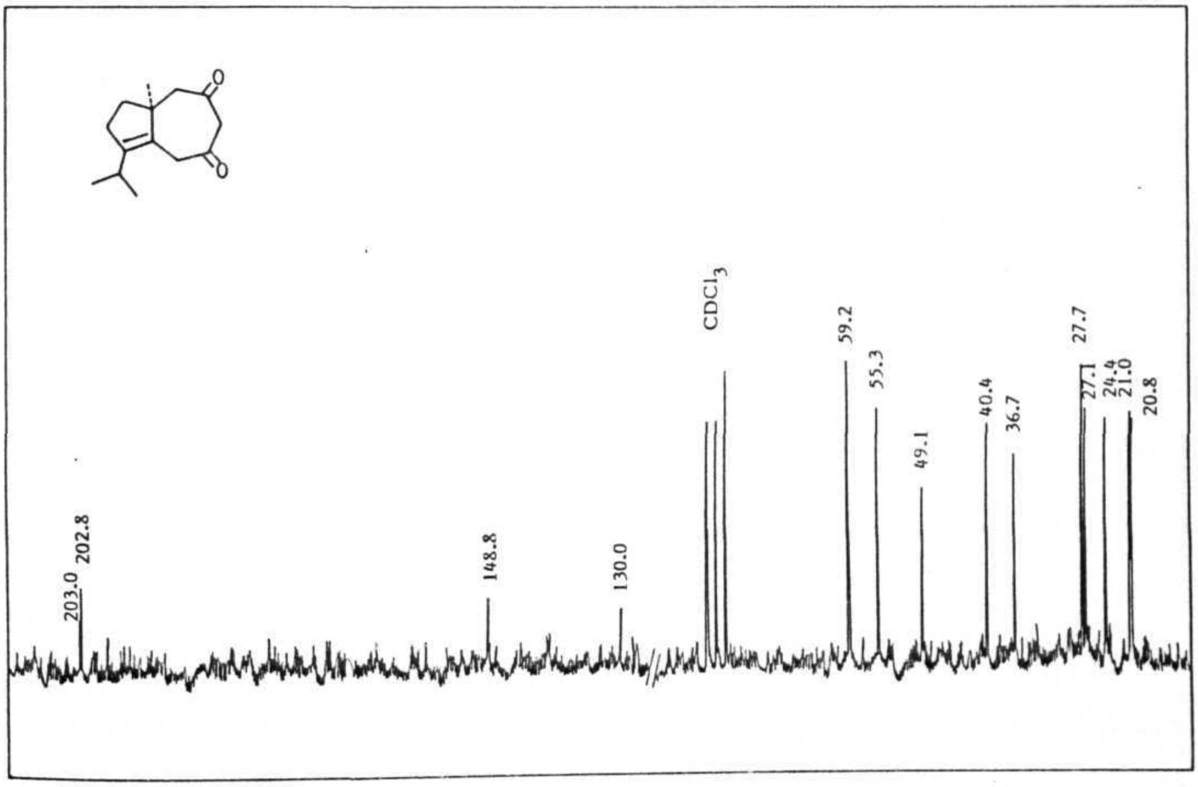


Fig. I.6 ^{13}C-NMR spectrum (25 MHz) of <u>44</u>

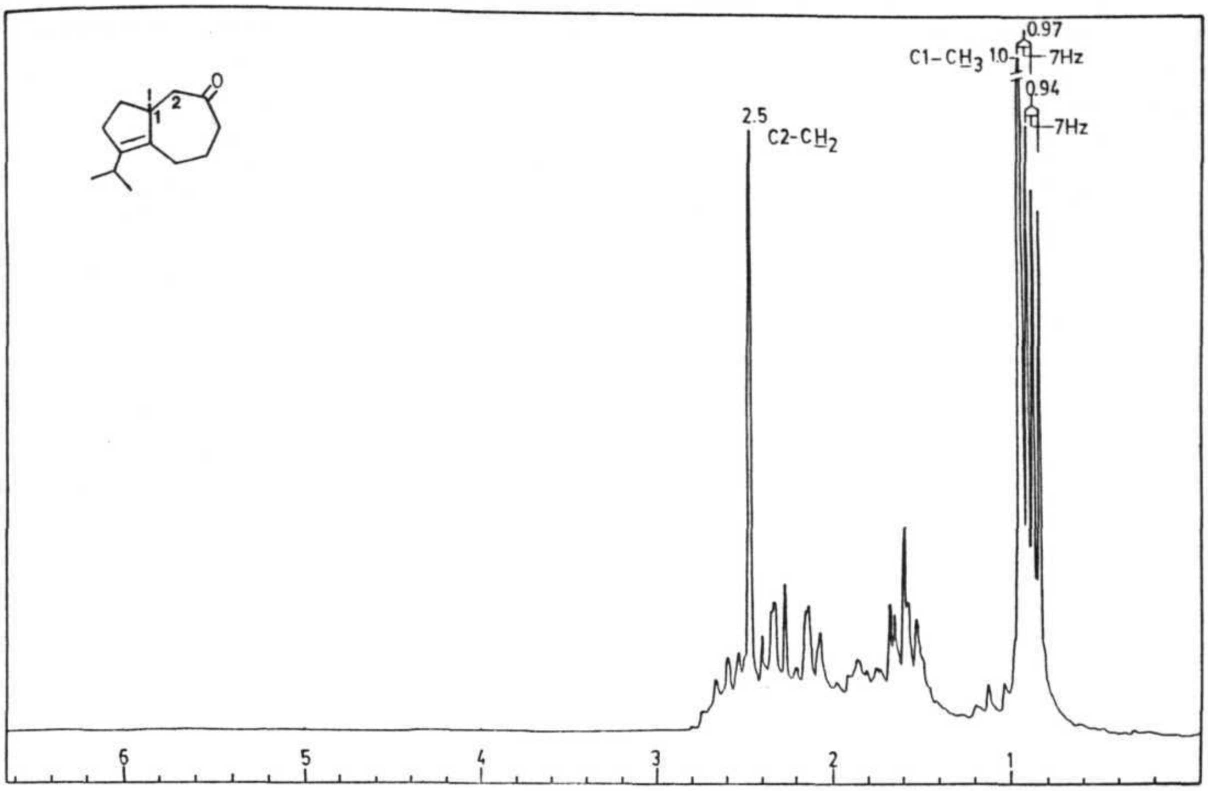


Fig. I.7 ^{1}H-NMR spectrum (100 MHz) of 30

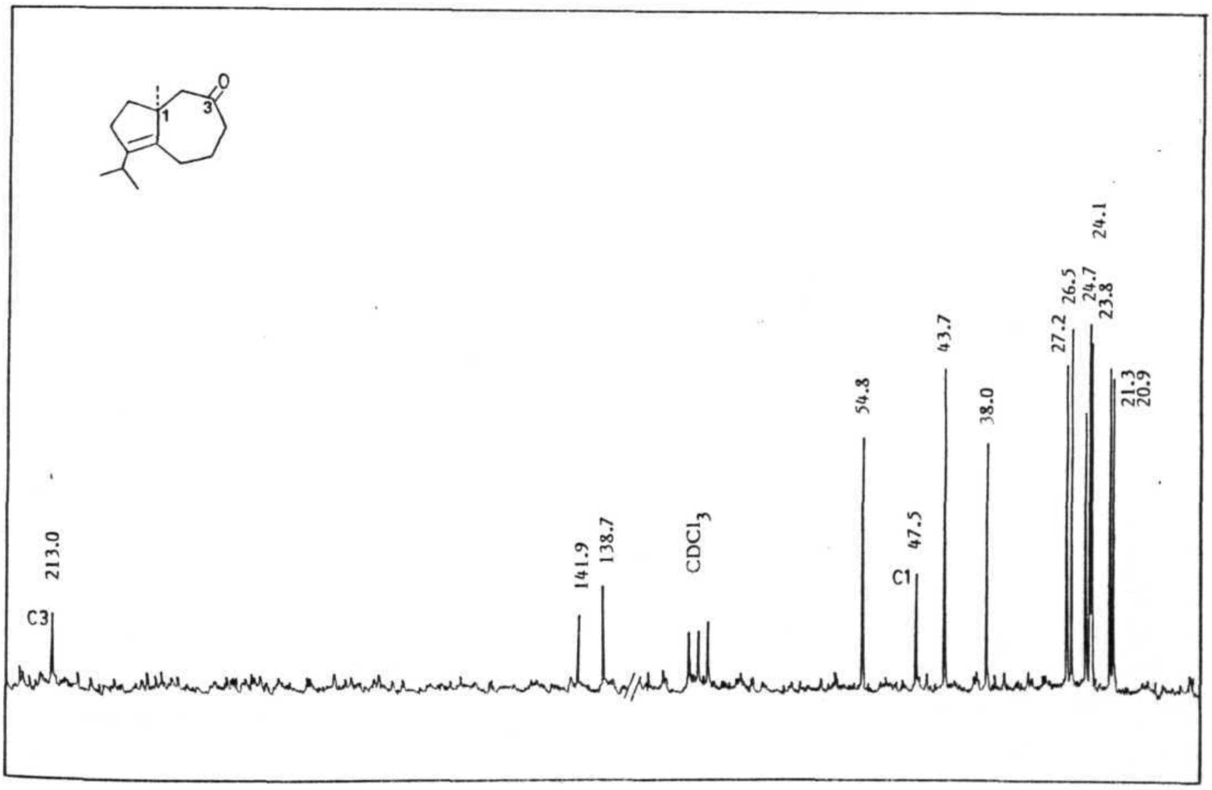


Fig. I.8 ^{13}C-NMR spectrum (25 MHz) of 30

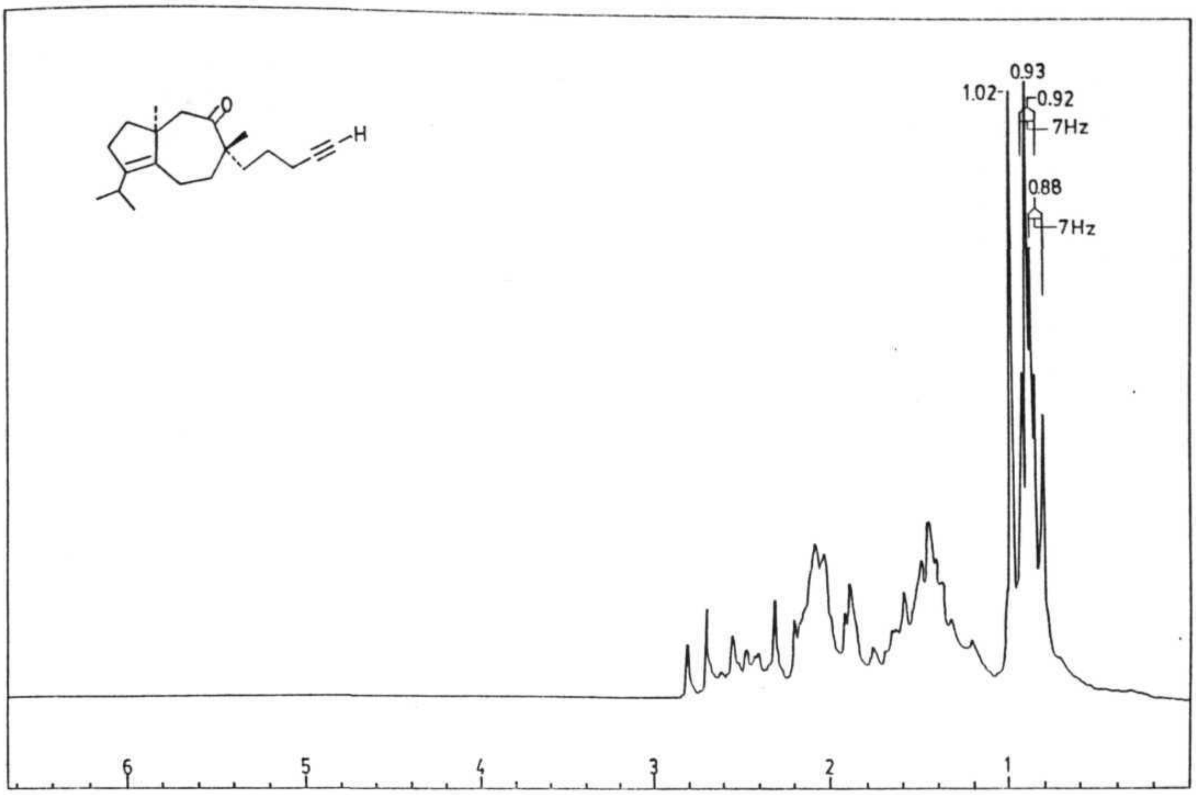


Fig. I.9 ^{1}H-NMR spectrum (100 MHz) of <u>72</u>

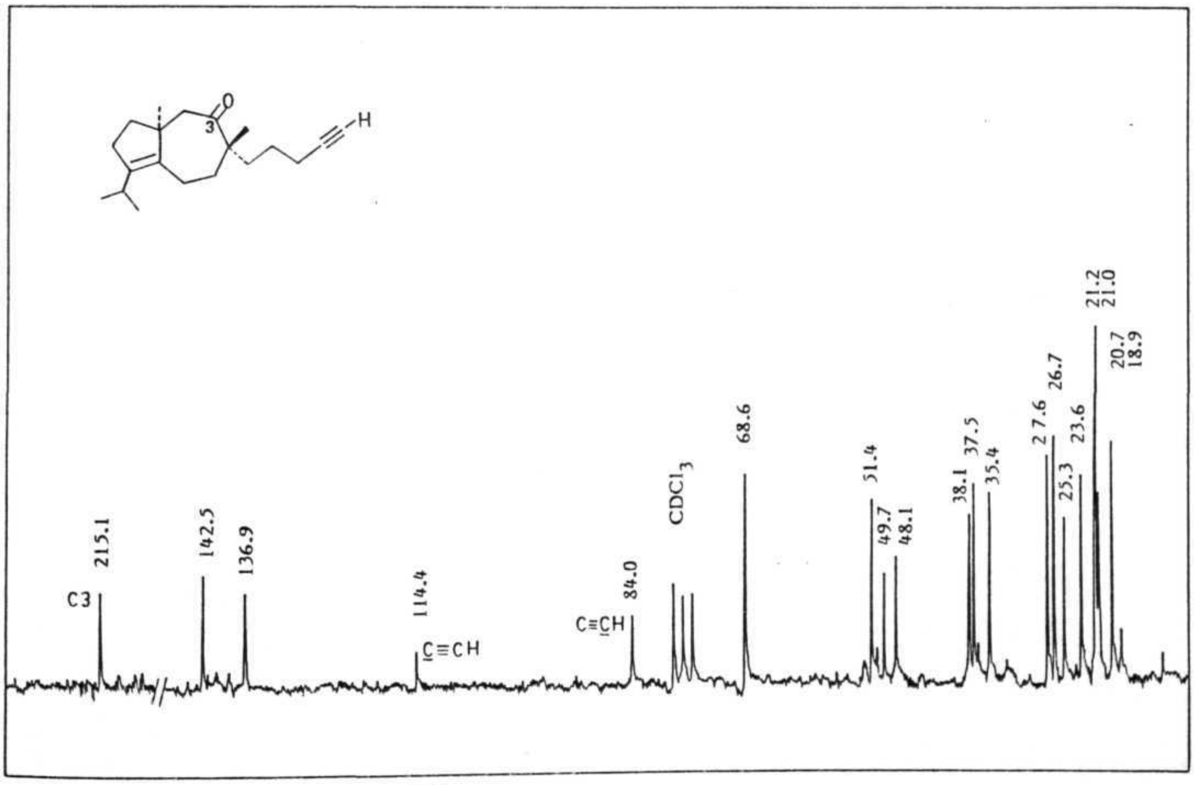


Fig. I.10 ^{13}C-NMR spectrum (25 MHz) of <u>72</u>

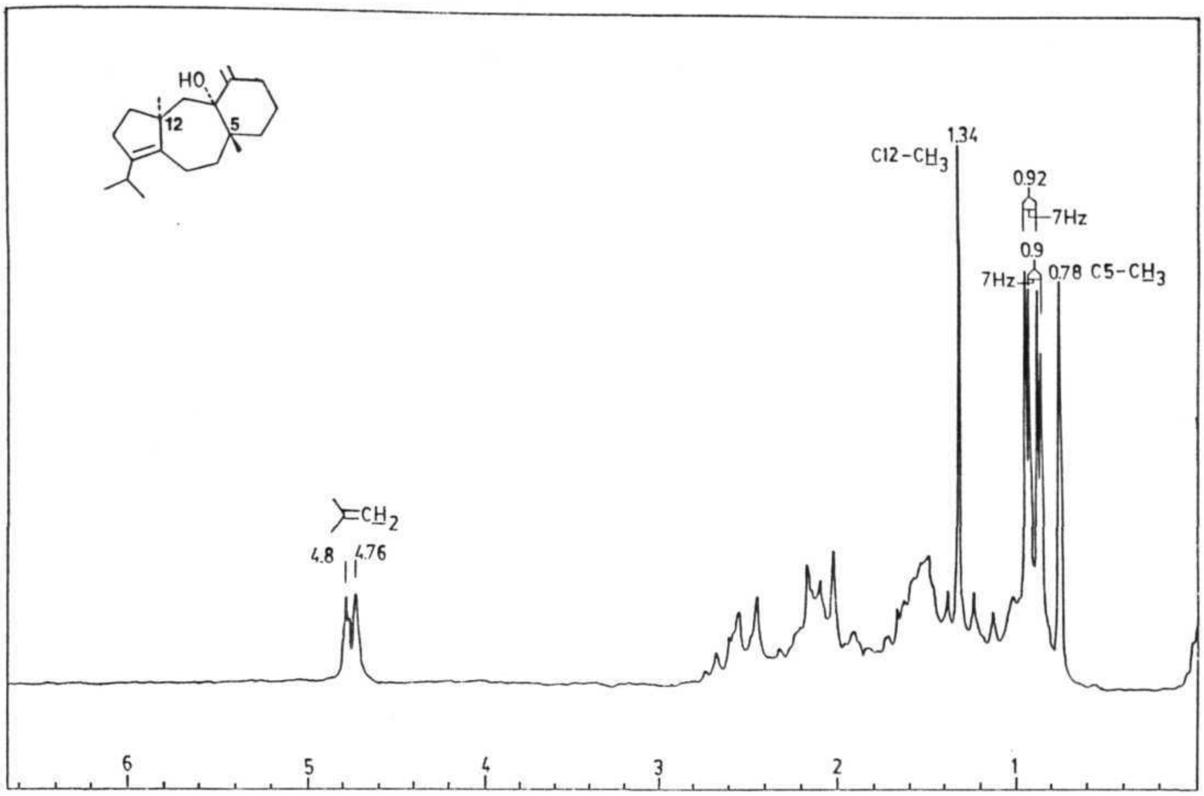


Fig. I.11 ^{1}H-NMR spectrum (100 MHz) of 71

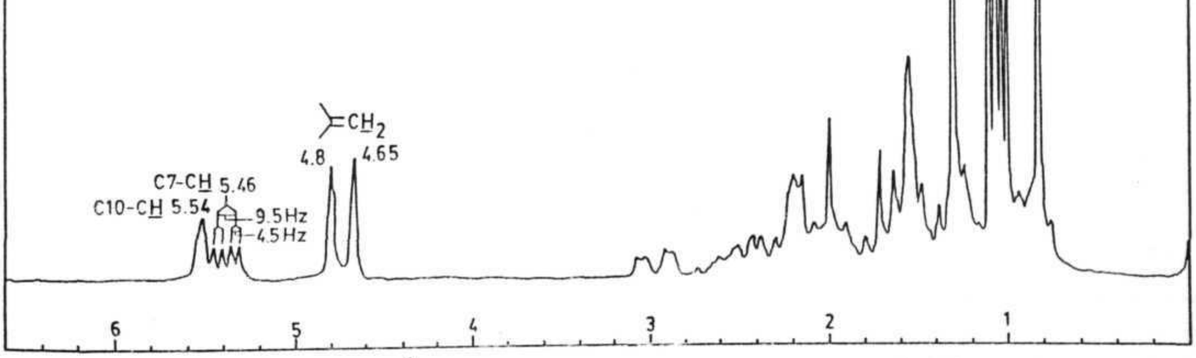


Fig. I.12 ^{1}H-NMR spectrum (100 MHz) of 29

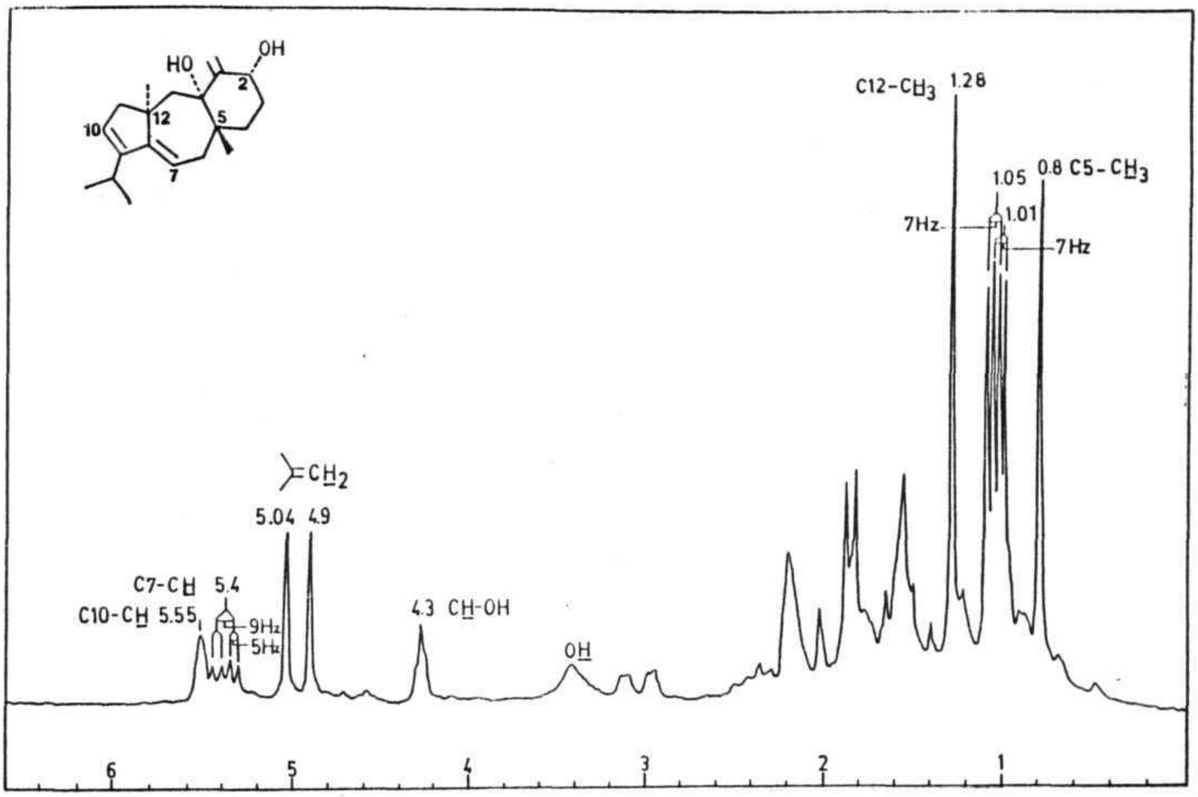


Fig. I.13 ^{1}H-NMR spectrum (100 MHz) of <u>82</u>

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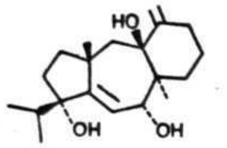
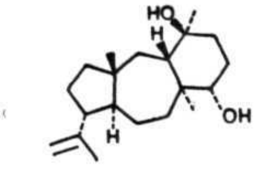
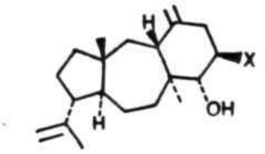
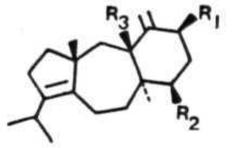
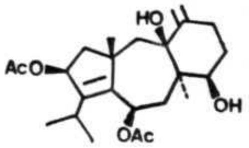
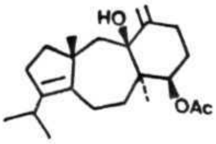
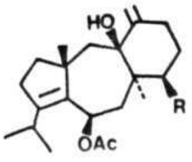
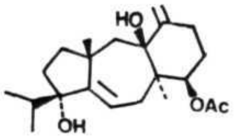
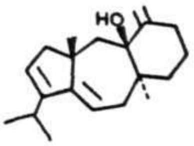
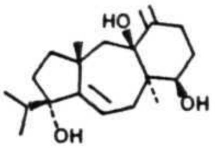
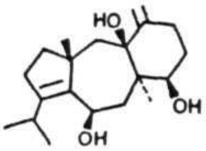
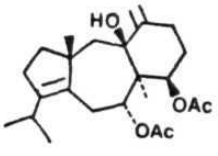
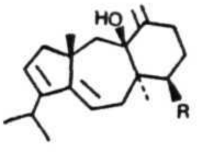
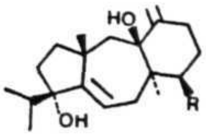
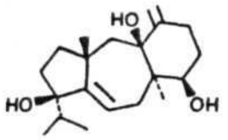
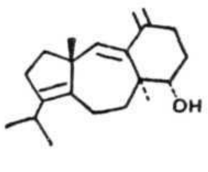
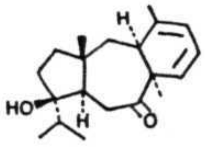
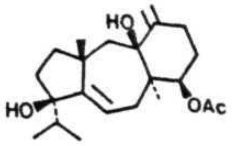
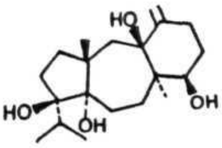
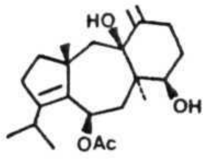
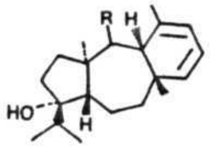
APPENDIX : A compilation of natural dolastane diterpenes

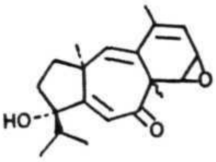
S. No.	Natural product	Species	Structure	Ref.
1	Dolatriol	*Dolabella auricularia*		1
2	(1R,4R)-Clavular-17-ene-1,4-diol	*Clavularia inflata*		2
3	(4R)-Clavulara-1(15),17-diene-4-ol	"	 X = H	2
4	(3S,4S)-Clavulara-1(15),17-diene-3,4-diol	"	X = OH	2
5	Amijiol	*Dictyota linearis*	 $R_1=H_2$, $R_2=R_3=OH$	3
6	Isoamijiol	"	$R_1=$ H, -OH $R_2=H$, $R_3=OH$	3
7	14-Deoxyamijiol	"	$R_1=H_2$, $R_2=OH$, $R_3=H$	3

8	Amijidictyol	"		4
9	(4S)-Acetoxy-(14S)-hydroxy dolasta-1(15),7,9-triene	Dictyota divaricata		5,7
10	(7S)-Acetoxy-(4S,14S)-dihydroxydolasta-1(15),8-diene	"		5
			R = OH	
11	(4S,7S)-Diacetoxy-(14S)-hydroxydolasta-1(15),8-diene	"	R = OAc	5,7
12	(7S)-Acetoxy-(14S)-hydroxy dolasta-1(15),8-diene	"	R = H	5,7
13	(4S,9R,14S)-4-Acetoxy-9,14-dihydroxydolasta-1(15),7-diene	Dictyota linearis & Dictyota divaricata		6,7

14	(14S,)-14-Hydroxydolasta-1(15),7,9-triene	"		6
15	(4S,9R,14S)-4,9,14-Trihydroxydolasta-1(15),7-diene	"		6
16	(4S,7S,14S)-4,7,14-Trihydroxydolasta-1(15),8-diene	"		6
17	(4S,6R,14S)-4,6-Diacetoxy-14-hydroxydolabella-1(15),8-diene	Clavularia inflata		6
18	(4S,7S)-Diacetoxy-(14S)-hydroxydolast-1(15),8-diene	Dictyota sp.	 R = OH	7

19	(4R,14S)-4-Acetoxy-14-hydroxydolast-1(15),7,9-triene	"	R = OAc	7
20	(4R,9S,14S)-4,9,14S-Trihydroxydolast-1(15),7-diene	"		7
			R = OH	
21	(4R,9S,14S)-4-Acetoxy-9,14-dihydroxydolast-1(15),7-diene	"	R = OAc	7
22	(4R,9R,14S)-4,9,14-Trihydroxydolasta-1(15),7-diene	"		7
23	Amijitrienol	Dictyota linearis		8
24	(5S,8S,9S,12S,14R)-9-Hydroxy dolasta-1,3-diene-6-one	Dictyota dichotoma		9

25		"		10
26		"		10
27		"		10
28	(5S,8S,9S,12S,14R)-9-Hydroxy dolasta-1,3-diene	Dictyota species	 R = H	11
29	(5S,8S,9S,12R,13S,14R)-9,13-Dihydroxy dolasta-1,3-diene	"	R = OH	11
30	(5S,8S,9S,12R,13R,14R)-9,13-Dihydroxy dolasta-1,3-diene	"	R = OH	11

31	(5S,8S,9S,12R,14R)-9-Hydroxy dolasta-1,3-dien-13-one	"	R = O	11
32	(5S,8S,9S,12R,13S,14R)-13-Acetoxy-9-hydroxy dolasta-1,3-diene	"	R = OAc	11
33	9-Hydroxy dolasta-1,7,13-trien-6-one	"		11

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Chapter II

Total Synthesis of Daucane Sesquiterpene (-)-Daucene and Isodaucane Sesquiterpene 2-Oxo-isodauc-5-en-12-al

II.1 ABSTRACT

Stereo- and enantioselective synthetic approaches towards bicyclic daucane and isodaucane sesquiterpenes, culminating in the total synthesis of (-)-daucene 7, (+)-aphanamol-I 13 and (+)-isodaucenal 15 are described. In these synthetic endeavours enantiomerically pure hydroazulenone 30, readily available from R-(+)-limonene 27 as described in the previous chapter of this thesis served as the common, advanced precursor.

Synthesis of (-)-daucene 7, the simplest member of the daucane (carotane) family was a straight forward affair. Regioselective methylation on 30, LAH reduction and dehydration furnished the natural product, Scheme II.10. An alternate approach to (-)-daucene 7 from the enal 28, a precursor of hydroazulenone 30, was also executed, Scheme II.11. A three step sequence involving addition of isopropenyl magnesium bromide, PCC-oxidation and enone-olefin cyclisation furnished the daucane skeleton 31. LAH reduction and dehydration completed the (-)-daucene 7 synthesis.

Synthesis of isodaucane sesquiterpene from hydroazulenone 30 involved a novel restructuring protocol. RuO_2-oxidation of 30 gave the triketone 33 which on regioselective aldol cyclisation furnished the restructured ene-dione 34, Scheme II.12, with amplified functionality and belonging to an enantiomeric series with respect to its precursor. Li-Liq.NH_3 reduction, catalytic hydrogenation and equilibration studies provided access to all four possible stereoisomeric hydroazulenones 38-41 from the ene-dione 34, Scheme II.15. The stereoisomer 38 having requisite stereochemistry at the three (C(1), C(7), C(8)) stereogenic centres was further elaborated to the natural products (+)-aphanamol-I 13 and (+)-isodaucenal 15 through

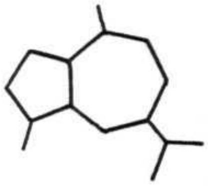
functional group manipulations indicated in Scheme II.18. This attainment of (+)-13 establishes the absolute stereochemistry of aphanamol-I 13 and aphanamol-II 14, the two important isodaucane natural products.

II.2. OBJECTIVE AND BACKGROUND:

Sesquiterpenes are most notable for the diversity of carbocyclic skeleta present in them. Indeed, a myriad combination of different ring sizes constitute the mono-, di-, tri- and tetracarbocyclic frameworks present in these C_{15}-compounds.[1] Besides this, many stereochemical subtleties and novel functionalisation patterns are associated with them. All these novel structural features make sesquiterpenes attractive and challenging targets of synthesis. In particular, they have provided the most popular forum for testing and developing new strategies in carbocyclic ring construction.[2] Over a thousand papers dealing with sesquiterpene syntheses have appeared in literature during the past two decades and synthetic chemists' enthusiasm for them shows no sign of abating.

Among the carbocyclic variations present in sesquiterpenoids, the 5,7-fused hydroazulenic system (bicyclo[5.3.0]decane) is the most abundantly distributed in Nature.[3] The commonly encountered skeleta based on the 5,7-fused ring system are those of guaiane 1 and pseudoguaiane 2, and the resulting family of guaianolides (eg. estafiatin 3) and pseudoguaianolides (eg. confertin 4)[4], Chart II.1, has received considerable attention from synthetic as well as biological activity point of view.

CHART II.1



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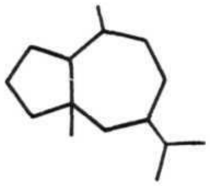

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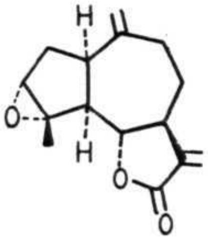

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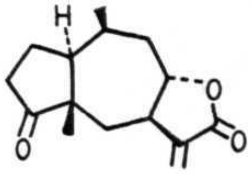

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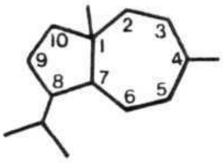
In addition to 1 and 2, there are two other types of 5,7-fused carbocyclic skeleta found in Nature. These are daucane (carotane) 5 and isodaucane 6, Chart II.2. Daucane skeleton 5 has been known for nearly three decades, with (+)-daucene 7[5], (+)-carotol 8[6] and (-)-daucol 9[6] isolated from carrot seeds (Daucus carota L) being the well known examples, Chart II.3. The daucane family is rapidly growing and lasidiol angelate 10[7] (ant repellent), and Jaeschkeanadiol 11[8] are some of the recently isolated natural products of interest, Chart II.3.

CHART II.2



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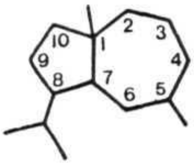

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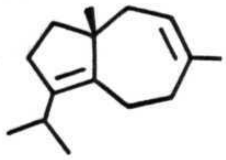
CHART II.3



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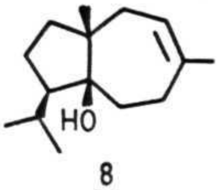

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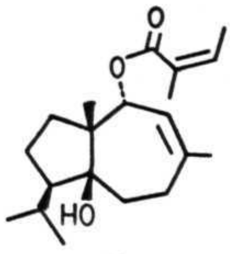

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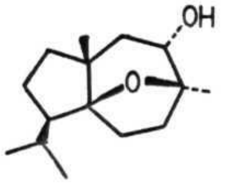

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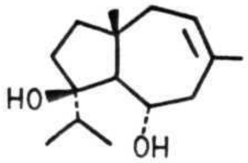

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However, isodaucane skeleton 6 has been discovered only about a decade ago and is of rare occurrence. So far, only six natural products based on this skeleton 6 are known, Chart II.4.[#] These include (-)-mintsulphide 12[11] from peppermint oil, (+)-aphanamol-I 13[12] and (+)-aphanamol-II 14[12,13] from

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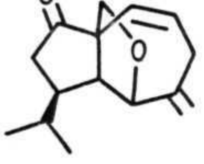
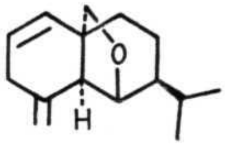
[#] Periplanone-A, one of the sex attractants of the American cockroach, was earlier shown to possess the isodaucane based structure (i).[9] However, recent studies have led to the revision of the structure of periplanone-A to (ii).[10]



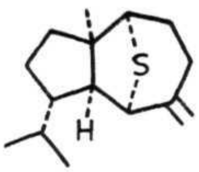
i



ii

the Meliaceous plant Aphanamixis grandifolia and 2-oxo-isodauc-5-en-12-al 15[13] from Chromolaen laevigata (Lam). Very recently, two more natural products 16 and 17 based on isodaucane skeleton 6 and bearing the novel isonitrile and thiocyanate functionalities, respectively, have been isolated[14] from the marine sponge Acanthella acuta.

CHART II.4



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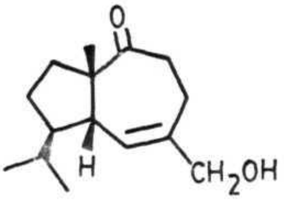

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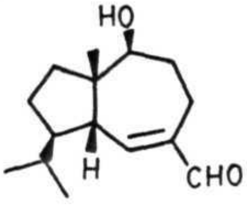

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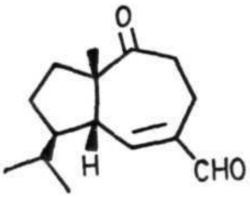

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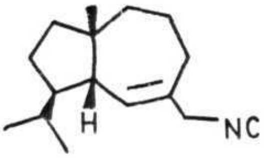

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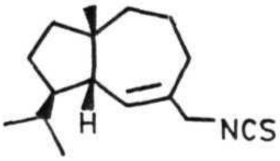
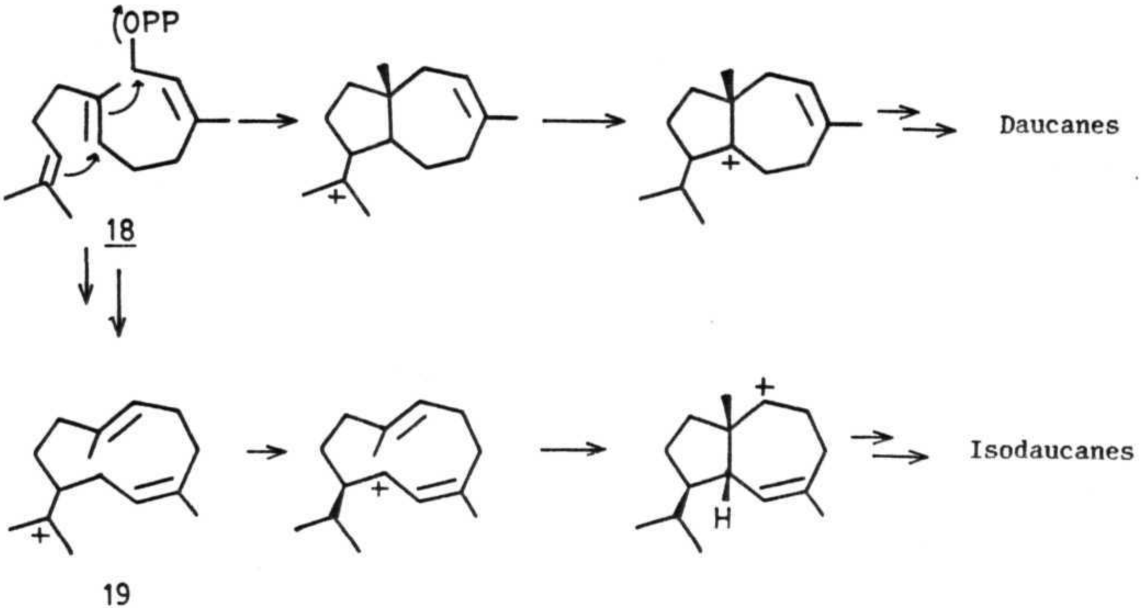


17

The structures of these isodaucane-based compounds have been mainly determined on the basis of high field NMR studies (NOE, 2D-NMR). With the exception of mintsulphide 12[11], the absolute configuration of other isodaucane sesquiterpenes has not been determined.

Daucane 5 and isodaucane 6 skeleta are structurally very closely related and differ only in the location of the methyl group on the seven membered ring. Despite such close structural relationship, 5 and 6 seem to have different biogenetic origin. While the daucane skeleton can be readily derived through double ring closure in a (2Z,6E)-farnesylpyrophosphate precursor 18, isodaucane probably arises through a germacrene precursor 19, Scheme II.1. The interesting, though less likely,

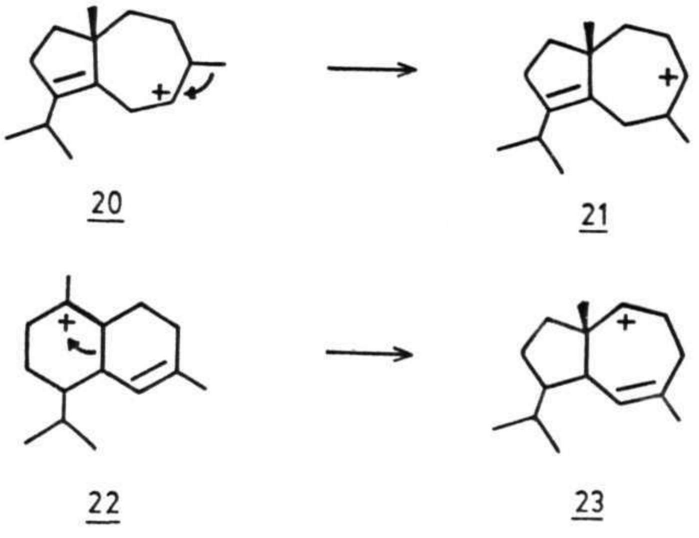
SCHEME II.1



possibility of isodaucanes arising through 1,2-methyl migration in a daucane cation (20 → 21) or ring contraction of a cadinane cation (22 → 23) cannot be completely ruled out at this stage, Scheme II.2. However, there is little experimental support for this proposal.

Daucane sesquiterpenes have aroused the interest of synthetic community and five syntheses of hydrocarbon daucene 7 have been reported through the efforts of Yamasaki[15] (1972), Naegeli et al.,[16] (1972), Levisalles et al.,[17] (1972), Seto et al.,[18] (1985) and Vandewalle et al.,[19] (1987). Of these, Yamasaki synthesis led to enantiomerically pure (-)-

SCHEME II.2

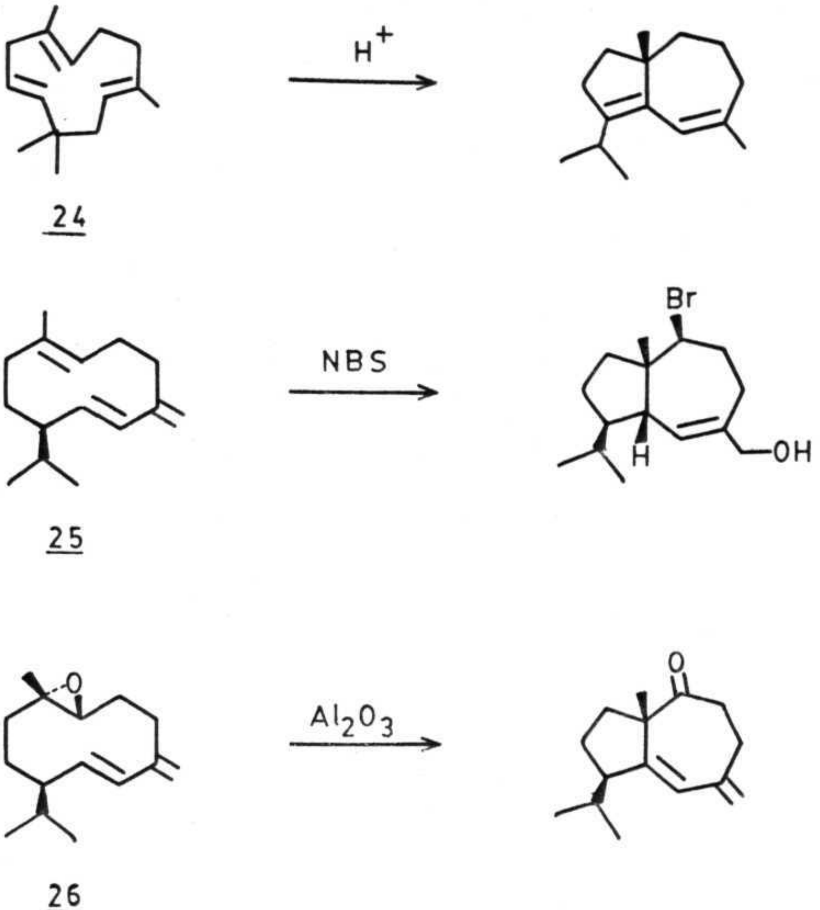


20 21 22 23

daucene 7 while Levisalles and Vandewalle syntheses led to (+)-daucene 7. Synthesis of other daucane sesquiterpenes, namely (+)-carotol 8[17], (-)-daucol 9[17] and lasidiol angelate 10[7] have also been reported.

On the other hand, successful total synthesis of any isodaucane sesquiterpene has not been achieved so far, although formation of isodaucane skeleton during acid catalysed cyclisation of humulene 24[20], germacrene-D 25[21] and epoxy germacrene-D 26[22] has been observed, Scheme II.3. A recent report[21] describes the formation of aphanamol-II 14 during biogenetic-type cyclisation of epoxy germacrene-D 26. In the cyclisation of 26 only (±)-14 was produced, Scheme II.4.

SCHEME II.3



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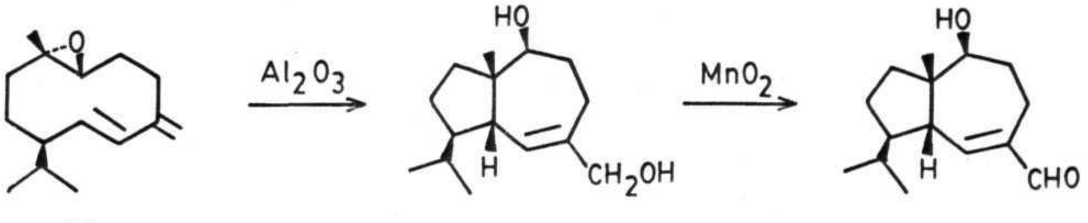
SCHEME II.4

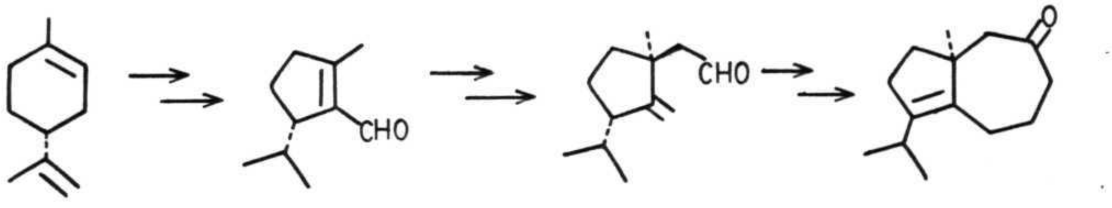


26

(±)-14

We became interested in the enantioselective total synthesis of daucane and isodaucane sesquiterpenes, particularly the later, as synthesis of this class has not yet been achieved. It was also our expectation that an enantioselective synthesis of isodaucane sesquiterpenes will enable us to elucidate the absolute stereochemistry of these natural products. The main impetus for undertaking this work was provided by the ready availability of the (-)-hydroazulenone 30[23], in quantity and in enantiomerically pure form, from R-(+)-Limonene 27, as detailed in the previous chapter of this thesis, Scheme II.5. The striking structural resemblance of 30 to the skeleta 5 and 6, and some of the natural products based on them, marked out 30 as an advanced precursor for their synthesis. Successful utilisation of (-)-hydroazulenone 30 for the total synthesis of (-)-daucene 7 and isodaucane sesquiterpenes (+)-aphanamol-I 13 and (+)-2-oxo-isodauc-5-en-15-al 15 is reported in this chapter. Realisation of 13 and 15 also establishes the absolute stereochemistry of these natural products.

SCHEME II.5

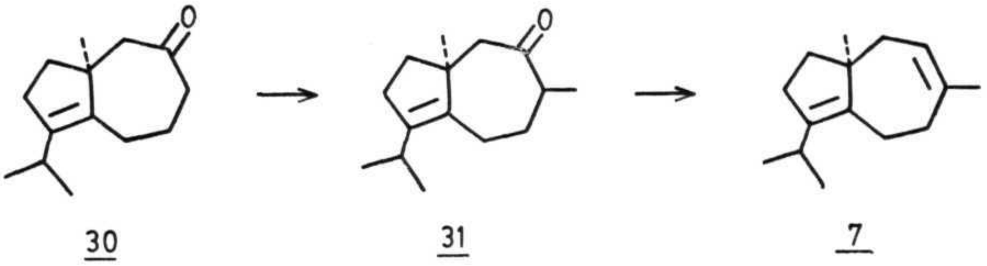


27 28 29 30

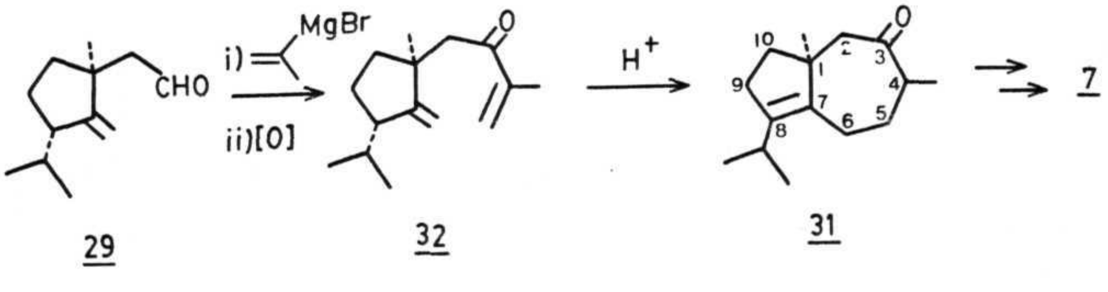
II.3. STRATEGY

As indicated above, C_{14}-hydroazulenone 30 was identified as the advanced, preformed precursor for the synthesis of (-)-daucene 7 as well as isodaucane sesquiterpenes 13 and 15. Conversion of 30 to (-)-daucene 7 looked like a fairly straight forward affair with the installation of the methyl group at C(4) in a regioselective manner to give 31. Further functional group adjustment (carbonyl → olefin) could then lead to the required hydrocarbon 7, Scheme II.6. As we shall see, this was achieved, as planned, without any encumbrance. However, we also considered the possibility of elaborating the C_{12}- enal 29, Scheme II.5, directly to 31 and hence to (-)-daucene 7 as shown in Scheme II.7. This was considered to be a shorter and more convenient approach and was duly realised (*vide infra*).

SCHEME II.6



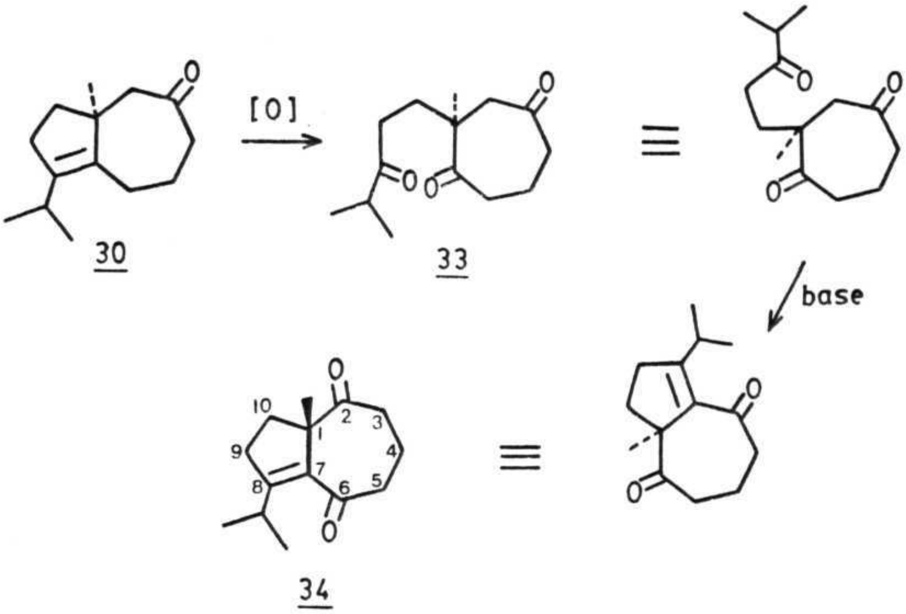
SCHEME II.7



Elaboration of 30 to the isodaucane sesquiterpenoids was, however, a more demanding proposition. This required formulation of a strategy to effect three main manipulations on the C_{14}- hydroazulenone 30. First and foremost was the question of generation and control of stereochemistry at (C(1), C(7), C(8)) stereogenic centres. Importantly, the *cis*-ring junction stereochemistry and the *cis*-relationship between the C(1)-methyl group and the C(8)-isopropyl group represent a thermodynamically less stable stereochemical arrangement. This stereochemical pattern is not accessible from 30 by simple hydrogenation as the C(7)-C(8) hydrogen atoms are *trans*-in isodaucane natural products. Moreover, we had observed that the considerably hindered tetrasubstituted double bond in 30 was completely resistant to hydrogenation even under moderate pressures. Therefore, some tactic had to be devised to secure the correct C(1), C(7) and C(8) stereochemical array. Secondly, completion of the isodaucane carbon skeleton required installation of the fifteenth carbon atom at C(5) in 30 at the desired oxidation level. It is to be noted that C(5)-methyl substituent is present at different oxidation levels in the isodaucane natural products 13 and 15. Lastly, isodaucane sesquiterpenes carry oxygen functionalisation across the seven membered ring and therefore methodology for the amplification and relocation of functionalisation in the hydroazulenone 30 was required.

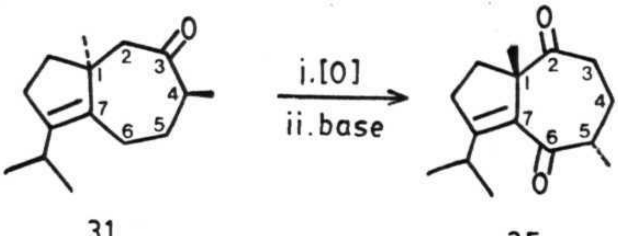
After considerable thought and much paper chemistry, it was possible to devise a synthetic stratagem that promised to provide a simple and satisfying solution to all the three strategic requirements mentioned above for the transformation of hydroazulenone 30 to isodaucane natural products. It occurred to us that restructuring of 30 through a two step sequence involving oxidation to triketone 33 and aldol-cyclisation would provide ene-dione 34, Scheme II.8. The restructured dione 34 now had amplified transannular functionalisation in the seven membered ring, an enone moiety with proclivity towards facile and stereochemically controlled reduction and a C(5)-pro-nucleophilic centre for the introduction of the fifteenth carbon atom at the desired oxidation level. Thus, 34 appeared to be an ideally suited substrate for elaboration into the isodaucane natural products.

SCHEME II.8



Besides these, there are two additional interesting features of the 30 → 34 transformation. During the restructuring process, C(3)-carbonyl of 30 becomes the C(6)-carbonyl in 34 and similarly the C(4) in 30 shows up as C(5) in 34. Thus, there is a way for the direct conversion of daucane skeleton 31 to isodaucane skeleton 35 through the two step oxidation-aldolisation sequence, Scheme II.9. Quite remarkably, the ene-diones 34

SCHEME II.9



31 35

and 35 now belong to the enantiomeric series with respect to the precursor hydroazulenones 30 and 31. This, as will be evident, enabled us to find entry to the naturally occurring enantiomer of aphanamol-I 13 from R-(+)-limonene 27.

Having delineated the conceptual framework for generating the daucane and isodaucane skeleta, it is time to describe the practical realisation of the total synthesis of sesquiterpenes (-)-daucene 7, (+)-aphanamol-I 13 and (+)-isodaucenal 15.

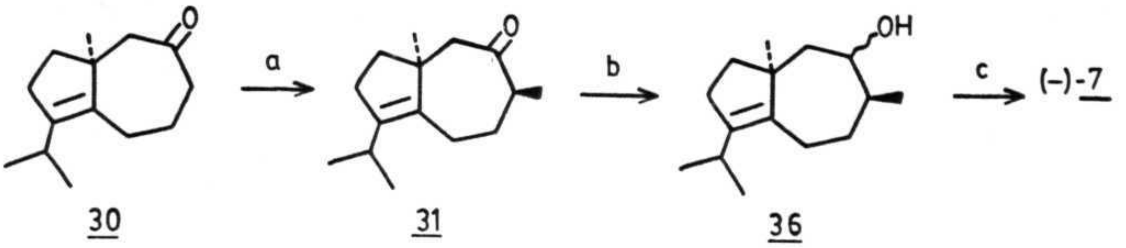
II.4. SYNTHESIS

A Short Synthesis of (-)-Daucene-(7)

At the outset, Scheme II.6 was implemented. Kinetically controlled deprotonation of 30 and quenching of the enolate anion with methyl iodide furnished 31 in a regio- and stereoselective fashion in 80% yield, Scheme II.10. Formation of a single stereoisomer was evident from the presence of a signal at δ 1.02 (d, J = 7Hz) in the ^{1}H NMR spectrum. Reduction of 31 with LAH gave a diastereomeric mixture of alcohol 36, which was dehydrated with $POCl_3$-pyridine to furnish (-)-daucene 7, $[\alpha]_D$-20 (C.08, $CHCl_3$ (Lit.

$[\alpha]_D$ +23)[5] in 50% yield, identical (IR, ^{1}H NMR, Fig.II.1) with the natural product.[#]

SCHEME II.10



Reagents, Conditions and Yields : a) LHMDS, THF, MeI, -78^{0}C, 80%; b) LAH, Et_2O, RT, 70%; c) $POCl_3$-pyridine, RT, 10h, 50%.

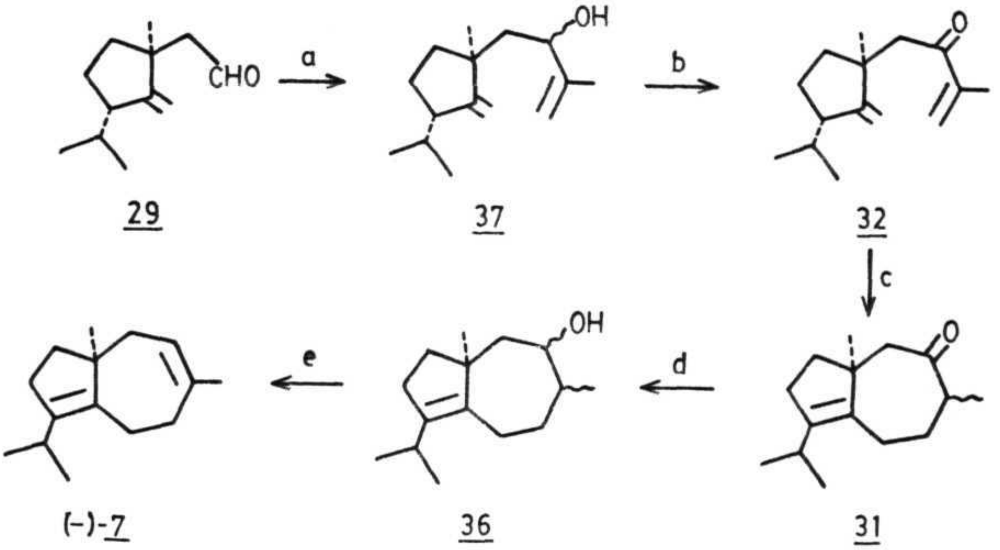
The synthesis of (-)-daucene 7 reported here is notable for its brevity and the fact that only a single required olefin is obtained in the last dehydration step. In other reported synthesis of 7, a mixture of olefins (daucene isomers) were generally encountered and required careful and tedious separation to obtain the natural product.[18,19]

Alternatively, (-)-daucene 7 was also synthesised from the enal 29 by direct construction of the daucane skeleton as indicated in Scheme II.11. Addition of isopropenyl magnesium bromide to 29 led to a diastereomeric mixture of allylic alcohols 37 in 83% yield. Careful oxidation of this mixture with PCC furnished a single enone 32 in 65% yield. The ^{1}H NMR

[#] We thank Professor Seto for the comparison spectra of daucene 7.

spectrum of 32 exhibited the presence of two β-protons of the enone moiety at δ 5.7 and 5.9 in addition to the exocyclic methylene protons at δ 4.75. The ^{13}C NMR spectrum had complimentary signals at δ 201.0, 162.7 & 123.8 due to the enone moiety in 32. Attention was now turned towards the key enone-olefin cyclisation step. Accordingly, exposure of enone 32 to catalytic amount of perchloric acid in ethyl acetate -acetic anhydride[24] furnished the hydroazulenone 31 in 70% yield, as a C(5)-epimeric mixture.

SCHEME II.11



Reagents, Conditions and Yields: a) isopropenyl magnesium bromide, THF, RT, 1h, 83%; b) PCC, DCM, 4 A^0 molecular sieves, RT, 1h, 65%; c) Cat. $HClO_4$, $EtOAc-Ac_2O$, RT, 0.5h, 70%; d) LAH, Et_2O, RT, 0.5 h, 70%; e) $POCl_3$-pyridine, RT, 12h, 50%.

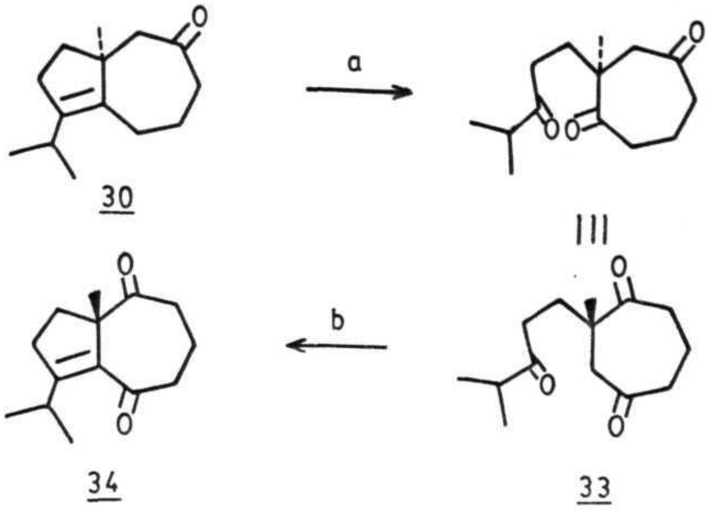
Absence of olefinic protons in the ^1H-NMR spectrum of 31 and the presence of ν_{max} 1700 cm^{-1} confirmed the predicted cause of the cyclisation process. The epimeric hydroazulenones 31 were reduced by LAH to alcohol 36 and then directly subjected to dehydration with $POCl_3$-pyridine to afford (-)-daucene 7 in 50% yield, Scheme II.11.[25]

Synthesis of (+)-Aphanamol-I (13) and (+)-2-oxo-Isodauc-5-en-12-al (15)

As described above, the successful pursuit of isodaucane sesquiterpene aphanamol-I relied heavily on the effective implementation of Scheme II.8. The tetrasubstituted double bond of bicyclic hydroazulenone 30 was smoothly cleaved following the Sharpless catalytic Ru(IV) oxidation procedure[26] to furnish the trione 33 in quantitative yield, Scheme II.12. The presence of three carbonyl resonances in the ^{13}C NMR at δ 213.4, 213.2 and 209.6, besides other spectral data, confirmed the monocyclic structure of 33. The trione 33 was readily induced to undergo intramolecular aldol cyclisation in the presence of 5% KOH-MeOH to furnish the bicyclic ene-dione 34 in 60% yield. The ene-dione formulation for 34, $[\alpha]_D$ + 177.1 (C 2.0, $CHCl_3$), was fully consonant with its IR (1700, 1670, 1590 cm^{-1}), ^1H-NMR (Fig.II.2) and ^{13}C NMR (Fig.II.3) spectra. The ^{13}C NMR spectrum in particular exhibited the presence of four diagnostic Sp^2 carbon resonances at δ 213.7, 199.8, 167.3 and 168.8 due to the conjugated enone moiety and a saturated carbonyl group. Thus, in a two-step synthetic stratagem, 30 was restructured to 34, as planned and was now set for the attempts to generate and control the stereochemistry at C(7) and C(8) stereogenic centres.

The enone moiety in 34 was subjected first to metal-ammonia reduction. Accordingly, the ene-dione 34 was treated with Li-liq.NH_3 and the resulting reduction products oxidised with PCC to furnish saturated diones 38 and 39 (9:1) in 70% yield, Scheme II.13, while the ^1H-NMR and ^{13}C-NMR spectra of

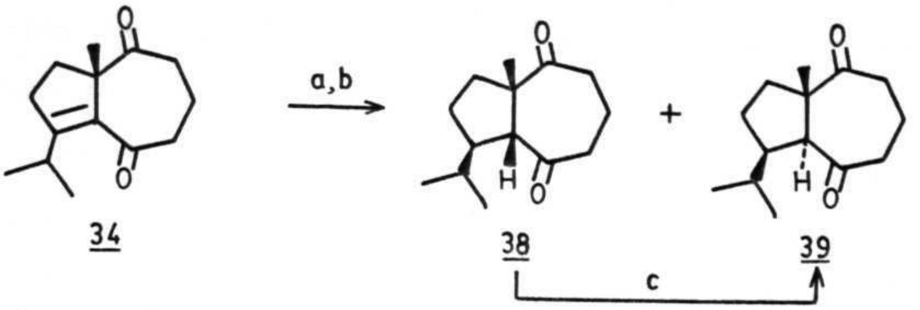
SCHEME II.12



Reagents, Conditions & Yields: a) RuO_2, $NaIO_4$, $H_2O-CH_3CN-CCl_4$, RT, 1h, quantitative; b) 5% KOH MeOH, Δ. 0.5 h, 60%

the major isomer 38 (Figs. II.4 & II.5) and minor isomer 39 (Figs. II.6 & II.7) fully supported their gross structures, they were not incisive enough for making stereochemical assignments. However, it was observed that the major isomer 38 on equilibration with base (NaOMe-MeOH) completely converted to the minor isomer 39 having more stable trans-ring junction stereochemistry, Scheme II.13. In the light of this observation, it is possible that the minor isomer 39 is a product of equilibration taking place during the isolation procedures rather than a true product of Li-liq.NH_3 reduction.

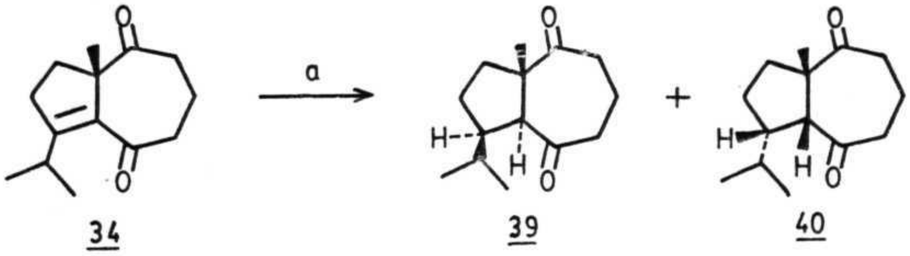
SCHEME II.13



Reagents, Conditions & Yields: a) Li, liq.NH_3, THF, MeOH,; b) PCC, DCM, 4 A^o molecular sieves, RT, 1h, 70%; c) 5% KOH-MeOH, 24h, RT, quantitative.

Catalytic hydrogenation of ene-dione 34 over Pd/C catalyst afforded two readily separable isomers 39 and 40 (5:4) in over 90% yield, Scheme II.14. In ^1H-NMR and ^{13}C-NMR of 39 and 40 fully supported their gross structure, particularly the later exhibited the presence of two saturated carbonyl groups in each of them. The ^1H and ^{13}C-NMR spectra of one of the isomer 40 are displayed in Fig.II.8 and II.9, respectively. The other isomer 39 from hydrogenation was found to be identical with the minor product 39 obtained during Li-liq.NH_3 reduction.

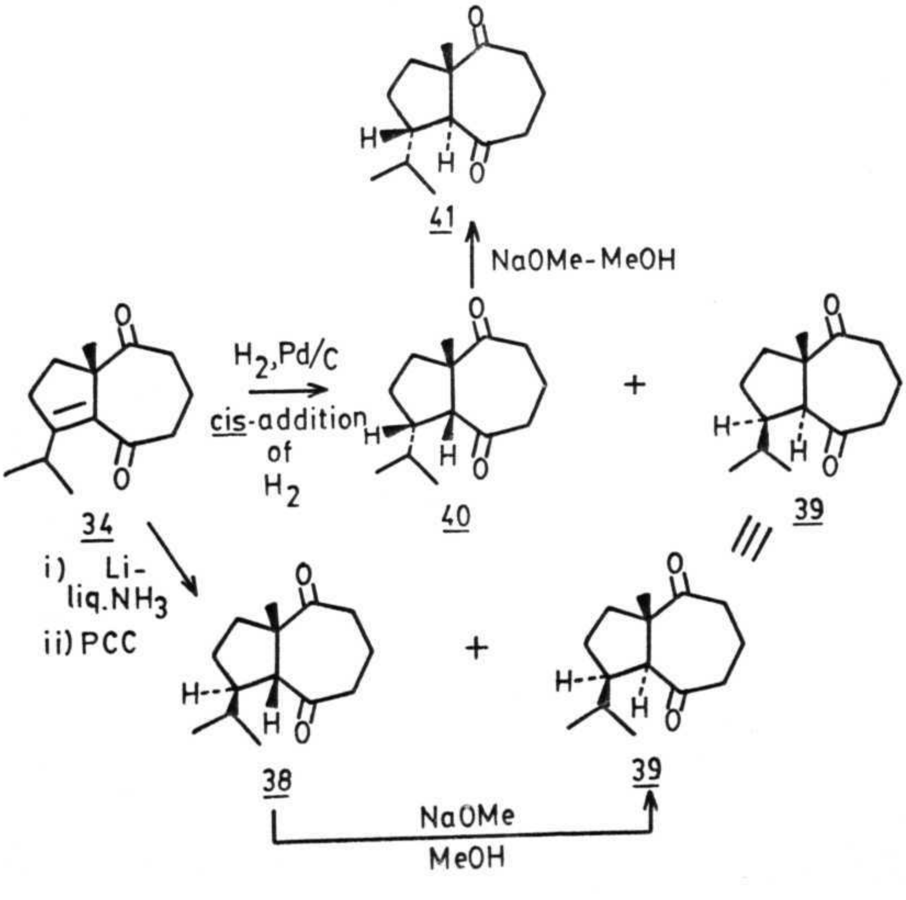
SCHEME II.14



Reagents, Conditions & yields: a) H_2, Pd/C, 20 psi, 1h, 90%.

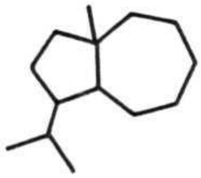
Keeping in mind the favoured cis-addition of hydrogen to the double bond, the two isomers obtained from 34 should be 40 and 39 having cis- and trans-ring junction stereochemistry, respectively. Since, the later isomer was found to be identical with the minor product of Li-liq.NH_3 reduction (also the product of epimerisation of 38), its identity was established. Expectedly, on exposure to NaOMe-MeOH, the trans- isomer 39 remained unchanged. Finally, the cis-ring junction isomer 40 from hydrogenation, on exposure to NaOMe-MeOH epimerised completely into a new stereoisomer 41 having trans- stereochemistry. This stereoisomer was different (^{1}H & ^{13}C NMR, Fig. II.10 & Fig. II.11) from the three other stereoisomers 38, 39 and 40 described earlier. Thus, it was possible to synthesise all the four possible stereoisomers 38, 39, 40 & 41 and their stereochemistries were rigorously secured on the basis of internally consistant correlation, Scheme II.15. To our knowledge, this is the first time that these bicyclic

SCHEME II.15

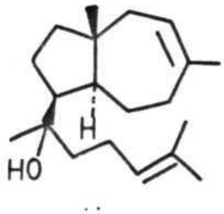


hydroazulenoids of well defined stereochemistry have become available and that too in enantiomerically form.[#]

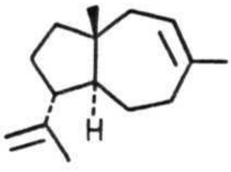
[#] Having access to all the four possible stereoisomers 38, 39, 40 & 41 of the bicyclic hydroazulenedione in enantiomerically pure form was quite significant. It may be noted that several sesqui- & diterpenes have been recently isolated in which perhydroazulenic moiety i is present in different stereochemical patterns ii - vi. Stereoisomers 38, 39, 40 & 41 can serve as advanced precursor for many of these through ring expansion and ring annulation protocols.



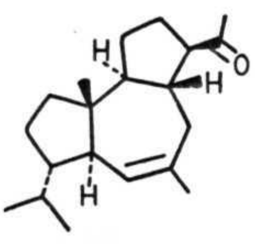
i



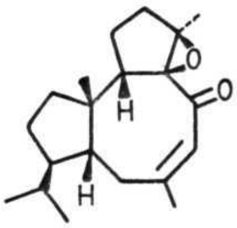
ii



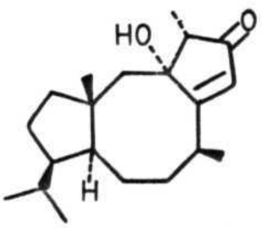
iii



iv



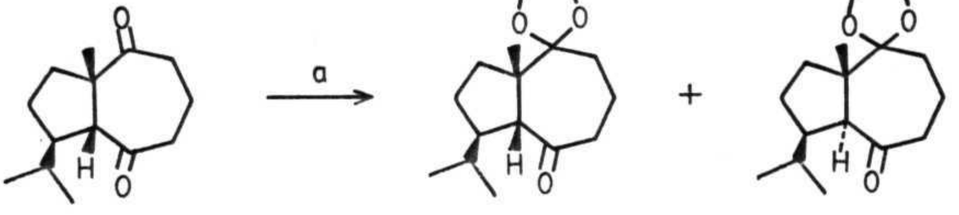
v



vi

With the acquisition of the saturated dione 38, having requisite stereochemistry at C(1), C(7) and C(8) centres, we had crossed the major hurdle in our quest for isodaucane sesquiterpenes. The next task enroute to the target molecules 13 and 15 was the functional group adjustment and introduction of the last carbon atom at C(5). For this purpose, the carbonyl group at C(2) in dione 38 was regioselectively protected as the monoacetal 42, Scheme II.16. However during the acetal protection operation, even in the presence of PPTS, considerable epimerisation occurred and the trans- 43 was also coproduced with 42. We therefore prepared 42 in a slightly modified manner to circumvent the complication due to epimerisation. Reverting back to ene-dione 34, we chemoselectively protected it as the enone-acetal 44 by exposure to ethylene glycol in the presence of PTS. Li-liq.NH_3 reduction of 44 and PCC oxidation of the product furnished a 7.5:1 mixture of 42 and 43, respectively, Scheme II.17.

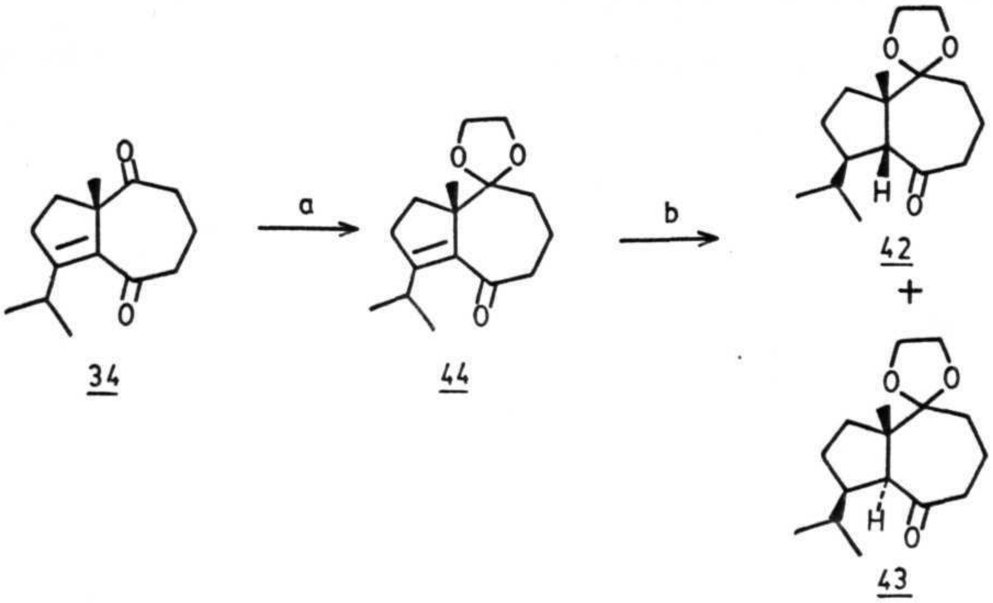
SCHEME II.16



38 42 43

Reagents, Conditions & Yields: a) $HOCH_2CH_2OH$, PPTS, benzene, Δ, 15 h, 20%.

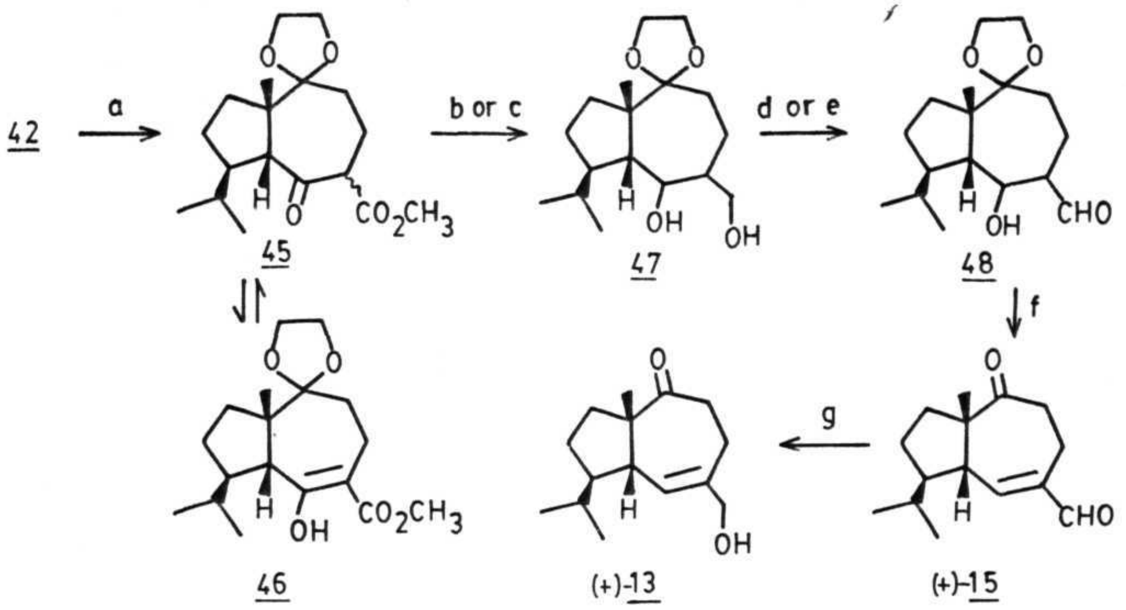
SCHEME II.17



Reagents, Conditions & Yields: a) HOCH$_2$CH$_2$OH, PPTS, benzene, Δ, 15h, 92%; b) Li-liq.NH$_3$, THF, PCC. DCM, 4 ^{0}A-molecular sieves, 74%.

Having secured 42 in a reasonable way, the seemingly straightforward functional group manipulation enroute to 13 and 15, proved quite cumbersome. Success was eventually achieved through the following reaction sequence. Kinetically controlled deprotonation of 42 with LHMDS and quenching with methyl chloroformate furnished the β-ketoester 45 in 80% yield, as a mixture of C(5)-diastereomers, Scheme II.18. There was also some indication (^{1}H-NMR) of the presence of tautomeric enol ester form 46. The keto ester 45 was directly reduced with LAH to afford the diol 47 in 40% yield. However, sodium borohydride surprisingly proved superior for this reduction and 47 was obtained in 62% yield from 45. The facile reduction of ester group in 45 to diol 47 with sodium borohydride probably takes place *via* the enol ester 46. No attempts were made to assign the stereochemistry at C(5) and C(6) centres in diol 47 because in subsequent steps these centres were going to be rehybridised by generation of the C(5)-C(6) double bond. Chemoselective oxidation of the primary hydroxyl group in 47 with PDC afforded the hydroxy aldehyde 48 in 25% yield. The

SCHEME II.18



Reagents, Conditions & yields: a) LHMDS, ClCOOMe, THF, -78°C, 0.5h, 86%; b) LAH, ether, RT, 1h, 40%; c) NaBH$_4$, MeOH, 0°C, 0.5h, 62%; d) PDC, DCM, 0°C, 0.5h, 25%; e) COCl$_2$-DMSO, Et$_3$N, DCM, -60°C, 1h, 70%; f) PTS, benzene, 80°C, 1h, 37%; g) NaBH$_4$, CeCl$_3$.6H$_2$O, MeOH, -5°C, 10 min, quantitative.

hydroxy aldehyde formulation for 48 was fully consonant with ν_{max} at 3500, 2720 and 1720 cm^{-1}, and the presence of a aldehydic proton signal at δ 9.72 (s) in its ^{1}H-NMR spectrum. However, Swern oxidation of 47 proved to be distinctly superior and hydroxy-aldehyde 48 could be obtained in 70% yield, Scheme II.18. Brief exposure of 48 to cat.PTS resulted in the dehydration as well as deacetalisation and furnished (+)-2-oxo-isodauc-5-en-12-al 15, [α]$_D$ + 33 (c 0.2, $CHCl_3$)[#] in 37% yield. The IR and ^{1}H-NMR spectra of 15 in $CDCl_3$ and C_6D_6 are displayed in Figs.II.12 & II.13, respectively. These values are in complete agreement with those reported in literature.[#]

Finally, chemoselective reduction of aldehyde functionality in 15 with $NaBH_4$-$CeCl_3.6H_2O$ reagent[27] led to aphanamol-I 13, [α]$_D$ +10 (c 0.4, $CHCl_3$; Lit. +13)[12] in quantitative yield. The identity of (+)-13 with the natural product was established through direct spectral (IR, ^{1}H-NMR; Fig.II.14) comparison.[@] Our synthesis of (+)- 13 also firmly establishes the absolute stereochemistry of this natural product. Since, aphanamol-I 13 has already been correlated with aphanamol-II 14, the synthesis of (+)- 13 establishes the absolute configuration of both the aphanamols.

Daucane → isodaucane skeletal transformation

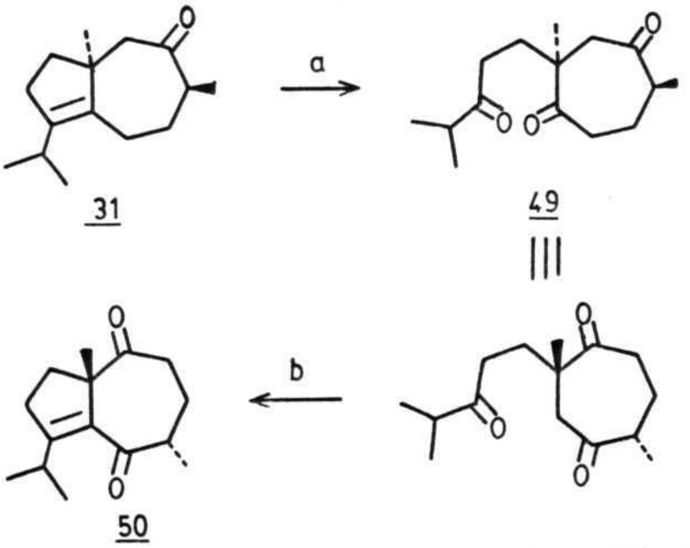
Having synthesised natural products based on daucane and isodaucane skeleta, it was our intent to demonstrate the direct chemical conversion of the daucane skeleton into isodaucane skeleton, as envisaged in Scheme II.9.

[#] The spectra of natural product could not be obtained from Professor F. Bohlmann for direct comparison despite many requests. Optical rotation of the natural product has not been reported.

[@] We thank Professor M. Nishizawa for providing comparison spectra of aphanamol-I 13.

For this purpose, the C_{15}-daucene derivative 31 (readily available as shown in Scheme II.10) was subjected to catalytic RuO_2-$NaIO_4$ oxidation to furnished the triketone 49 in quantitative yield. The three carbonyl resonances at δ 213.6 (2C) and 211.2 in its ^{13}C NMR were fully supportive of its formulation. The triketone 49 on intramolecular aldol condensation under the influence of 5% KOH-MeOH resulted in the smooth formation of the ene-dione 50 in 60% yield. The structure of ene-dione 50 was confirmed through its ^{13}C NMR and other spectral data summarised in the experimental section. The C_{15} ene-dione 50 $[\alpha]_D$-52(c 0.5, $CHCl_3$) has the complete carbon skeleton of isodaucane and it belongs to the enantiomeric series with respect to its daucane precursor. We have indicated above that daucane and isodaucane do not share common biogenetic origin despite extremely close structural relationship between them and Nature in its wisdom does not seems to convert one into another. However, through chemical manoeuvres, it has been possible to convert daucane derivative 31 to isodaucane 50 in a simple, straight forward manner.

SCHEME II.19



Reagents, Conditions & Yields: a) RuO_2, $NaIO_4$, CCl_4-H_2O-CH_3CN, RT, quantitative; b) 5% KOH-MeOH, 60°C, 1h, 60%.

II.5. SUMMARY AND OUTLOOK

The synthetic efforts reported here constitute the first total synthesis of isodaucane natural products. The attainment of stereo- and enantioselective synthesis of (+)-aphanamol I 13 establishes its absolute stereochemistry together with its sibling (+)-aphanamol II, 14. The strategy adopted for the synthesis of (+)-aphanamol I 13 and (+)-isodaucenal 15 is readily adaptable for the synthesis of other isodaucane sesquiterpenes.

A notable feature of the work described in this chapter is the preparation of four stereoisomeric perhydrozulenones 38 - 41 . The stereochemical patterns present in them have been encountered in many naturally occurring sesqui- and diterpenes. Thus, access to 38 - 41 augurs well for further synthetic activity in the area. This is the first time that a complete solution to the stereochemical subtleties present in daucane and isodaucane sesquiterpenes has been provided.

II.6. EXPERIMENTAL

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

Hydroazulenone 30 was prepared starting from R-(+)-limonene 27 according to the procedure described in the chapter I.

1S,4S-Dimethyl-8-isopropylbicyclo[5.3.0]dec-7-en-3-one (31):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal was placed n-butyl lithium (1.0 ml, 1.0 mmol, 1.0 m in hexane). The flask was cooled to $-78^{0}C$ and hexamethyldisilazane (ml, mmol) was added and the resulting slurry was dissolved in dry THF (1 ml) and stirred for 20 min. Then ketone 30 (100 mg, 0.5 mmol) in dry THF (1 ml) was added and stirring was continued for further 0.5 h. The resulting enolate was quenched by the addition of excess methyl iodide (1 ml). After stirring for further 0.5 h the reaction was stopped by the addition of brine (15 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (3 g) column. Elution with 5% ethyl acetate - pet ether furnished the C_{15}-ketone 31 (85 mg) in 80% yield.

$[\alpha]_D$: -74 (c 1.0, $CHCl_3$)

IR : 2950, 1700 cm^{-1}

^1H-NMR : δ2.8 - 1.4 (12H, series of m), 1.02 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 1.0 (3H, s, $-C-C\underline{H}_3$), 0.95 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.92 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ214.4, 141.5, 139.3, 53.3, 48.5, 47.2, 37.1, 34.4, 27.2, 26.7, 25.0, 23.3, 21.5, 21.0, 17.2

Analysis : $C_{15}H_{24}O$ Calcd: C, 81.76 ; H, 10.98
Found: C, 81.99 ; H, 10.88

1S,4S-Dimethyl-8-isopropylbicyclo[5.3.0]dec-7-en-3-ol (36):

Into a two necked 10 ml RB flask fitted with a rubber septum and mercury seal was placed lithium aluminium hydride (50 mg, excess) in dry ether (5 ml). To this suspension, bicyclic ketone 31 (50 mg, 0.24 mmol) in dry ether (1 ml) was slowly added through a syringe. The reaction mixture was stirred for 30 min. A few drops of ethyl acetate were then added to destroy the excess hydride, followed by saturated Na_2SO_4 solution. The reaction mixture was extracted with ether (25 ml x 3). The combined ethereal extract was washed and dried. Removal of the solvent gave crude mixture of hydroxy olefin which was charged on a silica gel (10 g) column and elution with 10% ethyl acetate-pet ether furnished the diastereomeric mixture of alcohols 36 (45 mg) in 90% yield.

IR : 3400, 2950, 1100 cm^{-1}

bp. : $150^{o}C/0.1$ mm

^{1}H-NMR : δ3.8 (1H, m, -CH-OH), 2.6 - 1.3 (13H, series of m), 1.05 - 0.08 (12H, series of s and d)

Analysis : $C_{15}H_{26}O$ Calcd: C, 81.02 ; H, 11.79
Found: C, 81.12 ; H, 11.81

(-)-Daucene (7):

The diastereomeric mixture of alcohols 36 (45 mg, 0.225 mmol) in dry pyridine (1.0 ml) was placed in a 5 ml RB flask fitted with a drying tube.

To this stirred solution was added phosphorous oxychloride (0.2 ml) at 0 - 5^oC and the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with pentane (10 ml) and slowly quenched with water to hydrolyse the excess phosphorous oxychloride. The reaction mixture was extracted with pentane (10 ml x 3), washed and dried. Removal of the solvent gave an oily residue which was charged on a silver nitrate impregnated silica gel (5 g) column. Elution with pentane removed less polar impurities. Further elution with 20% benzene - pentane furnished pure (-)-daucene 7 (23 mg) in 50% yield.

$[\alpha]_D$: -20 (c 1.0, $CHCl_3$)

IR : 2950, 1445, 830 cm^{-1}

^1H-NMR (fig. II.1) : δ5.43 (1H, br t, J = 6.6 Hz, C=C$\underline{H}$), 2.7 - 1.2 (11H, series of m), 1.74 (3H, br s, -C=C-C$\underline{H}_3$), 0.98 (3H, d, J = 7 Hz), 0.92 (3H, d, J = 7Hz), 0.91 (3H, s, -C-C$\underline{H}_3$)

The IR and ^1H-NMR spectra were found to be identical with the authentic spectra kindly provided by Professor Seto.

3S-Isopropyl-1S-methyl-2-methylene-1R-(3`-hydroxy-2`-methylbut-1`-en-4'-yl)cyclopentane (37):

Into a 50 ml three necked RB flask, fitted with a dry N_2 inlet, pressure equalising addition funnel and mercury seal, activated magnesium turnings (170 mg, 7.0 mmol) were placed and dry THF (5 ml) was introduced. To this mixture 2-bromopropene (970 mg, 8.0 mmol) in dry THF (5 ml) was slowly added and stirring was continued until all the magnesium had dissolved. A solution of the aldehyde 29 (1.0 g, 5.55 mmol) in dry THF (5 ml) was slowly added to it and the reaction mixture was stirred at room temperature for 1h. The reaction was quenched by addition of saturated NH_4Cl solution and extracted with ether (50 ml x 3). The combined organic extract was washed, dried and concentrated to give an oily residue which was charged on a silica gel (15 g) column. Elution with 10% ethyl acetate - pet ether furnished a diastereomeric mixture of allylic alcohols <u>37</u> (1.0 g) in 83% yield.

bp. : 160°C/0.1 mm

IR : 3400, 3050, 890 cm^{-1}

^{1}H-NMR : δ4.9 - 4.6 (8H, m, $-C{=}C\underline{H}_2$), 4.2 - 4.0(2H, m, $-C\underline{H}-OH$), 2.6 - 1.2 (22H, m), 1.08 (3H, s, $-C-C\underline{H}_3$), 1.0 (3H, s, $-C-C\underline{H}_3$), 0.95(3H, d, J=7Hz), 0.75 (3H, d, J=7Hz)

Analysis : $C_{15}H_{26}O$ Calcd: C, 81.02 ; H, 11.79

Found: C, 81.12 ; H, 11.81

3S-Isopropyl-1S-methyl-2-methylene-1R-(2'-methyl-1'-en-4'-yl-but-3'-one)cyclopentane (<u>32</u>):

To a suspension of pyridinium chlorochromate (1.1 g, 5.0 mmol) in dry dichloromethane (5 ml) containing 1.0 g of activated molecular sieves (4 $^{\circ}$A), was added allylic alcohol <u>37</u> (1.0 g, 4.5 mmol) in dry dichloromethane (5 ml) at 0°C. The reaction mixture was brought to room temperature, stirred for an additional 1h, diluted with dry ether (20 ml) and filtered through a small florisil (3 g) column. Removal of the solvent gave an oily liquid which was charged on a silica gel (20 g) column and elution with 10% ethyl acetate - pet ether furnished the enone <u>32</u> (645 mg) in 65% yield.

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

bp. : $146^{\circ}C/0.2$ mm

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

^{1}H-NMR : δ5.9 (1H, br s, $-C=C\underline{H}_2$), 5.70 (1H, br s, $-C=C\underline{H}_2$), 4.75 (2H, t, $-C=C\underline{H}_2$), 3.0 - 2.0 (3H, m), 1.8 (3H, s, $-C=C-C\underline{H}_3$), 1.75 - 1.2 (5H, m), 1.05 (3H, s, $-C-C\underline{H}_3$), 0.95 (3H, d, J=7Hz, $-CH-C\underline{H}_3$), 0.75 (3H, d, J=7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ201.0, 162.7, 145.8, 123.8, 103.3, 50.4, 47.4, 44.53, 36.9, 28.5, 27.0, 22.9, 21.6, 17.4, 16.1

Analysis : $C_{15}H_{24}O$ Calcd: C, 81.76 ; H, 10.98
Found: C, 81.82 ; H, 10.97

1S,4-Dimethyl-8-isopropylbicyclo[5.3.0]dec-7-ene-3-one (31):

Into a 25 ml RB flask, enone 32 (500 mg, 2.3 mmol) in dry ethyl acetate (10 ml) was taken and acetic anhydride (1 ml) and 70% perchloric acid (0.1 ml) were added.[24] The reaction mixture was stirred at room temperature for 5 min. The reaction mixture was then quenched with saturated $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was once again extracted with ethyl acetate (25 ml x 3) and the combined organic extract was washed, dried and concentrated to give an oily liquid which was chromatographed on a silica gel (20 g) column to furnish the bicyclic ketone 31 (350 mg) in 70% yield as a diastereomeric mixture.

bp : $110^{\circ}C/0.1$ mm

IR : 2950, 1700 cm^{-1}

^{1}H-NMR : δ2.7 - 1.4 (24H, m), 1.2 - 0.8 (24H, m, series of s and m)

(-)-Daucene (7):

Into a two necked 10 ml RB flask fitted with a rubber septum and mercury seal was placed lithium aluminium hydride (50 mg, excess) in dry ether (5 ml). To this suspension, bicyclic ketone 31 (50 mg, 0.24 mmol) in dry ether (1 ml) was slowly added through a syringe. The reaction mixture was stirred for 30 min. A few drops of ethyl acetate were then added to destroy the excess hydride, followed by saturated Na_2SO_4 solution. The reaction mixture was extracted with ether (25 ml x 3). The combined ethereal extract was washed and dried. Removal of the solvent gave crude mixture of hydroxy olefin which was charged on a silica gel (10 g) column and elution with 10% ethyl acetate-pet ether furnished the diastereomeric mixture of alcohols 36 (45 mg) in 90% yield.

IR : 3400, 2950, 1100 cm^{-1}

The above diastereomeric mixture of alcohols 36 (45 mg, 0.225 mmol) in dry pyridine (1.0 ml) was placed in a 5 ml RB flask fitted with a drying tube. To this stirred solution was added phosphorous oxychloride (0.2 ml) at 0 - 5^oC and the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with pentane (10 ml) and slowly quenched with water to hydrolyse the excess phosphorous oxychloride. The reaction mixture was extracted with pentane (10 ml x 3), washed and dried. Removal of the solvent gave an oily residue which was charged on a silver nitrate impregnated silica gel (5 g) column. Elution with pentane removed less polar impurities. Further elution with 20% benzene - pentane furnished pure (-)-daucene 7 (23 mg) in 50% yield.

1S-Methyl-1-(2'-methylpent-5'-yl-3'-one)cycloheptan-2,6-dione (33):

Into a 50 ml RB flask ketone 30 (1.0 g, 4.85 mmol) was taken in a mixture of carbontetrachloride, acetonitrile and water (each 5 ml). To this mixture were added sodium metaperiodate (1.28 g, 6.0 mmol) and ruthenium dioxide (10 mg).[26] After being stirred for 1 h, the reaction was diluted with dichloromethane (50 ml) and filtered through celite pad (3 g) and repeatedly washed with dichloromethane. The combined filtrate was washed and dried. The crude product obtained after removal of the solvent was filtered through a small silica gel (5 gm) column with 10% ethyl acetate - pet ether to furnish the triketone 33 (1.0 g) in quantitative yield.

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

bp. : $160^{o}C/0.1$ mm

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

^{1}H-NMR : δ3.1 - 2.2 (8H, m), 2.1 - 1.5 (5H, m), 1.12 (3H, s, $-C-C\underline{H}_3$), 1.05 (6H, d, J = 7Hz, $-CH(C\underline{H}_3)_2$)

^{13}C-NMR : δ213.4, 213.2, 209.6, 50.0, 47.3, 43.5, 40.4, 39.6, 34.2, 32.5, 21.4, 20.6, 17.7(2C)

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

Found: C, 70.87 ; H, 9.35

8S-Isopropyl-1S-methylbicyclo[5.3.0]dec-7-ene-2,6-dione (34):

Into a 50 ml RB flask fitted with a reflux condenser and mercury seal, triketone 33 (1.0 g, 4.5mmol) was placed and 5% methanolic KOH (25 ml) was added to it. The resulting reaction mixture was refluxed for 1 h.

Methanol was removed at reduced pressure and the residue left was diluted with water (10 ml) and extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was charged on silica gel (10 g) column. Elution with 15% ethyl acetate - pet ether furnished the ene-dione 34 (600 mg) in 60% yield.

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

bp. : $155^o/0.1$ mm

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

^1H-NMR (fig. II.2) : δ3.62 (1H, m), 3.1 - 1.45 (10H, series of m), 1.35 (3H, s, $-C-C\underline{H}_3$), 1.06 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 1.04 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR (fig. II.3) : δ213.7, 199.8, 167.3, 136.8, 61.3, 41.4, 37.2, 35.0, 29.7, 27.7, 20.9, 20.7, 20.5(2C)

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

Found: C, 76.51 ; H, 9.32

8R-Isopropyl-1S-methyl-7R-bicyclo[5.3.0]decan-2,6-dione (38) and 8R-Isopropyl-1S-methyl-7S-bicyclo[5.3.0]decan-2,6-dione (39):

Into a two necked 100 ml RB flask, fitted with a guard tube and septum, was taken freshly distilled liq.NH_3 (50 ml). To this was added freshly cut lithium metal (115 mg, 5 mmol) piece by piece. The resulting blue solution was stirred for 5 min and ene-dione 34 (200 mg, 0.90 mmol) in dry THF (5 ml) was added slowly. After stirring for 10 min the reaction mixture was quenched by careful addition of dry methanol (1 ml). After all the ammonia had evaporated, the reaction mixture was diluted with water (25 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude diol which was used directly for the next step.

To a suspension of pyridinium chlorochromate (220 mg, 1.0 mmol) in dry dichloromethane (5 ml) containing 1.0 g of activated molecular sieves (4 ^{o}A) was added the above crude diol (160 mg) in dry dichloromethane (5 ml) at 0^{o}C . The reaction mixture was brought to room temperature and stirred for an additional 1 h. Then the reaction mixture was diluted with dry ether (20 ml) and filtered through a small florisil (3 g) column. Removal of the solvent gave an oily liquid which was charged on a silica gel (2 g) column and elution with 10% ethyl acetate - pet ether furnished the <u>cis</u>-dione <u>38</u> (125 mg) in 63% yield.

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

bp. : 148^{o}C/0.1 mm

IR : 2950, 1700 cm^{-1}

^{1}H-NMR (fig. II.4) : δ3.5 (1H, d, J = 9Hz), 2.8 - 1.2 (12H, series of m), 1.0 (3H, s, -C-C$\underline{H}_3$), 0.85 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.74 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

^{13}C-NMR (fig. II.5) : δ212.9, 210.5, 56.5, 51.7, 51.3, 45.1, 40.8, 35.8, 29.7, 28.1, 23.7, 23.0, 21.6, 21.5

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

Further elution with 15% ethyl acetate - pet ether furnished the <u>trans</u>-dione <u>39</u> (15 mg) in 7% yield.

$[\alpha]_D$: -15 (c 1.0, $CHCl_3$)

bp. : 145^{o}C/0.1 mm

IR	:	2950, 1700 cm^{-1}
^1H-NMR (fig. II.6)	:	δ3.0 - 1.2 (13H, series of m), 1.4 (3H, s, $-C-C\underline{H}_3$), 0.95 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.82 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)
^{13}C-NMR (fig. II.7)	:	δ213.3, 211.1, 63.0, 59.2, 47.9, 42.8, 39.9, 34.8, 33.5, 27.5, 25.5, 21.5, 20.4, 20.2
Analysis	:	$C_{14}H_{22}O_2$ Calcd: C, 75.63 ; H, 9.97 Found: C, 75.33 ; H, 9.99

8R-Isopropyl-1S-methyl-7S-bicyclo[5.3.0]decan-2,6-dione (39):

Into a 10 ml three necked RB flask, fitted with a dry N_2 inlet, septum and mercury seal was placed dry methanol (2 ml). To this freshly cut sodium (5 mg, 0.2 mmol) was added and the reaction mixture was stirred until all the sodium had dissolved. Then the *cis*-dione 38 (25 mg, 0.11 mmol) was added with dry methanol (2 ml) and the contents were stirred at room temperature for 12 h. The methanol was removed at reduced pressure and the residue left was diluted with water (10 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product. The crude product was filtered through a small silica gel column with 5% ethyl acetate - pet ether to furnish the *trans*-dione 39 (25 mg) in quantitative yield.

8R-Isopropyl-1S-methyl-7S-bicyclo[5.3.0]decane-2,6-dione (39) and 8S-Isopropyl-1S-methyl-7R-bicyclo[5.3.0]decane-2,6-dione (40):

A solution of the ene-dione 34 (100 mg, 0.45 mmol) in dry ethyl acetate (3 ml) was hydrogenated (25 psi. pressure) over 10% Pd/C (20 mg) for 1 h. The catalyst was filtered-off and the solvent was removed to furnish the saturated dione mixture (100 mg). The mixture of products was chromatographed on a silica gel (5 g) column. Elution with 5% ethyl acetate - pet ether resulted in the removal of the less polar impurities and further elution with 10% ethyl acetate - pet ether furnished the trans-dione 39 (50 mg) in 50 % yield. This was found identical with the minor product obtained in the liq.NH_3 reduction of 34.

Further elution with 12% ethyl acetate - pet ether furnished the cis-dione 40 (40 mg) in 40% yield.

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

bp. : $145^oC/0.1$ mm

IR : 2950, 1700 cm^{-1}

^1H-NMR (fig. II.8) : δ3.25 - 1.2 (13H, series of m), 1.35 (3H, s, $-C-C\underline{H}_3$), 0.92 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.8 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR (fig. II.9) : δ214.5, 212.0, 59.4, 58.7, 49.8, 45.4, 40.1, 31.7, 29.0, 28.0, 26.4, 23.8, 22.7, 21.8

Analysis : $C_{14}H_{22}O_2$ Calcd: C, 75.63 ; H, 9.97
Found: C, 75.49 ; H, 9.91

8S-Isopropyl-1S-methyl-7S-bicyclo[5.3.0]decane-2,6-dione (41):

Into a 10 ml three necked RB flask, fitted with a dry N_2 inlet, septum and mercury seal was placed dry methanol (2 ml). To this freshly cut sodium (5 mg, 0.2 mmol) was added and the reaction mixture was stirred until all the sodium was dissolved. Then the cis-dione 40 (25 mg, 0.11 mmol) was added with dry methanol (2 ml) and the contents were stirred at room temperature for 12 h. The methanol was removed at reduced pressure and the residue left was diluted with water (10 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product. The crude product was filtered through a small silica gel column with 5% ethyl acetate - pet ether to furnish the <u>trans</u>-dione <u>41</u> (25 mg) in quantitative yield.

$[\alpha]_D$: -43 (c 1.0, $CHCl_3$)

bp. : $150^oC/0.1mm$

^1H-NMR (fig. II.10) : δ3.0 - 2.4 (5H, m), 2.1 - 1.2 (8H, m), 0.98 (3H, s, -C-$C\underline{H}_3$), 0.78 (3H, d, J = 7Hz, -CH-$C\underline{H}_3$), 0.70 (3H, d, J = 7Hz, -CH-$C\underline{H}_3$)

^{13}C-NMR (fig. II.11) : δ213.5, 210.3, 58.1, 57.3, 44.1, 43.4, 41.2, 35.6, 32.2, 24.3, 21.0, 20.7, 20.2, 19.7

Analysis : $C_{14}H_{22}O_2$ Calcd: C, 75.63 ; H, 9.97
Found: C, 75.92 ; H, 9.95

<u>2-Ethylene ketal-8R-isopropyl-1S-methyl-7R-bicyclo[5.3.0]decan-6-one</u> (<u>42</u>):

Into a 25 ml RB flask fitted with Dean-Stark water separator and reflux condenser, <u>cis</u>-dione <u>38</u> (100 mg, 0.45 mmol), ethylene glycol (0.2 ml) and PPTS (25 mg) in dry benzene (15 ml) were placed and the contents were refluxed for 15 h. The reaction mixture was diluted with benzene (25 ml), washed with aqueous $NaHCO_3$, water and then dried. The crude product obtained after removal of the solvent was charged on a silica gel (3 g) column. Elution with 5% ethyl acetate - pet ether removed the less polar impurities. Further elution with 10% ethyl acetate - pet ether furnished the <u>cis</u>-acetal <u>42</u> (24 mg) in 20% yield.

$[\alpha]_D$: 17.5 (c 1.0, $CHCl_3$)

bp. : $165^{o}/0.1$ mm

IR : 1700, 1380, 1120 cm^{-1}

^{1}H-NMR : δ4.0 (4H, m, $-O-C\underline{H}_2-C\underline{H}_2-O-$), 3.72 (1H, br d, J = 9Hz), 2.6 - 1.2 (12H, m), 0.9 (3H, s, $-C-C\underline{H}_3$), 0.84 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.72 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ212.8, 113.1, 65.4(2C), 52.7, 52.0, 50.8, 44.0, 34.4, 33.5, 30.0, 28.0, 23.5, 22.1, 21.8, 19.4

Analysis : $C_{16}H_{26}O_3$ Calcd: C, 72.14 ; H, 9.84
Found: C, 72.09 ; H, 9.79

Further elution with 15% ethyl acetate - pet ether furnished the <u>trans</u>-acetal <u>43</u> (46 mg) in 30% yield.

$[\alpha]_D$: -15.5 (c 1.0, $CHCl_3$)

bp. : $176^{o}C/0.1$ mm

^{1}-NMR : δ4.0 - 3.6 (4H, m, $-O-C\underline{H}_2C\underline{H}_2-O-$), 2.8 - 1.4 (13H, series of m), 1.29 (3H, s, $-C-C\underline{H}_3$), 0.85 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.76 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ210.8, 113.4, 65.3, 64.6, 62.6, 54.1, 45.9, 40.7, 33.8, 33.0, 32.7, 26.35, 24.7, 21.7, 19.7, 18.8

Analysis : $C_{16}H_{26}O_3$ Calcd: C, 72.14 ; H, 9.84
Found: C, 71.98 ; H, 9.74

<u>2-Ethylene ketal-8R-isopropyl-1S-isopropylbicyclo[5.3.0]dec-7-en-6-one</u> (<u>44</u>):

Into a 25 ml RB flask fitted with Dean-Stark water separator and reflux condenser, ene-dione <u>34</u> (100 mg, 0.45 mmol), ethylene glycol (0.2 ml) and PTS (25 mg) in dry benzene (15 ml) were placed and the contents were refluxed for 15 h. The reaction mixture was diluted with benzene (25 ml), washed with aqueous $NaHCO_3$, water and then dried. The crude product obtained after removal of the solvent was charged on a silica gel (3 g) column. Elution with 5% ethyl acetate - pet ether removed the less polar impurities. Further elution with 10% ethyl acetate - pet ether furnished the enone-acetal <u>44</u> (110 mg) in 92% yield.

$[\alpha]_D$: +84.26 (c 1.0, $CHCl_3$)

mp. : 83-84^{o}C

IR : 1670, 1615, 1340, 875 cm^{-1}

^{1}H-NMR : δ4.0 (4H, br s), 3.36 - 3.04 (1H, m), 2.6 - 1.2 (10H, m), 1.28 (3H, s, $-C-C\underline{H}_3$), 1.06 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 1.0 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ204.5, 164.3, 138.7, 113.9, 65.2, 65.0, 57.1, 43.4, 33.8, 33.7, 29.1, 28.2, 23.2, 21.0, 19.3

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

Found: C, 72.56 ; H, 9.20

<u>2-Ethylene ketal-8R-isopropyl-1S-methyl-7R-bicyclo[5.3.0]decan-6-one</u> (<u>42</u>) and <u>2-Ethylene ketal-8R-isopropyl-1S-methyl-7S-bicyclo[5.3.0]decan-6-one</u> (<u>43</u>):

Into a two necked 100 ml RB flask, fitted with a guard tube and septum, was taken freshly distilled liq.NH_3 (50 ml). To this was added freshly cut lithium metal (115 mg, 5 mmol) piece by piece. The resulting blue solution was stirred for 5 min and enone-acetal <u>44</u> (200 mg, 0.72 mmol) in dry THF (5 ml) was added slowly to it. After stirring for 10 min the reaction mixture was quenched by careful addition of dry methanol (1 ml). After all the ammonia had evaporated, the reaction mixture was diluted with water (10 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was used directly for the next step.

To a suspension of pyridinium chlorochromate (500 mg, 2.3 mmol) in dry dichloromethane (5 ml) containing 1.0 g of activated molecular sieves (4 °A), was added the above crude aclcohol (200 mg, 0.72 mmol) in dry dichloromethane (5 ml) at 0°C. The reaction mixture was brought to room temperature, stirred for an additional 1h, diluted with dry ether (20 ml) and filtered through a small florisil (3 g) column. Removal of the solvent gave an oily liquid which was charged on a silica gel (20 g) column and elution with 10% ethyl acetate - pet ether furnished the cis-acetal 42 (125 mg) in 65% yield.

Further elution with 15% ethyl acetate - pet ether furnished the trans-acetal 43 (17 mg) in 9% yield.

5-Carbomethoxy-2-ethylene ketal-8R-isopropyl-1S-methyl-7R-bicyclo[5.3.0]-decan-6-one (45):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal, was introduced n-butyllithium (0.6 ml, 0.6 mmol, 1.0 m in hexane) and cooled to -78°C. Hexamethyldisilazane (0.25 ml, 1.2 mmol) was carefully added and the resulting slurry was dissolved by the addition of dry THF (2 ml) and stirred for 20 min. A solution of cis-acetal 42 (100 mg, 0.3 mmol) in dry THF (2 ml) was then slowly added through a syringe and the contents were stirred for 0.5 h at -78°C. The resulting enolate was quenched by addition of methyl chloroformate (0.5 ml, excess) and the stirring was continued for further 10 min. The reaction mixture was diluted with brine and extracted with ether (50 ml x 3). The ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel column. Elution with 5% ethyl acetate - pet ether furnished the keto-ester 45 (105 mg) in 86% yield as diastereomeric mixture.

bp. : 163°C/ 0.11 mm

IR : 1730, 1720, 1160 cm^{-1}

^1H-NMR : δ4.05 - 3.8 (8H, m, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 3.78 (3H, s, -O-C$\underline{H}_3$), 3.73 (3H, s, -O-C$\underline{H}_3$), 3.6 - 1.0 (24H, series of m), 0.98 - 0.7(18H, series of s and d)

Analysis : $C_{18}H_{28}O_5$ Calcd: C, 66.64 ; H, 8.70
Found: C, 66.01 ; H, 8.29

8R-Isopropyl-1S-methyl-2-ethylene ketal-7R-bicyclo[5.3.0]decan-6-ol-5-methanol (47):

Reduction of 45 with lithium aluminium hydride:

Into a 25 ml RB flask keto-ester 45 (100 mg, 0.3 mmol) was placed in dry ether (10 ml) and cooled in an ice-bath. To this lithium aluminium hydride (120 mg, excess) was added and the contents were stirred at room temperature for 1 h. The excess lithium aluminium hydride was destroyed by careful addition of ethyl acetate followed by sat. Na_2SO_4 solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 ml x3). The combined organic extract was washed, dried, concentrated and the crude product thus obtained was charged on a silica gel (5 g) column. Elution with 25% ethyl acetate - pet ether resulted in the removal of less polar impurities and further elution with 50% ethyl acetate - pet ether furnished the diol 47 (32 mg) in 40% yield.

IR : 3450, 1460 cm^{-1}

^{1}H-NMR : δ4.16 - 4.02 (1H, m, -C$\underline{H}$-OH), 3.92 (4H, br s, O-C$\underline{H}_2$C$\underline{H}_2$-O), 3.68 - 3.44 (2H, m, -C$\underline{H}_2$OH), 2.56 - 1.28 (14H, m), 1.30 (3H, s, -C-C$\underline{H}_3$3), 0.96 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.86 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

^{13}C-NMR : δ114.7, 75.0, 69.1, 65.2, 65.0, 53.8, 51.7, 50.2, 44.2, 35.7, 34.8, 29.7, 28.2, 24.7, 23.2, 23.0, 22.5

Analysis : $C_{17}H_{30}O_4$ Calcd: C, 68.42 ; H, 10.13

Found: C, 68.39 ; H, 10.09

Reduction of 45 with sodium borohydride:

Into a dry 25 ml RB flask keto-ester 45 (100 mg, 0.3 mmol) was placed in dry methanol (5 ml) and cooled in ice bath. To this reaction mixture sodium borohydride (100 mg, excess) was added slowly in small portions and the contents were stirred at for 30 min. Then methanol was removed at reduced pressure and the residue left was diluted with water (10 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed and dried. The crude product obtained after removal of the solvent was charged on a small silica gel (5 g) column. Elution with 40% ethyl acetate - pet ether resulted in the removal of the less polar impurities and further elution with 50% ethyl acetate - pet ether furnished the diol 47 (55 mg) in 62% yield.

2-Ethylene ketal-5-formyl-8R-isopropyl-1S-methyl-7R-bicyclo[5.3.0]decan-6-ol (48):

Oxidation of 47 with PDC:

Into a 10 ml RB flask diol 47 (50 mg, 0.16 mmol) was placed in dry dichloromethane (5 ml) and pyridinium dichromate (70 mg, 0.2 mmol) added at 0°C and stirred for 0.5 h. The reaction mixture was diluted with dry ether (50 ml), filtered through a small florisil (3 g) column and concentrated. The crude product obtained was chromatographed on a silica gel (3 g) column. Elution with 10% ethyl acetate - pet ether furnished the hydroxy aldehyde 48 (20 mg) in 40% yield.

IR : 2720, 1690, 800 cm^{-1}

^{1}H-NMR : δ9.72 (1H, s, O=C-$\underline{H}$), 4.48 - 4.72 (1H, m, -C$\underline{H}$-OH), 2.68 - 1.12 (13H, m), 1.28 (3H, s, -C-C$\underline{H}_3$), 1.02 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.92 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

Analysis : $C_{17}H_{28}O_4$ Calcd: C, 68.89 ; H, 9.52

Found: C, 68.79 ; H, 9.46

Oxidation of 47 by Swern method:

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet septum and mercury seal, oxalyl chloride (0.1 ml, 1.0 mmol) dissolved in dry dichloromethane (2 ml) was placed and the contents were cooled to -60°C. To this reaction mixture DMSO (0.2 ml) in dry dichloromethane (2 ml) was added to it over 5 min. and the stirring was continued for further 10 min. Then the diol 47 (50 mg, 0.16 mmol) in dry dichloromethane was introduced slowly over a period of 5 min. After stirring for further 10 min triethyl amine (1 ml) was added to the reaction mixture at $-60^{0}C$. The reaction mixture was brought to room temperature and quenched with water (10 ml) and extracted with ether (50 ml x 3). The combined organic layer was washed, dried and concentrated to a crude product which was charged on a silica gel (5 g) column. Elution with 5% ethyl acetate - pet ether resulted in the removal of the less polar impurities and further elution with 10% ethyl acetate - pet ether furnished the hydroxy aldehyde 48 (35 mg) in 70% yield.

(+)-2-Oxo-isodauc-5-en-12-al (15):

Into a 10 ml RB flask fitted with a reflux condenser hydroxy aldehyde 48 (10 mg, mmol) was placed in dry benzene (5 ml) and cat. amount of PTS was added. The reaction mixture was refluxed for 2 h then cooled and quenched by the addition of sat. $NaHCO_3$ solution. The benzene layer was separated and the aqueous layer was extracted with benzene (25 ml x 3). The combined benzene extract was washed, dried and concentrated. The crude product thus obtained was filtered through a small silica gel (1 g) column. Elution with 5% ethyl acetate - pet ether furnished (+)-15 (4 mg) in 37% yield.

$[\alpha]_D$: +33 (c 0.5, $CHCl_3$; lit. not reported)[13]

IR : 2950, 2740, 1680, 1630 cm^{-1}

^1H-NMR (fig. II.12) : δ9.35 (1H, s, O=C-$\underline{H}$), 6.63 (1H, br d, -C=C$\underline{H}$-), 2.8 - 1.5 (11H , series of m), 1.33 (3H, s, -C-C$\underline{H}_3$), 0.94 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$)

^{1}H-NMR(C_6D_6) (fig. II.13) : δ9.15 (1H, s, O=C-H), 6.01 (1H, br d, -C=CH-), 2.7 - 1.1 (11H, series of m), 0.89 (3H, s, -C-CH_3), 0.73 (3H, d, J = 7Hz, -CH-CH_3), 0.71 (3H, d, J = 7Hz, -CH-CH_3)

The spectral data of this product (both in $CDCl_3$ and C_6D_6) was found to be identical with those reported in the literature.[13]

(+)-<u>Aphanamol I</u> (13):

Into a 10 ml RB flask (+)-2-oxo-isodauc-5-en-12-al 15 (4 mg) was placed in dry methanol (2 ml) and $CeCl_3.6H_2O$ (5 mg) was added and the reaction mixture was cooled to -5°C. To this sodium borohydride was added in small amounts and the reaction was followed by tlc. When the starting material was completely consumed, the reaction was quenched by addition of acetone (0.1 ml). The reaction mixture was concentrated under reduced pressure and the residue was diluted with water (5 ml) and extracted with ether (25 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (1 g) column by eluting with 5% ethyl acetate - pet ether to furnish (+)-aphanamol I 13 (4 mg) in quantitative yield.

$[\alpha]_D$: +10 (c 0.3, $CHCl_3$) (lit. +13)[12]

IR : 3400, 1690 cm^{-1}

^{1}H-NMR (fig. II.14) : δ5.51 (1H, br d, -C=CH), 4.0 (2H, br s, -CH_2-OH), 3.0 - 1.4 (11H, series of m), 1.22 (3H, s, -C-CH_3), 0.9 (3H, d, J = 7Hz, -CH-CH_3), 0.91 (3H, d, J = 7Hz, -CH-CH_3)

Direct comparison of our spectra with those supplied by Professor Nishizawa established the identity of our synthetic material with the natural product.

1S,5S-Dimethyl-1-(2'-methylpent-5'-yl-3'-one)cycloheptan-2,6-dione (49):

Into a 50 ml RB flask the ketone 31 (100 mg, 0.4 mmol) was placed in a mixture of carbontetrachloride, acetonitrile and water (each 5 ml). To this mixture were added sodium metaperiodate (128 mg, 0.6 mmol) and ruthenium dioxide (10 mg). After being stirred for 1 h, the reaction was diluted with dichloromethane (50 ml) and filtered through celite pad (3 g) and repeatedly washed with dichloromethane. The combined filtrate was washed and dried. The crude product obtained after removal of the solvent was filtered through a small silica gel (5 gm) column with 10% ethyl acetate - pet ether to furnish the trione 49 (100 mg) in quantitative yield.

$[\alpha]_D$: +51.1 (c 1.0, $CHCl_3$)

IR : 2950, 1700 cm^{-1}

^1H-NMR : δ2.8 - 2.2 (8H, m), 2.1 - 1.5 (4H, m), 1.1 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 1.08 (3H, s, $-C-C\underline{H}_3$), 1.05 (6H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ213.6(2C), 211.2, 48.9, 47.3, 46.5, 40.5, 38.4, 34.4, 31.5, 28.5, 22.7, 17.9(2C), 15.6

Analysis : $C_{15}H_{24}O_3$ Calcd: C, 71.39 ; H, 9.59
Found: C, 71.30 ; H, 9.63

1S,5S-Dimethyl-8-isopropylbicyclo[5.3.0]dec-7-ene-2,6-dione (50):

Into a 50 ml RB flask fitted with a reflux condenser and mercury seal, trione (100 mg, 0.4 mmol) was placed and 5% KOH in methanol (25 ml) was added to it. The resulting reaction mixture was refluxed for 1 h.

Methanol was removed at reduced pressure and the residue left was diluted with water (10 ml) and extracted with ether (100 ml x 3). The combined extract was washed, dried and concentrated to a crude product which was charged on silica gel (10 g) column. Elution with 15% ethyl acetate - pet ether furnished the ene-dione <u>50</u> (65 mg) in 60% yield.

$[\alpha]_D$: -44 (c 1.0, $CHCl_3$)

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

^{1}H-NMR : δ3.8 (1H, m), 3.2 - 1.4 (9H, series of m), 1.3 (3H, s, $-C-C\underline{H}_3$), 1.09 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 1.07 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 1.06 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ215.0, 200.5, 168.5, 137.1, 60.8, 43.2, 36.7, 35.5, 30.0, 29.8, 27.9, 20.8, 20.5, 19.7, 15.3

Analysis : $C_{15}H_{22}O_2$ Calcd: C, 76.88 ; H, 9.46
Found: C, 76.95 ; H, 9.40

II.7. SPECTRA

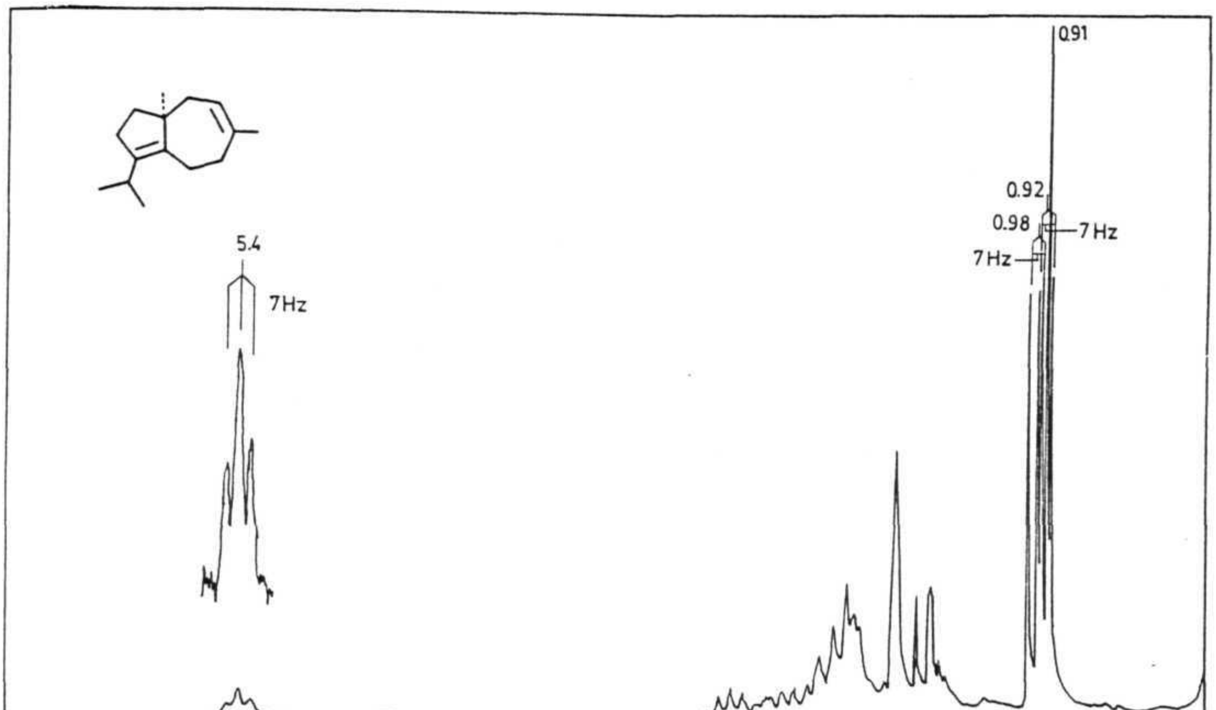


Fig. II.1 ^{1}H-NMR spectrum (100 MHz) of 7

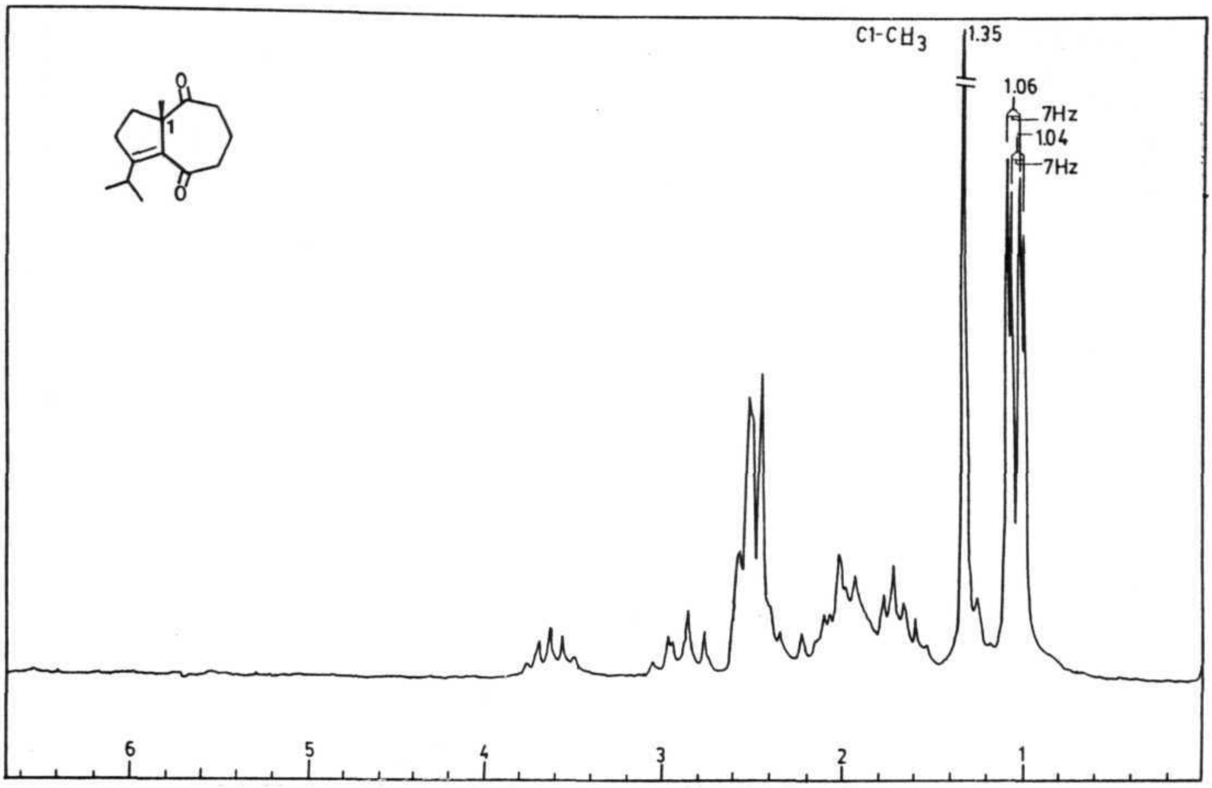


Fig. II.2 ^{1}H-NMR spectrum (100 MHz) of <u>34</u>

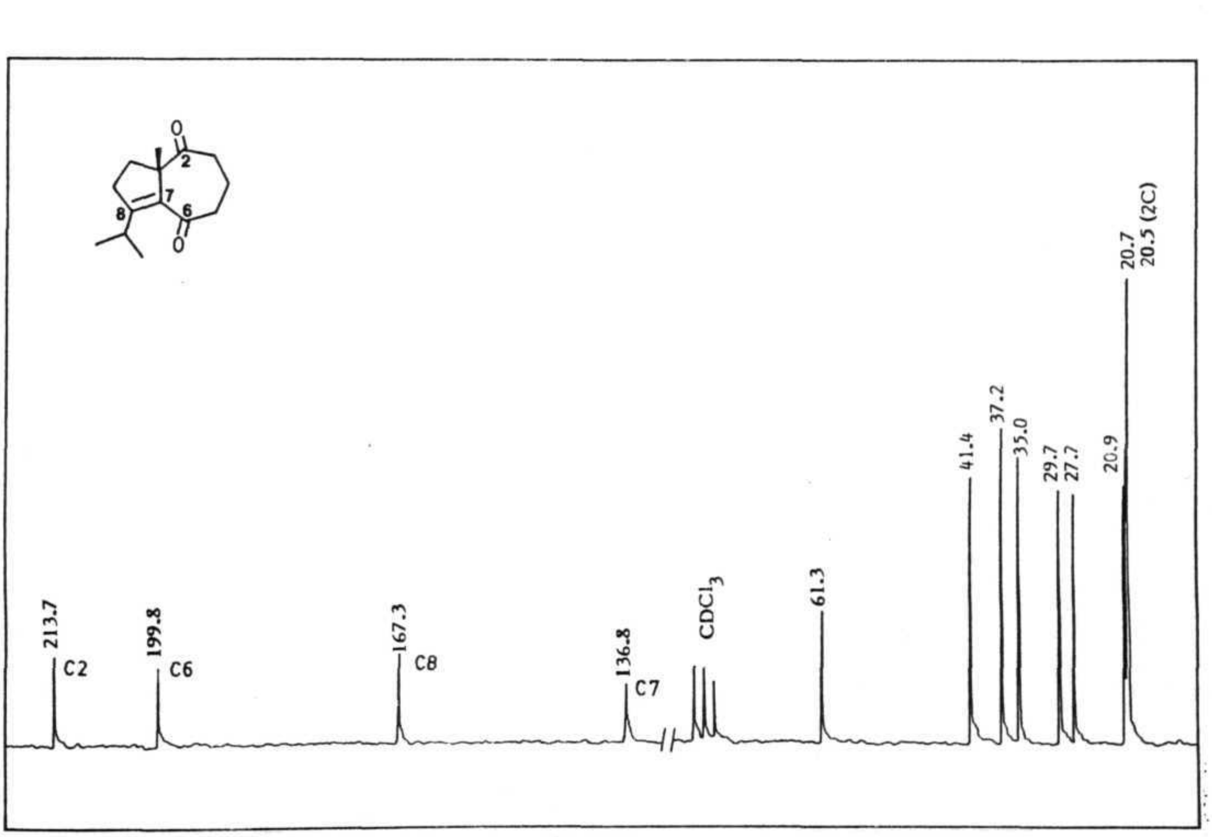


Fig. II.3 ^{13}C-NMR spectrum (25 MHz) of 34

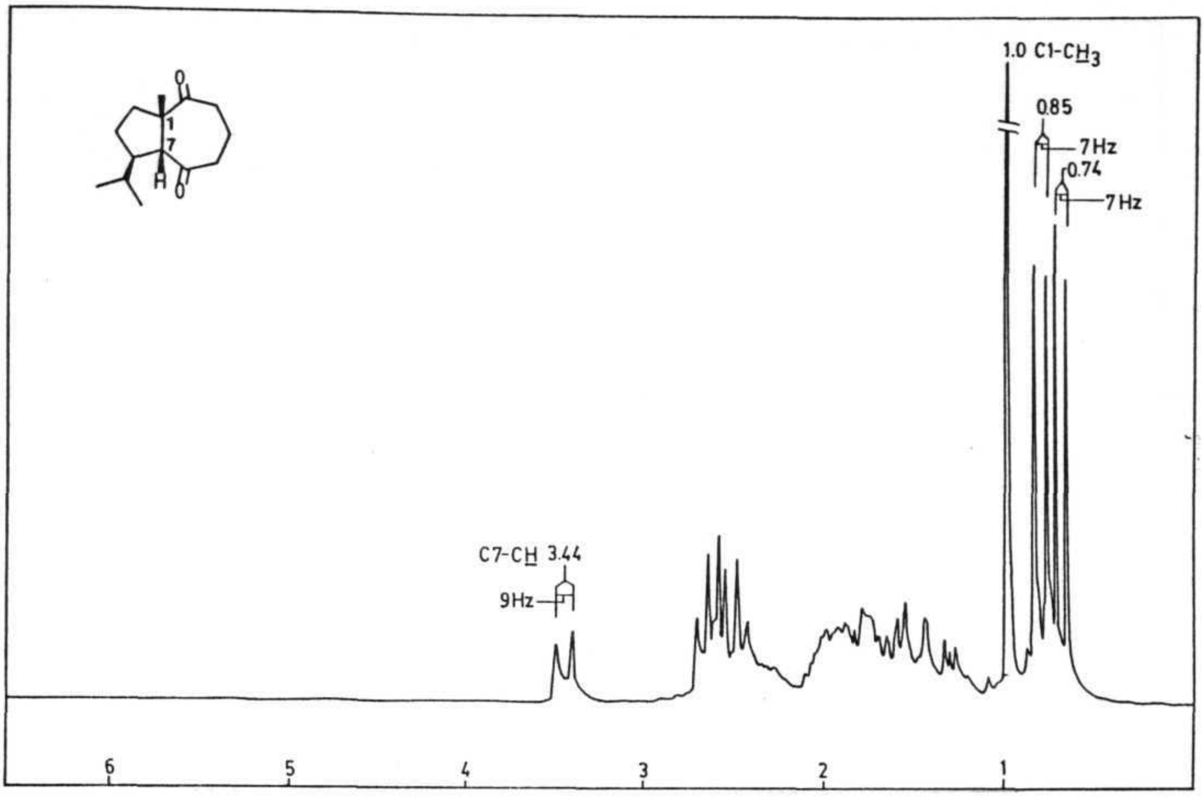


Fig. II.4 ^{1}H-NMR spectrum (100 MHz) of 38

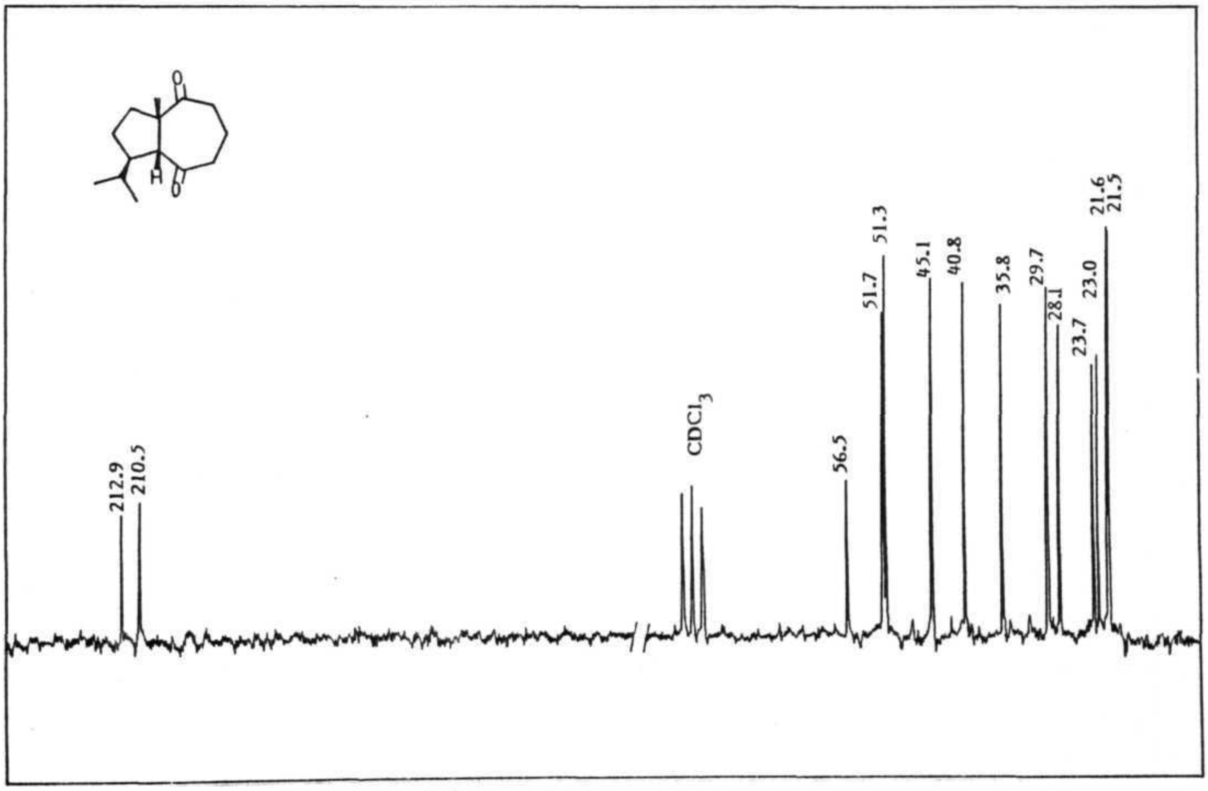


Fig. II.5 ^{13}C-NMR spectrum (25 MHz) of 38

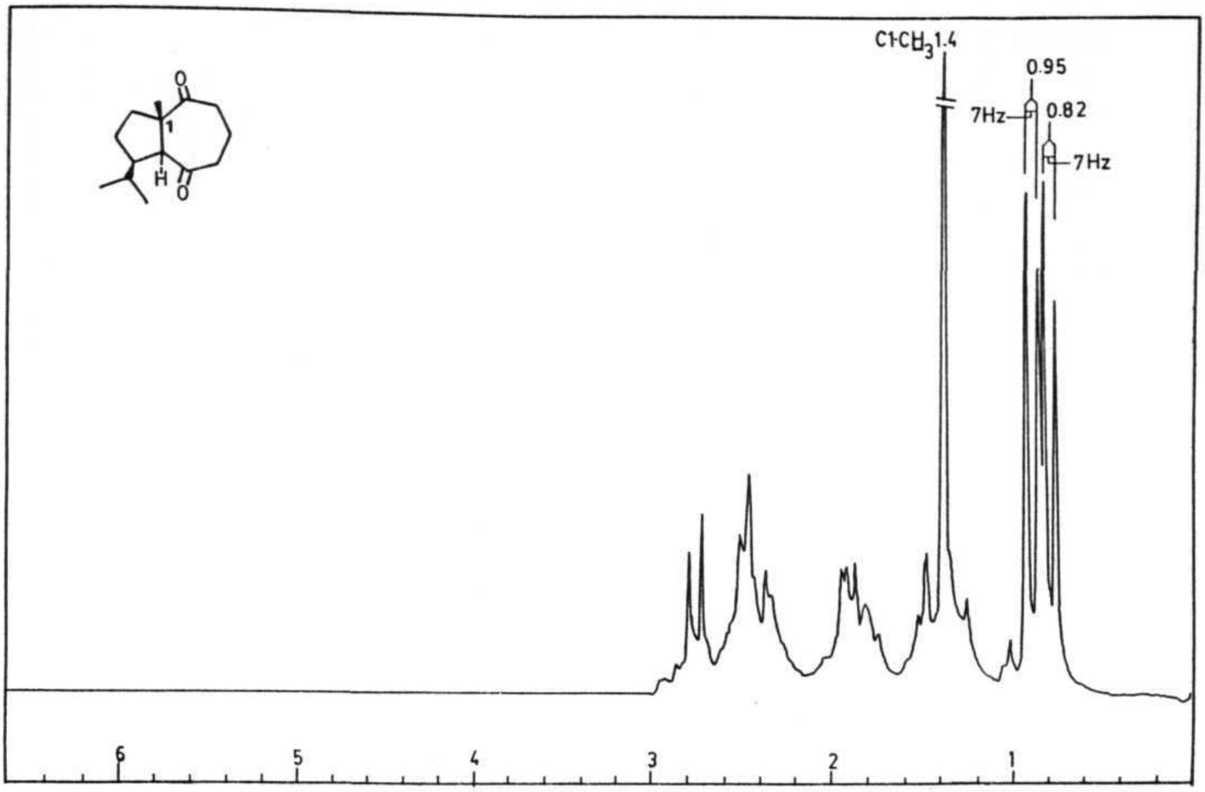


Fig. II.6 ^{1}H-NMR spectrum (100 MHz) of 39

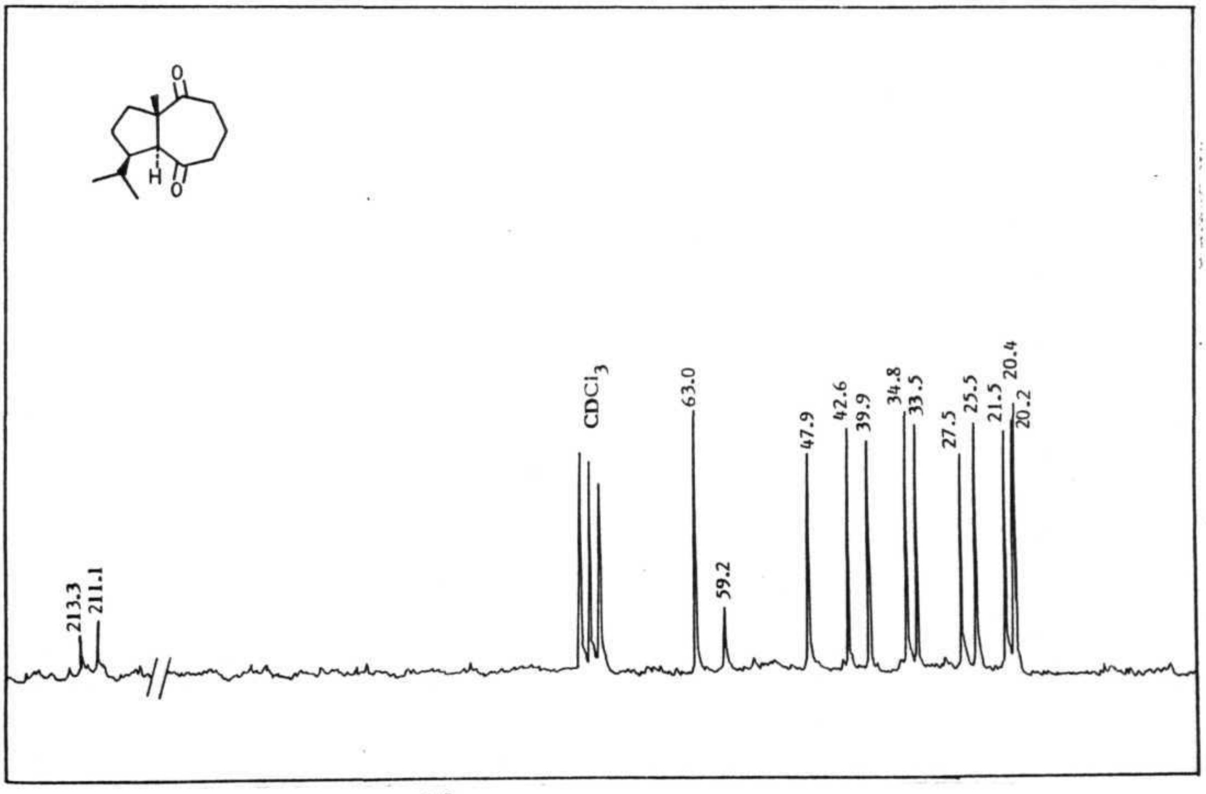


Fig. II.7 ^{13}C-NMR spectrum (25 MHz) of 39

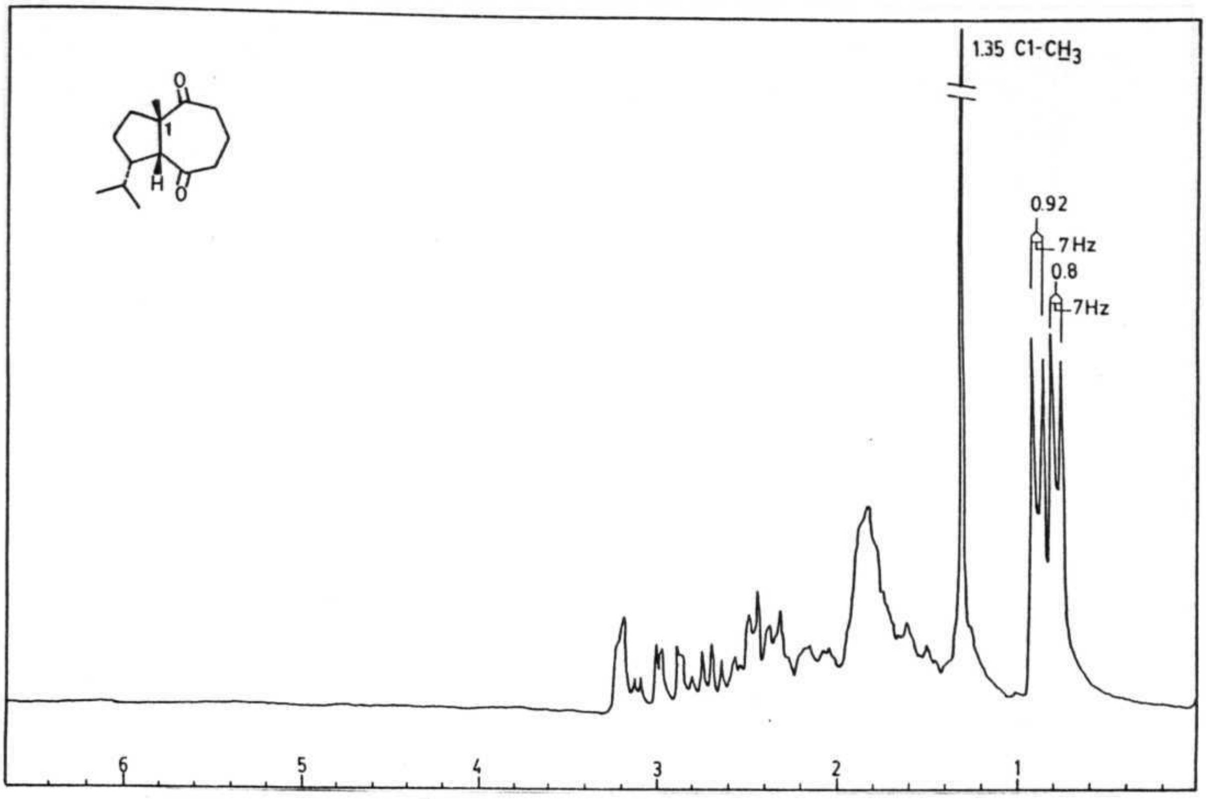


Fig. II.8 ^{1}H-NMR spectrum (100 MHz) of 40

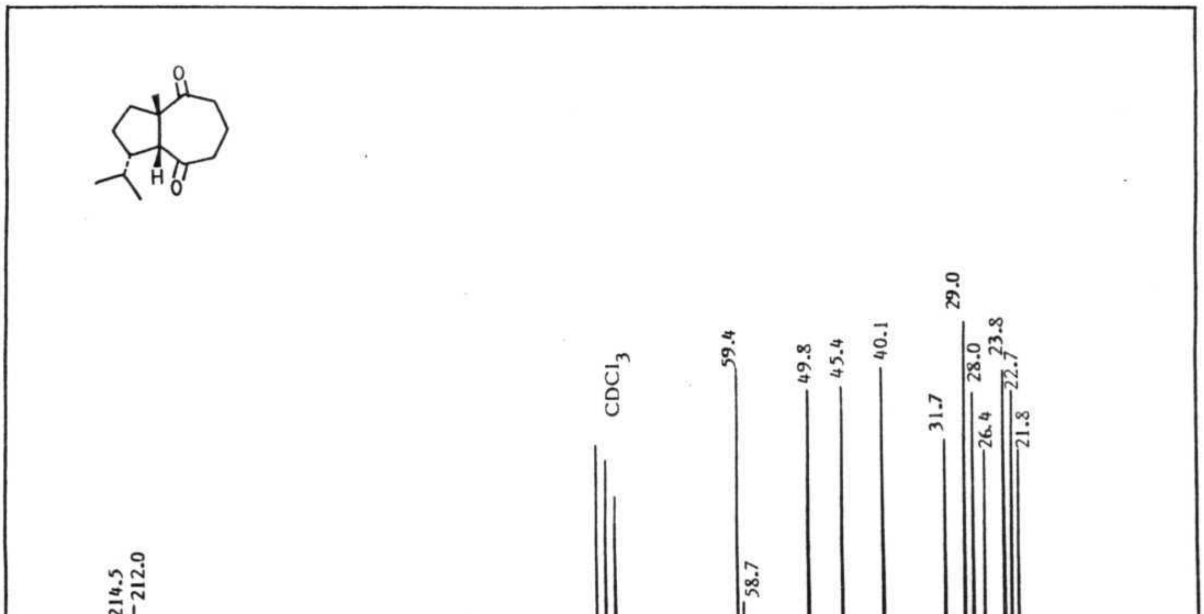


Fig. II.9 ^{13}C-NMR spectrum (25 MHz) of 40

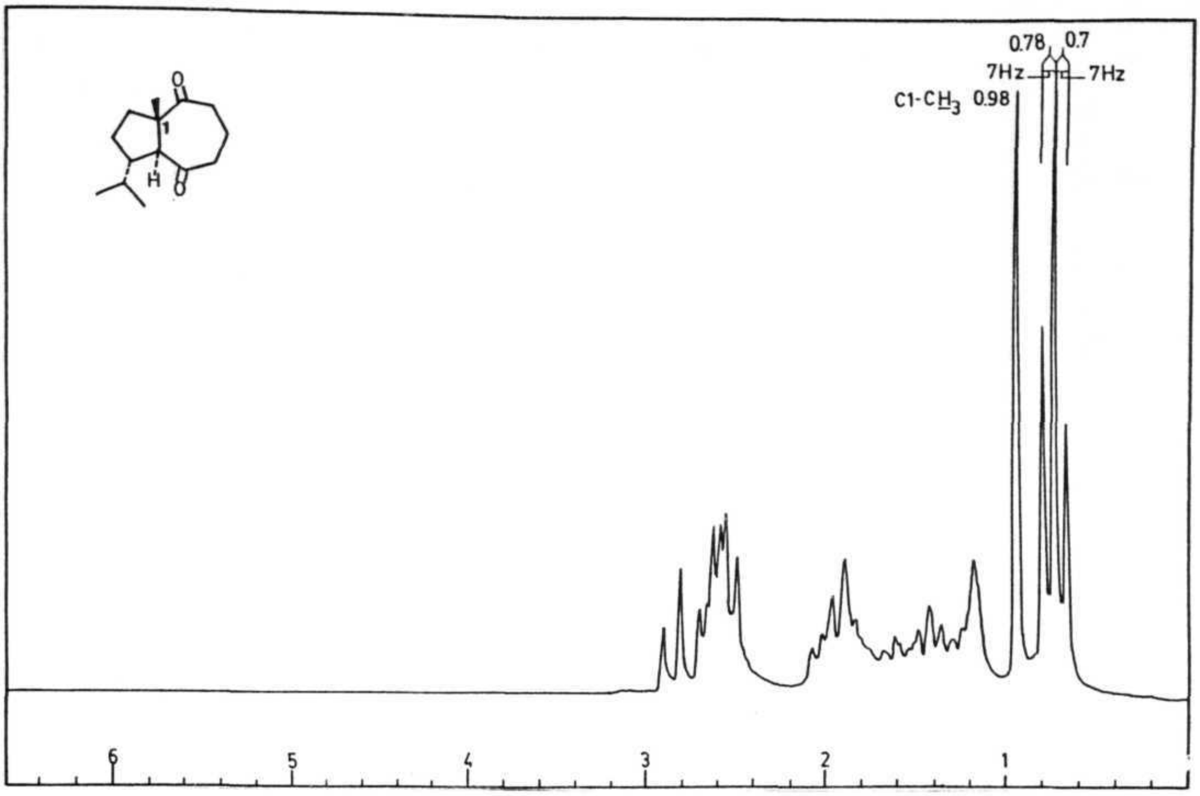


Fig. II.10 ^{1}H-NMR spectrum (100 MHz) of 41

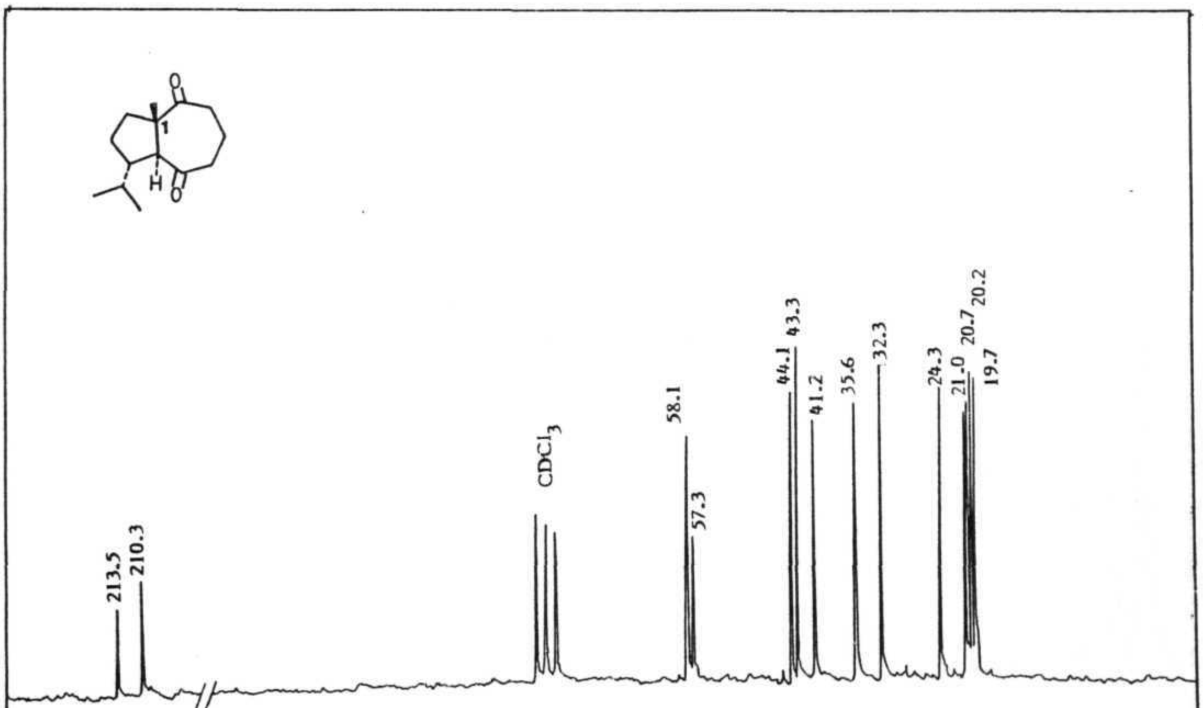


Fig. II.11 ^{13}C-NMR spectrum (25 MHz) of 41

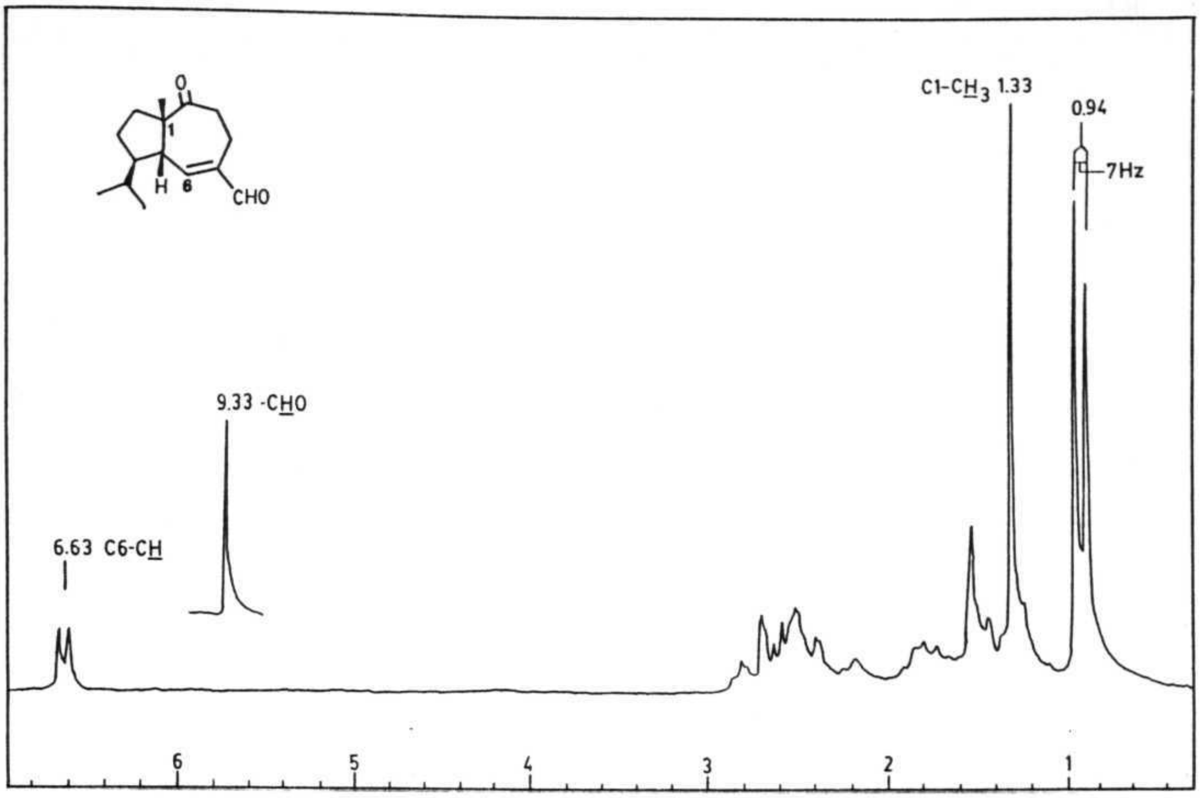


Fig. II.12 ^{1}H-NMR spectrum (100 MHz, $CDCl_3$) of <u>15</u>

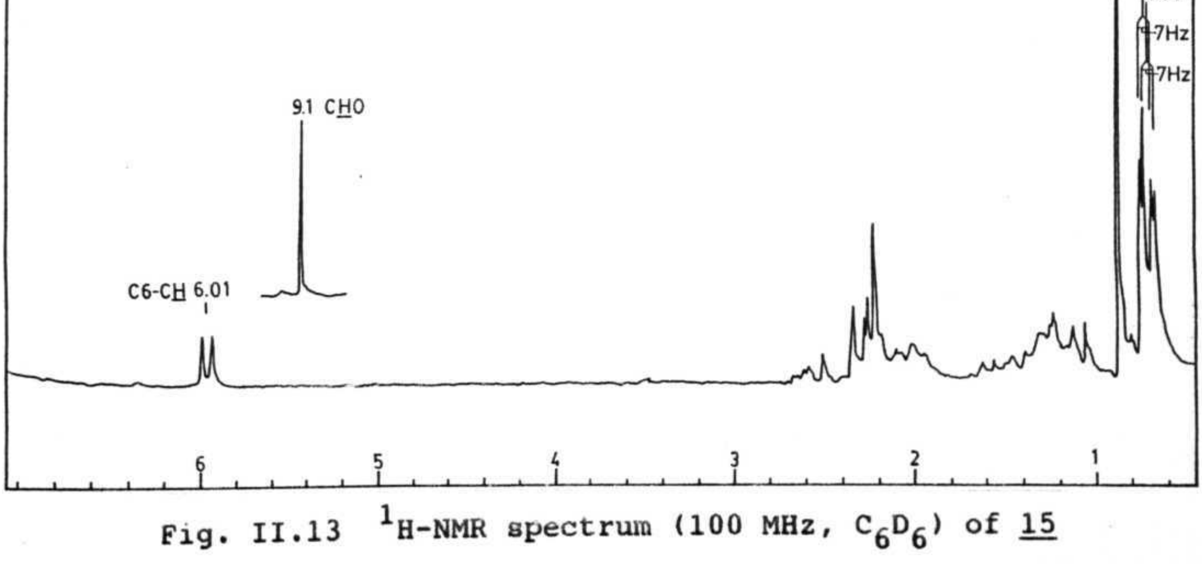


Fig. II.13 ^{1}H-NMR spectrum (100 MHz, C_6D_6) of <u>15</u>

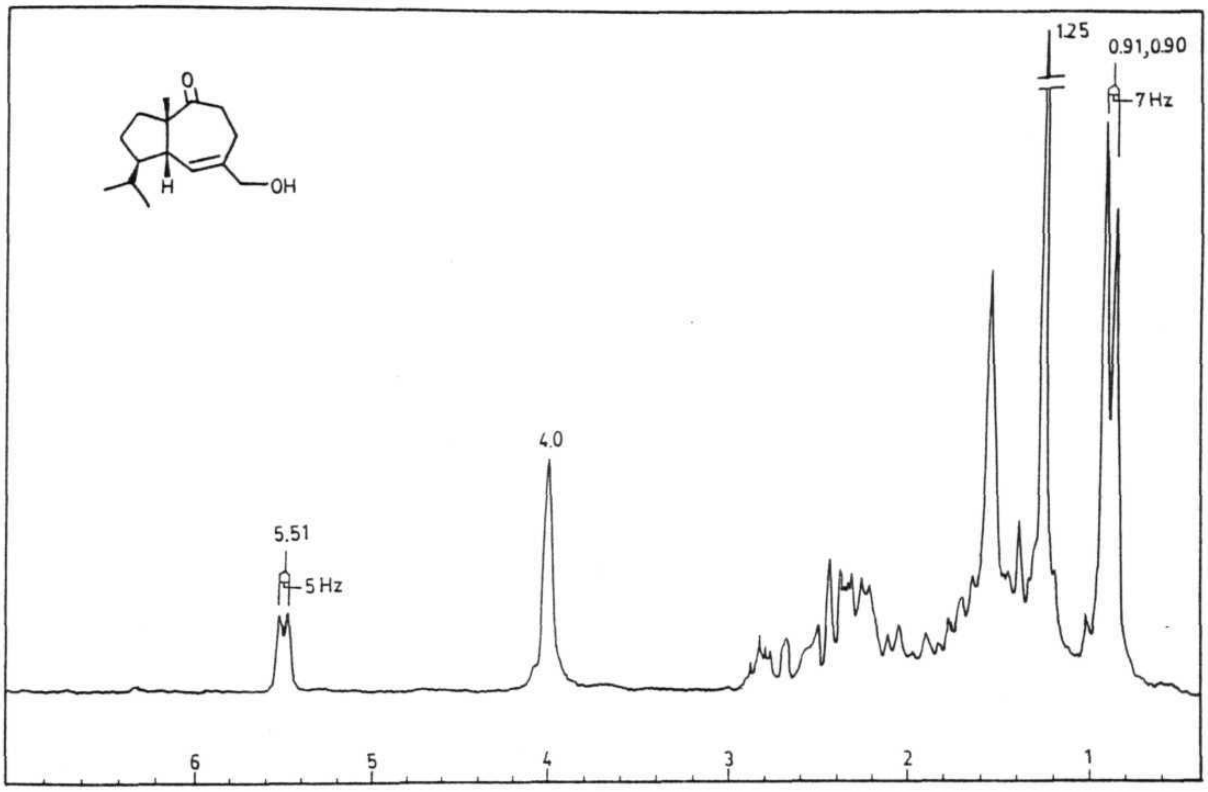


Fig. II.14 ^{1}H-NMR spectrum (100 MHz) of <u>13</u>

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Chapter III

An Oxy-Cope Rearrangement Route to 5,11-Fused Bicyclic dolabellane diterpenes.

III.1. ABSTRACT

A synthetic approach to the 5,11-fused bicyclic dolabellane framework of wide nature occurrence has been conceived. The key concept in this approach is the 4-carbon ring expansion of the enantiomerically pure bicyclic hydroazulenone (-)-11 *via* oxy-Cope rearrangement to generate a 11-membered ring in a stereoselective manner.

Bicyclic hydroazulenone (-)-11 was elaborated to set-up an oxy-Cope system. Regioselective α-carbomethoxylation followed by methylation on 11 furnished 16 as a mixture of C(4)-stereoisomers. The carboxymethyl group was elaborated to a vinyl group *via* the following sequence. 16 (ester) → 17 (alcohol) → 18 (aldehyde) → 14 (vinyl), Scheme III.5. The C_{17}-dienone 14 was reacted with vinyl magnesium bromide to furnish the divinyl carbinol 19. Thermal rearrangement of 19 proceeded smoothly to furnish the nor-dolabellane (+)-20 in good yield, Scheme III.6.

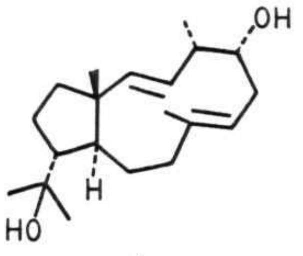
For elaboration to the dolabellane skeleton, 14 was treated with isopropenyl magnesium bromide and the resulting C_{20}-divinyl carbinol 13 on thermal conditions furnished dolabellane ketones (-)-12a,(-)-12b. Attempt to convert (-)-12a, (-)-12b to the natural product δ-araneosene 5 did not meet with success despite many efforts. Cationic cyclisation of the bicyclic alcohol 25 obtained from 12a,12b to the tricyclic 5,8,5-fused hydrocarbon 26 was observed and the structure of this product needs further scrutiny.

III.2. OBJECTIVE AND BACKGROUND

In this chapter of the thesis, we continue with the theme of developing new synthetic routes to novel terpene frameworks. The focus here is on a unique 5,11- fused bicyclic diterpenoid skeleton.

The C_{20}-diterpenoids are only a shade behind sesquiterpenoids in the diversity of carbocyclic skeleta present in them. In the case of diterpenes, increased number of carbon atoms and double bonds in the precursor geranylgeraniol pyrophosphate enhances the propensity towards the formation of larger rings. Therefore, compounds containing 7-,8-,9-,10-,11- and 14-membered rings are quite prevalent among diterpenes.[1] The resulting carbocyclic frameworks containing uncommon assembly of rings are particularly attractive targets for synthesis.

While a good many carbocyclic frameworks among diterpenes have been known for a long time, recent isolation studies from exotic sources like, insects, tobacco, microbes and marine organisms have unravelled new carbocyclic skeleta in great abundance. In particular, marine flora and fauna have proved to be an unusually rich source of novel diterpenes in the past decade or so.[2] In 1976, Faulkner et al.,[3] reported the isolation of a novel diterpenoid 1 from the digestive glands of sea hare Dolabella californica sterns. The parent 5,11-fused bicarbocyclic skeleton 2 was named dolabellane. At about the same time, unknown to most researchers in the area, H.J. Borschberg at ETH isolated[4] three closely related hydrocarbons α-,β- and δ-araneosenes 3, 4 and 5, respectively, from Sordaria araneosa cain, having a 5,11-fused bicyclic skeleton[#] 2. Since



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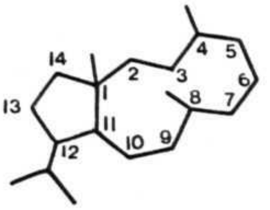

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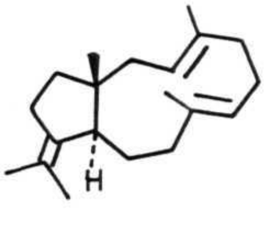

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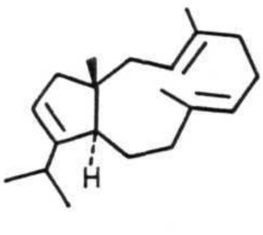

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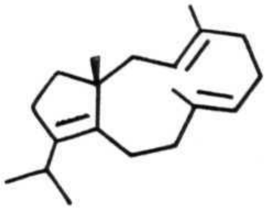

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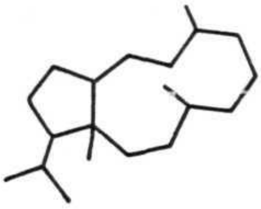
then, dolabellanes have frequently surfaced from marine sources and have emerged as one of the largest group among the diterpenoids. Nearly, sixty dolabellane natural products are presently known and are summarised in the appendix of this chapter. More recently, 'isodolabellane' skeleton 6, having 5,11-fused system and readily derivable from dolabellanes via a 1,2-methyl migration, has also been encountered in the form of natural products 7 and 8 from the soft coral Clavularia inflata.[5]

[#] There results have not appeared so far in any Journal. We thank Professors R.M. Coates, University of Illinois, Urbana, USA and H. Takeshita, Kyushu University, Kasuga-koen, Kasuga, Japan, for making available to us the xerox copies of relevant pages of H.J. Borschberg's Ph.D thesis.



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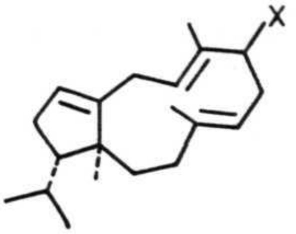


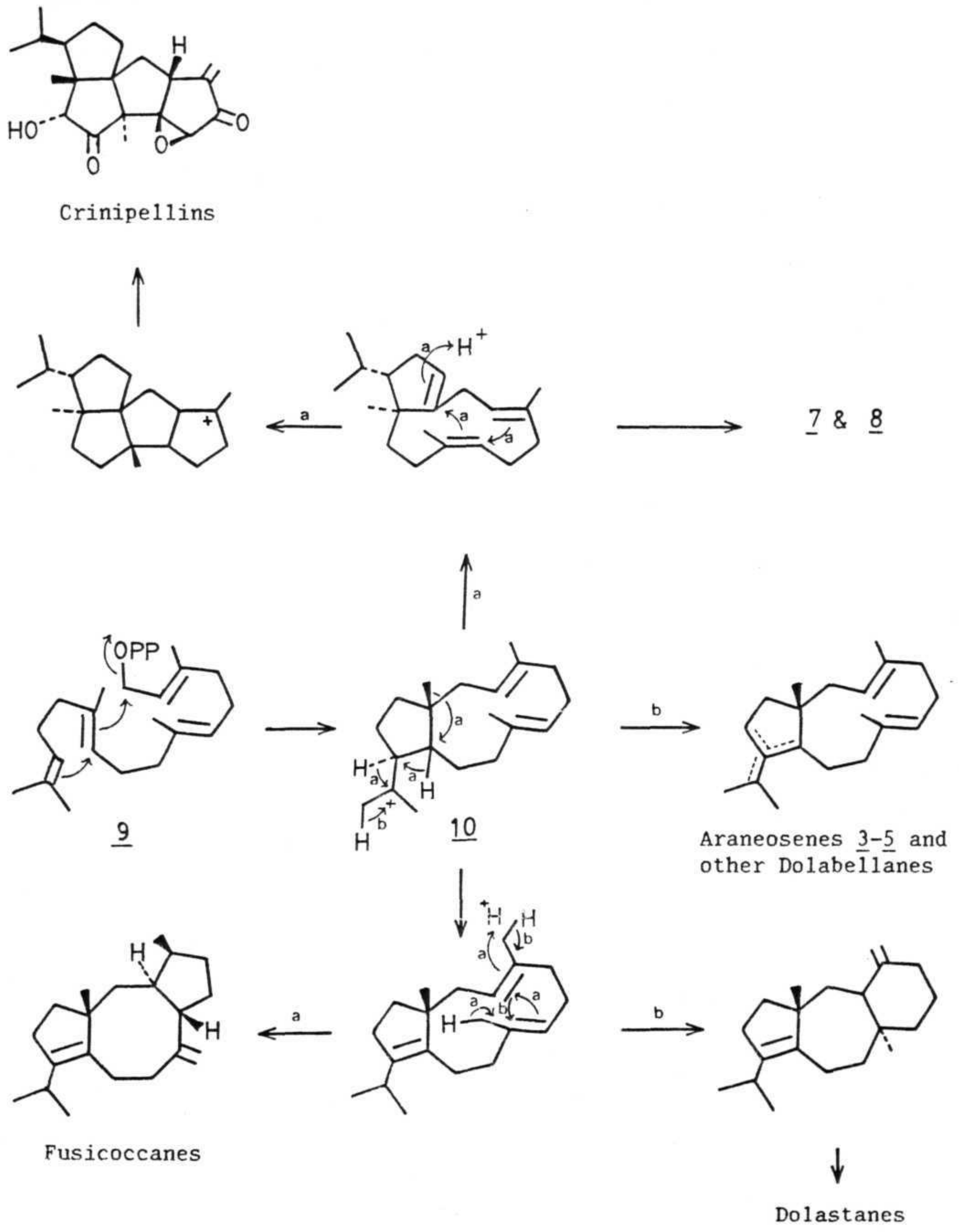
7, X= αOH
8, X= βOH

The structures of most of these dolabellanes have been elucidated employing ^{1}H- and ^{13}C-NMR, X-ray crystallography techniques and chemical correlations. Several groups have independently arrived at the absolute configuration of many of the dolabellanes employing Nakanishi's exiton chirality method and X-ray difraction studies. However, absolute stereochemistry of araneosenes 3 - 5 has not been determined.

A majority of dolabellane natural products, exhibit wide ranging biological activity. For example, all the dolabellane derivatives isolated from Dictyota dichotoma possess antimicrobial activity against gram positive and gram negative organisms. They also possesses significant cytotoxicity and show in vivo activity against virus of influenza and adenovirus.[6]

Biogenetically, the dolabellanes can be readily derived through the cyclisation of E,E,E-geranylgeraneol pyrophosphate 9 as shown in Scheme III.1. However, what makes dolabellanes biogenetically significant is the pivotal position, the cation 10 occupies in the biogenesis of several novel diterpenes like dolastanes, fusicoccanes and crinipellins. Various modes of transannular cyclisation in the eleven membered ring account for the formation of these diverse skeleta, Scheme III.1.

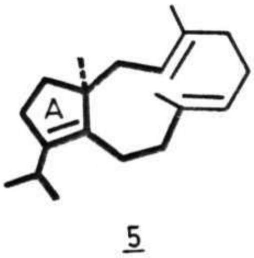
SCHEME III.1



Despite wide occurrence of dolabellanes in Nature and interesting structural and stereochemical features associated with them, no synthetic venture directed towards them has appeared so far in literature. We were fascinated by dolabellanes for several reasons. Besides the construction of the novel carbocyclic ring system, the prospect of inducing suitably designed dolabellane derivative towards biogenetic type of cyclisation was a tempting proposition. For this purpose araneosenes 3 -5 appeared to be particularly worthy candidates. We therefore initiated synthetic studies aimed at simplest dolabellane hydrocarbon δ-araneosene 5. In this chapter of the thesis, first successful construction of the complete dolabellane frame in the form of the bicyclic ketone 12 is described. Some preliminary studies on the cationic cyclisation of the dolabellane ring system are also reported.

III.3. STRATEGY

In considering various strategic options for the construction of dolabellane diterpenes eg. δ-araneosene 5, we were once again influenced by the ready availability of the enantiomerically pure hydroazulenone (-)-11[7] in our hands (see chapter I, Scheme I.15). It became at once apparent that δ-araneosene 5 and (-)-11, not only shared on exactly identical ring 'A', but 14-carbon atoms of the later could be exactly superimposed on the former (see heavy line in 5 and 11). Thus, hydroazulenone (-)-11 could



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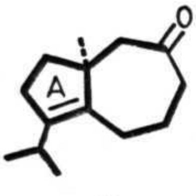

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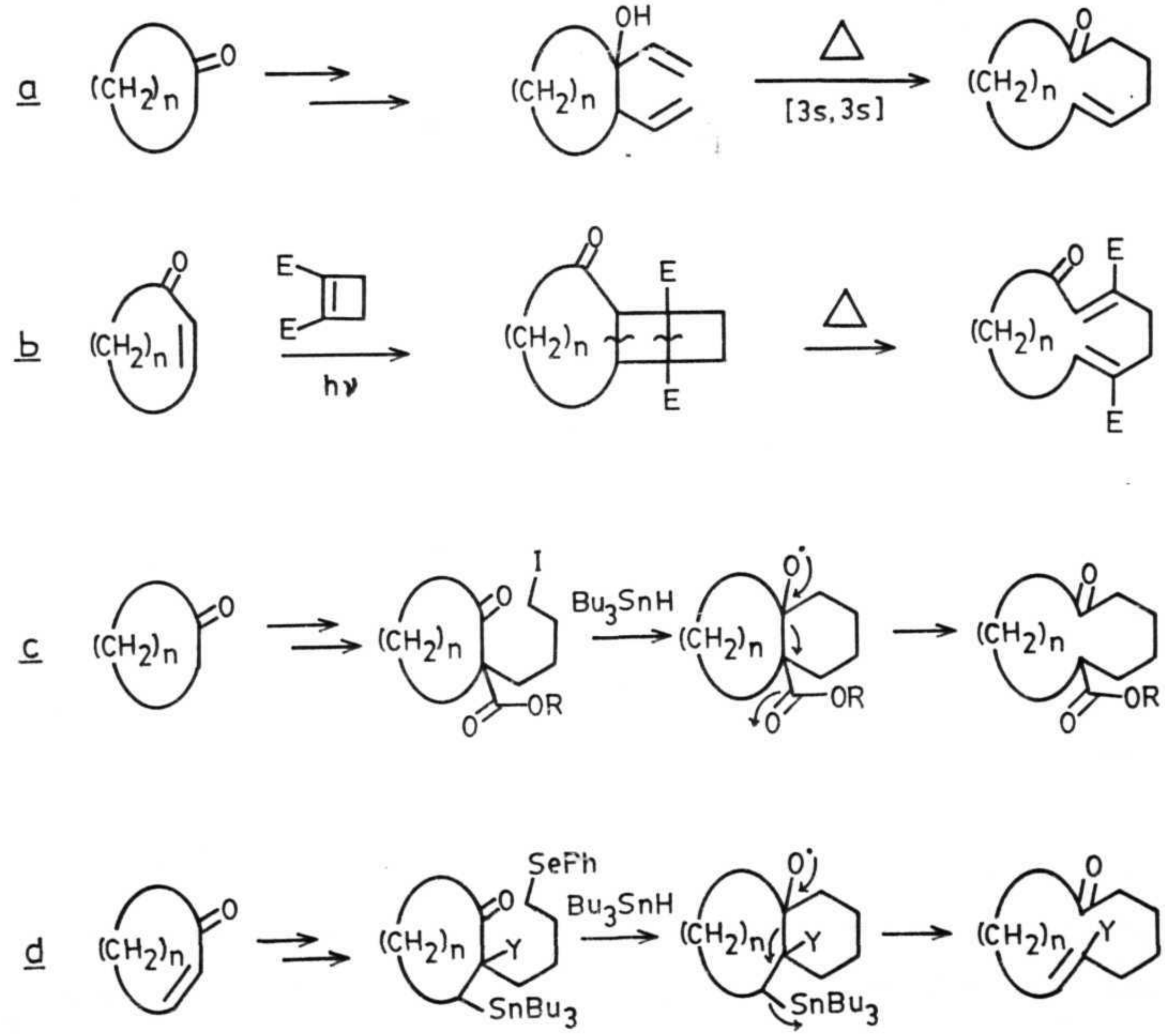
serve as a potential precursor for dolabellanes, provided a four carbon annulative ring-expansion in its 'B' ring could be effected (7 membered → 11-membered) and in addition two methyl groups and two trans-double bonds installed at appropriate locations. Thus, the primary requirement for the elaboration of 11 to dolabellane framework was the choice of a proper four-carbon ring expansion methodology. A literature scan led to the identification of several protocols that have been developed for this purpose and are displayed in Scheme III.2a-d.

SCHEME III.2



Anionic oxy-Cope rearrangement (Scheme III.2a) or even simple Cope rearrangement offers convenient 4-carbon ring expansion with adequate functionalisation. Clark Still has very elegantly demonstrated the efficacy of this strategy in his brilliant synthesis of periplanone-B[8] and acoragermacrene[9] sesquiterpenes.

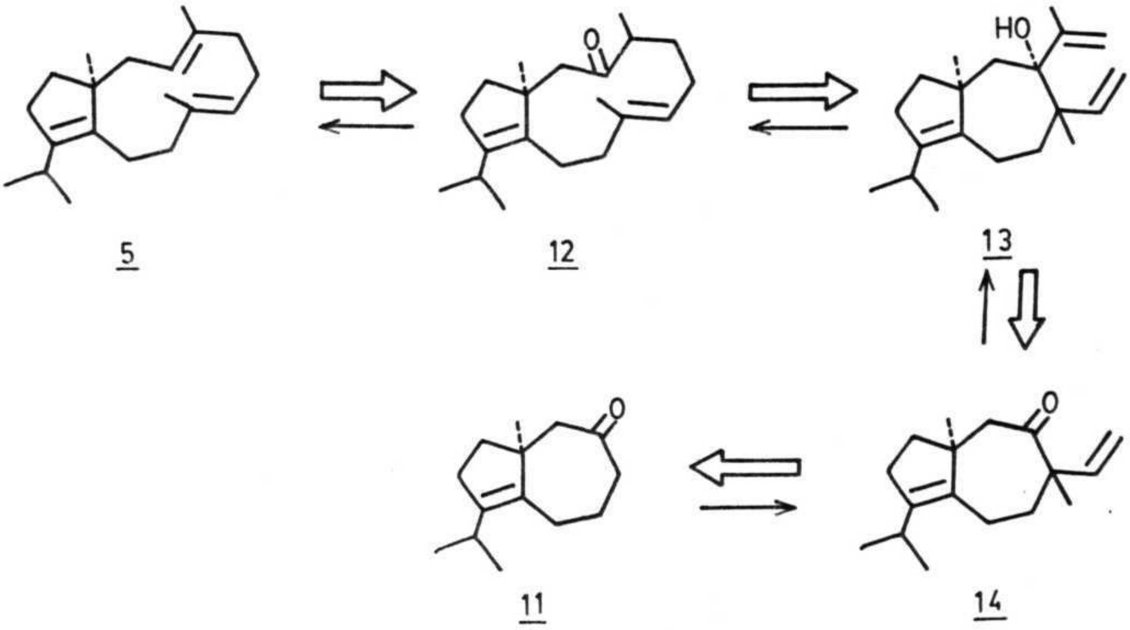
Photo-thermal metathesis, involving photochemical 2+2-cycloaddition between an enone and a substituted cyclobutene followed by regioselective fragmentation of the intermediate bicyclo[2.2.0]hexane moiety is a pleasant way of effecting 4-carbon ring expansion, Scheme III.2b. Wender,[10] Lange,[11] Vandewalle[12] and Williams[13] have cleverly employed this strategy for the synthesis of several sesquiterpenes, particularly those incorporating a 10-membered carbocycle.

Dowd[14] has described a radical-based 4-carbon annulation strategy Scheme III.2c, involving radical addition to a carbonyl group followed by fragmentation. This methodology is notable for its brevity as it can be set-up through two simple alkylations of a carbonyl precursors. Finally, a closely related variant of the Dowd methodology has been outlined by Baldwin[15] based on organo-tin chemistry, Scheme III.2d.

From the above described 4-carbon ring expansion methodologies, the oxy-Cope rearrangement protocol appeared to be suited for our purpose, particularly employing the hydroazulenone precursor (-)-<u>11</u>. Indeed, a retrosynthetic analysis from δ-araneosene <u>5</u>, keeping in view a [3s,3s]-shift as the key transformation leads to <u>11</u> as the key building block, Scheme III.3. The advantage of this reaction lay in the fact that the

C(7)-trans-double bond can be correctly positioned in the resulting eleven membered ring.

SCHEME III.3

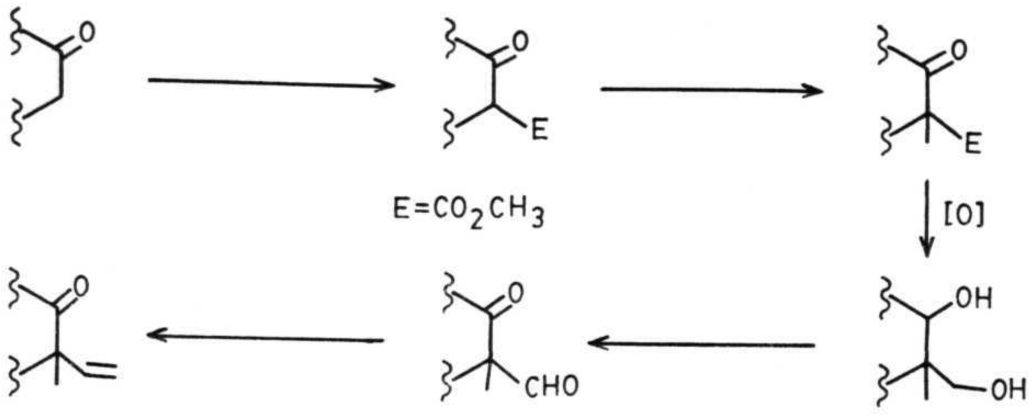


Having identified the EPC (-)-11 as the key precursor and oxy-Cope rearrangement as the pivotal ring expansion reaction, the stage was set to give practical shape to the theme indicated in Scheme III.3.

III.4. SYNTHESIS

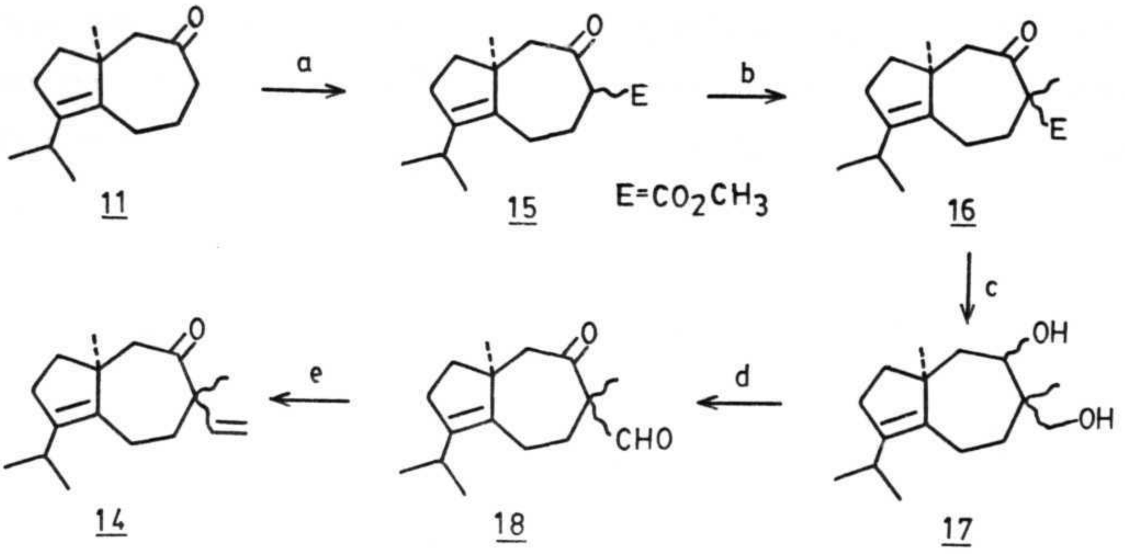
As indicated in Scheme III.3, the first task was the transformation of 11 to 14. For this purpose a five step sequence indicated in Scheme III.4 was envisaged. Accordingly, the enolate generated by reacting (-)-11 with sodium hydride was quenched with dimethylcarbonate to furnish the keto-ester 15 in 78% yield as a diastereomeric mixture, Scheme III.5. The gross

SCHEME III.4



structure of 15 was confirmed on the basis of IR spectrum exhibiting ester frequency (1730 cm^{-1}) and ^{1}H-NMR spectrum showing a set of ester methyl protons at δ 3.78 (3H, s) and δ 3.7 (3H, s) corresponding to two diastereomers. Quaternisation at C(4) in 15 was readily achieved *via* methylation with methyl iodide in the presence of K_2CO_3-acetone to furnish 16 in 85% yield as a 2:3 diastereomeric mixture. As would be expected, 16 had two additional singlets due to C(4)-angular methyl group at δ 1.38 and 1.24 in its ^{1}H-NMR spectrum corresponding to the two diastereomers. Since, the diastereomeric mixture was inseparable, it was carried as such throughout the Scheme III.5. As will be seen, this had little bearing as the final outcome as this centre was subsequently destroyed. LAH reduction of 16 gave the diol 17 in 65% yield. The diol was carefully oxidised with PCC to furnish the keto-aldehyde 18 some what poor yield (30%). The presence of IR bands at 2750, 1710, 1695 cm^{-1} corresponding to the aldehyde and cycloheptanone moieties were in agreement with its formulation. This was further supported by its ^{1}H-NMR spectrum which had two signals corresponding to two diastereomeric aldehyde protons at δ 9.7

SCHEME III.5



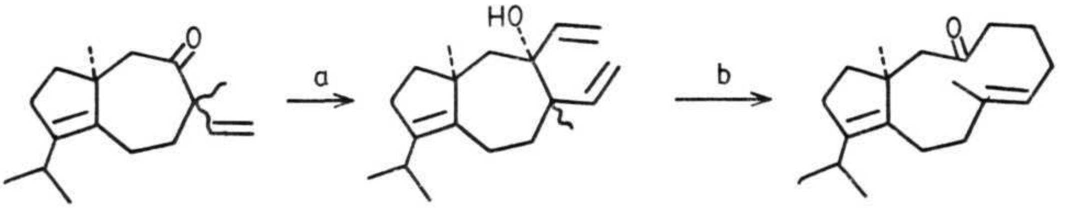
Reagents, Conditions & Yields: a) NaH, $(CH_3O)_2C{=}O$, Δ, 6h, 78%; b) K_2CO_3-Acetone, MeI, Δ, 24h, 85%; c) LAH, Et_2O, RT, 1h, 65%; d) PCC, DCM, 4 A^{o} molecular sieves, RT, 1h, 30%; e) $Ph_3P^{+}CH_3Br^{-}$, Na-t-amyloxide, RT, 10 min., 90%.

(s) and 9.58 (s). A chemoselective Wittig olefination was now considered for the conversion of the aldehyde functionality in 18 to a vinyl group. The keto-aldehyde 18 was exposed to the ylide, generated by treatment of methylenetriphenylphosphonium bromide with sodium-t-amyloxide to furnish the vinyl ketone 14 in a very satisfying 90% yield. The ^{1}H-NMR spectrum of 14 now had the characteristic ABC pattern of the vinyl group in the olefinic proton region.

As planned, addition of isopropenyl Grignard reagent to 14 was expected to deliver 13 for the key oxy-Cope rearrangement (13 → 12, Scheme III.3).

However, to avoid stereochemical problems associated with the creation of an additional chiral centre at C(4) during the oxy-Cope process, initial study was carried through the addition of vinyl magnesium bromide. This also enabled us to establish the conditions for the oxy-Cope rearrangement. Addition of this Grignard reagent to 14 gave the labile divinyl carbinol 19 (IR: 3400 cm^{-1}), Scheme III.6. The divinyl carbinol 19 when heated in a sealed tube at 200^{o}C for 1h, underwent smooth [3s,3s]-shift and furnished 1s,8-dimethyl-12-isopropylbicyclo[9.3.0]tetradeca-7Z,11-diene-3-one 20 in 70% yield from 14 as a single stereoisomer. The structure of 20 rests on its IR (ν_{max} 1700 cm^{-1}), ^{1}H-NMR (Fig.III.1) and ^{13}C-NMR (Fig.III.2)

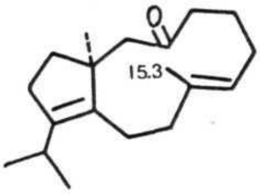
SCHEME III.6



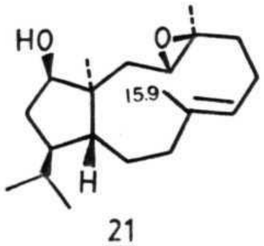
14 19 20

Reagents, Conditions & Yields: a) ⁄⁄‾Br, Mg, THF, Δ , 1h; b) sealed tube, (neat) 200^{o}C, 1h, 70% from 14.

spectral data. The ^{13}C-NMR spectrum showed the presence of five sp^{2} carbons at δ 209.0, 144.4, 136.1, 134.7 and 128.5 in consonance with its formulation. The trans-stereochemistry of the C(7) double bond in 20 was established through the characteristic signal of the olefinic proton in the ^{1}H-NMR spectrum and the appearance of the vinyl methyl group carbon resonance at δ 15.35. These are diagnostic of dolabellanes having *trans*-C(7) double (cf 21).[16]



20



21

We observed some what to our surprise, that on exposure to KH[17] at various temperatures 19 did not furnish any 20 . In this particular case, the thermal oxy-Cope rearrangement seems to be distinctly superior to the anionic oxy-Cope process. The stereochemistry of the oxy-Cope rearrangement, although expected, is important as the C(7)-double bond is installed in correct configuration.

Having demonstrated the formation of 5,11-fused system 20, we carried out the addition of isopropenyl magnesium bromide on 14 to furnish the divinyl carbinol 13 in 40% yield. This reaction proved to be extremely sensitive to the reaction conditions. Use of isopropyl lithium instead of the Grignard reagent did not improve things. The labile trienol 13 was directly subjected to rearrangement in a sealed tube at 170°C for 1h to furnish the C_{20}-dolabellane skeleton in the form of ketones (-)-12a and (-)-12b(3:2) in 70% yield, Scheme III.7. The two C(4)-epimers were readily separable on column chromatography and their ^{1}H-NMR (Fig III.3, major isomer & Fig III.4, minor isomer) and ^{13}C- NMR (Fig.III.5, major isomer & Fig.III.6, minor isomer) data fully supported their gross structure including *trans*-geometry of C(7)-double bond.[#] When the mixture of isomers 12a,12b or the minor isomer 12a or 12b was exposed to base (NaOMe-MeOH) it readily converted to the other major isomer 12a or 12b. Clearly, one of the isomers was considerably more stable than the other.[@] However, it was

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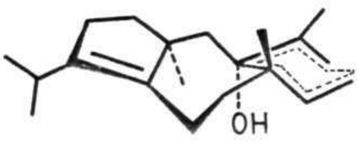
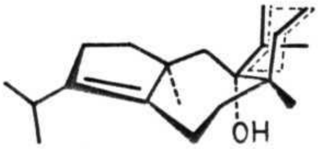
[#] Among the various diastereomeric transition states that are possible for this facile oxy-Cope rearrangement, the two chair like transition states i and ii appear to be more favourable. We have assumed, not without reason, that isopropyl magnesium bromide should add predominantly from the face opposite to the angular methyl group. The chair-like transition states i and ii account for the observed E-geometry of the C(7)-double bond in the dolabellane derivatives 12a, 12b.



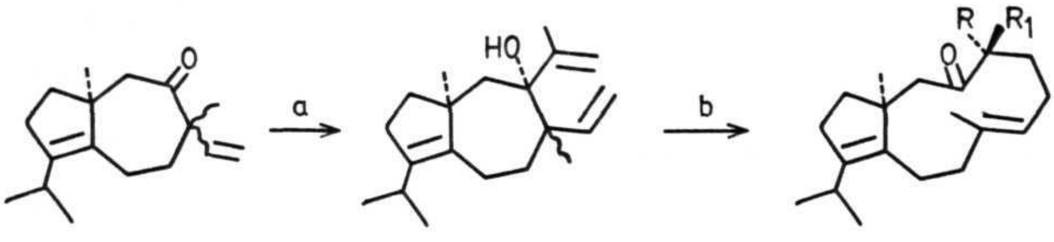
i



ii

[@] MM2 calculations on 12a & 12b did not prove very helpful due to the presence of large number of closely related conformations. However, employing the newly developed molecular mechanics programme CONFLEX which generates and takes into account all significant conformations, it has been possible to calculate the E_{strain} for 12a and 12b. According to the calculations, kindly performed be Professor E. Osawa and his student E. Goto, 12a is marginally (0.7 K cal) more stable than 12b. We thank Professor Osawa for making available to us these results from his programme which is very much in the trial stage.

SCHEME III.7



14 13 12a, $R=CH_3, R_1=H$

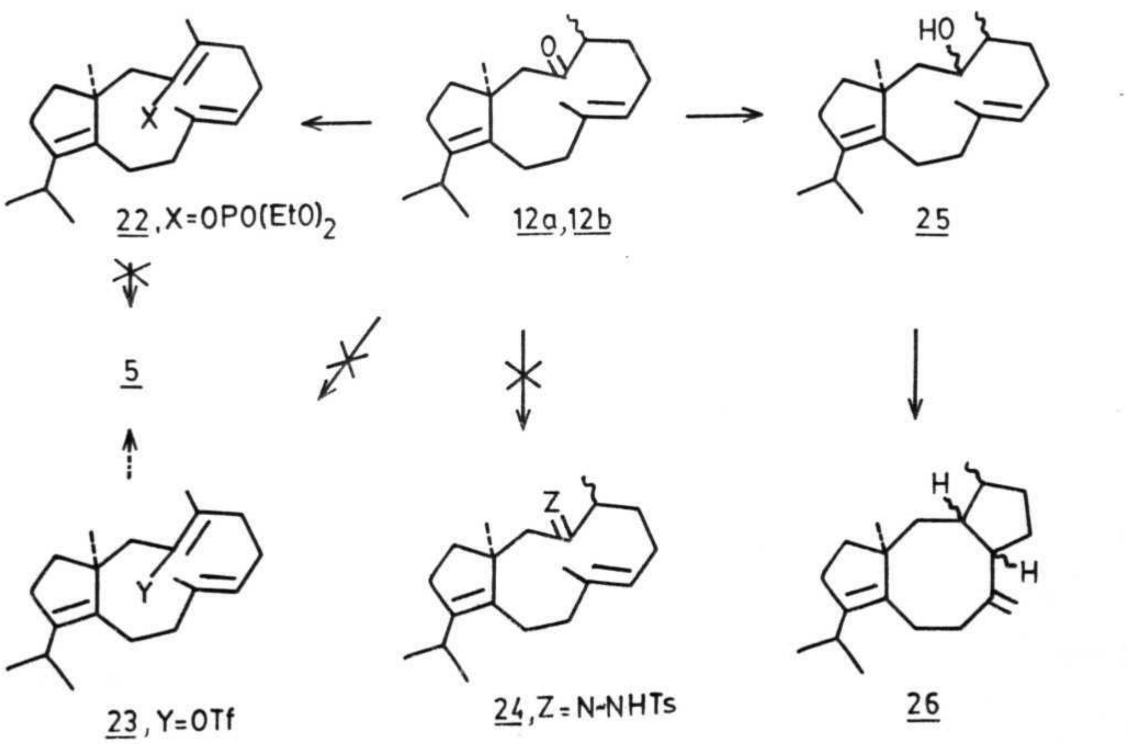
12b, $R=H, R_1=CH_3$

Reagents, Conditions & Yields: isopropenyl magnesium bromide, THF, Δ, 0.5h, 40%; b) sealed tube, 170°C, 1h, 70%

not possible to distinguish between them. The bicyclic dolabellane ketones 12a, 12b appeared to be all set for convertion to δ-araneosene 5 through a regioselective carbonyl → olefin functional group adjustment. We tried several methods to effect this change as shown in Scheme III.8, but without any success. We were aware of the possibility of transannular interaction/cyclisation during the chemical manipulation of the carbonyl group in 12a, 12b. We therefore chose reactions that clearly avoided such possibilities. At first, we attempted to convert the ketones 12a, 12b to the enol-phosphate 22 to be followed by metal ammonia reduction[18] to furnish δ-araneosene 5. Although an enol-phosphate product 22 was obtained from 12a, 12b on exposure to LDA and quenching with diethyl chlorophosphate, further reduction led to intractable products. Alternatively, we sought to convert 12a, 12b to the enol triflate 23 followed by tri-n-butyl stannane reduction[19] to give the natural product 5. However, in this case, despite several attempts enol-triflate could not be prepared. Finally, we attempted a Caglioti reaction[20] via the tosylhydrazone 24. But, once again 12a, 12b were found to be unreactive towards the preparation of this straightforward derivative.

Despite reservations, we attempted an alternative sequence from 12, 12b. Reduction of 12a, 12b with LAH readily furnished a diastereomeric mixture of alcohols 25. Several attempts employing heating in HMPA,[21] MsCl-py , $POCl_3$-py, anhydrous $CuSO_4$,[22] Burgess salt[23] etc. to dehydrate 25 to the δ-araneosene 5 proved futile. In most of these case, there were definitive indications of formation of transannular cyclised hydrocarbon products having the gross tricyclic structure 26. This indication for the formation of novel 5,8,5-fused product was available from the ^{1}H-NMR spectra of the product(s) which exhibited olefinic proton resonances due to an exocyclic methylene group (δ 4.6-4.8) and showed the absence of trisubstituted double bond. However, definitive characterisation could not be done due to paucity of the material.

SCHEME III.8



III.5. SUMMARY AND OUTLOOK

The novel 5,11-fused bicyclic framework of biogenetically important dolabellane diterpenes has been synthesised in the form of ketones (-)-12a and (-)-12b. Although, 12a, 12b could not be converted into a natural product like δ-araneosene 5, the methodology outlined here from bicyclohydroazulenone 11 is amenable to tactical modifications to synthesise other members of this family (appendix).

Preliminary observation of biogenetic-type cationic cyclisations of the dolabellane framework to 5,8,5-fused tricyclic system 26 has been made. Further studies and clarification of the stereochemistry of the cyclised product 26 should prove worthwhile.

III.6. EXPERIMENTAL

For general write-up see the experimental of the first chapter.

Bicyclic hydroazulenone (-)-11 was prepared from R-(+)-limonene as described in the first chapter.

4-Carbomethoxy-8-isopropyl-1S-methylbicyclo[5.3.0]dec-7-en-3-one 15:

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal was placed sodium hydride (240 mg, 50% dispersion in oil, 5.0 mmol). The oil was removed by washing sodium hydride with dry benzene (2 ml). Then the hydride was covered with dry dimethyl carbonate (10 ml). enone 11 (1.0 g, 4.85 mmol) in dry dimethyl carbonate (5 ml) was added slowly to it. The contents were stirred at room temperature for 6 h. Then the reaction mixture was diluted with ether (100 ml) and the excess sodium hydride was destroyed by careful addition of water (25 ml). The ethereal layer was separated and the aqueous layer was once again extracted with ether (50 ml x3). The combined ethereal extract was washed, dried and concentrated to a crude product (1.5 g) which was charged on a silica gel (15 g) column. Elution with 5% ethyl acetate - pet ether resulted in removal of oil impurities and further elution with 10% ethyl acetate - pet ether furnished the keto-ester 15 (1.0 g) in 78% yield.

bp. : $160^oC/0.1$ mm

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

^1H-NMR : δ3.78 (s, -O-C$\underline{H}_3$), 3.7 (s, -O-C$\underline{H}_3$), 2.8 - 2.5 (series of m), 1.05 - 0.85 (series of s and d)

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

Found: C, 72.97 ; H, 9.35

4-Carbomethoxy-1S,4-dimethyl-8-isopropylbicyclo[5.3.0]dec-7-en-3-one (16):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, a reflux condenser and septum was placed anhydrous potassium carbonate (1.33 g, 10.0 mmol). To this keto-ester 15 (1.0 g, 3.78 mmol) in dry acetone (25 ml) was added and the contents were refluxed for 1 h. Then methyl iodide (2 ml, excess) was added and refluxing was continued for 12 h. Acetone was removed at reduced pressure and the residue left was diluted with water (25 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to give the crude product (1.2 g) which was filtered through a small silica gel (5 g) column to furnish the methylated keto-ester 16 (895 mg) in 85% yield as a diastereomeric mixture.

bp. : 165°C/0.1mm

IR : 2950, 1700, 1440, 1250, 1210, 1110 cm^{-1}

^{1}H-NMR : δ3.7 (s, $-O-C\underline{H}_3$), 3.65 (s, $-O-C\underline{H}_3$), 2.9 - 1.5 (series of m), 1.38 (s, $-C-C\underline{H}_3$), 1.24 (s, $-C-C\underline{H}_3$), 1.05 - 0.8 (series of s and d)

Analysis : $C_{17}H_{26}O_3$ Calcd: C, 73.34 ; H, 9.41
Found: C, 73.71 ; H, 9.41

1S,4-Dimethyl-8-isopropylbicyclo[5.3.0]dec-7-en-3-one-4-farmaldehyde (18):

Into a 50 ml RB flask lithium aluminium hydride (300 mg, excess) was placed and dry ether (20 ml) was added. To this keto-ester 16 (800 mg, 2.9 mmol) in dry ether (2 ml) was slowly added at 0°C and the contents were stirred at room temperature for 1 h. Then the excess lithium aluminium hydride was destroyed by careful addition of ethyl acetate followed by saturated Na_2SO_4 solution (5 ml). The reaction mixture was extracted with ethyl acetate (50 ml x 3). Combined organic extract was washed, dried and concentrated to a crude diol (600 mg) which was filtered through a small silica gel (5 g) column. Elution with ethyl acetate furnished the diol 17 (500 mg) as a diastereomeric mixture in 65% yield which was used directly for the next step.

IR : 3450, 2950 cm^{-1}

Into a 50 ml RB flask pyridinium chlorochromate (4.3 g, 20.0 mmol) and activated molecular sieves (4 ^{o}A) were placed in dry dichloromethane (10 ml) and cooled to 0^{o}C. To this the above diol 17 (1.0 g, 4.0 mmol) was added with dry dichloromethane (5 ml) and stirred for 5 h at room temperature. Then the reaction mixture was diluted with dry ether (50 ml) and filtered through a small florisil (10 g) column. The crude product obtained after removal of solvent was charged on a silica gel (10 g) column. Elution with 3% ethyl acetate - pet ether removed the less polar impurities and further elution with 10% ethyl acetate - pet ether furnished the keto-aldehyde 18 (300 mg) in 30% yield as a mixture of diastereomers.

IR : 2950, 2700, 1710, 1695, 1450, 1060 cm^{-1}

^{1}H-NMR : δ9.7 (1H, s, O=C-H), 9.58 (1H, s, O=C-H), 3.0 - 1.3 (22H, series of m), 1.25 - 0.85 (18H, series of s and d)

Analysis : $C_{16}H_{24}O_2$ Calcd: C, 77.37 ; H, 9.74

Found: C, 77.11 ; H, 9.77

1S,4-Dimethyl-8-isopropyl-4-vinylbicyclo[5.3.0]dec-7-en-3-one (14):

Into a 50 ml three necked RB flask fitted with a dry N_2 inlet, mercury seal and septum, methyltriphenylphosphium bromide (570 mg, 1.6 mmol) was placed and dry benzene (10 ml) was added. To this stirring suspension freshly sublimed sodium t-amyloxide (88 mg, 0.8 mmol) in dry benzene (3 ml) was added. The resulting lemon coloured reaction mixture was stirred for 30 min at room temperature. Keto-aldehyde 18 (200 mg, 0.8 mmol) in dry benzene (3 ml) was added at once to the reaction mixture and stirring was continued for 15 min. Then the reaction mixture was quenched with water and extracted with benzene (50 ml x 3). The combined benzene extract was washed, dried and concentrated to a crude product (300 mg) which was filtered through a small silica gel column (5 gm) to get rid of the polar triphenylphosphine oxide impurities. The vinyl ketone 14 (180 mg) was obtained in 90% yield as a diastereomeric mixture.

IR : 3050, 2950, 1695, 1630, 1450, 910 cm^{-1}

^1H-NMR : δ6.0 - 5.6 (2H, m, $-C\underline{H}=CH_2$), 5.15 - 4.85 (4H, m, $-CH=C\underline{H}_2$), 2.8 - 1.5 (22H, series of m), 2.2 - 0.8 (18H, series of s and d)

Analysis : $C_{17}H_{26}O_2$ Calcd: C, 77.82 ; H, 9.99
Found: C, 78.08 ; H, 9.81

1S,8-Dimethyl-12-isopropylbicyclo[9.3.0]tetradeca-7Z,11-dien-3-one (20):

Vinyl bromide (THF solution) was prepared according to procedure described in the experimental section of the first chapter of this thesis.

Into a 25 ml three necked RB flask fitted with dry N_2 inlet, septum and mercury seal were placed activated magnesium turnings (40 mg, 1.6 mmol and a small piece of iodine. To this dry THF (5 ml) was added followed by vinyl bromide (THF solution) until all the magnesium had reacted. If necessary, the reaction mixture was refluxed to initiate the reaction. To this vinyl ketone 14 (200 mg, 0.8 mmol) in dry THF (2 ml) was added and stirring was continued for further 30 min. The reaction mixture was quenched by addition of saturated ammonium chloride solution (25 ml) and extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude labile divinyl carbinol 19 (200 mg) which was directly used for next step.

The above divinyl carbinol 19 (200 mg) was taken in a corning glass tube and sealed under N_2 atmosphere. This sealed tube was heated at 200°C for 1 h. Then the sealed tube was cooled to room temperature and opened and the crude product was filtered through a small silica gel (3 g) coulmn by eluting with 5% ethyl acetate - pet ether furnish a C_{19}-ketone 20 (140 mg) in 70% yield.

$[\alpha]_D$: +6 (c 1.0, $CHCl_3$)

IR : 2950, 1700, 1440, 1350, 1060 cm^{-1}

^{1}H-NMR (fig. III.1) : δ4.9 - 4.7 (1H, m, -CH=C-), 2.8 - 1.8 (17H, series of m), 1.66 (3H, br s, $-C=C-CH_3$), 1.09 (3H, d, J = 7Hz, $-CH-CH_3$), 0.96 (3H, d, J = 7Hz, $-CH-CH_3$), 0.92 (3H, s)

^{13}C-NMR (fig. III.2) : δ209.0, 144.4, 136.1, 134.7, 128.6, 53.2, 48.7, 41.9, 40.9, 34.7, 30.6, 28.9, 28.1, 27.2, 25.1, 21.5, 21.0(2C), 15.3

Analysis : $C_{19}H_{30}O$ Calcd: C, 83.15 ; H, 11.02
Found: C, 83.66 ; H, 11.01

12-Isopropyl-1S,4,8-trimethylbicyclo[9.3.0]tetradeca-7Z,11-dien-3-ones (12a,12b):

Into a 25 ml three necked RB flask fitted with a dry N_2 inlet, mercury seal and septum, activated magnesium turnings (40 mg, 1.6 mmol) and iodine (2 mg) were placed. To this dry THF (5 ml) was added followed by isopropenyl bromide (0.16 ml, 1.8 mmol) in dry THF (5 ml) was added drop by drop. The reaction mixture was initially heated to reflux to initiate the reaction, then heating was removed and the reaction mixture was stirred until all the magnesium had reacted. Vinyl ketone 14 (200 mg, 0.8 mmol) in dry THF (5 ml) was added to this and stirring was continued for further 30 min. The reaction mixture was quenched by addition of saturated NH_4Cl

solution (50 ml) and extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product (200 mg) which was chromatographed on a silica gel (5 g) column to get rid of some more polar impurities. Elution with 2% ethyl acetate-pet ether furnished the labile divinyl carbinol 13 (100 mg) in 40% yield, which was used directly for the next step.

The above divinyl carbinol 13 (100 mg, neat) was taken into a corning glass tube and sealed under N_2 atmosphere. The sealed tube was heated at $170^{o}C$ for 1h, cooled and opened. On tlc examination after the reaction is over, it showed two clear products but no starting material. The crude product was charged on a silica gel (5 g) column. Elution with 3% ethyl acetate - pet ether furnished one of the methyl epimers 12a,12b (42 mg, major).

$[\alpha]_D$: -51 (c 1.0, $CHCl_3$)

IR : 2950, 1700, 1450, 1350, 1020 cm^{-1}

^1H-NMR (fig. III.3) : δ4.92 (1H, t, J = 8Hz, $-C\underline{H}=C-$), 2.8 - 1.4 (16H, series of m), 1.65 (3H, br s, $-C=C-C\underline{H}_3$), 1.08 (3H, s, $-C-C\underline{H}_3$), 1.06 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 1.04 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.95 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR (fig. III.4) : δ213.6, 143.6, 138.5, 136.1, 127.3, 50.3, 48.7, 47.5, 39.2, 37.8, 34.6, 27.3, 27.1(2C), 26.4, 23.6, 21.0, 20.8, 18.2, 17.7

Analysis : $C_{20}H_{32}O$ Calcd: C, 83.27 ; H, 11.18

Found: C, 83.56 ; H, 11.21

Further elution with 5% ethyl acetate - pet ether furnished the other methyl epimer 12a,12b(28 mg, minor) in an over all yield of 70%.

$[\alpha]_D$: -54 (c 1.0, $CHCl_3$)

IR : 2950, 1700, 1450, 1040 cm^{-1}

^{1}H-NMR (fig. III.5) : δ4.75 (1H, m, $-C\underline{H}=C-$), 2.85 - 1.4 (16H, series of m), 1.65 (3H, br s, $-C=C=C\underline{H}_3$), 1.1 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.98 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.96 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.95 (3H, s, $-C-C\underline{H}_3$)

^{13}C-NMR (fig. III.6) : δ212.7, 144.5, 135.7, 134.0, 128.8, 52.2, 48.4, 46.3, 41.0, 34.5, 34.1, 31.0, 28.3, 27.2, 21.3, 21.0, 19.5, 15.1

Analysis : $C_{20}H_{32}O$ Calcd: C, 83.27 ; H, 11.18

Found: C, 83.10 ; H, 11.16

Equilibration of the minor ketone epimer (12a,12b):

Into a 10 ml three necked RB flask, fitted with a dry N_2 inlet, septum and mercury seal was placed dry methanol (5 ml). To this freshly cut sodium (20 mg) was added piece by piece and the reaction mixture was stirred until all the sodium had reacted. Then the ketone 12a,12b (minor) was added in dry methanol (2 ml) and the reaction mixture was stirred at room temperature for 12 h. The methanol was removed at reduced pressure and the residue left was diluted with water (10 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product. The crude product was filtered through a small silica gel column by eluting with 5% ethyl acetate - pet ether to furnish 12a,12b(major) in quantitative yield.

Preparation of enol phosphonate (22):

Into a 25 ml three necked RB flask fitted with a dry N_2 inlet, mercury seal and septum was placed diisopropylamine (.05 ml, 0.3 mmol) and dry THF (1 ml). The contents were cooled to $-78^{\circ}C$ and then n-butyllithium (0.2 ml, 0.2 mmol in hexane) was added. The reaction mixture was stirred for 30 min and ketone 12a,12b (10 mg, 0.03 mmol) in dry THF (1 ml) was added and reaction mixture was brought to $0^{\circ}C$ and stirring was continued for further 30 min. The resulting enolate was quenched by the addition of diethyl chlorophosphate (0.2 ml, excess) with dry THF (1 ml). After stirring for 20 min at $0^{\circ}C$ - $10^{\circ}C$ the reaction was stopped by the addition of brine (10 ml) and the resulting aqueous layer was extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated. The crude product thus obtained was filtered through a small silica gel (3 g) column. Elution with 5% ethyl acetate furnished the enol-phosphate 22 (7 mg) 50% yield.

IR : 2950, 1030, 980 cm^{-1}

^{1}H-NMR : δ5.0 (1H, m, $-C\underline{H}=C-$), 4.2 (4H, q, J = 7Hz, $-O-C\underline{H}_2CH_3$), 2.6 - 1.2 2(8H, series of m), 1.1 - 0.8 (9H, series of s and d)

Attempted reduction of enol-phosphate (22):

Into a 50 ml three necked RB flask fitted with guard tube and septum was placed freshly distilled liq.NH_3 (20 ml). To this freshly cut sodium (20 mg, excess) was added piece by piece and the resulting blue coloured solution was stirred for 5 min and enol-phosphate 22 (10 mg, 0.2 mmol) was added. Stirring was continued for further 15 min and liq.NH_3 was allowed to evaporate. The residue was diluted with water (10 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude mixture of unidentifiable products.

Attempted preparation of enol-triflate (23):

Into a 25 ml three necked RB flask fitted with a dry N_2 inlet, mercury seal and septum was placed diisopropylamine (.05 ml, 0.3 mmol) and dry THF (1 ml). The contents were cooled to -78°C and then n-butyllithium (0.2 ml, 0.2 mmol in hexane) was added. The reaction mixture was stirred for 30 min and ketone 12a,12b (10 mg, 0.03 mmol) in dry THF (1 ml) was added and reaction mixture was brought to 0°C and stirring was continued for further 30 min. The resulting enolate was quenched by the addition of n-phenyl triflamide (25 mg, excess) with dry THF (1 ml). After stirring for 20 min at 0°C - 10°C the reaction was stopped by the addition of brine (10 ml) and the resulting aqueous layer was extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated. Only starting material was recovered.

12-Isopropyl-1S,4,8-trimethyl bicyclo[9.3.0]tetradeca-7,11-dien-3-ol (25):

Into a 25 ml RB flask one of the ketones 12a,12b (25 mg, 0.086 mmol) in dry ether (5 ml) was placed. The reaction mixture was cooled to 0°C and excess lithium aluminium hydride (25 mg) was added. Then the reactants were stirred at room temperature for 30 min and excess lithium aluminium hydride was distroyed by careful addition of ethyl acetate followed by saturated Na_2SO_4 solution. The aqueous layer was extracted with ethyl acetate (25 ml x 3) and the combined organic extract was washed and dried. The crude product obtained after removal of the solvent was charged on a small silica gel (2 g) column. Elution with 10% ethyl acetate - pet ether furnished the alcohol <u>25</u> (23 mg) in 95% yield as a diastereomeric mixture.

IR : 3400, 1460, 1380, 1100 cm^{-1}

^{1}H-NMR : δ5.28(1H, t, J = 7Hz, -C=C$\underline{H}$-), 3.88 (1H, m, -C$\underline{H}$-OH), 2.9 - 1.3 (19H, series of m), 1.24 - 0.9 (12H, series of s and d)

<u>Attempted mesylation of</u> (<u>25</u>):

Into a 5 ml RB flask fitted with guard tube alcohol <u>25</u> (10 mg, 0.03 mmol) was placed in dry pyridine (1 ml). The reaction mixture was cooled to 0^oC in an ice bath and freshly distilled mesyl chloride (0.2 ml) was added to it. The contents were stirred at 0^oC for 1 h. The reaction mixture was quenched by addition of water (5 ml) and then extracted with pentane (50 ml x 3). The combined pentane extract was washed, dried and concentrated to a crude product, which showed two components on $AgNO_3$ impregnated tlc. The crude product was charged on a $AgNO_3$ impregnated silica gel (3 g) column. Elution with pet ether furnished one of the transannular cyclised product <u>26</u> (3 mg) in 35% yield.

IR : 2950, 890 cm^{-1}

^{1}H-NMR : δ4.67 and 4.61 (2H, br s, -C=C$\underline{H}_2$), 2.8 - 1.2 (18H, series of m), 0.99 (3H, s, -C-C$\underline{H}_3$), 0.96 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.95 (3H, d, J = 7Hz, -CH-C$\underline{H}_3$)

Further elution with 5% benzene - pet ether furnished another isomer of 26 (1 mg) in 12% yield.

IR : 2950, 890 cm^{-1}

^{1}H-NMR : δ4.75 and 4.65 (2H, br s, $-C{=}C\underline{H}_3$), 2.6 - 1.4 (18H, series of m), 9.6 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 9.2 (3H, s, $-C-C\underline{H}_3$), 0.9 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

Full characterisation of the two transannular cyclised products was not possible due to paucity of material and lack of facility to perform high field ^{1}H-NMR and NOE experiment.

III.7. SPECTRA

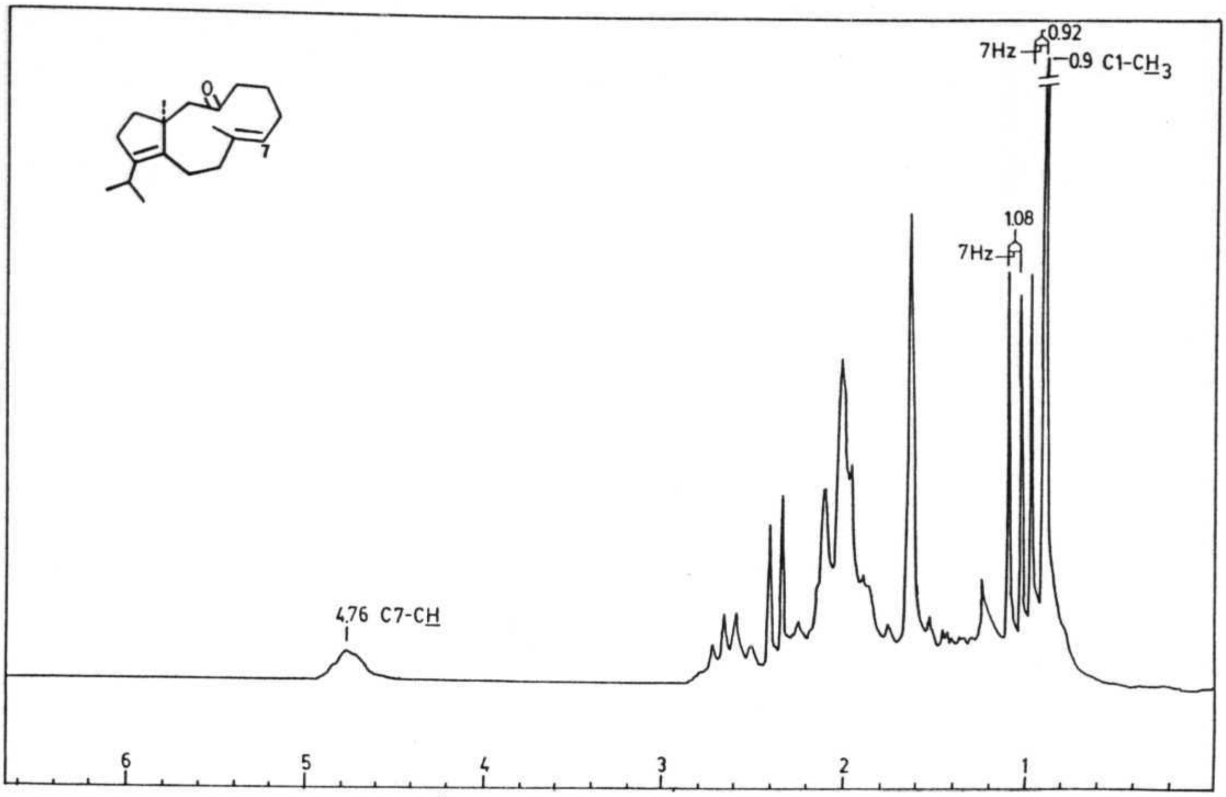


Fig. III.1 ^{1}H-NMR spectrum (100 MHz) of <u>20</u>

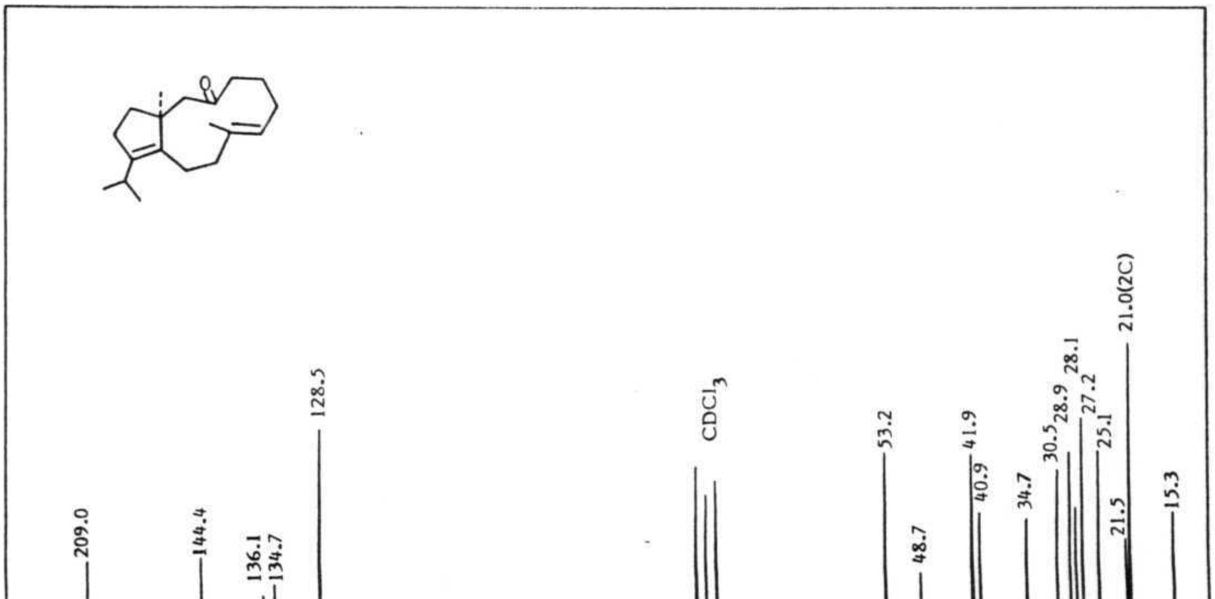


Fig. III.2 ^{13}C-NMR spectrum (25 MHz) of <u>20</u>

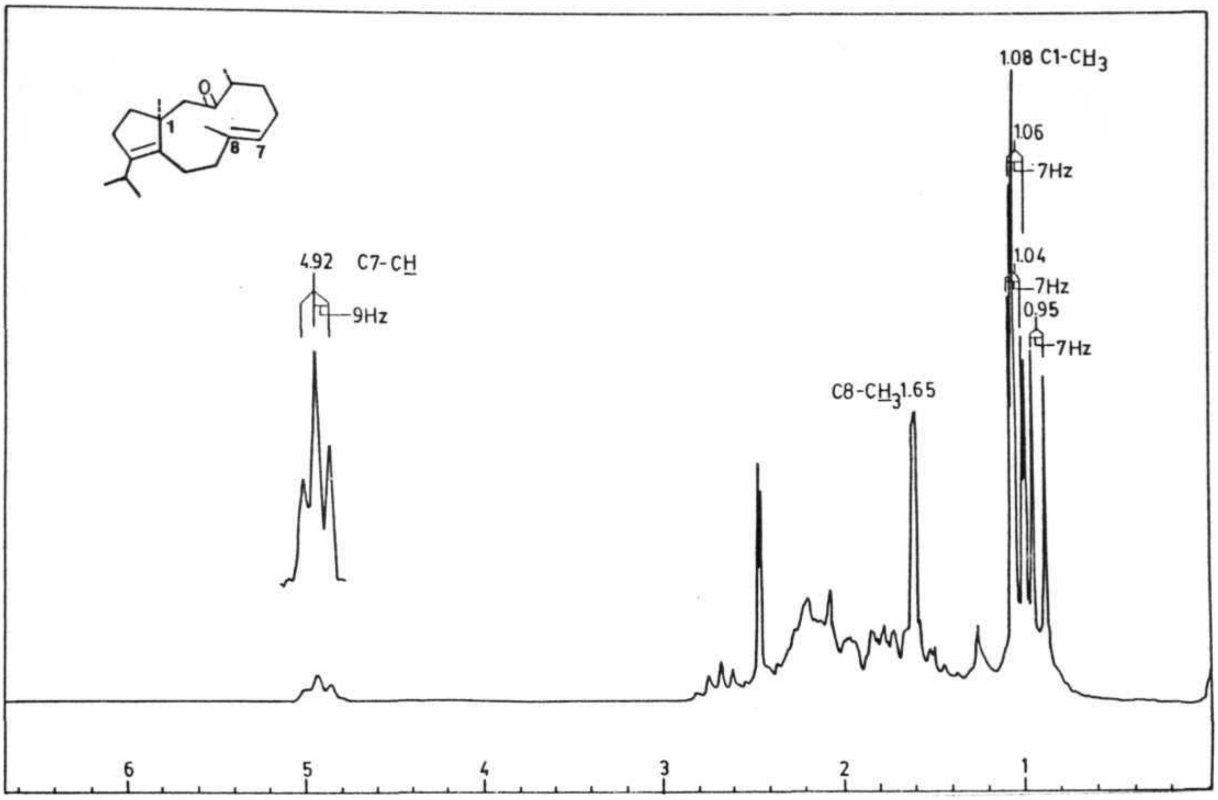


Fig. III.3 ^{1}H-NMR spectrum (100 MHz) of 12a,12b (major isomer)

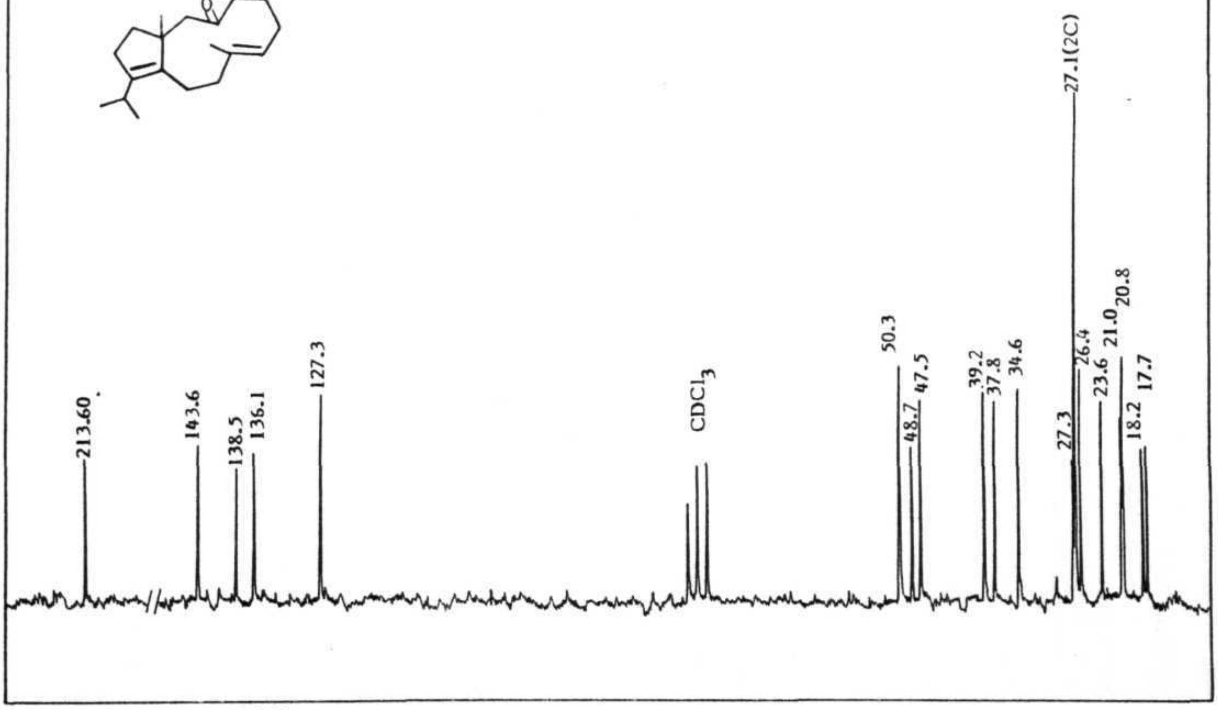


Fig. III.4 ^{13}C-NMR spectrum (25 MHz) of 12a,12b (major isomer)

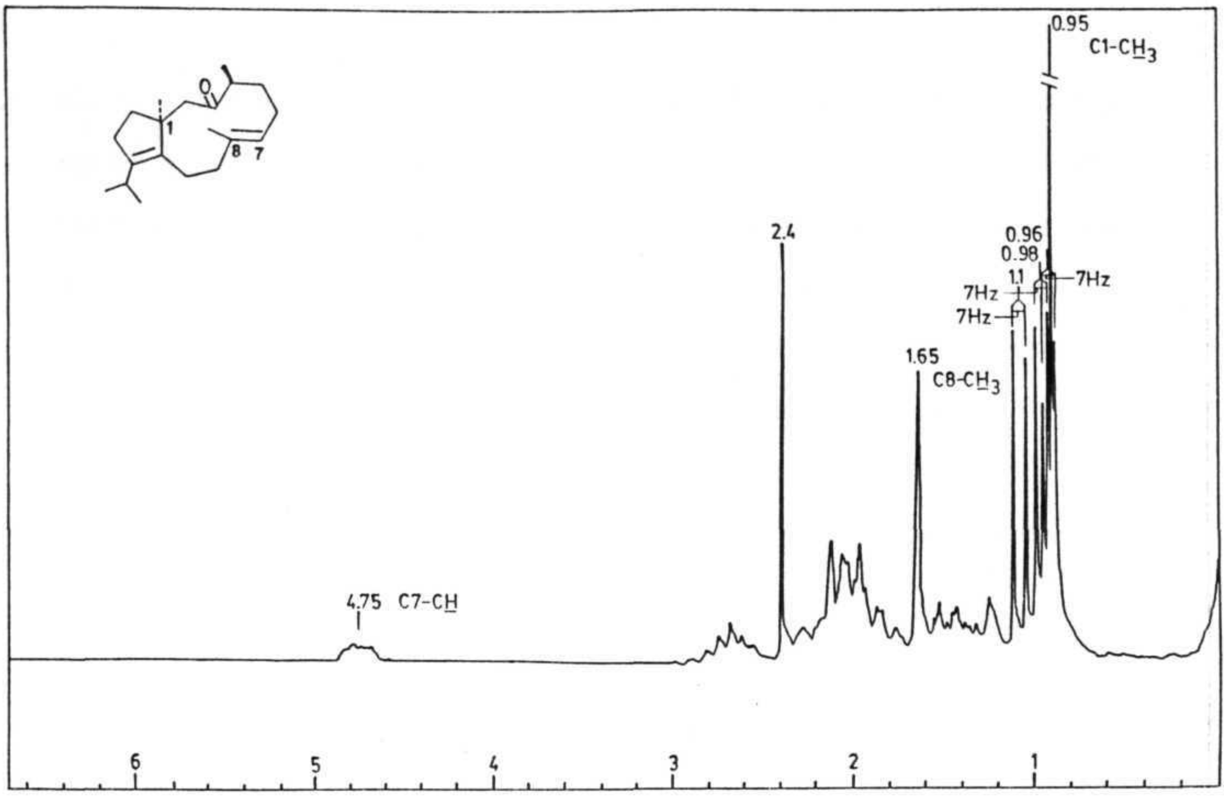


Fig. III.5 ^{1}H-NMR spectrum (100 MHz) of 12a,12b (minor isomer)

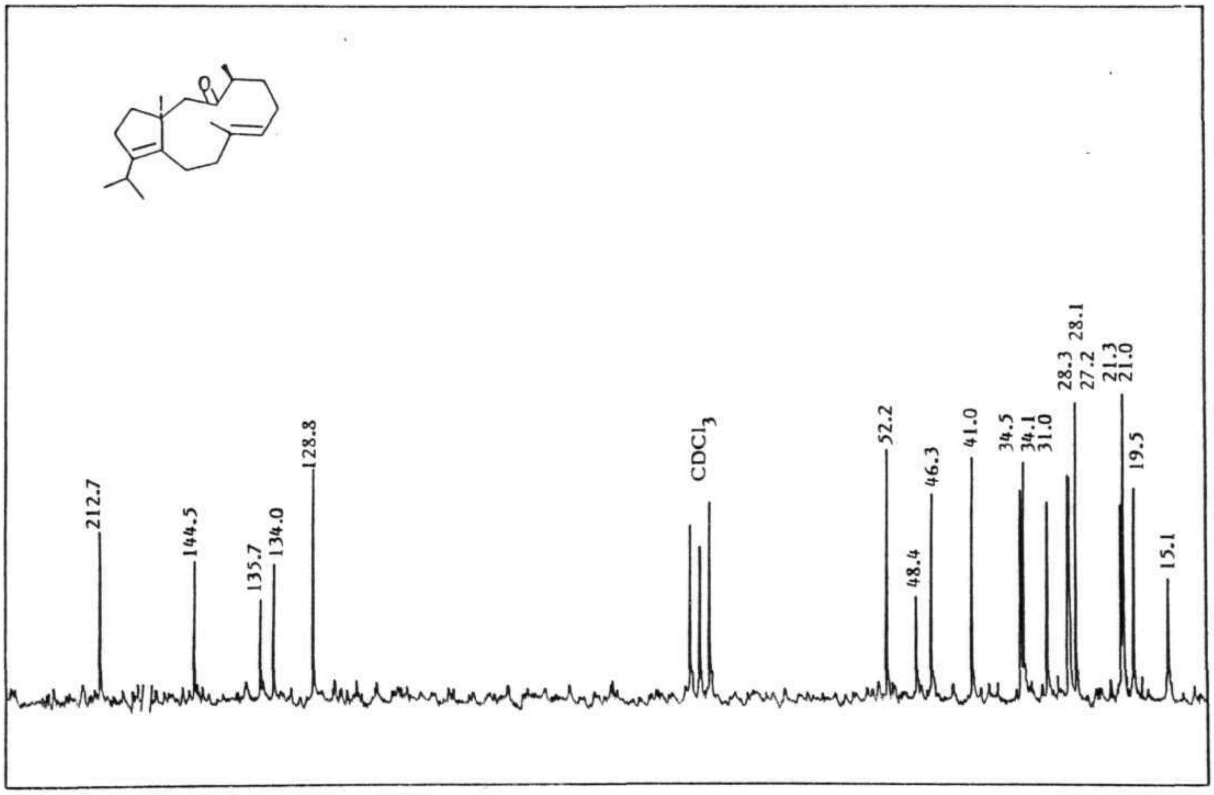


Fig. III.6 ^{13}C-NMR spectrum (25 MHz) of 12a,12b (minor isomer)

III.8. REFERENCES

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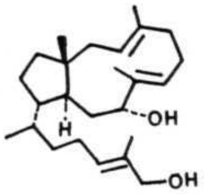
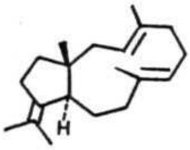
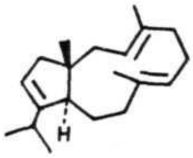
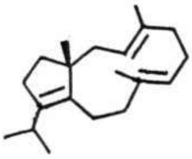
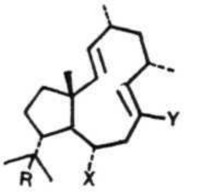
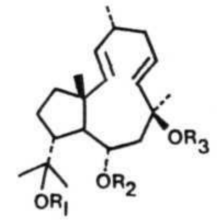
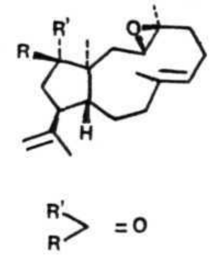
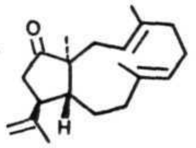
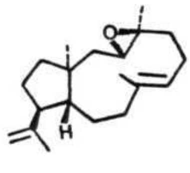
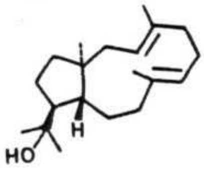
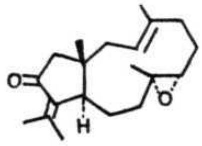
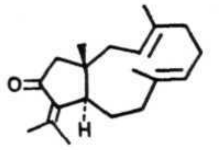
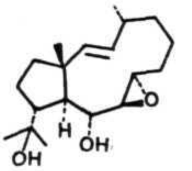
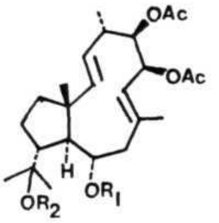
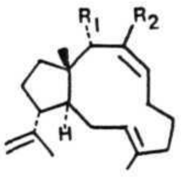
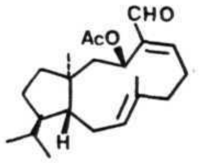
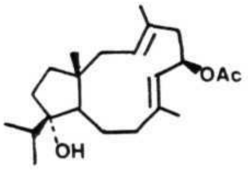
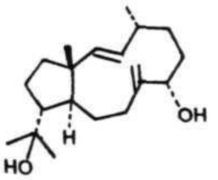
APPENDIX : A compilation of natural dolabellane diterpenes

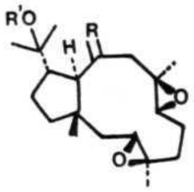
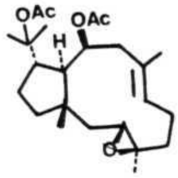
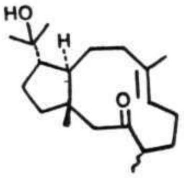
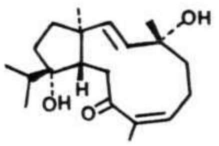
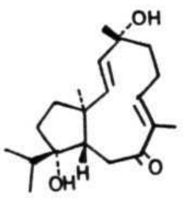
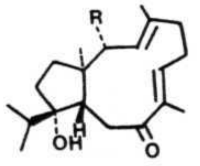
S. No.	Natural Product	Species	Structure	Ref.
1.	Albolineaol	*Ceroplastes albolineatus*		1
2.	β-Araneosene	*Sordoria araneosa*		2
3.	γ-Araneosene	"		2
4.	δ-Araneosene	"		2
5.	(1R,2E,4R,7E,10S,11R,12R)-10-Acetoxy-18-hydroxy-2,7-dolabelladiene	*Dictyota californica*	 R=H, X=OAc, Y=H	3
6.	(1R,2E,4R,7E,10S,11S,12R)-10,18-Diacetoxy-2,7-dolabelladiene	"	R=Ac, X=OAc, Y=H	4
7.	(1R,2E,4R,7E,10S,11S,12R)-10,18-Dihydroxy-2,7-dolabelladiene	"	R=H, X=OH, Y=H	4

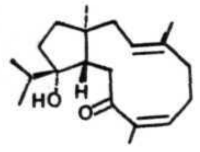
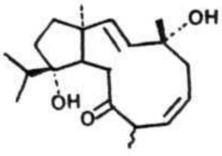
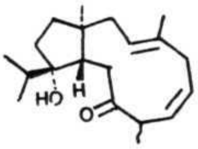
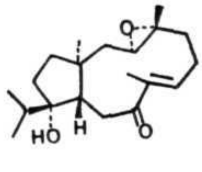
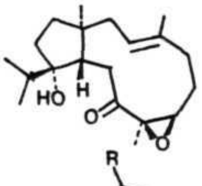
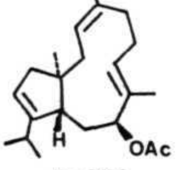
8. (1R,2E,4R,6R,7E,10S,11S,12R)-6,10-Diacetoxy-18-hydroxy-2,7-dolabelladiene	"	R=H, X=OAc, Y=OAc	4
9. (1R,2E,4R,6R,7E,10S,11S,12R)-10-Acetoxy-6,18-dihydroxy-2,7-dolabelladiene	"	R=H, X=OAc, Y=OH	4
10. (1R,2E,4R,6R,7E,10S,11S,12R)-18-Acetoxy-6,10-dihydroxy-2,7-dolabelladiene	"	R=Ac, X=OH, Y=OH	4
11. (1R,2E,4R,6R,7E,10S,11S,12R)-6,10,18-Trihydroxy-2,7-dolabelladiene	"	R=H, X=OH, Y=OH	4
12. (1R,2E,4R,7E,11S,12R)-18-Hydroxy-2,7-dolabelladiene	"	R=H, X=H, Y=H	4
13. (1R,2E,4R,6E,8S,10S,11S,12R)-8,10,18-Triacetoxy-2,6-dolabelladiene	"	 R_1=Ac, R_2=Ac, R_3=Ac	4
14. 1R,2E,4R,6E,8S,10S,11S,12R)-10,18-Diacetoxy-8-hydroxy-2,6-dolabelladiene	"	R_1=Ac, R_2=Ac, R_3=H	4
15. (1R,2E,4R,6E,8S,10S,11S,12R)-8,18-Diacetoxy-10-hydroxy-2,6-dolabelladiene	"	R_1=Ac, R_2=H, R_3=Ac	4
16. (1R,2E,4R,6E,8S,10S,11S,12R)-8,10-Diacetoxy-18-hydroxy-2,6-dolabelladiene	"	R_1=H, R_2=Ac, R_3=Ac	4

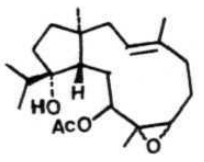
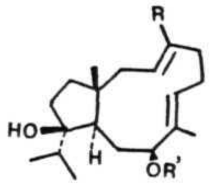
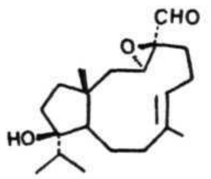
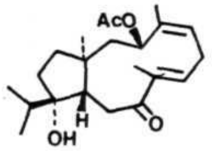
17. (1R,2E,4R,6E,8S,10S,11S,12R)-18-Acetoxy-8,10-dihydroxy-2,6-dolabelladiene	"	R_1=Ac, R_2=H, R_3=H	4
18. (1R,2E,4R,6E,8S,10S,11S,12R)-8,10,18-Trihydroxy-2,6-dolabelladiene	"	R_1=H, R_2=H, R_3=H	4
19. 3,4-Epoxy-14-oxo-7,18-dolabelladiene	Dictyota dichotoma		5
20. 3,4-Epoxy-14-hydroxy-7,18-dolabelladiene	"	R=OH, R'=H	5
21. 14-Oxo-3,7,18-dolabellatriene	"		5
22. 3,4-Epoxy-7,18-dolabelladiene	"		5
23.			5
24. (7S,8S)-Epoxy-13-keto-(1S,11R)-dolabell-3E,12(18)-diene	Eunicea calyculata		6

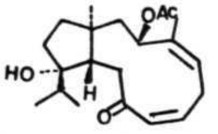
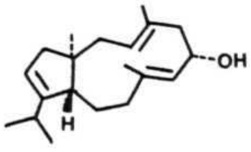
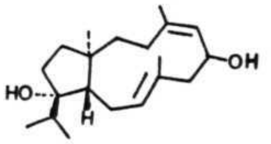
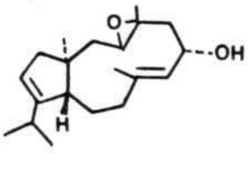
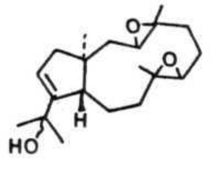
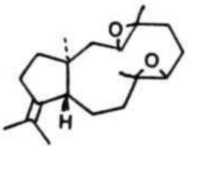
25. 13-Keto-1S,11R-dolabell-3E,7E,12(18)-triene	"		6
26. (1R,2E,4S,7R,8R,10R,11R,12S)-10,18-Dihydroxy-7,8-epoxy-dolabell-2-ene	Aplysia dactylomela		7
27. (1R,2E,4S,5R,6S,7E,10S,11S,12R)-5,6-Diacetoxy-10,18-dihydroxy-2,7-dolabelladiene	Dilophus fasciola	 $R_1=R_2=H$	8
28. (1R,2E,4S,5R,6S,7E,10S,11S,12R)-5,6,10-Triacetoxy-18-hydroxy-2,7-dolabelladiene	"	$R_1=Ac$, $R_2=H$	8
29. (1R,2E,4S,5R,6S,7E,10S,11S,12R)-5,6,10,18-Tetraacetoxy-2,7-dolabelladiene	"	$R_1=R_2=Ac$	8
30. (3R)-Acetoxy-16-hydroxy-(1S,11R,12S)-dolabell-(4E.8E,18)-triene	Dictyota sp.	 $R_1=Ac$, $R_2=CH_2OH$	9

31. (3R,16)-Dihydroxy-(1S,11R,12S)-dolabell-(4E,8E,18)-triene	"	R_1=OH, R_2=CH_2OH	9
32. (3R)-Acetoxy-(1S,11R,12S)-dolabell-(4Z,8E,18)-triene-16-al	"	R_1=Ac, R_2=CHO	9
33. (3S)-Hydroxy-(1R,11S,12R)-dolabell-(4E,8E,18)-triene	Dictyota sp.	R_1=OH, R_2=CH_3	10
34. (16)-Hydroxy-(1R,11S,12R)-dolabell-(4E,8E,18)-triene	"	R_1=H, R_2=CH_2OH	10
35. (1R,11S,12R)-Dolabell-(4Z,8E,18)-trien-16-al	"	R_1=H, R_2=CHO	10
36.	"	R_1=OH, R_2=OAc	11
37.	"		11
38. (1R,6R,11R,12R)-6-Acetoxy-12-hydroxydolabella-(3E,7E)-diene	Odontoschisma denudatum		12
39.	Dictyota species		13

40. (10R,18)-Diacetoxy-(3S,4S;7S,8S)-diepoxydolabelladiene	Barbilophozia floerkei	 R= β OAc, R'=Ac	14
41. (18)-Acetoxy-(3S,4S;7S,8S)-diepoxydolabellane	"	R=H_2, R'=Ac	14
42. (10R,18)-Diacetoxy-3S,4S-epoxydolabell-7E-ene	"		14
43. (18)-Hydroxydolabell-7E-en-3-one	"		14
44. (1S,2E,4R,7Z,11S,12S)-4,12-Dihydroxydolabella-2,7-dien-9-one	Dictyota dichotoma		15
45. (1S,2E,4R,7E,11S,12S)-4,12-Dihydroxydolabella-2,7-dien-9-one	"		15
46. (1S,3E,7E,11S,12S)-12-Hydroxydolabella-3,7-dien-9-one	"	 R=H	15

47.	(1R,2R,3E,7E,11S,12S)-2-Acetoxy-12-hydroxydolabella-3,7-dien-9-one	"	R = OAc	15
48.	(1S,3E,7Z,11S,12S)-12-Hydroxydolabella-3,7-dien-9-one	"		15
49.	(1S,2E,4R,6Z,11S,12S)-4,12-Dihydroxydolabella-2,6-dien-9-one	"		15
50.	(1S,3E,6Z,11S,12S)-12-Hydroxydolabella-3,6-dien-9-one	"		15
51.	(1S,3S,4R,7E,11S,12S)-3,4-Epoxy-12-hydroxy dolabella-7-en-9-one	"		15
52.	(1S,3E,7R,8R,11S,12S)-7,8-Epoxy-12-hydroxy dolabella-3-en-9-one	"		15
53.	(1R,3E,7E,9S,11S)-9-Acetoxydolabella-3,7,12-trien-16-al	"	 R=CHO	15

54. (1R,3E,7E,9S,11S)-9-Acetoxydolabella-3,7,12-trien-16-oic acid	"	R=COOH	15
55. (1S,3E,11S,12S)-9-Acetoxy-7,8-epoxy dolabella-3-en-12-ol	"		15
56. (1R,6R,11R,12R)-6,12-Dihydroxy dolabella-3E,7E-diene	Odontoschisma denudatum	 R=R'= H	16
57. (1R,6R,11R,12R)-6-Acetoxy-12,16-dihydroxy dolabella-3E,7E-diene	"	R=OH, R'=Ac	16
58. (1R,6R,11R,12R)-6,16-Diacetoxy-12-hydroxy dolabella-3E,7E-diene	"	R=OAc , R'=Ac	16
59. (1R,3S,4S,6R,11R,12R)-6-Acetoxy-3,4-epoxy-12-hydroxy dolabella-7E-en-16-al	"		16
60. (1S,3R,4Z,7E,11S,12S)-3-Acetoxy-12-hydroxy dolabella-4,7-diene-9-one	Dictyota bartyriciana		17

61. (1S,3R,4Z,7Z,11S,12S)-3-Acetoxy-12-hydroxy dolabella-4,7-dien-9-one	"		17
62. (1R,3E,6S,7E,11S)-6-Hydroxy dolabella-3,7,12-triene	Dictyota species		17
63. (1R,11S,12S)-6,12,-Dihydroxy dolabella-4(E/Z),8(E/Z)-diene	"		17
64. (1S,6S,7E,11S)-3,4-Epoxy dolabella-7,12-dien-6-ol	"		17
65. (1S,11S)-3,4;7,8-Diepoxy-dolabella-12-en-18-ol	"		17
66. (1S,11S)-3,4;7,8-Diepoxy-dolabella-12(18)-ene	"		17

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Chapter IV

Model Studies Towards Fusicoccane diterpenes: Construction of the 5,8,5-Fused Tricarbocyclic Ring System

IV.1. ABSTRACT

A new stereocontrolled approach to cis,anti,cis-5,8,5- tricarbocyclic ring system from 5,5,5,5-fused tetraquinenes is delineated. The basic concept in this approach is the recognition of a bicyclo[3.3.0]oct-1(5)-ene moiety as a masked cyclooctane-1,5-dione equivalent, Scheme IV. 1. Thus, a C_{14}-tetraquinene 14 emerged as the equivalent of a 5,8,5- fused system, Scheme IV.3 and was readily obtained from simple building blocks, cyclopentyl chloride and bicyclo[3.3.0]octan-2-carboxaldehyde 19 employing Nazarov cyclisation as a key step, Scheme IV.7. Oxidation of 14 with RuO_2-$NaIO_4$ furnished the desired C_{14}-5,8,5-dione 15 in excellent yield. The same strategy was further extended towards the enantioselective construction of the fusicoccane framework.

For this purpose, the chiron (-)-42, readily obtained from R-(+)-limonene 43, Scheme IV.11 was coupled with 3-bromobicyclo[3.3.0]octane in the presence of lithium in a Barbier-type of reaction to furnish allylic alcohol 46, Scheme IV.13. Barium manganate oxidation of 46 furnished the enone 47 which was converted in to cross-conjugated dienone 49 through bromination-dehydrobromination sequence. Nazarov cyclisation of 49 afforded tetraquinane based enone 51. Thioacetalisation-reductive desulphurisation on 51 furnished the C_{18}-tetraquinene 53, Scheme IV.14. Oxidation with RuO_2-$NaIO_4$ furnished the tricyclic C_{18}-dione (+)-54 bearing the 5,8,5- skeleton present in fusicoccanes.

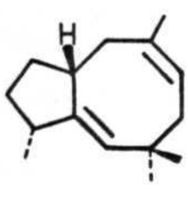
IV.2. OBJECTIVE AND BACKGROUND

The eight membered ring is the newest entrant into the diverse assemblage of carbocyclic rings present among isoprenoid natural products. In the recent past, the number of terpene carbon frameworks is which a cyclooctane ring is present as a part of condensed or bridged polycyclic system have proliferated rapidly. The cyclooctane bearing carbon frameworks have now been located among C_{15} - sesqui-, C_{20}-di- and C_{25}-sesterterpenes. Currently, nearly sixty natural products compose the structurally novel and complex family of cyclooctanoid natural products.[1]

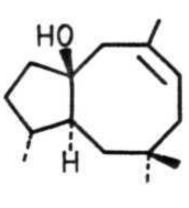
The eight membered ring bearing natural products are fairly widely distributed in Nature and have been encountered in terrestrial plants, marine organisms, pathogenic fungi and insects. These natural products are derived through interesting biosynthetic pathways and many of them exhibit promising biological active profile.

Among the more interesting carbocyclic variations that have surfaced in recent years embodying an eight membered ring are the uncommon 5,8- and 5,8,5- fused ring systems. Indeed, an eight membered ring shows an intriguing predilection towards partnering a five membered ring. Three sesquiterpenoids of marine origin, precapnelladiene 1,[2] dactylol 2[3] and asteriscanolide 3[4] are examples of 5,8-fused cyclopentacycloctane nucleus, Chart IV.1. The diterpenoids basmenone 4[5] from tobacco, cycloaraneosene 5[6] from a fungus and epoxydictymene 6[7] from a brown alga are based on the more intricate 5,8,5-assembly. Sesterterpenoids ophiobolins (eg. ophiobolin. H 7)[8] and ceroplastols (eg. ceroplastic acid 8[9]) also incorporates the 5,8,5 system.

CHART IV.1



1



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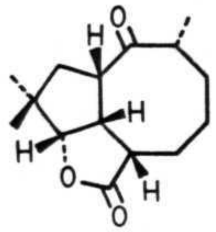

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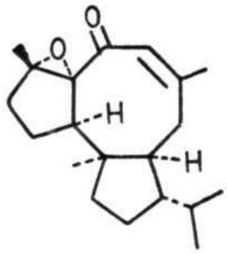

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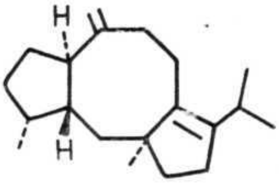

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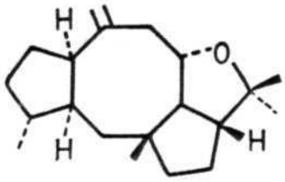

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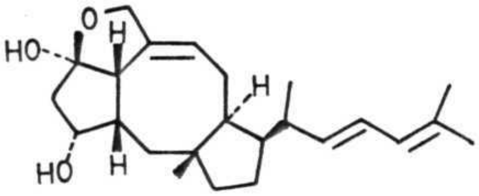

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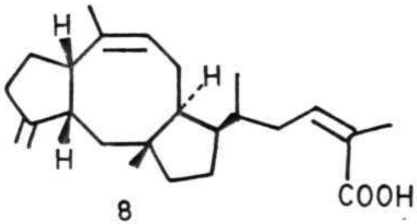

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The cyclooctanoid terpenes bearing 5,8- and 5,8,5-ring system pose considerable synthetic challenge due to the presence of uncommon assembly of carbocyclic rings, many stereogenic centres and complex functionalisation patterns. Synthetic quest for them presents a combination of unique synthetic problems. First of all, because of unfavourable entropic factors, commonly used method of ring formation are not conducive for the construction of cyclooctanes and new methodologies nead to be developed for their creation. Secondly, cyclooctanes displayed marked propensity towards transannular reaction and therefore synthetic manipulations on them have to be effected with marked/latent functionalities. Lastly, eight membered ring and its fused systems are conformationally flexible and therefore prediction and control of stereochemistry is rendered uncertain. This is a major problem in stereoselective synthesis as many of the cyclooctanoid natural products contain remote methyl group bearing stereogenic centres.

Largely, on account of the factors mentioned above, progress towards the total synthesis of cyclooctanoid natural products has been relatively slow. Dutta in 1976 was the first to describe an attempt towards the construction of the 5,8,5-ring system.[10] This was followed by several other approaches for the realisation of 5,8- and 5,8,5-carbocyclic systems. However, it was in 1984 that the first synthesis of cyclooctanoid terpenes appeared in literature.[11] Almost simultaneously, Mehta[12] (precapnelladiene 1), Paquette[13] (precapnelladiene 1) and Gadwood[14] (dactylol 2) described the total synthesis of 5,8-fused bicyclic natural products. More recently, Wender[15] has achieved the synthesis of the novel 5,8-fused natural product asteriscanolide 3.

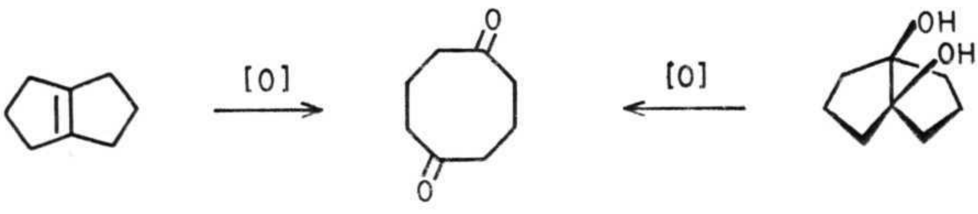
In the meantime, synthetic efforts towards the construction of fused cyclooctanoid systems are continuing with much vigour.[16] Up-to-date references to these studies have been provided. So far, only Takeshita's group has succeeded in the total synthesis of 5,8,5 - natural products. His efforts have culminated in the synthesis of cycloaraneosene 5[17a] in 1986 and ceroplastic acid 8[17b] in 1988. Our own efforts in the area, leading to the construction of 5,8,5-ring systems were completed in 1985 and reported in 1986.[18]

For reasons delineated earlier the natural products based on 5,8,5-fused ring system appeared to us attractive and challenging targets of synthesis. To begin with our prime concern was to develop a general and flexible methodology for the construction of the basic 5,8,5-carbocyclic framework of well defined stereochemistry and substitution pattern. Efforts directed towards the successful realisation of this objective are described below.

IV.3. STRATEGY AND MODEL STUDIES

It was recognised, at the very outset that the main problem in constructing the 5,8,5-ring system resides in the formation of the eight membered ring and control of the stereochemistry on the flexible 5,8- and 5,8,5-ring systems. A solution therefore lay in designing a rigid substrate which is a cyclooctane equivalent and exhibits definite stereochemical preference in its reactivity. At the conceptual level, the bicyclo[3.3.0]octane ring system appeared to be an ideal and versatile cyclooctane equivalent. Oxidative or equivalent cleavage of the central bond in the bicyclic system (9 → 10 and 11 → 10) would furnish the functionalised cyclooctane ring, Scheme IV.1. More importantly, the

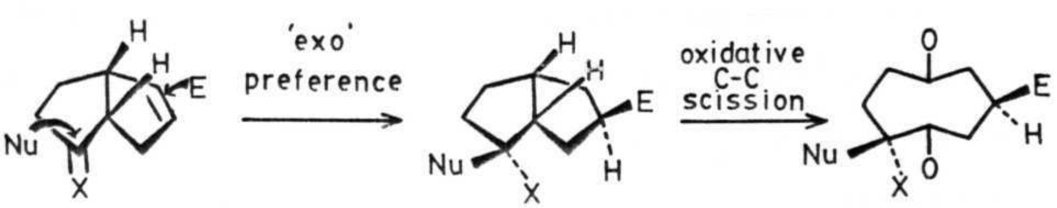
SCHEME IV.1



9 10 11

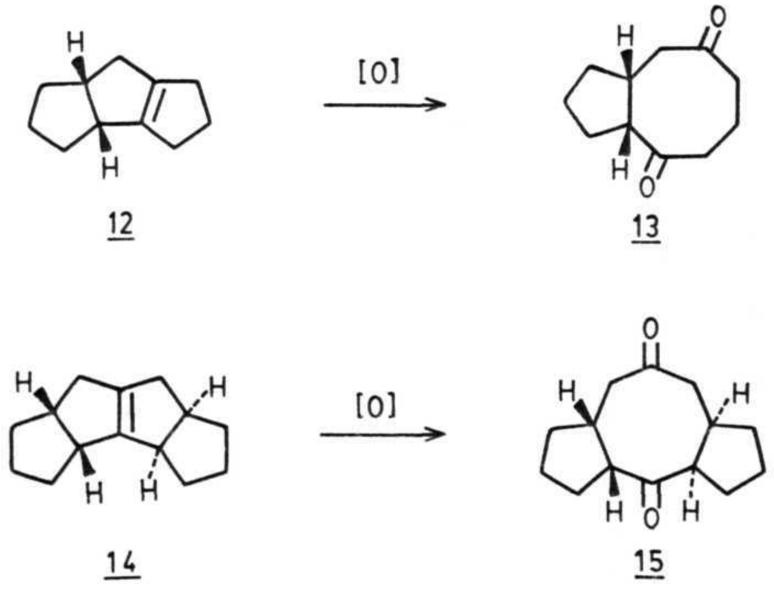
spacial geometry of the cis-fused bicyclo[3.3.0]octane imparts its preferential reactivity on the exo-face (convex surface). Thus, in principle the requisite stereochemical features of the eight membered ring can be built into the bicyclic frame, Scheme IV.2.

SCHEME IV.2



The strategic theme of our 5,8,5-approach emerged from the extension of Scheme IV.1. If 5,5-fused bicyclic system is equivalent to an eight membered ring, then a 5,5,5-fused system should be equivalent to a 5,8-ring system (12 → 13) and 5,5,5,5-fused system should be equivalent of a 5,8,5-fused system (14 → 15), Scheme IV.3. Since polyquinanes prefer the

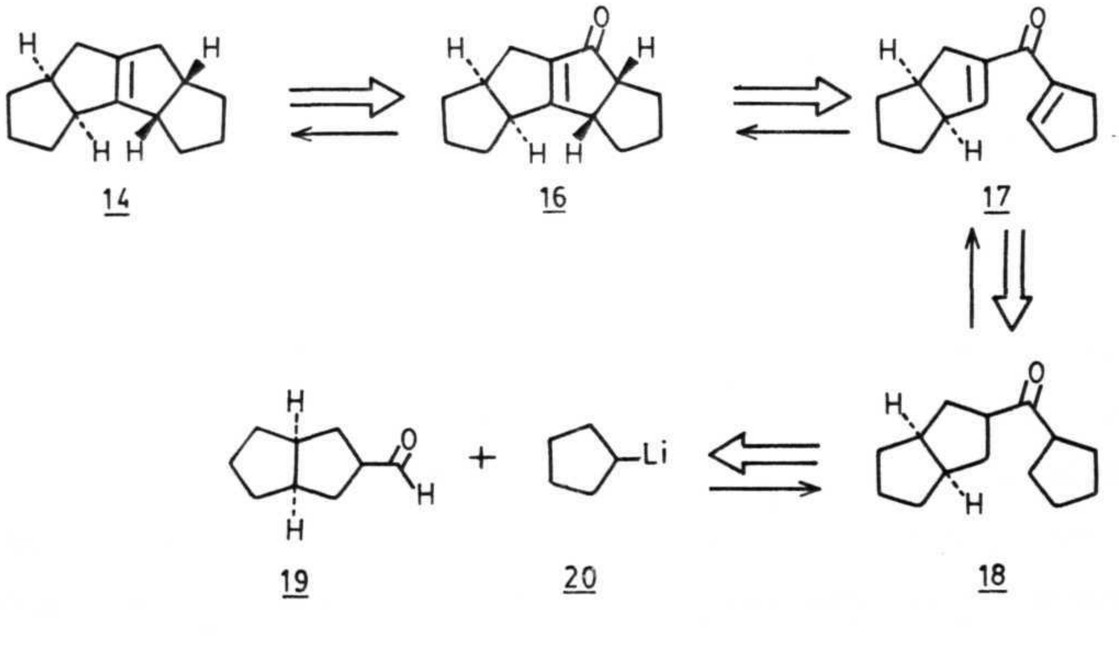
SCHEME IV.3



stable *cis*, *anti*, *cis*-type ring fusion pattern and exhibit *exo*-selectivity, these stereochemical controls can be transcribed from them into the dicyclopenta[a,d]cyclooctane system during the unravelling oxidative step. Therefore, the design of tetraquinene 14 became our first objective and a new approach was envisaged towards this end.

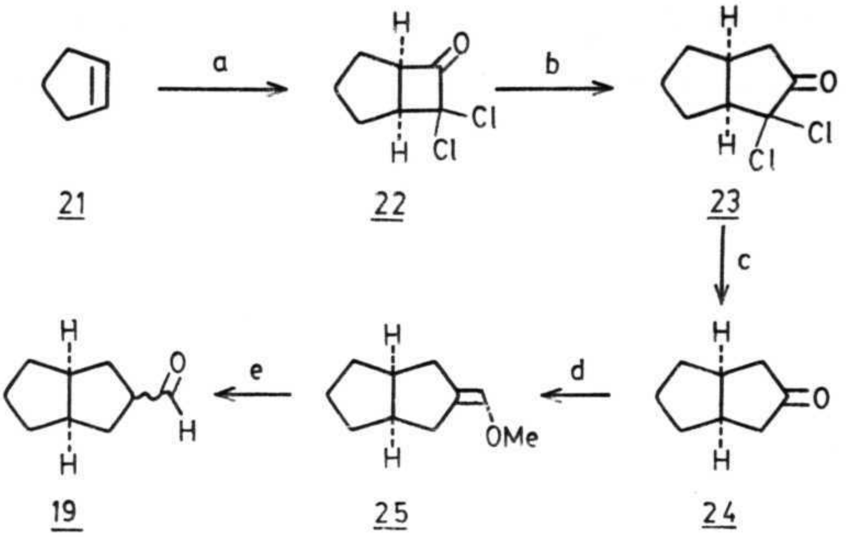
Prior to the present work only few synthetic entries into the C_{14}-tetraquinane system had been recorded in the literature[19] and none of these was particularly suitable for the synthesis of 14. Hence, a new reaction sequence for the construction of this linearly fused tetraquinene 14 was conceived based on the retrosynthetic analysis, in which a Nazarov cyclisation on 17 to give 16 was contemplated as the pivotal step. Efforts were immediately initiated to build the tetraquinene 14 as per the theme indicated in Scheme IV.4.

SCHEME IV.4



The required bicyclo[3.3.0]octane-2-carboxaldehyde 19[20] synthon was prepared as shown in Scheme IV.5. Cyclopentene was cyclopentannulated following the dichloroketene addition-diazomethane ring expansion-dechlorination methodology of Greene[21] to furnish bicyclo[3.3.0]]octan-3-one 24.[22]

SCHEME IV.5

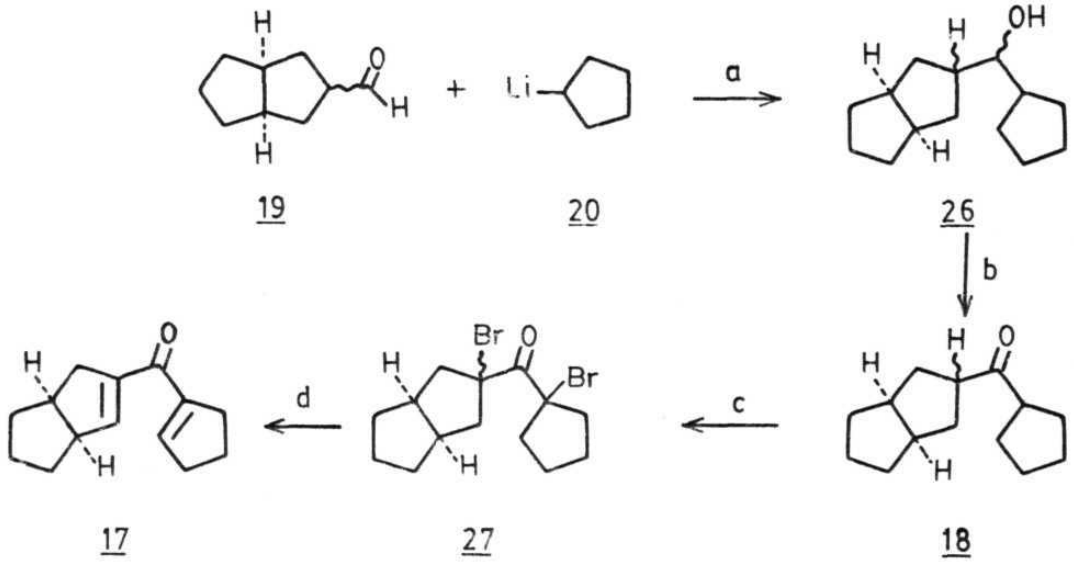


Reagents, Conditions & Yields: a) Cl_3COCl, Zn-Cu, Ether,12h; b) CH_2N_2, MeOH, Ether, 5^oC; c) Zn,CH_3COOH, RT, 55% from 21; d) $Ph_3P^+CH_2OCH_3Cl$, Ether, Na-t-amyloxide, RT, 1h; e) Cat.35%, $HClO_4$,Ether, 82% from 24.

Reaction of the bicyclic ketone 24 with the ylide derived from methoxy methyl triphenyl phosphonium chloride and sodium-t-amyloxide gave the enol ether 25 which was directly hydrolysed with 35% perchloric acid to afford aldehyde 19 in 82% yield. Although at this state the aldehyde 19 was a mixture of both exo- and endo isomers, we proceeded further without recourse to any separation since in subsequent steps the C(3)-stereogenic centre was going to be destroyed. The gross structure of 19 was fully commensurate with its IR and ^{1}H-NMR data (vide experimental).

The two pieces 19 and 20 identified in Scheme IV.4 were now put together. Ultrasound promoted condensation of cyclopentyllithium 20 and aldehyde 19 furnished a mixture of epimeric alcohols 26 in 35% yield, Scheme IV.6. This alcoholic mixture 26 was directly subjected to PCC oxidation to afford the epimeric ketones 18 (ν_{max} 1700 cm^{-1}) in 85% yield. This epimeric mixture of ketones 18 was transformed into a single dienone

SCHEME IV.6



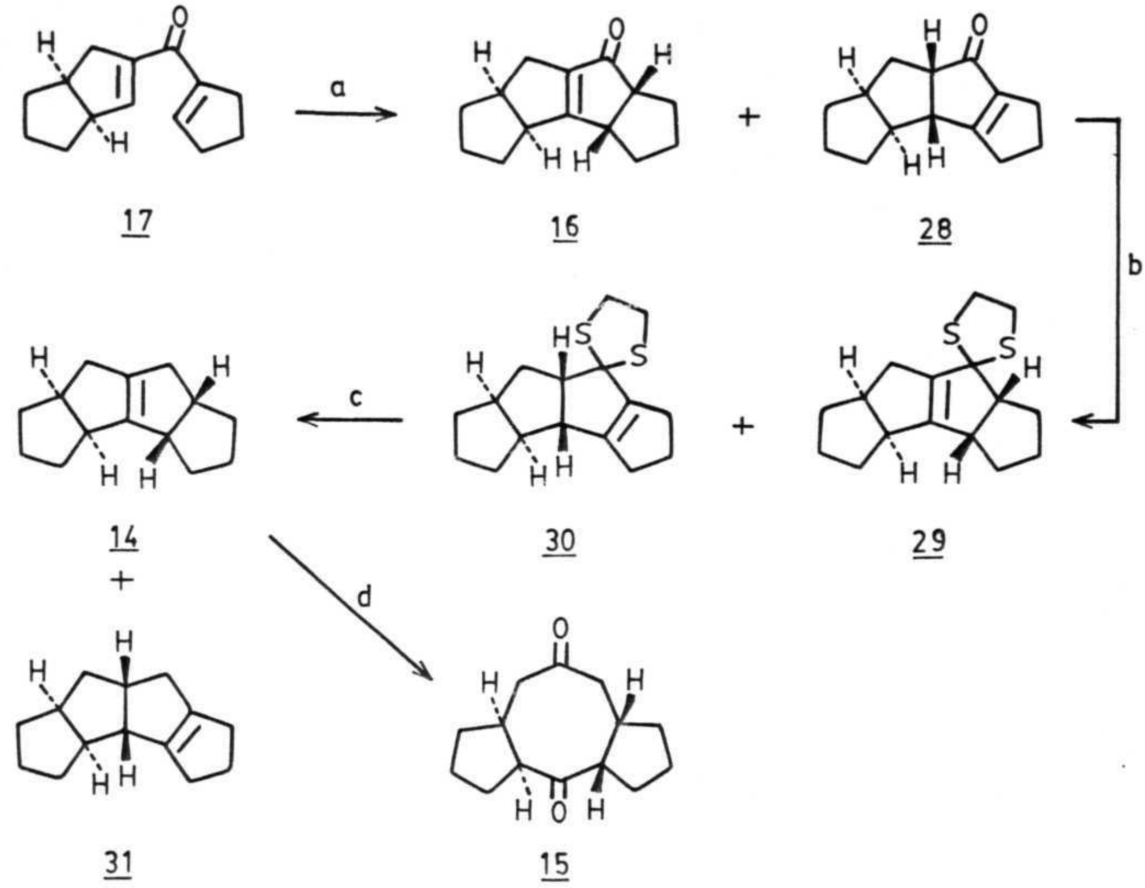
Reagents, conditions & yields: a) THF,))), RT, 10 min, 35%; b) PCC, DCM, 4 A^{o} molecular sieves, RT, 2h, 85%; c) Br_2, CCl_4, 15h, RT, 91%; d) Li_2CO_3-LiBr, DMF, 80^{o}C, 4h, 80%.

17 through a classical protocol. Addition of bromine to 18 resulted in the formation of α, α,dibrominated product 27 in 91% yield. The dibromide 27 was directly double dehydrobrominated in the presence of Li_2CO_3-LiBr in DMF to furnish the dienone 17 in 80% yield. The ν_{max} 1610 cm^{-1} in its IR spectrum, the presence of signals at δ 6.6 & 6.4 due to two β-olefinic protons of the enone moiety and the resonances at δ 190.6, 145.6, 144.7, 142.9, 141.6, in its ^{13}C-NMR firmly confirmed the structure of this key product 17, Scheme IV.6.

The dienone 17 was now well set for a Nazarov cyclisation. Heating the dienone 17 in PPA at $100^{o}C$ resulted in the expected cyclisation and a 4:1 mixture of tetraquinane-based enones 16 and 28 in a combined yield of 60% was realised, Scheme IV.7. The two enones were not separable by column chromatography or preparative tlc but some separation could be effected by MPLC. However, only the major isomer 16 was obtained pure and was characterised. The presence of ^{13}C-resonances δ 207.3, 190.2, 147.6 in its ^{13}C-NMR (Fig. IV.1) characteristic of a tetrasubstituted cyclopentenone moiety confirmed the structure of 16. Since these two enones were not readily separable, the mixture was carried through for the next deoxygenation step.

The enone mixture of 16 and 28 was converted into the corresponding thioacetals 29 & 30 (87%) and subjected to Na-Liq.NH_3 reduction to furnish a mixture of tetracyclic olefins 14 & 31, Scheme IV.7. As anticipated by by us the two olefins were now readily separable on $AgNO_3$-SiO_2 gel and both both of them were now fully characterised. The required C_{14}-tetraquinene hydrocarbon 14 of C_2-symmetry exhibited the expected 8-line ^{13}C-NMR

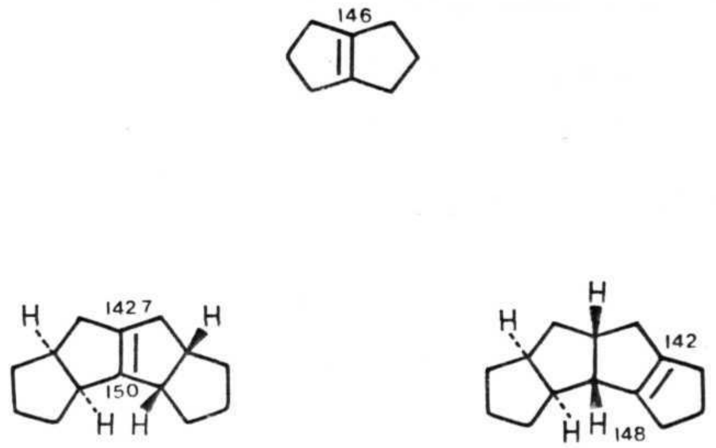
SCHEME IV.7



Reagents, conditions & yields: a) PPA, 100^{o}C, 1h, 60%; b) $HSCH_2CH_2SH$, PTS-C_6H_6, Δ , 0.5h, 87%; c) Li.Liq.NH_3, Na, 74%; d) RuO_2, $NaIO_4$, CCl_4-MeCN-H_2O, RT, 1h, 92%.

spectrum (Fig.IV.2) with diagnostic resonances at δ 150.2, 142.7, 47.4, 45.4, 37.6, 35.9, 30.2, 26.1. On the other hand the other minor tetraquinene hydrocarbon 31 had 14-resonances in its ^{13}C-NMR (Fig.IV.3), which confirmed its unsymmetrical structure. It is interesting to compare the characteristic ^{13}C-NMR chemical shifts of the bridgehead sp^2 carbon atoms in the polyquinanes displayed in Chart IV.2.[24]

CHART IV.2

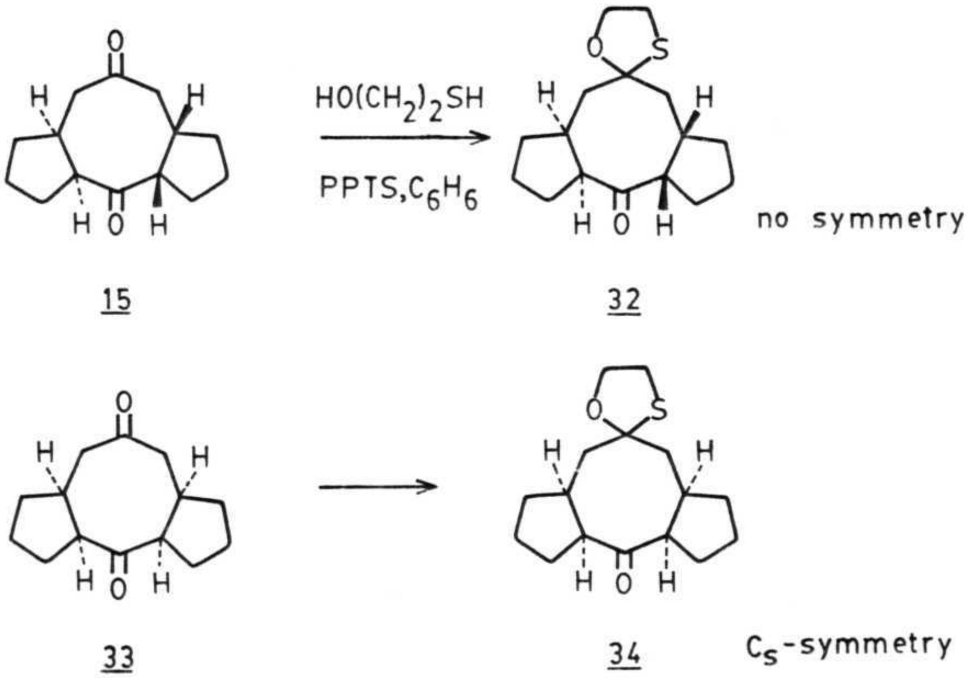


The required symmetrical tetraquinene 14 was oxidised with RuO_2-$NaIO_4$ according to the procedure of Sharpless[25] to furnish the crystalline 5,8,5-tricarbocyclic dione 15 in 92% yield. The ν_{max} 1680 cm^{-1} and 8-line ^{13}C-NMR spectrum (Fig. IV.4) with signals at δ 216.01, 211.8, 53.6, 45.0, 40.5, 33.9, 28.0, 24.0 were fully consonant with its structure. While the gross structure of 15 was fully secured, we had so far not addressed ourselves to the stereochemical question in 15 as well as its precursor tetraquinene 14. Although it is known that in polyquinanes the cis, anti, cis- stereochemistry is thermodynamically more stable, and it might have been generated during Nazarov cyclisation step, it needed to be established unambiguously.

The structure of 15 was secured through an interesting experiment. Dione 15 was readily and regioselectively transformed to the mono-1,3-

oxathiolane derivative 32 on treatment with 2-mercaptoethanol in the presence of PPTS. The ^{13}C-NMR of 32 was devoid of any symmetry and exhibited a 16-line spectrum (Fig. IV.5) which showed that 32 has *cis*, *anti*, *cis* ring fusion with C_2-symmetry, Scheme IV.8. If the ring junction had been *cis*, *syn*, *cis*-33 then the resulting mono-1,3-oxa thiolane 34 would have exhibited a 10-line spectrum due to C_s-symmetry. This result conclusively rules out *cis*, *syn*, *cis*-structure for 15 and establishes it and its tetraquinene precursor 14 as having *cis*, *anti*, *cis*-stereochemistry.

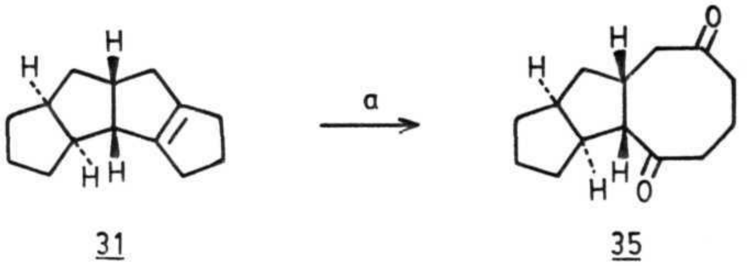
SCHEME IV.8



The isomeric olefin 31 was like-wise oxidised with RuO_2-$NaIO_4$ to furnish the interesting ring system 35 in 92% yield, Scheme IV.9. Once again the presence of ν_{max} 1680 cm^{-1} in its IR and resonances at δ 213.8 and 212.9 corresponding to two carbonyl groups in its ^{13}C-NMR spectrum

(Fig. IV. 6) confirmed the structure of the dione 35. The stereochemistry of the ring junction was assigned as cis, anti, cis on the basis of previous analogy.

SCHEME IV.9



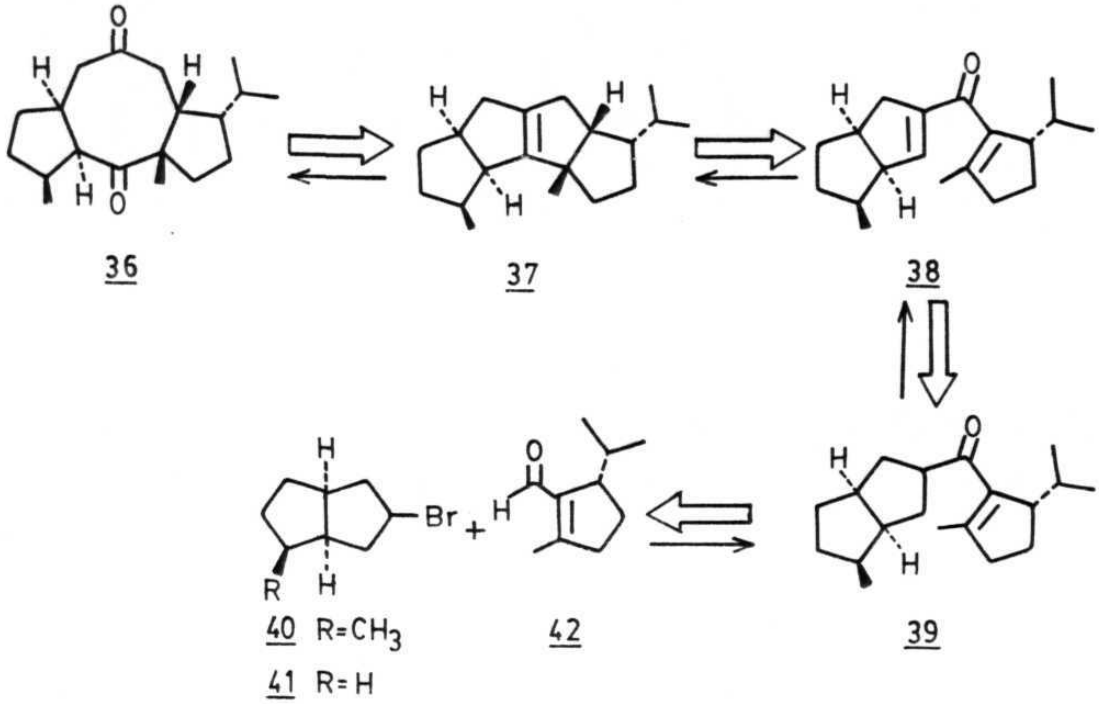
Reagents, Conditions & Yields: a) RuO_2, $NaIO_4$, CCl_4-MeCN-H_2O, 92%.

Having established a viable methodology for the construction of the 5,8,5- dione 15 employing a model tetraquinene 14, we ventured to amplify the scope of this theme for the construction of the carbocyclic framework of fusicoccane diterpenes.

IV.4. SYNTHESIS: Towards the Enantioselective Construction of the Fusicoccane Framework

Construction of the functionalised fusicoccane framework 36 following the 5,5,5,5 → 5,8,5 strategy demonstrated above required the generation of the appropriately substituted tetraquinene 37. The tetraquinene 37, in turn could be assembled through a pivotal Nazarov cyclisation as indicated in the retrosynthetic Scheme IV.10. Thus, 40 and 42 were indicated as two

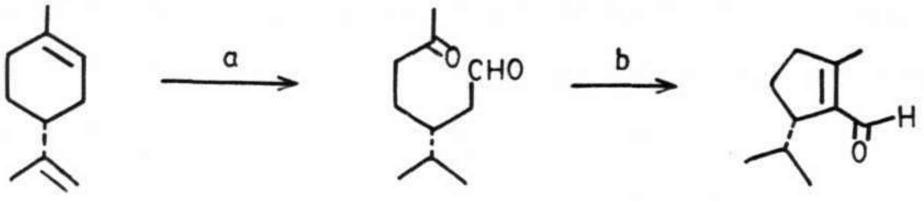
SCHEME IV.10



starting synthons. An advantage of this theme was that employing a chiron 42 an enantioselective approach to the tricyclic fusicoccane framework 36 could be developed. We therefore decided to put in practice the retrosynthetic theme shown in Scheme IV.10. However, in order to avoid regeochemical problems, we decided to employ 3-bromobicyclo[3.3.0]]octane 41 instead of its methyl substituted derivative 40.

Of the two pieces, chiron 42 ([α]$_D$-7.9 ; c.1.0, $CHCl_3$) was readily prepared from R-(+)-limonene 43 as shown in Scheme IV.11. Experimental details about its preparation have been described earlier in the first

SCHEME IV.11

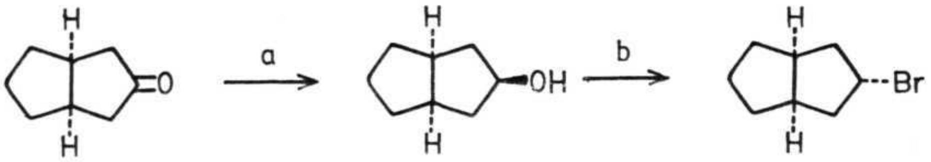


43 44 42

Reagents, Conditions & Yields: a) i. m-CPBA, $CHCl_3$; ii. 1% H_2SO_4, THF-H_2O; iii. $NaIO_4$, THF-H_2O; iv. PtO_2, EtOAc, H_2, 20 psi; b) CH_3COOH, Piperidine, benzene.

chapter of this thesis. The other piece, the exo-3-bromobicyclo[3.3.0]octane 41[26] was prepared from bicyclo[3.3.0]octan-3-one 24 as shown in Scheme IV.12.

SCHEME IV.12



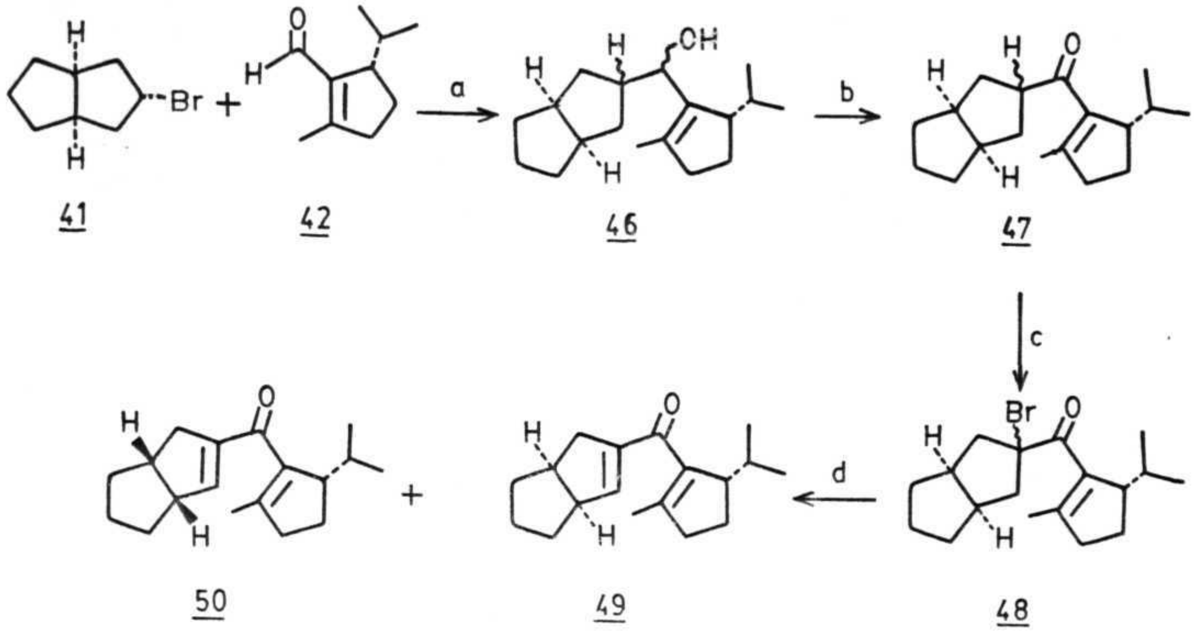
24 45 41

Reagents, Conditions & Yields: a) LAH, ether, RT, 1h, 80%; b) PBr_3, 0°C, 1h, quantitative.

Barbier-type reaction between chiral enal 42 and bromide 41 in the presence of lithium chips and under ultrasound irradiation led to the formation of diastereomeric mixture of allylic alcohols 46 in 40% yield, Scheme IV.13. Oxidation of this mixture of alcohols 46 was attempted with many oxidising agents like PCC, PDC, MnO_2 etc., but none of them gave the required enone 47. Only uncharacterisable complex mixtures were obtained in the reactions. However, this problem could be overcome by employing barium manganate[27] as the oxidising agent which clearly gave the enone 47 (60:40) in 55% yield, as a mixture of diastereomers. Separation of stereoisomers was considered unnecessary at this stage. Carefully controlled mono-bromination α to the carbonyl group in 47 with 2,4,4,6-tetrabromocyclohexa-2,5-dienone[28] gave the bromo-enone 48 which was directly subjected to dehydrobromination with Li_2CO_3-LiBr in DMF to furnish dienones 49 & 50 (1:1) in 26% yield. The IR spectrum (ν_{max} 1620 cm^{-1}) and the presence of ^1H-NMR resonances at δ 6.4 and δ 1.8 due to the β-proton and β-methyl groups of the two enone moieties confirmed its structure, Scheme IV.13.

The stage was now set for the Nazarov cyclisation step. However, the conditions employed earlier for the Nazarov-type cyclisation (PPA, 100^oC) failed to effect the cyclisation in this case. Recourse to P_2O_5, methane sulphonic acid, BF_3-etherate, $SnCl_4$ etc. did not prove encouraging. After many trials, it was obsereved that PTS effected the desired cyclisation but in poor (20%) yield. Thus, exposure of 49 & 50 to PTS in refluxing toluene

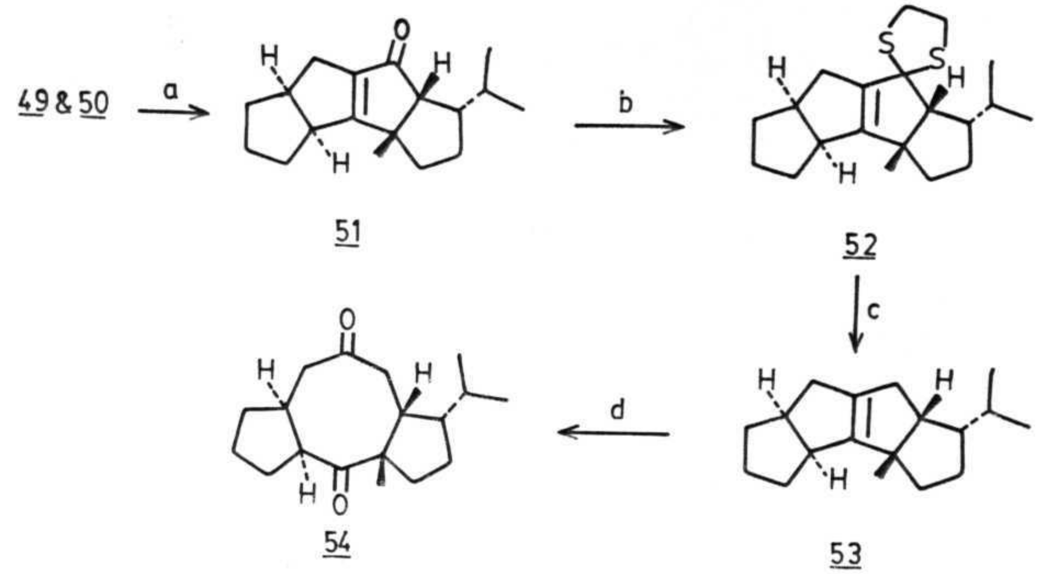
SCHEME IV.13



Reagents, Conditions & Yields: a) Li, THF,))), 0-10^{0}C, 1h, 40%; b) $BaMnO_4$, DCM, 15h, RT, 55%; c) 2,4,4,6-tetrabromocyclohexa-2,5-dienone, cat.HCl(gas), ether, RT, 12h; d) Li_2CO_3-LiBr, DMF, 80^{0}C, 2h, 26% from 47.

provided the required tetracyclic enone 51, surprisingly as a single stereoisomer Scheme IV.14. This was a fortuitous outcome in same sense as it avoided the difficulty in separation but it did render the stereochemical assigned somewhat difficult. The structure of enone 51 was clearly indicated by its IR (ν_{max} 1700, 1640 cm^{-1}), ^{1}H-NMR (δ 1.24 (3H, s), 0.97 (3H, d) and 0.88 (3H, d), Fig. IV.7) and ^{13}C-NMR (Fig. IV.8) spectrum. However, delineation of its stereochemistry presented some difficulties. Since 51 is formed from 49 during thermodynamically controlled conditions, a more stable cis, anti, cis stereochemistry for the

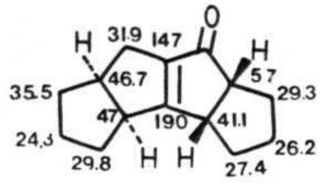
SCHEME IV.14



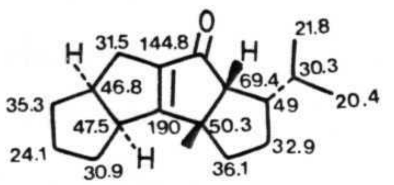
Reagents, Conditions & Yields: a) PTS, toluene, 2h, 20%; b) HS-CH_2CH_2SH, PTS, C_6H_6, Δ ; c) Li-Liq.NH_3, Na; d) RuO_2, $NaIO_4$, CCl-MeCN-H_2O, 0.5, RT, 82%.

polyquinane fusion appears reasonable. Stereochemistry to the C(6)-isopropyl group is based on the comparison of ^{13}C-NMR chemical shifts between enone 51 and the enone 16 and model compounds[24] 55, 56 & 57 as shown in Chart IV.3. However, this stereochemical assignment should be regarded as only tentative.

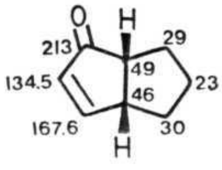
CHART IV.3



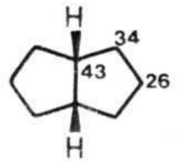
16



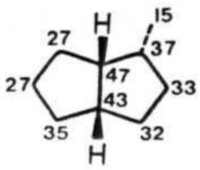
51



55



56

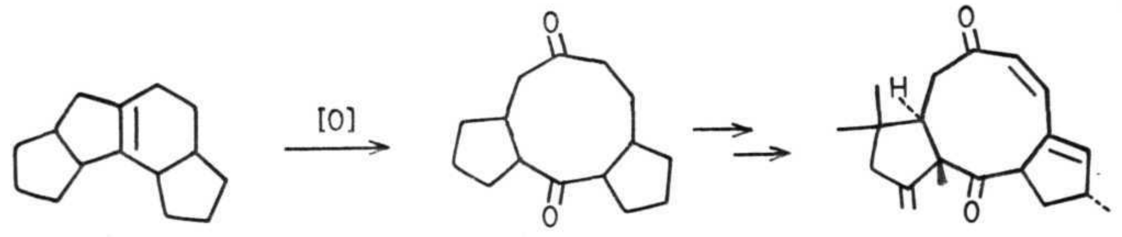


57

The enone 51 was now prepared for the cyclooctane revelation protocol. Deoxygenation of 51 via thioacetalisation-desulphurisation sequence gave the labile olefin 53 which was directly subjected to RuO_2-$NaIO_4$ oxidation to furnish the crystalline (+)-dione 54 ($[\alpha]_D$ + 15 ;c 0.1 $CHCl_3$) in 82% yield Scheme IV.14. The structure of dione 54 was fully secured through its IR (ν_{max} 1680 cm^{-1}) and ^1H-NMR spectrum (Fig. IV.9) which exhibited methyl signals at δ 1.25 (3H, s), 1.0 (3H, d), 0.87 (3H, d). Thus, tricyclic C_{18}-dione 54 bearing the basic carbon skeleton of fusicoccanes and having desirable functionalisation in the eight membered ring became available from readily available building blocks.

IV.5. SUMMARY AND OUTLOOK

A short and general approach to functionalised *cis*, *anti*, *cis* 5,8,5-fused ring system 15 from the readily available bicyclo-[3.3.0]octan-3-one 24 has been developed *via* the novel tetraquinene hydrocarbon 14. A similar 5,5,5,5 → 5,8,5 methodology has been applied for the enantioselective construction of the fusicoccane carbon skeleton 54 employing the chiron (-)-42. The general protocol delineated here has built-in flexibility and can be readily adapted for the synthesis of ophiobolins and other 5,8,5-fused systems. The concept of using bicyclo[3.3.0]octene 9 as a cyclooctane dione equivalent can be extended to higher homologues and exploited for related complex syntheses. For example, homologue 58 of tetraquinene 14 can generate a 5,9,5-system 59 present in biologically important natural product jatrophatrione 60.[29]



58 59 60

IV.6. EXPERIMENTAL

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

cis-Bicyclo[3.3.0]octan-8-one (24):[22]

Into a 500 ml three necked RB flask fitted with a dry N_2 inlet, an addition funnel and mercury seal was placed cyclopentene (10 g, 0.15 mol) in dry ether (250 ml). To this activated Zn-Cu couple (19.5 g, 0.3 mol) was added followed by trichloroacetyl chloride (17.7 ml, 0.18 mol) through an addition funnel over a period of 1 h. After the addition was over the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water (100 ml) and the organic layer was separated. The aqueous layer was once again extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude bicyclic dichloroketone 22 (20 g) which was directly used for the next step.

To a solution of above crude bicyclic dichloroketone 22 (10 g,60mmol) in ether (100 ml) catalytic amount of methanol (1 ml) was added followed by an ethereal solution of diazomethane prepared by treating nitrosomethyl urea with KOH. The reaction mixture was kept at 5°C for 1 h and excess diazomethane was destroyed with a few drops of acetic acid. Removal of the solvent furnished the crude ring expanded dichloroketone 23 (12 g) which was used as such for the next reaction.

Into a 100 ml RB flask the above crude bicyclic dichloroketone 23 (10 g, 57.0 mmol) was placed in acetic acid (50 ml) and cooled in an ice-bath.

To this zinc (4.0 g, 60.0 mmol) was added in small portions and the reaction mixture was stirred for 5 h. Then the reaction mixture was diluted with water (200 ml) and extracted with ether (250 ml x 3). The combined ethereal extract was washed with sat. $NaHCO_3$, water, dried and concentrated to crude product which was distilled at reduced pressure to afford the bicyclo[3.3.0]octan-3-one <u>24</u> (10 g) in 55% yield. The IR and ^1H-NMR data of <u>24</u> was found identical with the reported in the literature.[22]

IR : 1725 cm^{-1}

^1H-NMR : $\delta 3.0 - 2.4$ (4H, m), 2.0 - 1.0 (8H, m)

<u>cis-Bicyclo[3.3.0]octane-3-carboxaldehyde (19)</u>:[20]

Into a 50 ml three necked RB flask fitted with dry N_2 inlet, septum and mercury seal, methoxymethyltriphenylphosphonium chloride (10.3 g, 17.0 mmol) was placed. The solid was suspended in of dry ether (10 ml) and freshly sublimed sodium t-amyloxide (1.87g, 17.0 mmol) in dry ether (5 ml) was added and the resulting dark red reaction mixture was stirred for 45 min at room temperature. To this the bicyclic ketone <u>24</u> (2.0 g, 15.6 mmol) in dry ether (5 ml) was added and the contents were stirred for 1 h. The reaction mixture was quenched by addition of water and extracted with ether (100 ml x 3). The combined ethereal extract was washed, dried and concentrated. The crude enol ether <u>25</u> thus obtained was used as such for the next step.

Into a 50 ml RB flask the above crude enol ether <u>25</u> was placed in ether (25 ml) and cooled in an ice -bath. To this 0.5 ml of 35%

perchloric acid was added and the reaction mixture was stirred for 6 h at room temperature. Then the reaction mixture was diluted with ether and quenched by careful addition of 5% $NaHCO_3$. The ethereal layer was separated and the aqueous layer was once again extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was charged on a silica gel (20 g) column. Elution with pet ether resulted in the removal of triphenylphosphine derived impurities and further elution with 5% ethyl acetate - pet ether furnished the aldehyde 19 (1.81 g,mixture of epimers) in 82% yield. The IR and ^{1}H-NMR spectral values of 19 were found identical with the reported in the literature.[20]

bp. : 110^o/1.0 mm
IR : 2950, 2750, 1750, 1450, 1110 cm^{-1}
^{1}H-NMR : δ9.57 (2H, d, J = 4Hz, O=C-H), 2.8 - 1.0 (m, 26H)

3-cis-Bicyclo[3.3.0]octan-1-cyclopentyl methanol (26):

Into a 50 ml three necked RB flask, fitted with dry N_2 inlet, pressure equalising addition funnel and mercury seal, freshly cut lithium pieces (140 mg, 20.0 mmol) were placed and dry THF (5 ml) was introduced. To this mixture chlorocyclopentane (2.1 g, 15 mmol) in dry THF (5 ml) was slowly added through addition funnel and the reaction was subjected to ultrasound by placing the RB flask in ultrasound generator containing water, where it gives maximum agitation. After all the lithium metal had reacted a solution of the aldehyde (1.5 g,10.5 mmol) in dry THF (5 ml) was slowly added to it and the reaction mixture was sonicated for further 10 min. The reaction mixture was quenched by addition of saturated NH_4Cl solution (50 ml) and extracted with ether (100 ml x 3). The combined organic extract was washed, dried and concentrated to a crude product (1.5 g) which was filtered through a silica gel (10 g) column to furnish the alcohol 26 (760 mg, epimeric mixture) in 35% yield.

bp. : 160^{o}C/0.1 mm

IR : 3400, 2950, 1450, 1060, 1010 cm^{-1}

^{1}H-NMR : δ3.30 (2H, t, J = 7Hz, -C$\underline{H}$-OH), 2.4 - 0.8 (44H, series of m)

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

Found: C,80.42 ; H,11.60

3-cis-Bicyclo[3.3.0]octan-1-cyclopentyl ketone (18):

To a suspension of pyridinium chlorochromate (1.0 g, 7.0 mmol) in dry dichloromethane (10 ml) containing activated molecular sieves (4 ^{o}A, 1. g) was added the alcohol (760 mg, 3.65 mmol) at ice-bath temperature. The contents were stirred for 2 h and diluted with dry ether (50 ml). Then the contents were filtered through a florisil pad and repeatedly washed with dry ether. Removal of the solvent gave the crude product which was filtered through a silica gel (5 g) column by eluting with 10% ethyl acetate - pet ether to furnish the ketone 18 (640 mg) in 85% yield as an epimeric mixture.

bp. : 140^{o}C/0.1 mm

IR : 2950, 1700, 1450, 1100 cm^{-1}

^{1}H-NMR : δ3.2 - 2.8 (4H, m), 2.7 - 2.3 (4H, m), 2.2 - 1.0 (36H, m)

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

Found: C, 81.47 ; H, 10.73

1,1'-Dibromo-3-cis-bicyclo[3.3.0]octan-1'-cyclopentyl ketone (27):

In to a 25 ml three necked RB flask fitted with a dry N_2 inlet, pressure equalising addition funnel and mercury seal, ketone 18 (600 mg, 2.9 mmol) was placed in dry carbontetrachloride (5ml). Bromine (1.0 g, 6.2 mmol) solution in dry carbontetrachloride (5 ml) was added slowly through addition funnel and stirred for 15 h at room temperature. The reaction mixture was quenched by addition of saturated $NaHCO_3$ and extracted with dichloromethane (25 ml x 3). The combined organic extract was washed, dried and concentrated. The crude product thus obtained was filtered through a silica gel (15 g) column to furnish the dibromoketone 27 (960 mg) in 91% yield. The pure product was recrystallised from pet ether.

mp. : $53^{o}C$

IR : 2950, 1700, 1450, 1220, 940 cm^{-1}

^1H-NMR : δ3.0 - 2.2 (8H, series of m), 2.1 - 1.4 (12H, series of m)

Analysis : $C_{14}H_{20}Br_2O$ Calcd: C, 46.17 ; H, 5.53

Found: C, 46.34 ; H, 5.58

3-cis-Bicyclo[3.3.0]octan-1'-cyclopentyl-2,1'-dienone (17):

Into a 25 ml three necked flask fitted with a dry N_2 inlet, septum and mercury seal, LiBr (865 mg, 10 mmol),Li_2CO_3 (740 mg, 10 mmol) were placed. The solid mixture was suspended in dry dimethylformamide (5 ml) and dibromoketone 27 (1.0 g, 2.75 mmol) in dry dimethylformamide (5 ml) was added. The reaction mixture was heated at $80^{o}C$ for 4 h with stirring. Then the reaction mixture was poured into ice-cold water (50 ml) and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (5 g) column. Elution with 10% ethyl acetate - pet ether furnished the dienone 17 (385 mg) in 80% yield.

bp. : 140°C/0.1 mm
IR : 3050, 2950, 1440, 1370 cm^{-1}
^{1}H-NMR : δ 6.6 (1H, br s, -CH=C-), 6.4 (1H, br s, -CH=C-), 3.7 - 3.1 (1H, m), 3.0 - 1.4 (15H, series of m)
^{13}C-NMR : δ190.6, 145.0, 144.7, 142.9, 141.6, 51.4, 39.6, 39.3, 35.0, 33.5, 31.5, 25.1, 22.3
Analysis : $C_{14}H_{18}O$ Calcd: C, 83.12 ; H, 8.97
Found: C, 83.02 ; H, 8.99

cis,anti,cis-Tetra cyclo[6.6.0.0^{2,6}.0^{10,14}]tetradec-1(8)-en-7-one (16) and cis,anti,cis-tetracyclo[6.6.0^{2,6}.0^{10,14}]tetradec-2(6)-en-7-one (28):

Into a 25 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal, polyphosphoric acid (5 ml) was placed and heated to 100°C. Then the dienone 17 (300 mg, 1.5 mmol) was added and heating was continued with vigorous stirring at 100°C for 1 h. The reaction mixture was brought to room temperature, and poured into ice and extracted with ether (50 ml x 3). The combined ethereal extract was washed, dried and concentrated to give a crude product which was filtered through a silica gel (5 g) column. Elution with 5% ethyl acetate - pet ether furnished the tetracyclic enones 16 and 28 (120 mg) in 60% yield (regio isomeric mixture of enones in approximately 4:1 ratio from which only major isomer 16 could be separated in small amounts using MPLC and characterised).

bp. : 140°C/0.1 mm

IR : 2950, 1690, 1640, 1450, 1390 cm^{-1}

^1H-NMR : δ3.4 - 2.9 (3H, m), 2.8 - 1.0 (15H, series of m)

^{13}C-NMR (fig. IV.1) : δ207.2, 190.2, 147.6, 57.2, 47.2, 46.7, 41.3, 35.4, 32.0, 29.8, 29.4, 27.7, 26.2, 24.3

Analysis : $C_{14}H_{18}O$ Calcd: C, 83.12 ; H, 8.97
Found: C, 83.15 ; H, 8.93

7,7-Ethylenedithio-cis,anti,cis-tetracyclo[6.6.0.$0^{2,6}$.$0^{10,14}$]tetradec-1(8)-ene (29) and 6,6-Ethylenedithio-cis,anti,cis-tetracyclo[6.6.$0^{1,5}$,$0^{9,13}$]-tetradec-1(5)-ene (30):

Into a 50 ml RB flask fitted with a reflux condenser tetracyclic enone mixture 16 and 28 (200 mg, 1.5 mmol) was placed in dry benzene (25 ml). To this ethane dithiol (0.5 ml) and PTS(15 mg) were added and the contents were refluxed for 30 min. Then reaction mixture was diluted with benzene (50 ml) and washed with saturated $NaHCO_3$ solution. The crude product obtained was charged on a silica gel (3 g) column. Elution with pet ether resulted in the removal of ethane dithiol impurities and further elution with 5% ethyl acetate - pet ether furnished the mixture of thioacetals 29 and 30 (200 mg, mixture of regio isomers) in 87% yield.

IR : 2950, 1450, 1270 cm^{-1}

^1H-NMR : δ3.25 (8H, s, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 3.3-1.2 (36H, series of m)

cis,anti,cis-Tetracyclo[6.6.0.$0^{2,6}$.$0^{10,14}$]tetradec-1(8)-ene (14) and cis,anti,cis-Tetracyclo[6.6.0.$0^{2,6}$.$0^{10,14}$]tetradec-2(6)-ene (31):

Into a two necked 100 ml RB flask, fitted with a guard tube and septum, was taken freshly distilled liq.NH_3 (50 ml). To this was added freshly cut sodium metal (115 mg, 5 mmol) piece by piece. The resulting blue solution was stirred for 5 min and thioacetal (200 mg, 0.72 mmol) in dry ether (5 ml) was added slowly to it. The reaction mixture was quenched with saturated NH_4Cl solution after all the ammonia had evaporated. The reaction mixture was diluted with water (25 ml) and the aqueous layer was extracted with n-pentane (50 ml x 3). The combined pentane extract was washed, dried and concentrated to a crude product which showed two componants on silver nitrate impregnated tlc plate. The crude product was chromatographed on a silver nitrate impregnated silica gel (20 g) column. Elution with pentane furnished the symmetric tetraquinene hydrocarbon 14 (80 mg).

bp.	: $130^{\circ}C/0.1$ mm
IR	: 2950, 1440 cm^{-1}
^{1}H-NMR	: δ3.1 - 2.6 (4H, m), 2.5 - 2.2 (2H, m), 1.9 - 1.2 (14H, m)
^{13}C-NMR (fig. IV.2)	: δ150.2, 142.7, 47.4, 45.4, 37.6, 35.9, 30.2, 26.1
Mass	: $C_{14}H_{20}$ M/e Calcd: 188.1564 Found: 188.1584

Further elution with 10% bezene - pentane furnished unsymmetric tetraquinene hydrocarbon 31 (20 mg) in a combined yield of 74% (4:1).

bp.	: $130^{\circ}C/$ 0.1 mm
IR	: 2950, 1450, 1000 cm^{-1}
^{1}H-NMR	: δ3.2 - 2.9 (1H, m), 2.6 - 1.2 (19H, series of m)
^{13}C-NMR (fig. IV.3)	: δ148.3, 142.4, 55.1, 48.1, 47.0, 44.5, 40.7, 35.7, 33.9, 32.1, 29.1, 27.9, 27.4, 25.8
Mass	: $C_{14}H_{20}$ M/e Calcd: 188.1564 Found: 188.1586

cis,anti,cis-Tricyclo[9.3.0.0^{3,7}]tetradec-2,9-dione (15):

Into a 25 ml RB flask the symmetric tetraqinene hydrocarbon 14 (80 mg, 0.42 mmol) was taken in a mixture of carbontetrachloride, acetonitrile and water (each 2 ml). To this mixture were added sodium metaperiodate (213 mg, 1.0 mmol) and ruthenium dioxide (3 mg). After being stirred for 30 min, the reaction was diluted and extracted with dichloromethane (25 ml x 3). The combined organic extract was washed and dried. The crude product obtained after removal of the solvent was filtered through a small silica gel (5 gm) column with 10% ethyl acetate - pet ether to furnish the dione 15 (85 mg) in 92% yield. The dione was recrystallised from pet ether - dichloromethane mixture.

mp. : 66^{o}C

IR : 2950, 1690, 1440, 1250, 1180 cm^{-1}

^{1}H-NMR : δ3.05 (2H, t, J = 8Hz), 2,6 - 1.4 (18H, series of m)

^{13}C-NMR (fig. IV.4) : δ216.1, 211.8, 53.6, 45.0, 40.5, 33.9, 28.0, 24.0

Analysis : $C_{14}H_{20}O_2$ Calcd: C, 76.32 ; H, 9.15

Found: C, 76.40 ; H, 9.17

9,9-(Ethylene oxathio)-cis,anti,cis-Tricyclo[6.9.0.0^{3,7}]tetradec-2-one (32):

A solution of diketone 15 (75 mg, 0.34 mmol), 2-mercapto ethanol (0.2 ml) and PPTS (25 mg) in dry benzene (20 ml) was refluxed with a Dean-Stark water separator for 3 h. The reaction mixture was diluted with benzene (25 ml), washed with aqueous $NaHCO_3$ and water, then dried. The crude product obtained after removal of the solvent was charged of a silica gel (10 g) column. Elution with 5% ethyl acetate - pet ether removed sulfur impurities. Further elution with 10% ethyl acetate - pet ether furnished the 1,3-oxathioacetal ketone 32 (72 mg) in 72% yield, which was recrystallised form hexane.

mp. : $91^{o}C$

IR : 2950, 1680, 1440, 1200, 1100, 1060, 840 cm^{-1}

^1H-NMR : δ4.4 - 4.0 (2H, m, $-O-C\underline{H}_2CH_2-S-$), 3.2 - 2.9 (4H, m, $-O-Ch_2C\underline{H}_2-S$), 2.6 - 1.2 (18H, series of m)

^{13}C-NMR (fig. IV.5) : δ218.7, 98.5, 70.2, 53.4, 52.1, 43.2, 42.2, 41.6 39.9, 35.5, 35.2, 33.1, 29.1, 28.6, 24.0, 23.8

Analysis : $C_{16}H_{24}O_2S$ Calcd: C, 68.52 ; H, 8.62

Found: C, 68.56 ; H, 8.59

cis,anti,cis-Tricyclo[6.6.0.$0^{2,6}$]tetradeca-10,14-dione (35):

Into a 25 ml RB flask the unsymmetric tetraquinene hydrocarbon 31 (20 mg, 0.1 mmol) was placed in a mixture of carbontetrachloride, acetonitrile and water (each 1 ml). To this mixture were added sodium metaperiodate (110 mg, 0.5 mmol) and ruthenium dioxide (3 mg). After being stirred for 30 min the reaction mixture was diluted and extracted with dichloromethane (25 ml x 3). The combined organic extract was washed and dried. The crude product obtained after removal of solvent was filtered through a small silica gel (5 g) column with 10% ethyl acetate - pet ether to furnish the dione 35 (21 mg) in 90% yield, which was recrystallised from hexane - dichloromethane mixture.

mp. : $129^{o}C$

IR : 2950, 1680, 1450, 1260 cm^{-1}

^1H-NMR : δ3.0 - 2.0 (11H, series of m), 1.9 - 1.1 (9H, m)

^{13}C-NMR (fig. IV.6) : δ213.8, 212.9, 62.2, 45.2, 43.5(2C), 42.7, 41.7, 40.0(2C), 33.9, 33.5, 26.1, 23.9

Analysis : $C_{14}H_{20}O_2$ Calcd: C, 76.32 ; H, 9.15

Found: C, 76.30 ; H, 9.14

3-endo-Hydroxy-cis-bicyclo[3.3.0]octane (45):

Into a 100 ml RB flask ketone 24 (5 g, 40.3 mmol) was placed in dry ether (60 ml) and cooled in ice bath. To this lithium aluminium hydride (1.5 g, excess) was added. The reaction mixture was stirred at room temperature for 30 min and then excess lithium aluminium hydride was destroyed by careful addition of ethyl acetate followed by saturated Na_2SO_4 solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml x 3). The combined organic extract was washed, dried and concentrated. The crude product thus obtained was dilstilled at reduced pressure to furnish endo alcohol 45 (4.5 g) in 90 % yield.

IR : 3450, 2950, 1100 cm^{-1}

^{1}H-NMR : δ3.97 (1H, m, C<u>H</u>-OH), 3.0 - 1.0 (13H, series of m)

exo-3-Bromo-cis-bicyclo[3.3.0]octane (41):[26]

Into a 50 ml two necked RB flask fitted with a pressure equalising addition funnel and mercury seal, bicyclic alcohol 45 (5 g, 40 mmol) was placed and cooled in ice-bath. To this phosphorous tribromide (5.4 g, 20 mmol) was added drop wise and the reaction mixture was stirred for 1h. Then the reaction mixture was poured into ice cold water and extracted with ether (50 ml x 3). The combined ethereal extract was washed with saturated $NaHCO_3$, water and dried. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish bromide <u>41</u> (6.0 g) in 80% yield. The IR and ^{1}H-NMR spectral values of <u>41</u> were found identical with the reported in the literature.[26]

bp. : 110°C/0.1 mm

IR : 2950, 1200, 910 cm^{-1}

^{1}H-NMR : δ4.5 (1H, m, -C<u>H</u>Br), 2.9-2.6 (2H, m), 2.4-1.1 (10H, series of m)

<u>5S-Isopropyl-2-methyl cyclopent-1-ene-1-carboxaldehyde</u> (<u>42</u>):

Enantiomerically pure enal <u>42</u> was prepared from R-(+)-limonene according to the procedure described in the experimental section of the chapter I.

<u>3'-cis-Bicyclo[3.3.0]octa-2-methyl-5-isopropyl-1-ene-1-cyclopentyl methanol</u> (<u>46</u>):

Into a 50 ml three necked RB flask, fitted with dry N_2 inlet, a rubber septum and mercury seal, freshly cut lithium pieces (140 mg, 20.0 mmol) were placed and dry THF (10 ml) was introduced. To this mixture bromide <u>41</u> (4.6 g, 25 mmol) and enal <u>42</u> (1.5 g, 10.0 mmol) in dry THF (5 ml) were added. Then the reaction mixture was subjected to ultrasound by placing the RB flask in an ultrasound generator containing water, where it gives maximum agitation for 1 h. Occasionally crushed ice was added to the water present in the sonicator to maintain the temperature constantly at 15-20°C.

The reaction mixture was quenched with saturated NH_4Cl solution and then extracted with ether (50 ml x 3). The combined ethereal extract was washed and dried. The crude material obtained after removal of the solvent was chromatographed on a silica gel (25 g) column. Elution with 5% ethyl acetate - pet ether removed the unreacted bromide impurities and further elution with 10% ethyl acetate - pet ether furnished the allylic alcohol 46 (1.0 g) in 40% yield as a diastereomeric mixture.

bp. : $160^{o}C$/ 0.1 mm

IR : 3450, 2950, 1440, 1000 cm^{-1}

^{1}H-NMR : δ 4.2 (2H, br d, J = 12 Hz, -C$\underline{H}$-OH), 3.8 - 1.2 (40H, series of m), 1.63 (6H, br s, -C=C-C$\underline{H}_3$), 0.92 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.75 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$)

Analysis : $C_{18}H_{30}O$ Calcd: C, 82.38 ; H, 11.52
Found: C, 82.30 ; H, 11.55

3'-cis-Bicyclo[3.3.0]octa-2S-isopropyl-1-en-1-cyclopentyl ketone (47):

Into a 100 ml RB flask allylic alcohol 46 (1.0 g, 3.8 mmol) in 50 ml of dry dichloromethane was placed. To this freshly prepared dry barium manganate[27] was added and the reaction mixture was stirred vigorously for 15h. Then the reaction mixture was filtered through a buchner funnel and the solid remained was washed repeatedly with dichloromethane (50 ml). The filtrate was concentrated to give a crude product which was filtered through a small silica gel (10 g) column with 10% ethyl actate - pet ether to furnish enone 47 (540 mg) in 55% yield as diastereomeric mixture.

bp. : $150^{o}C$/0.1 mm

IR : 2950, 1660, 1450, 1360, 1150 cm^{-1}

^{1}H-NMR : δ3.2 - 2.9 (2H, m), 2.6 - 2.0 (6H, m), 1.95 (6H, br s, -C=C-C$\underline{H}_3$), 1.8 - 1.0 (30H, m), 0.95 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.75 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$)

Analysis : $C_{18}H_{28}O$ Calcd: C, 83.02 ; H, 10.84
Found: C, 83.15 ; H, 10.90

3-cis-Bicyclo[3.3.0]octa-2-methyl-5S-isopropyl-1,2-dien-1-cyclopentyl ketone (49) and (50):

Into a 50 ml three necked flask fitted with a dry N_2 inlet, septum and mercury seal, was placed 2,4,4,6-tetrabromocyclohexa-2,5-dienone[28] (1.23 g, 3.0 mmol) in dry ether (20 ml). To this suspension enone 47 (500 mg, 1.9 mmol) in dry ether (10 ml) was added and catalytic amount of HBr gas was bubbled through the reaction mixture to initiate the reaction. Then the reaction mixture was stirred for 12 h at room temperature , quenched with aqueous $NaHCO_3$ solution and extracted with ether (25 ml x 3). The combined extract was washed, dried and concentrated to give an oily crude bromo-enone 48 which was directly used for further reaction.

Into a 25 ml three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal LiBr (430 mg, 5 mmol), Li_2CO_3 (370 mg, 5 mmol) were placed. This solid mixture was suspended in 5 ml of dry dimethylformamide and the above crude bromo-enone 48 in dry dimethylformamide (5 ml) was added. The reaction mixture was heated at 80°C for 2 h. Then the reaction mixture was poured into ice cold water (10 ml) and extracted with ether (25 ml x 3). The combined ethereal extract was washed, dried and concentrated. The crude product thus obtained was charged on a silica gel (10 g) column.

Elution with 10% ethyl acetate - pet ether removed less polar impurities and further elution with 15% ethyl acetate - pet ether furnished the dienones 49 and 50 (130 mg) in 26% yield as a diastereomeric mixture.

bp. : $150^{0}C/0.1$ mm

IR : 2950, 1620, 1440, 1360 cm^{-1}

^{1}H-NMR : δ6.35 (2H, br s, -C=C$\underline{H}$), 3.2 - 1.8 (12H, series of m), 1.75 (6H, br s, -C=C-C$\underline{H}_3$), 1.7 - 1.2 (20H, series of m), 0.88 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$), 0.75 (6H, d, J = 7Hz, -CH-C$\underline{H}_3$)

Analysis : $C_{18}H_{26}O$ Calcd: C, 83.66 ; H, 10.14
Found: C, 83.69 ; H, 10.17

2-Methyl-5-isopropyl-cis,anti,cis-tetracyclo[$6.6.0.0^{2,6},0^{10,14}$]tetradec-1(8)-en-7-one (51):

Into a 25 ml RB flask dienoned 49 and 50 (150 mg, 0.58 mmol) in dry toluene (10 ml) were placed. To this mixture catalytic amount of PTS (5 mg) was added and the reaction mixture was refluxed for 2 h. Then the reaction mixture was diluted with benzene (50 ml) and washed with saturated $NaHCO_3$, water and dried. The crude product obtained after removal of the solvent was filtered through a small silica gel (5 g) column. Elution with 5% ethyl acetate- pet ether furnished a single tetracyclic enone 51 (30 mg) in 20% yield.

$[\alpha]_D$: +25.5 (c 0.5, $CHCl_3$)

bp. : $150^{0}C/0.1$ mm

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

^{1}H-NMR (fig. IV.7) : δ3.3 - 2.8 (2H, m), 2.7 - 1.4 (15H, m), 1.24 (3H, s, $-C-C\underline{H}_3$), 0.97 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.88 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR (fig. IV.8) : δ206.2, 190.9, 144.8, 69.4, 50.3, 49.0, 47.5, 46.8, 36.1, 35.3, 32.3, 31.5, 30.9, 30.3, 26.9, 24.1, 21.8, 20.4

Analysis : $C_{18}H_{26}O$ Calcd: C, 83.66 ; H, 10.14
Found: C, 83.64 ; H, 10.11

7,7-Ethylenedithio-2-methyl-5-isopropyl-cis,anti,cis-tetracyclo[6.6.0.-$0^{2,6}.0^{10,14}$]tetrdec -1(8)-ene (52):

Into a 25 ml RB flask fitted with a reflux condenser, tetracyclic enone 51 (100 mg, 0.39 mmol) was placed in dry benzene (10 ml). To this was added ethane dithiol (0.5 ml) and p-toluenesulfonic acid (15 mg) and the reaction mixture was refluxed for 30 min. The reaction mixture was diluted with benzene (25 ml) washed with saturated $NaHCO_3$ solution and dried. The benzene extract was concentrated to give the crude product which was charged on a silica gel (15 g) column. Elution with 5% ethyl acetate - pet ether removed the ethane dithiol derived impurities. Further elution with 10% ethyl acetate - pet ether furnished the thioacetal 52 (110 mg) in 90% yield.

IR : 2950, 1460, 1370, 1020 cm^{-1}

^{1}H-NMR : δ3.2 - 3.0 (4H, m, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 3.0 - 1.3 (17H, series of m), 1.08 (3H, s, $-C-C\underline{H}_3$), 0.95 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.85 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

3-methyl-6S-isopropyl-cis,anti,cis-tricyclo[9.3.0.$0^{3,7}$]tetradeca-2,9-dione (54):

Into a two necked 100 ml RB flask, fitted with a guard tube and septum, was taken freshly distilled liq.NH_3 (50 ml). To this was added freshly cut sodium metal (60 mg, 2.7 mmol) piece by piece. The resulting blue solution was stirred for 5 min and the thioacetal 52 (100 mg, 0.3 mmol) in dry ether (2 ml) was added slowly to it. After stirring for 1 h, the reaction mixture was quenched by careful addition of NH_4Cl. After all the ammonia had evaporated, the reaction mixture was diluted with water (25 ml) and extracted with pentane (50 ml x 3). The combined pentane extract was washed, dried and concentrated to a crude tetracyclic hydrocarbon 53 which was directly used for further reaction.

Into a 25 ml RB flask, the above crude hydrocarbon 53 was taken in a mixture of carbon tetrachloride, acetonitrile and water (each 2 ml). To this mixture were added sodium metaperiodate (213 mg, 1.0 mmol) and ruthenium dioxide (3 mg). After being stirred for 30 min the reaction mixture was diluted and extracted with dichloromethane (25 ml x 3). The combined organic extract was washed and dried. The crude product obtained after removal of the solvent was filtered through a small silica gel (5 g) column to furnish the dione 54 (50 mg) in 82% yield, which was recrystallised form hexane - dichloromethane mixture.

$[\alpha]_D$: +15 (c 0.3, $CHCl_3$)

mp. : 61^oC

IR : 2950, 1690, 1450, 1020 cm^{-1}

^{1}H-NMR (fig. IV.9) : δ3.4 - 3.2 (1H, m), 2.6 - 1.3 (16H, series of m), 1.25 (3H, s, $-C-C\underline{H}_3$), 1.0 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$), 0.87 (3H, d, J = 7Hz, $-CH-C\underline{H}_3$)

^{13}C-NMR : δ58.59, 55.89, 53.19, 49.02, 48.55, 46.55, 43.7, 34.5, 34.4, 32.9, 30.7, 26.6, 25.1, 24.4, 22.1, 19.6

Analysis : $C_{18}H_{28}O_2$ Calcd: C, 78.21 ; H, 10.21
Found: C, 78.27 ; H, 10.31

IV.7. SPECTRA

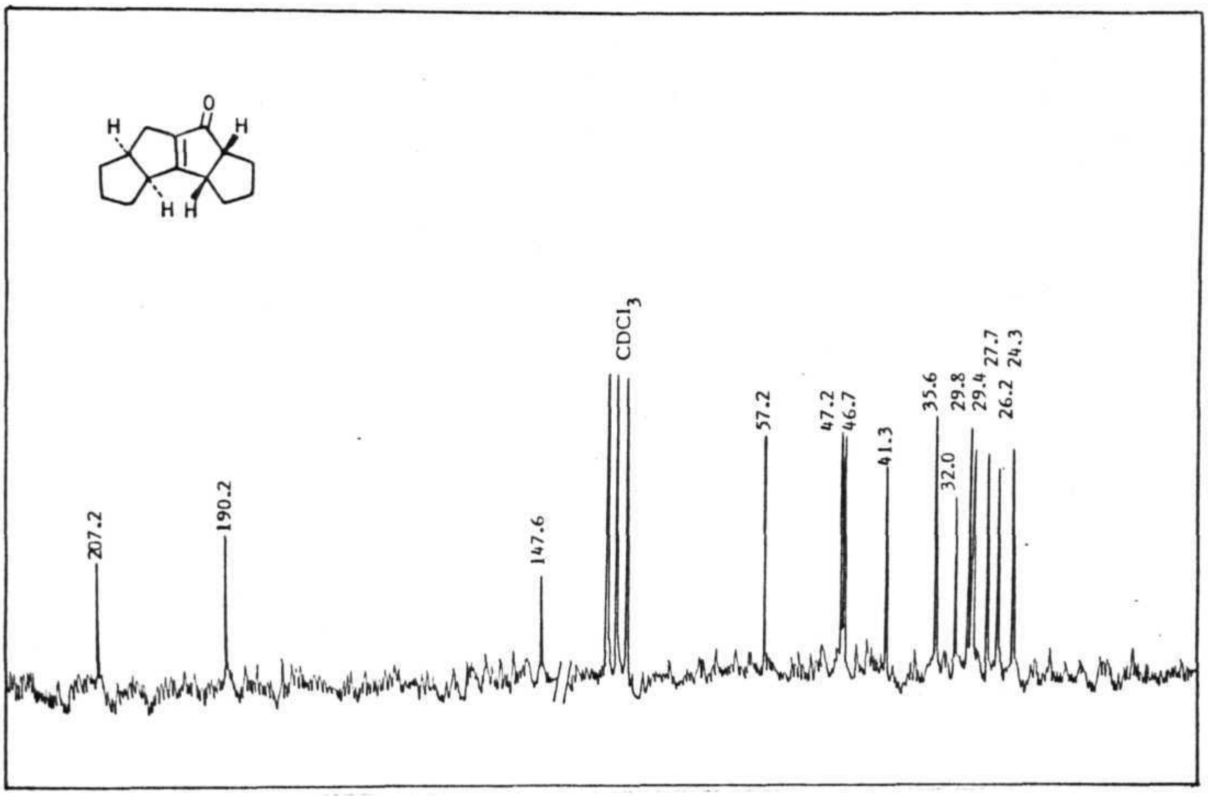


Fig. IV.1 ^{13}C-NMR spectrum (25 MHz) of 16

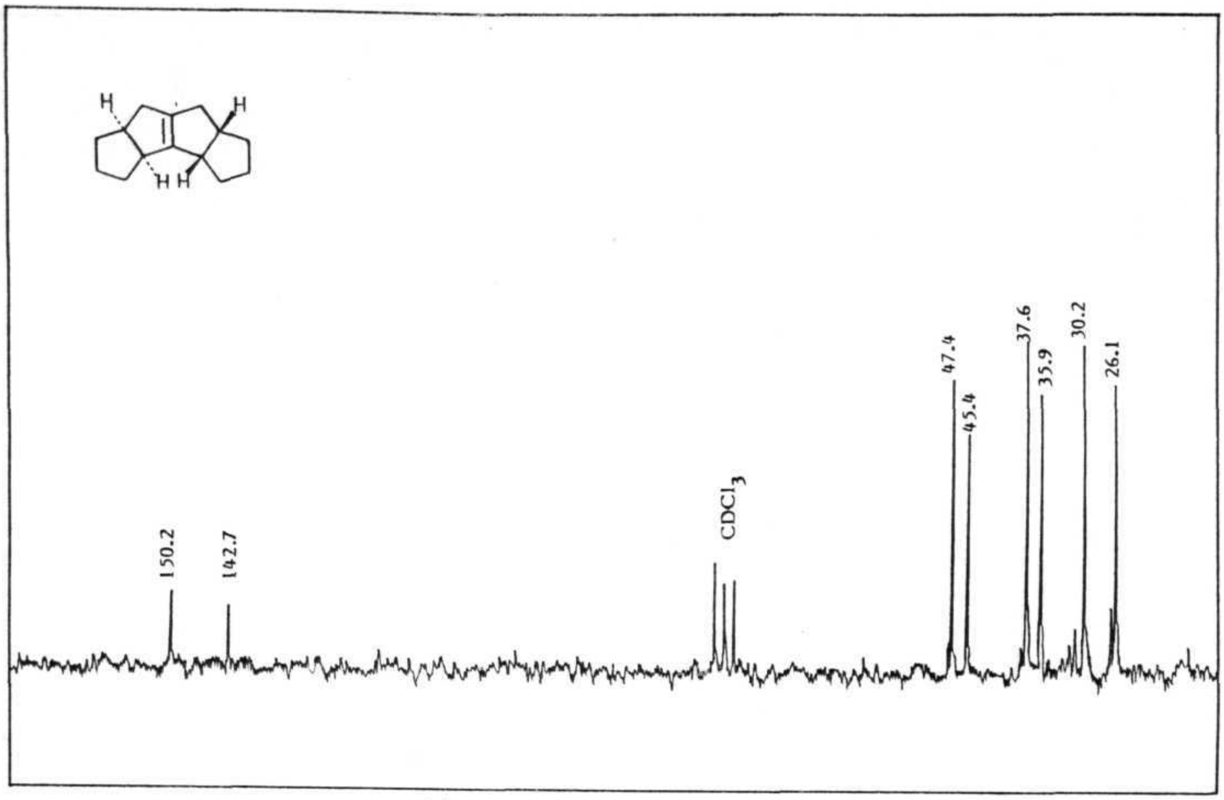


Fig. IV.2 ^{13}C-NMR spectrum (25 MHz) of 14

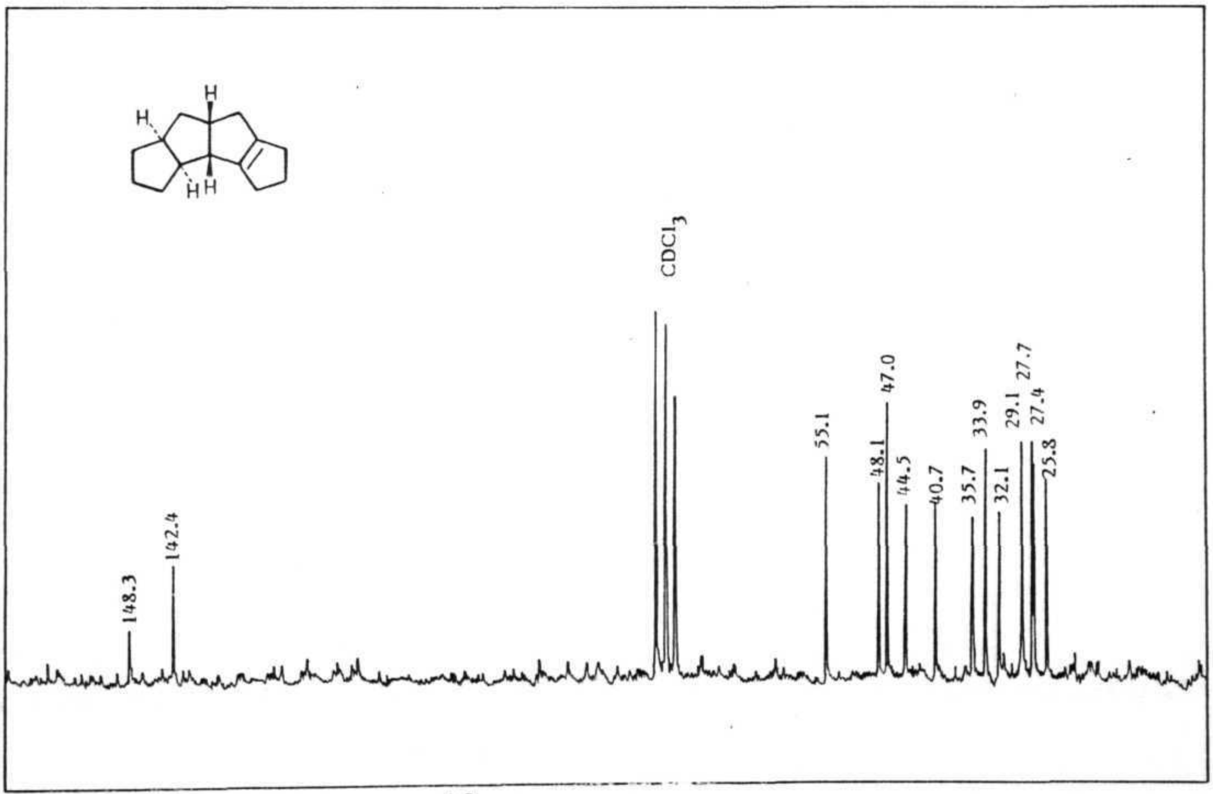


Fig. IV.3 ^{13}C-NMR spectrum (25 MHz) of 31

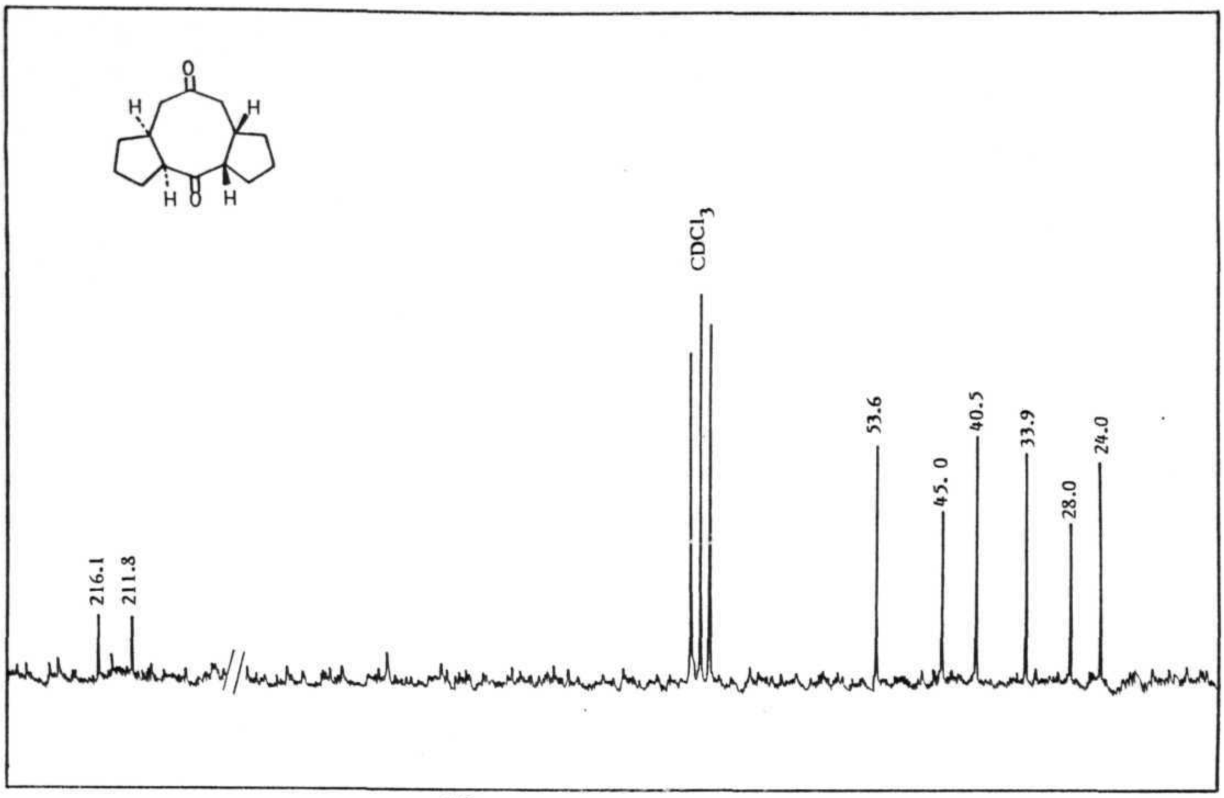


Fig. IV.4 ^{13}C-NMR spectrum (25 MHz) of <u>15</u>

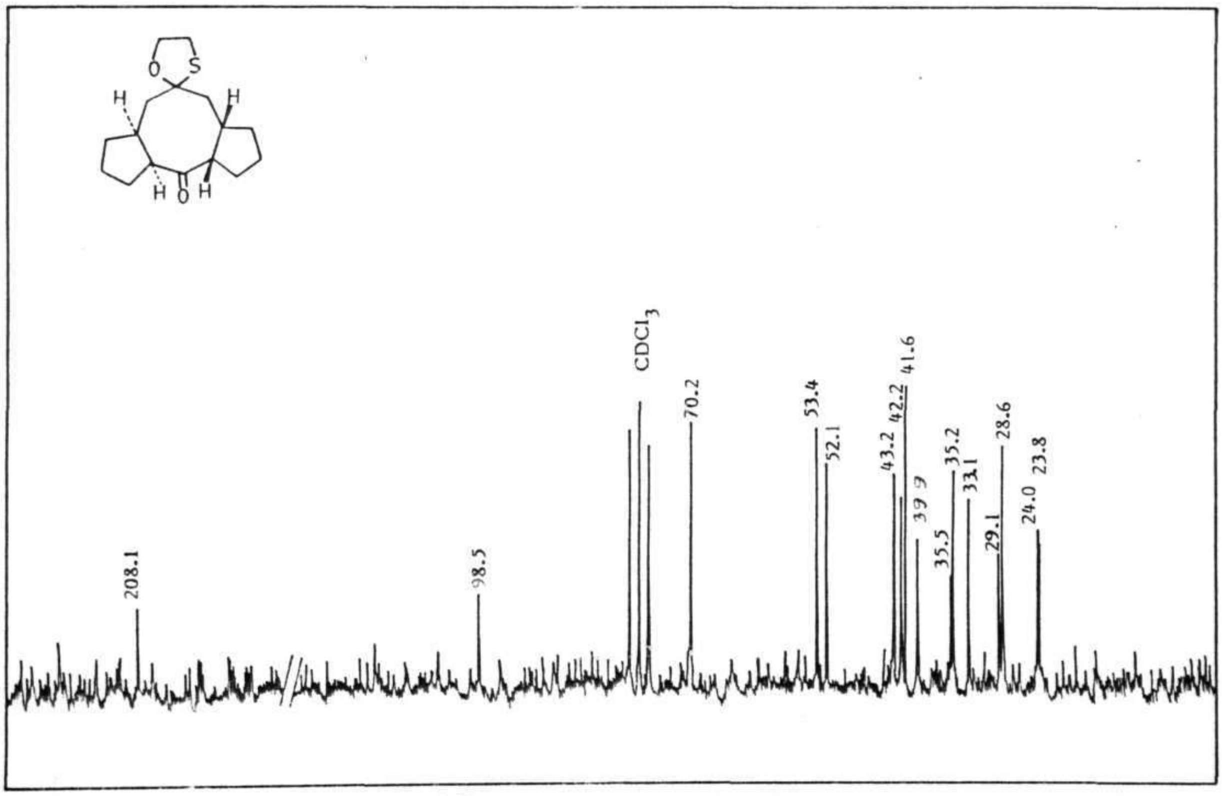


Fig. IV.5 ^{13}C-NMR spectrum (25 MHz) of <u>32</u>

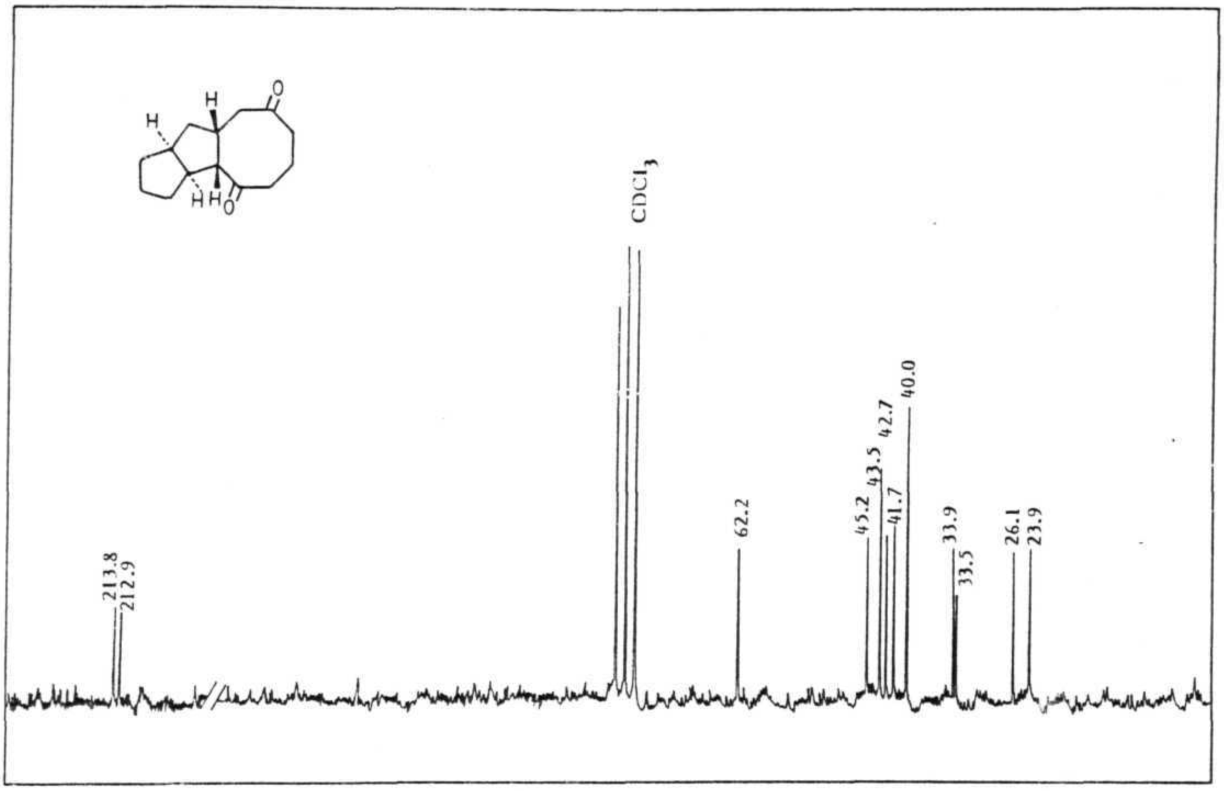


Fig. IV.6 ^{13}C-NMR spectrum (25 MHz) of <u>35</u>

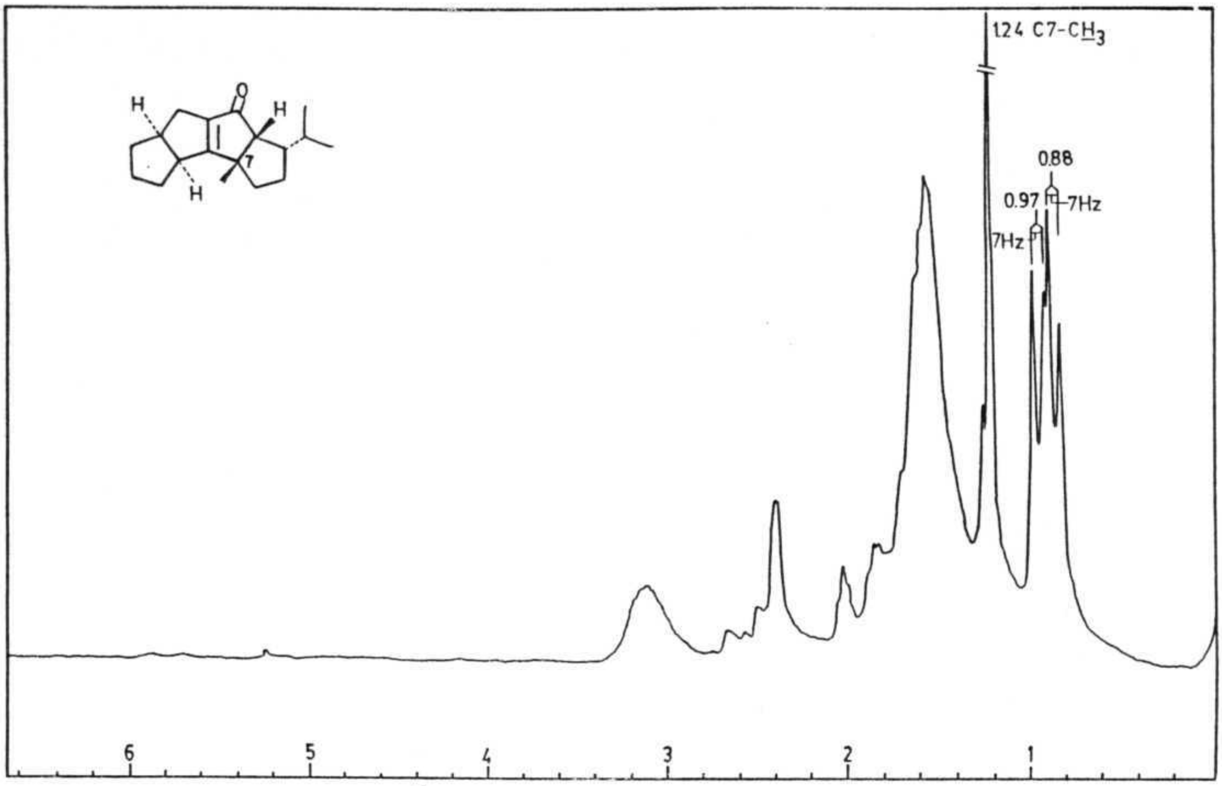


Fig. IV.7 ^{1}H-NMR spectrum (100 MHz) of 51

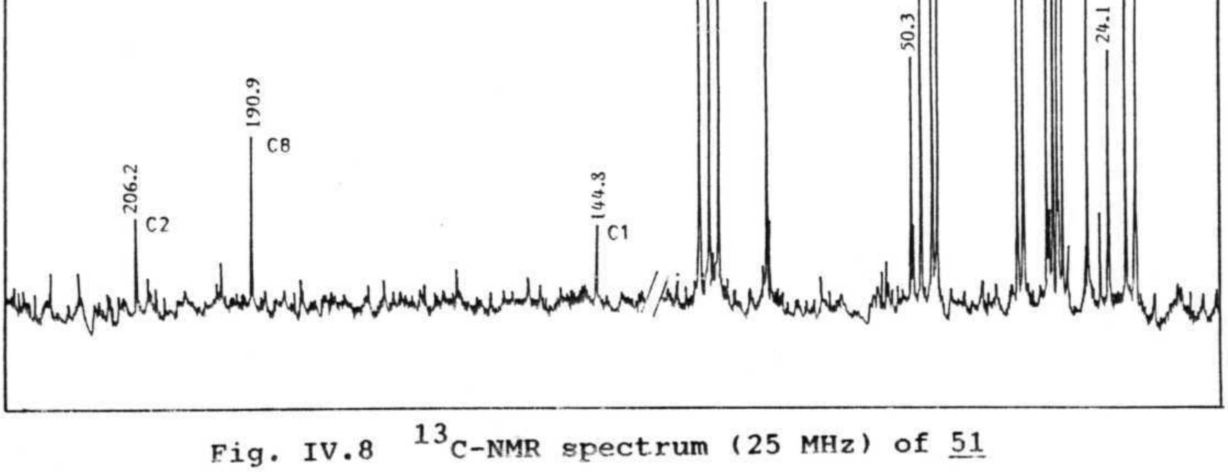


Fig. IV.8 ^{13}C-NMR spectrum (25 MHz) of 51

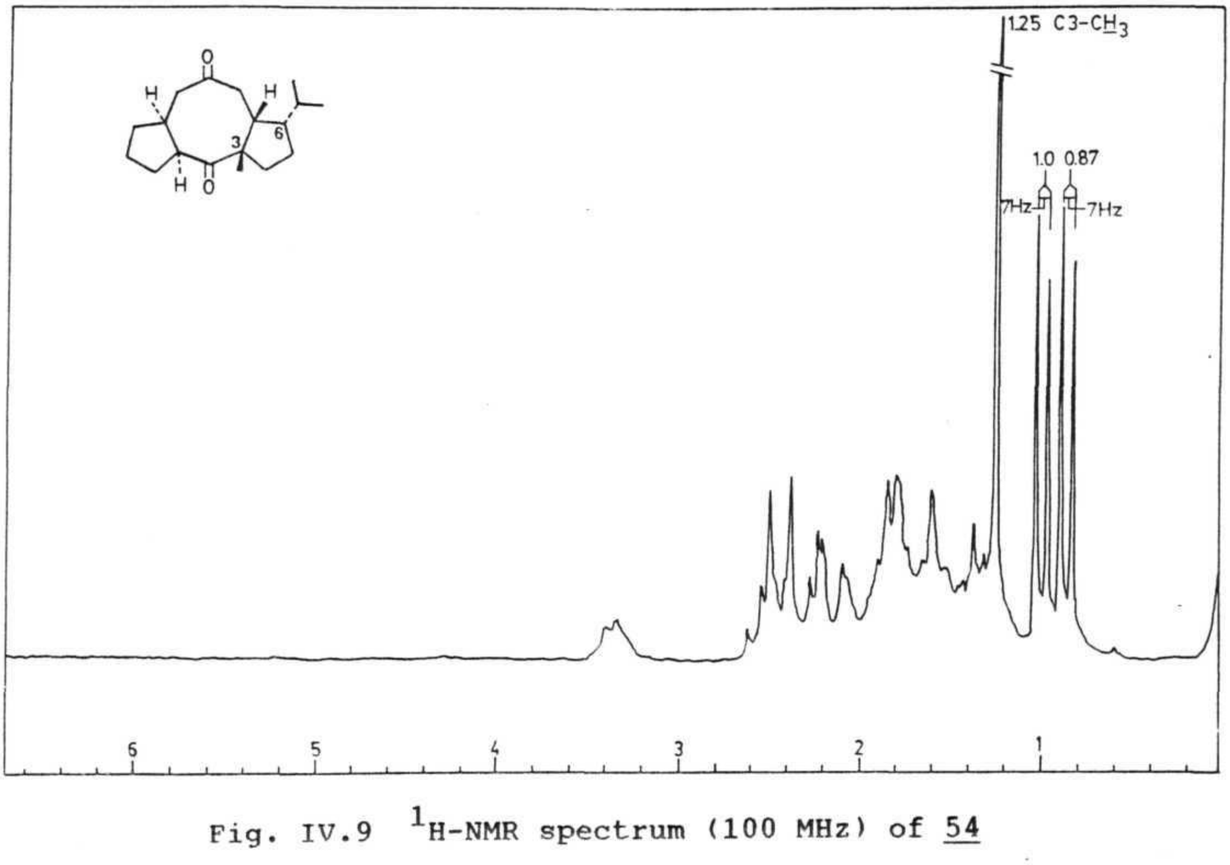


Fig. IV.9 ^{1}H-NMR spectrum (100 MHz) of <u>54</u>

VI.8. REFERENCES

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VITAE

The author was born on August 24th 1961, at Hyderabad, Andhra Pradesh. After completing his B.Sc. Degree in 1981 from C.K.M. College, Warangal, he joined the University of Hyderabad, Hyderabad and received the M.Sc. Degree in 1983. He joined the same University for the Ph.D. Programme in July, 1983 and presently is continuing in the same School as a Senior Research Fellow.

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