TOTAL SYNTHESIS OF NATURAL PRODUCTS : TOWARDS CAPNELLENE, PRECAPNELLADIENE, LONGIPENOL AND IKARUGAMYCIN

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

BY
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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 G. 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 other investigators.

A. Narayana Murty

CERTIFICATE

Certified that the work contained in this thesis entitled: 'TOTAL SYNTHESIS OF NATURAL PRODUCTS : TOWARDS CAPNELLENE, PRECAPNELLADIENE, LONGIPENOL AND IKARUGAMYCIN' has been carried out by Mr.**A. Narayana Murty,** under my supervision and the same has not been submitted elsewhere for a Degree.

G. Mehta

GOVERDHAN MEHTA
(Thesis Supervisor)

R. Jagannathan.

D E A N
SCHOOL OF CHEMISTRY

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ABREVIATIONS

Ac	acetyl
AIBN	azobisisobutyronitrile
Bu	butyl
MCPBA	meta-chloroperbenzoic acid
Et	ethyl
LAH	lithium aluminium hydride
LDA	lithium diisopropyl amide
Li-HMDS	lithium hexamethyldisilazide
Me	methyl
MeOH	methanol
PCC	pyridinium chlorochromate
Ph	phenyl
Py	pyridine
TBDMS	tertiary butyldimethylsilyl
THF	tetrahydrofuran

PREFACE

The synthesis, chemical reactivity and biological activity of polycondensed frameworks bearing one or more five membered rings have received a great deal of attention in the past decade. This can be attributed to the discovery of several natural products bearing an uncommon assembly of rings, e.g., 5-5-5, 5-6-5, 5-8, 5-8-5, 5-5-5-5, 5-8-5-5 etc., from terrestrial plants, marine organisms, phytopathogenic fungi and insects. The design of these novel polycarbocyclic arrays, adorned with complex functionalities and stereochemical intricacies, constitutes considerable challenge. Their acquisition requires development of new and imaginative strategies for carbocyclic ring construction and many groups around the world have joined the fray. We too have been enticed by the clarion-call and the results reported herein are therefore of topical interest in a competitive area.

The thesis entitled "TOTAL SYNTHESIS OF NATURAL PRODUCTS: TOWARDS CAPNELLENE, PRECAPNELLADIENE, LONGIPENOL AND IKARUGAMYCIN" is divided into four chapters : I. Total synthesis of the marine natural product (±)-capnellene, II. A general stereocontrolled approach to the 5-8 fused systems: Total synthesis of marine natural product (±)-precapnelladiene, III. Synthetic studies towards the ABD ring system of longipenol, and IV. Synthetic studies towards the construction of the perhydro-as-indacene moiety of ikarugamycin. The subject matter of each chapter has been organised under the following headings: Abstract, Objective and Background, Strategy, Synthesis, Summary and Outlook, Experimental, Spectra and References.

The first chapter of the thesis deals with the total synthesis of the linear triquinane based sesquiterpene marine natural product (±)-capnellene.

The synthesis has been achieved by two different routes deviating from a common triquinane intermediate. The key step in the approach pursued here is the photo-thermal metathesis of the Diels-Alder adduct obtained from 2-methylcyclopentadiene and p-benzoquinone to generate the functionalised triquinane framework. The cis,syn,cis triquinane bisenone thus obtained has 12 of the 15 carbon atoms of the natural product and valuable functionality for further manipulation. Elaboration of the C_{12}-triquinane bisenone to the hydrocarbon (±)-capnellene has been successfully achieved through several interesting functional group manipulations. The methodology developed in the context of capnellene synthesis is a general one and can be conveniently adapted for the synthesis of the more complex capnellanols.

In the second chapter, a general methodology for the construction of cis- and trans-bicyclo [6.3.0]undecane systems and its further application to the first total synthesis of the marine natural product (±)-precapnelladiene is described. The key 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. Thus, a general 5-5-5 → 5-8 theme emerged and tricyclo[6.3.0.$0^{2,6}$]undeca-1(8)-ene (C_{11}-triquinene) was identified as the equivalent of a bicyclo [6.3.0]undecane system. Several linear triquinenes have been synthesised and transformed into the corresponding 5-8 fused diones via catalytic ruthenium dioxide oxidation. For the synthesis of precapnelladiene, a readily available 5-5-5 fused ene-dione has been employed as the starting material. Through a series of regio- and stereoselective operations, the ene-dione furnished the pivotal C_{12}-triquinene having the desired stereochemistry at the three stereogenic centres. The bicyclo[6.3.0]undecane moiety was generated from this triquinene through RuO_2 mediated oxidative scission. Functional group readjustments on the resulting 5-8 diketone led to the stereoselective synthesis of (±) precapnelladiene. An appendix at the end of this chapter lists all the known

cyclooctanoid natural products for ready reference.

Synthetic studies directed towards the ABD ring system of the tetracyclic diterpene longipenol is the subject matter of the third chapter. Here again, the general 5-5-5 → 5-8 methodology has been applied for the synthesis of the AB rings of longipenol to which ring D can be appended. To begin with, the readily available triquinane based ene-dione was subjected to some functional group transformations to generate a triquinene with the desired side chain. Ruthenium dioxide oxidation of the triquinene furnished the 5-8 fused AB ring system. Several attempts were made to construct the D ring on to the AB framework. Limited success was achieved through an intramolecular Mukaiyama reaction and a functionalised tricyclo[5.4.2.$0^{4,12}$]tridecane derivative having the ABD ring system present in longipenol was obtained. However, stereochemical difficulties thwarted further progress towards the target molecule.

In the fourth chapter, a new photo-thermal metathesis based synthesis of as-perhydroindacene ring system is described. Attempts to apply this methodology for the construction of the 5-6-5 carbocyclic fragment of the antibiotic ikarugamycin are detailed. The carbocyclic portion of ikarugamycin has trans,-anti,cis-stereochemistry at the ring junction and as many as eight stereogenic centres. The present effort resulted in the construction of the 5-6-5 tricarbocyclic frame with the required alkyl substituents and the trans,anti,cis-stereochemistry. However, stereochemistry at one of the carbon centres (methyl group bearing) could not be controlled. Still, the methodology developed here is a promising one and can be further exploited with tactical adjustments.

CHAPTER I

TOTAL SYNTHESIS OF THE MARINE NATURAL PRODUCT (±)-CAPNELLENE

I. 1. ABSTRACT

A novel and short synthetic approach to the capnellane group of triquinane sesquiterpenes, culminating in the total synthesis of hydrocarbon capnellene 6 is presented. The key element in the approach was the stepwise photo-thermal metathesis of the readily available Diels-Alder adduct 12a of 1-methylcyclopentadiene and p-benzoquinone. Thus UV irradiation of the tricyclic adduct 12a resulted in smooth $_{\pi}2_{s}+_{\pi}2_{s}$ cyclisation and led to the caged pentacyclic dione 13a. Regiospecific fragmentation of cyclobutane ring in 13a using flash vacuum pyrolysis technique gave the cis-syn-cis-triquinane bisenone 14. The C_{12}-bisenone 14, bearing 12 of the 15 carbons of capnellene 6 on treatment with base (DBU) underwent relocation of one of its enone moieties to furnish the transposed bisenone 20. From the bisenone 20, two different routes were pursued for further elaboration to the natural product. The essential difference between the routes lay in the strategy adopted for the installation of the gem-dimethyl group.

In the first approach [Scheme I.7] the bisenone 20 was transformed to the exo-methylene compound 30, through the Wittig olefination reaction on the partially hydrogenated ene-dione 29. The exo-methylene compound 30 was smoothly transformed to the nor-capnellanone 32 via Simmons-Smith cyclopropanation and

catalytic hydrogenation sequence. Since 32 has been previously transformed into the natural product in one step, achievement of the nor-capnellanone 32 constituted a total synthesis of the capnellene 6 in 9 steps.

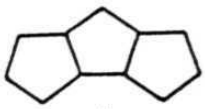
In the second approach [Scheme I.8] the key intermediate 20 was converted to a new bisenone 33, through alkylative enone transposition protocol. Chemo- and stereoselective 1,4-reduction of the bisenone 33 delivered the hydroxy-enone 34, which was transformed to the gem-dimethylated hydroxy-ketone 35, through conjugate addition of lithium dimethyl cuprate reagent. PCC oxidation of 35 furnished the diketone 36, in which the two carbonyl groups were readily chemo-differentiated. Wittig olefination of 36 occurred preferentially at the less hindered carbonyl and the keto-olefin 37 was obtained. Finally, the undesired carbonyl group was discarded through reduction to the hydroxy-olefin 38 and Barton deoxygenation sequence involving conversion to the S-methylthiocarbonate 39 and tri-n-butylstannane reduction. Synthesis of capnellene 6 through this route was accomplished in 13 steps.

I. 2. OBJECTIVE AND BACKGROUND

While molecular arrays composed of fused five membered rings (polyquinanes)* have been known to Nature since time immemorial, they were revealed to man only recently. Despite this belated discovery, polyquinane natural products have rapidly proliferated[1]. They have been isolated from plant, marine and microbial sources. They have also elicited widespread interest from synthetic chemists in recent years, primarily on account of the diverse and architecturally unique assembly of five-membered rings present in them and the promising biological activity exhibited

*Poly + quin + anes (quin, abbreviation of quintet or quintuplet, meaning five, fl. quintus. This colloquial name has been commonly accepted for the rapidly growing family of polyfused cyclopentanoids.

by some members of this family. Among the various naturally occurring polyquinanes, the two C_{11}-tricyclopentanoid skeleta 1** and 2***, incorporating three linearly[2] and angularly[3] fused five membered rings, respectively, as the fundamental ring systems are the most commonly encountered. A recent and novel addition to the polyquinane family has been the discovery of the tetraquinane framework 3****, embodying both 1 and 2, in the crinipellin group of diterpenoids[4].



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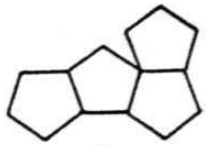
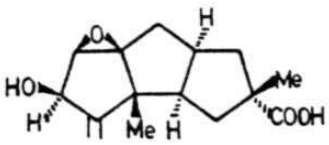


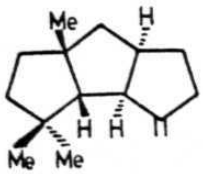
3

Presently, three carbocyclic skeleta based on 1 and five based on 2 are known. Representative examples of each of these are displayed in Chart I.1[2,10] and I.2[3], respectively. In addition, novel natural products bearing annulated triquinane

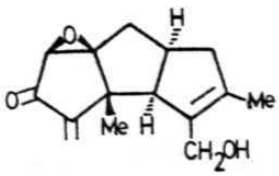
Chart I.1



HIRSUTIC ACID [2a]



CAPNELLENE [2b]



PLEUROTELLOL[2c]

frameworks have also been isolated. These include the diterpenes laurenene[5] and crinipellins[4], and sesterterpene retigeranic acid[6], Chart I.3. The galaxy of polyquinane natural products exhibited in Charts I.1-3 have caught the imagination of a large number of synthetic chemists around the world and provided a very popular testing

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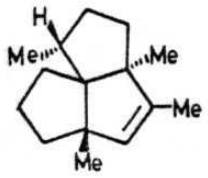
** Tricyclo $(6.3.0.0^{2,6})$ undecane.

*** Tricyclo $(6.3.0.0^{1,5})$ undecane.

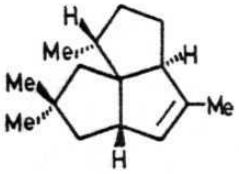
**** Tetracyclo $(6.6.0.0^{4,8}, 0^{10,14})$ tetradecane.

ground for the development of new cyclopentane annulation technologies as well as strategies for the rapid and simultaneous creation of two or more five membered

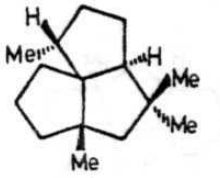
Chart I.2



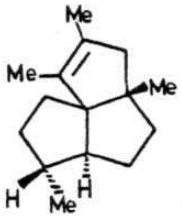
ISOCOMENE [3a]



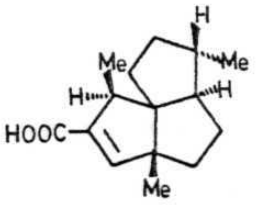
PENTALENENE [3c]



SILPHINENE [3e]



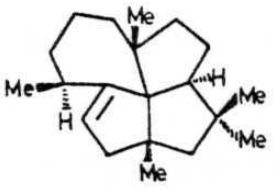
SILPHIPERFOLENE [3e]



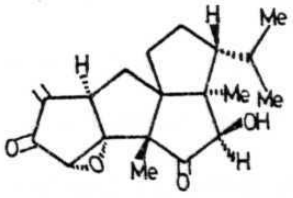
SUBERGORGIC ACID [3f]

rings. Indeed polyquinane synthesis has been referred to as one of the 'vibrant' areas in contemporary organic chemistry research[7].

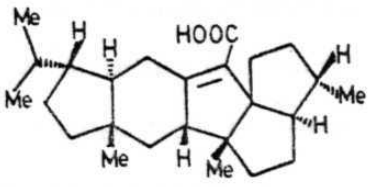
Chart I.3



LAURENENE [5]



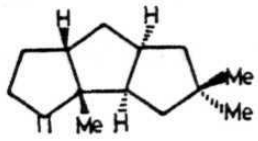
CRINIPELLIN A [4]



RETIGERANIC ACID [6]

In our research group, a programme directed towards the total synthesis of polyquinane natural products was initiated in 1980. As a part of this endeavour, linearly fused triquinanes, hirsutene 4[8], coriolin 5[9] (both from the fermentation broth of Coriolus consors) and capnellene 6[10] (from the soft coral Capnella imbricata)

were selected as synthetic objectives. While the total synthesis of hirsutene 4 and coriolin 5 were pursued and completed[16a,b] by other colleagues in the group, the total synthesis of capnellene 6 was selected as a synthetic goal to form a part of



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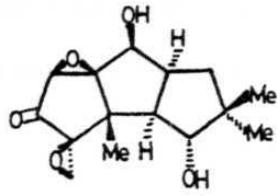

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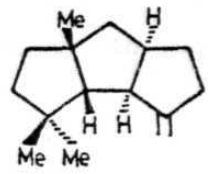


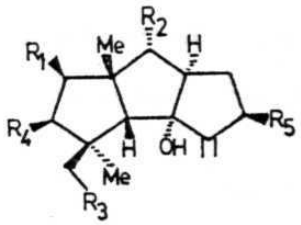
6

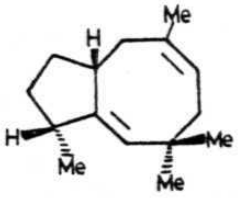
this dissertation. Happily, the synthesis of the sesquiterpene hydrocarbon (±)-capnellene* was achieved in 1983[16c,d] but some related work was carried out subsequently. In this chapter of the thesis, a full account of the work directed towards capnellene 6 is given.

The capnellanes are a group of C_{15}-sesquiterpenoids of marine origin, composed of three five membered rings fused linearly in a cis-anti-cis fashion and were reported by Djerassi et. al. in 1974. The first member of this family was isolated[11a] from the dichloromethane extract of the soft coral Capnella imbricata (Coelenterata, octacorallia) collected off Sewaru, Leti island, Indonesia. This was identified as $\Delta^{9,12}$-capnellene-3β,8β,10α-triol 7d by single crystal x-ray structure determination. After a few years, other 'capnellanols' 7a-f[11a,b] were revealed from the same soft coral species collected nearby and at Laing island, Papua-New Guinea. Interestingly, the composition of sesquiterpene fractions containing 'capnellanols' varied

*The hydrocarbon 6 has always been referred to as $\Delta^{9,12}$-capnellene in literature. However, as 6 is the only known hydrocarbon of this type, we prefer to refer it simply as capnellene, like hirsutene, etc.

in composition from colony to colony and site of collection. Along with these polyhydroxylated compounds, two hydrocarbons were also isolated. These were capnellene 6, the likely biogenetic precursor of 'capnellanols' 7a-f and precapnelladiene 8[12], the presumed immediate precursor of the tricyclopentanoid skeleton found in 6 and 7a-f. The 'capnellanols' exhibit some biological activity and in particular their role in supporting the marine eco-system has been noted. There is evidence to suggest





7a $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = OH$

b $R_1 = R_2 = R_3 = H$; $R_4 = R_5 = OH$

c $R_1 = R_3 = H$; $R_2 = R_4 = R_5 = OH$

d $R_2 = R_3 = R_4 = H$; $R_1 = R_5 = OH$

e $R_2 = R_4 = H$; $R_1 = R_3 = R_5 = OH$

f $R_1 = R_3 = R_4 = H$; $R_2 = R_5 = OH$

PRECAPNELLADIENE 8

that these polyhydroxylated sesquiterpenes act as chemical defence agents in the coral reef biomass to ward off algal and microbiol growth and to prevent larval settlement[11c-e].

The capnellane group of sesquiterpenes pose a considerable synthetic challenge. It emanates from the presence of a linear triquinane framework with cis-anti-cis stereochemical disposition at the ring junctions and the presence of

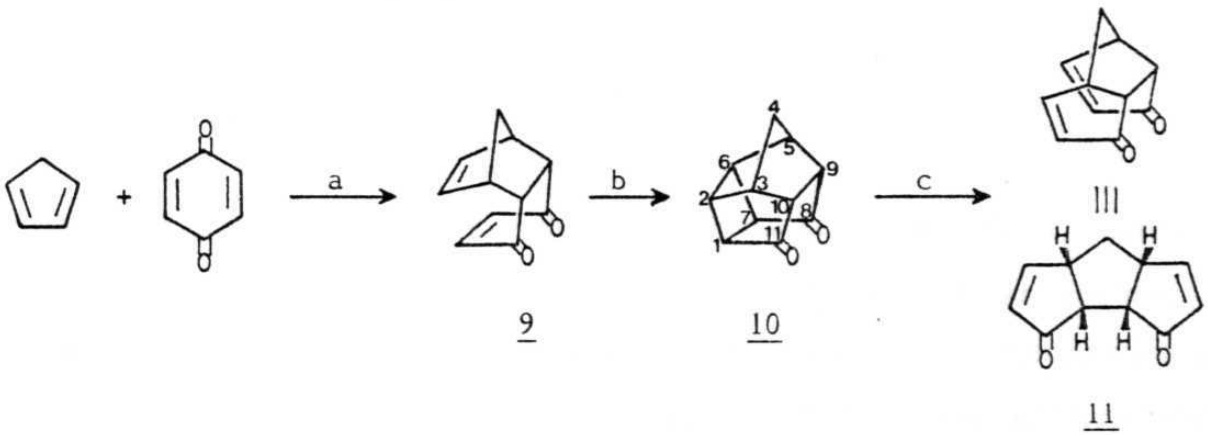
quaternary carbon centres. The more complex 'capnellanols' 7a-f have a network of oxygen functionalities and upto seven stereogenic centres. Their creation is a much more daunting task requiring generation and management of multiple oxygen functionalities with high level of stereochemical control. In particular, the ubiquitous presence of the bisallylic alcohol moiety in 7a-f requires development of new synthetic protocols. However, by comparison the hydrocarbon capnellene 6 is a much less formidable, but yet substantially appealing synthetic target. It embodies the primary challenge of all capnellanes as far as carbocyclic ring construction with quaternary centres and establishment of cis-anti-cis stereochemistry is concerned. Therefore, initial synthetic forays were all targeted towards capnellene 6.

Between 1982 and 1987, nearly a dozen syntheses of capnellene 6 and derivatives have been reported[13-17]. These have been accomplished by the research groups led by Dreiding[13a], Oppolzer[13b], Little[14], Paquette[15], Mehta[16], Piers[17a], Stille[17b], Liu[17c], Curran[17d] and Grubbs[17e]. While some of these syntheses evolved around the more obvious sequential cyclopentannulation strategy, others employed synthetic strategems for simultaneous generation of two or three five membered rings. In addition, construction of the capnellene skeleton along the biogenetically postulated route has been achieved by the groups of Matsumoto[18] and Pattenden[19]. Very recently, efforts have been mounted towards 'capnellanols', and Shibasaki et. al.[20] have accomplished the syntheses of $\Delta^{9,12}$-capnellene-8 β,10α-diol 7a and $\Delta^{9,12}$-capnellene-3β,8β,10 α-triol 7d. A synthesis of the diol 7a has also been achieved by Pattenden's group[21]. Several recent reviews[1d,22] adequately catalogue synthetic efforts towards capnellane group of sesquiterpenes and these are therefore not discussed in detail here. However, up-to-date references to these works have been provided above. With this background, we now venture to describe our total synthesis of (±)-capnellene 6.

I. 3. GENERAL STRATEGY

The cornerstone of our synthetic strategy was the recognition that the pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione (Cookson's caged dione 10)[23], readily available from 1,3-cyclopentadiene and p-benzoquinone in two high yielding steps, is a rich repository of five-membered rings which can be extracted through a thermally induced regioselective cyclobutane fragmentation (C_1-C_7 and C_2-C_6 cleavage) to furnish cis-syn-cis-triquinane bisenone 11, scheme I.1 [24]. Quite remarkably, commercially available cyclopentadiene and p-benzoquinone can be transformed

Scheme I.1

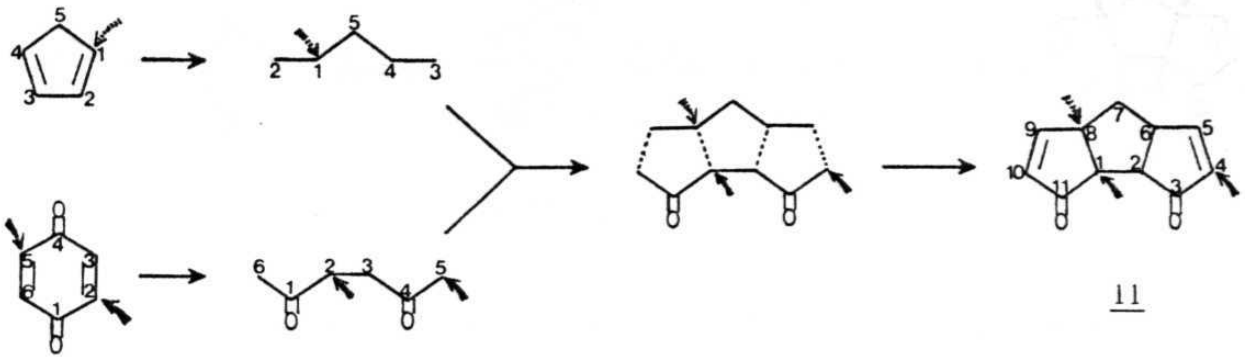


Reagents : (a) Heat, (b) Light, (c) Heat.

in three steps into three linearly fused five-membered rings using only heat, light and heat, respectively, as the reagents. The key chemical change involved in this approach is the stepwise (photo-thermal) metathesis of the Diels-Alder adduct 9 to 11[24]. Adaptation of scheme I.1 to the synthesis of triquinane natural products requires installation of appropriate methyl substituents on the carbocyclic framework, change of cis-syn-cis stereochemistry of the triquinane to the desired cis-anti-cis pattern and functional group adjustments.

A scrutiny of the origin of the carbon atoms of the triquinane system 11 from its precursors revealed that its top half (C_5-C_9) was derived from 1,3-cyclopentadiene and the bottom half (C_{10}, C_{11}, C_1-C_4) from p-benzoquinone, as shown in scheme I.2[16d]. This provided direct, more or less unlimited scope for the induction

Scheme I.2

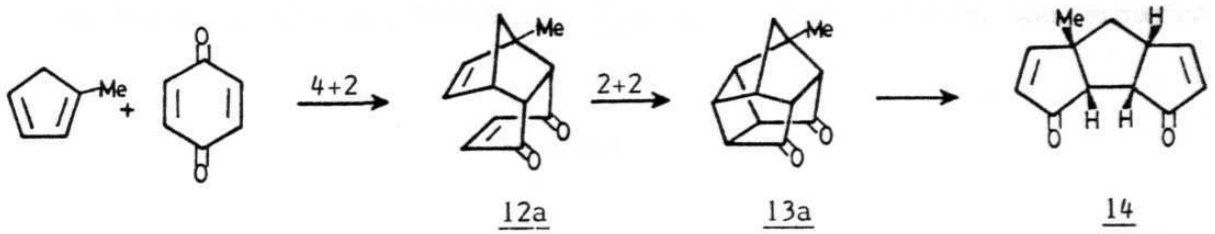


11

of methyl or other groups on the carbocyclic framework, particularly at quaternary centres. For example, the methyl groups at C_1 and C_4 (dark arrows) required to generate the hirsutene 4 skeleton could be readily traced to the 2,5-positions of p-benzoquinone. Similarly, the methyl group at C_8 (dotted arrow) required to construct the desired capnellene 6 skeleton could be built into the complementary C_1 position of the starting 1,3-cyclopentadiene. The stereochemical problem could be readily sorted out as the cis-syn-cis-triquinane system 11 has a folded shape and is sterically crowded, it should be amenable to epimerization to the less hindered and thermodynamically more stable cis-anti-cis form of natural products either directly or through transposition of the enone double bond to the tetrasubstituted position and stereoselective reduction. Finally, the bisenone moieties on the triquinane framework constituted excellent functionalities with desirable location and oxidation level for further manipulation. Thus, a general protocol for the synthesis of all triquinane natural products emerged.

The foregoing analysis identified p-benzoquinone and 1-methylcyclopentadiene as the starting materials for obtaining the pivotal C_{12}-triquinane bisenone 14 precursor of capnellene via the three step photo-thermal metathesis as shown in scheme I.3. Some difficulties during the Diels-Alder cycloaddition were anticipated

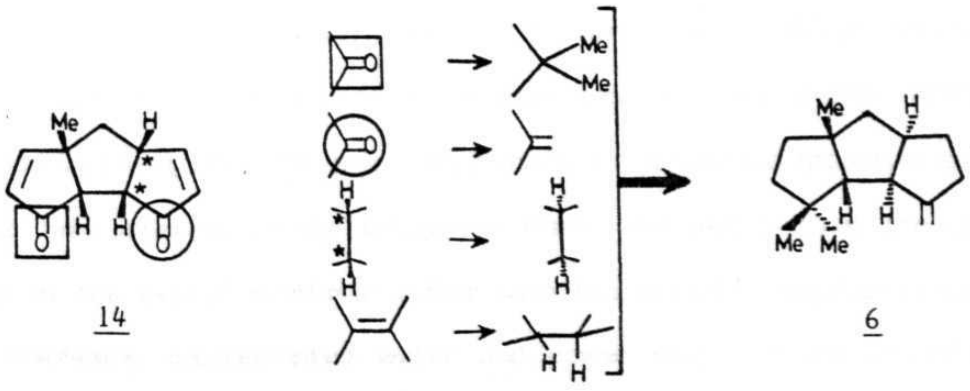
Scheme I.3



12a 13a 14

because of the intervention of the thermal [1s, 5s]-sigmatropic processes in 1-methylcyclopentadiene[25]. These were sought to be overcome through the separation of regioisomeric products at an appropriate stage. Further elaboration of bisenone 14 to the natural product required four key operations, scheme I.4. These were identified

Scheme I.4

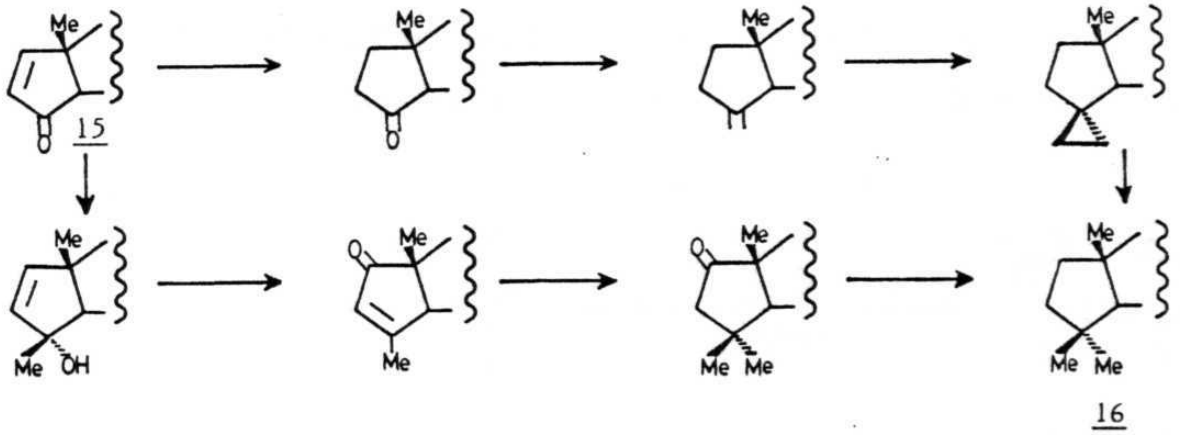


14 6

as gem-dimethylation of the boxed carbonyl, methylenation of the circled carbonyl, inversion of stereochemistry at the starred centres and elimination of the redundant functionalities. Reducing the scheme I.4 into practice required selection of appropriate

reactions and their orchestration in a logical sequence. While the methylenation of the circled carbonyl in the scheme I.4 was a fairly straight forward proposition through the Wittig reaction, the gem-dimethylation of the other carbonyl had to be a multistep sequence. Two approaches emanating from the enone moiety 15 were considered for this purpose and the reactions leading to the dimethyl compound 16 are indicated in scheme I.5. Finally, the cis-anti-cis stereochemistry was expected

Scheme I.5

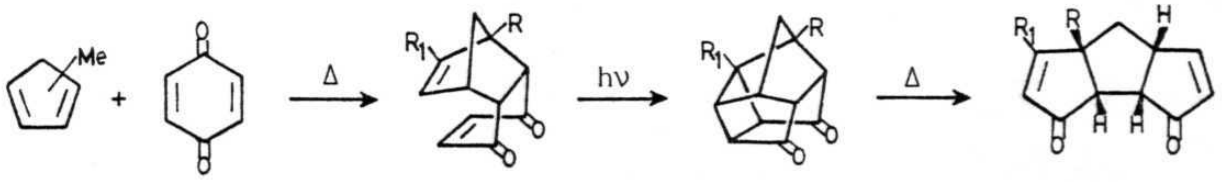


to result from the stereoselective reduction of the tetrasubstituted double bond. The guiding influences in the choice of reactions were to have overall economy in terms of steps involved, minimal or no deployment of protective groups, exploitation of the steric bias inherent in the triquinane frame and last but not the least the compatibility of the overall synthetic effort with the available logistics support (e.g., number of manhours, uninterrupted water and power supply in the laboratory and availability of chemicals and reagents in India!).

Thus, with a short, direct way to the key C_{12}-triquinane synthon 14 of capnellene on the anvil and the conceptual framework for functional group alterations leading to the natural product defined, the stage was set for the execution of the synthetic plan.

I. 4. SYNTHESIS OF (±)-CAPNELLENE

As already mentioned, the first major stride towards capnellene 6 had to be the successful implementation of the scheme I.3 leading to the rapid and efficient acquisition of the C_{12}-triquinane bisenone 14. For this purpose 1-methylcyclopentadiene and p-benzoquinone were identified as the cheap and abundantly available starting materials. Diels-Alder reaction between them furnished a 60:40 mixture[26] of two regioisomeric endo-adducts 12a and 12b, as indicated by the ^1H NMR spectrum of the total reaction mixture. As apprehended, 4+2 adduct formation from 1-methylcyclopentadiene and its [1,5] sigmatropy derived isomer (2-methylcyclopentadiene) had occurred. Luckily, the major, required adduct 12a could be obtained pure through fractional crystallisation of the mixture albeit in poor yield

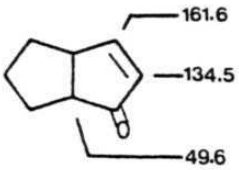


12a R=Me; R_1=H 13a R=Me; R_1=H 14 R=Me; R_1=H

b R=H; R_1=Me b R=H; R_1=Me 17 R=H; R_1=Me

and was readily characterised on the basis of its quaternary methyl singlet at δ1.40 in the ^1H NMR spectrum. Irradiation of an ethyl acetate solution of 12a in a pyrex vessel with a 450-W Hanovia lamp led to a smooth intramolecular $\pi^2_s+\pi^2_s$ photocycloaddition and the pentacyclic dione 13a, mp 176°C, was obtained in high yield. The photocycloaddition of 12a could also be carried out efficiently in the bright sunlight of Hyderabad but much longer reaction time was required. The structure of the pentacyclic dione 13a was fully consistant with its ^1H NMR and ^{13}C NMR spectral data.

Having obtained the pentacyclic dione 13a, attention was turned to the critical thermal fragmentation of the cyclobutane ring to complete the two step photo-thermal metathesis of 12a to the triquinane bisenone 14. This was successfully achieved employing the flash vacuum pyrolysis (FVP) technique previously described by us[16d,24]. Slow sublimation of 13a through a home built quartz column, packed with quartz chips, at 530°C (0.1 mm) resulted in its near quantitative conversion to the triquinane system 14, mp 94-97°C. The UV spectrum: λ_{max}^{MeOH} 216nm and IR spectrum: ν_{max} 1730 and 1600 cm^{-1} of 14 indicated the presence of 2-cyclopentenone substructure. The ^{1}H NMR spectrum [Fig.I-1] of the bisenone 14 showed the presence of two characteristic β-proton resonances at δ 7.48 and 7.40 of the 2-cyclopentenone moiety along with quaternary methyl resonance at δ 1.30. The ^{13}C NMR spectrum [Fig.I-2] of 14 revealed a striking similarity to the other structurally related polyquinanes 18 and 19[24,27]. The assignment of folded cis-syn-cis stereochemistry



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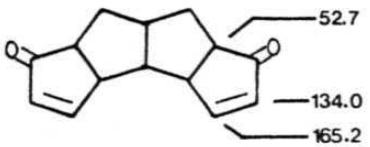

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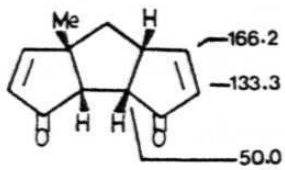
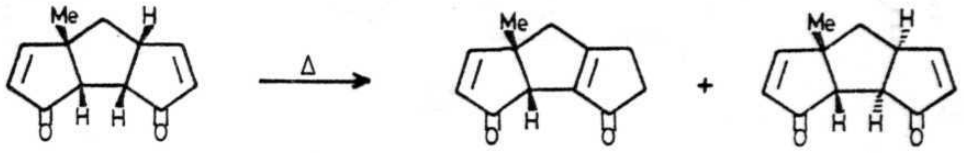


14

of 14 follows from its genesis from the caged pentacyclic dione 13a and was further supported by its conversion to the pentacyclic dione 13a on exposure to UV irradiation.

Although, we demonstrated the sequence from 12a to 14 using pure 12a, the loss of material during purification of 12a by fractional crystallisation was too severe and therefore, in practice, we carried the mixture of 12a and 12b to the FVP stage through 13a and 13b, where bisenones 14 and 17 were readily separable by column chromatography. In this manner the required cis-syn-cis-bisenone 14 could be routinely prepared in 20-30g quantities. The unrequired isomeric bisenone

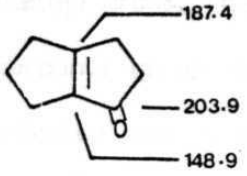
17 was characterised on the basis of its UV spectrum: λ_{max}^{MeOH} 222 and 217 nm, IR spectrum: ν_{max} 1720, 1620 and 1600 cm^{-1}, ^1H NMR spectrum [Fig.I-3, β-proton of the enone moiety



14 20 21

at δ 7.44 as a 'dd' and β-methyl of the enone moiety at δ2.08] and ^{13}C NMR spectrum [Fig.I-4, vinylic β-carbons of the enone moiety at δ 178.5(s) and 165.3(d)].

With the assured supply of the key C_{12}-bisenone 14, attention was turned to the important operation, namely, inversion of stereochemistry at the ring junction to generate the desired cis-anti-cis-triquinane system. The most straight forward expedient by which such an inversion at the ring junction stereochemistry could be achieved was through the isomerisation of one of the enone moieties in 14 to the more substituted bridgehead position of 20 and catalytic hydrogenation or re-isomerisation back to the original position by taking advantage of the greater thermodynamic stability of the cis-anti-cis-isomer over the folded cis-syn-cis-isomer. Thus, it became necessary to first find suitable conditions for the relocation of double bond in 14 to 20 and destroying the ring junction stereochemical array before recreating it in the desired cis-anti-cis fashion. Earlier experience[16d,24] with triquinane precursors of hirsutene encouraged us to attempt a thermal isomerisation of the enone moiety. When a solution of cis-syn-cis-bisenone 14 was heated in benzyl benzoate for 7 min. at 316°C, an equilibrium mixture (12:1) of 20 and 21 was obtained. The structure of the major product 20, mp 97-98°C, followed from the ^{13}C NMR spectrum which showed the carbon resonances of the tetrasubstituted enone moiety at δ 183.8(s) and 147.6(s). These resonances are characteristic and similar to those exhibited by the structurally related polyquinanes 22 and 23[24,27].



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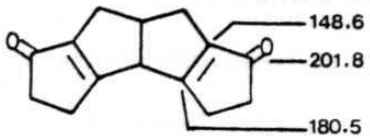
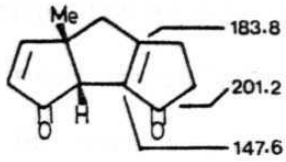


23



20

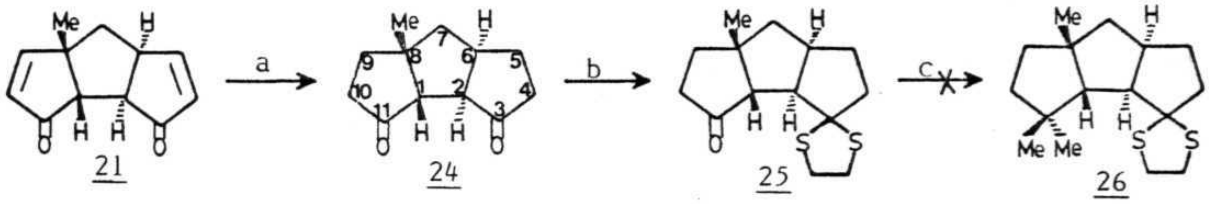
The minor product of the thermal isomerisation reaction, isolated in very small amounts, turned out to be the cis-anti-cis-bisenone 21, mp 67-68°C. The assignment of cis-anti-cis structure 21 followed from its spectral data and in particular from the ^{1}H and ^{13}C NMR spectra [Fig.I-5 and I-6, respectively] which were similar to the cis-syn-cis-isomer 14. When the cis-anti-cis-bisenone 21 was exposed to UV irradiation it did not undergo intramolecular (2+2) cyclisation to the caged system. This further confirmed its formulation.

Although the cis-anti-cis-bisenone 21 of required stereochemical pattern was realised, it constituted <10% of the reaction mixture. Furthermore, the product recovery from the high temperature isomerisation reaction was also unsatisfactory. Therefore, an alternate avenue for efficiently carrying out the enone transposition was sought. After some exploratory experiments, it was discovered that 1,5-diazabicyclo[5.4.0]undeca-5-ene (DBU) smoothly converted 14 into the tetrasubstituted bisenone 20 in >90% yield. However, in the case of formation of 20 the cis-anti-cis-isomer was not observed.

At this stage, two options were available. Either we could employ the scarce 21 with correct stereochemistry and transform it in very few steps to capnellene 6 or use the more abundant 20, along the route indicated in scheme I.4. We decided to first try out with the cis-anti-cis-bisenone 21. Catalytic hydrogenation of 21 gave the tetrahydro-dione 24. The carbonyl groups in 24 were readily chemo-differentiated due to the steric shielding of the C_{11} carbonyl by the angular

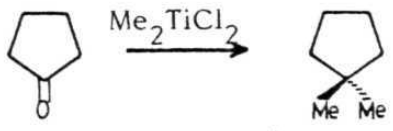
methyl group. Thus, 24 was selectively thioacetalised to 25 quite readily. The exposed carbonyl group now had to be gem-dimethylated to give 26. For this purpose, we selected the single-shot reaction reported recently by Reetz[28] for transforming cyclopentanone 27 into 1,1-dimethylcyclopentane 28 using organo-titanium reagents. The reaction conditions for this transformation are known to tolerate a thioacetal protective group and that is why it was installed. However, several attempts to

Scheme I.6



Reagents & Yields : (a) H_2 - 10% Pd/C, ethyl acetate, quantitative; (b) Ethanedithiol, PTS, benzene, 55%; (c) Me_2TiCl_2.

gem-dimethylate 25 with dimethyltitanium dichloride led no where. We even decided to draw upon the expertise of the Reetz group for effecting this reaction*, but



27 28

the reaction failed in Marburg as well. We attribute this to the considerable steric interference of the angular methyl group on the convex face to the approach of the bulky titanium reagent.

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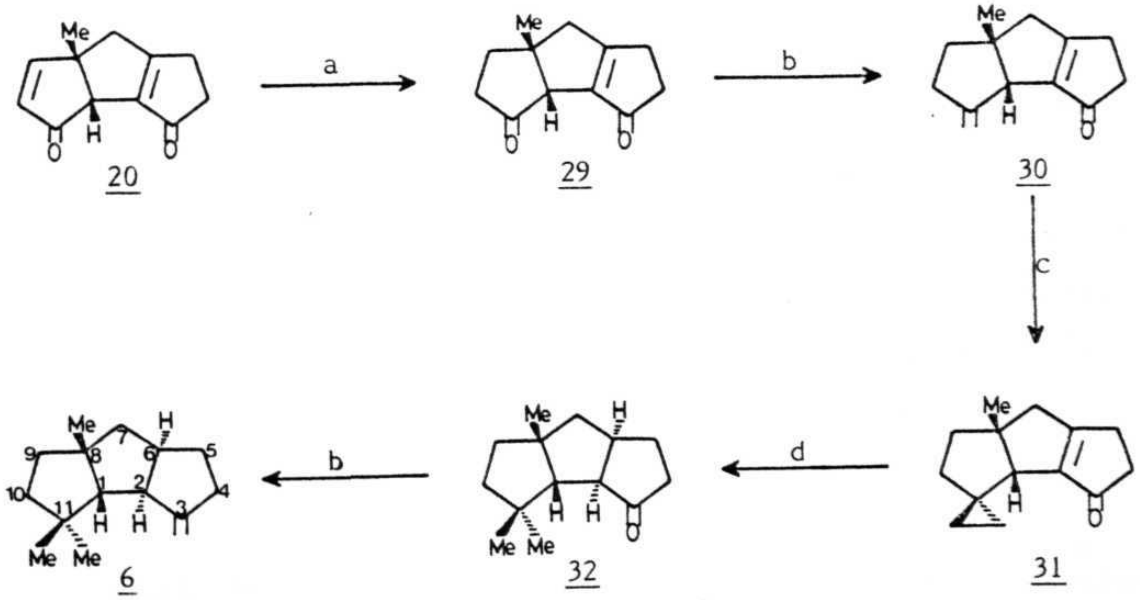
*We thank Professor M.T.Reetz, Fachbereich Chemie der Universitat, Marburg, for performing this reaction for us.

We therefore, decided to switch back to the implementation of scheme I.4. The C_{12}-bisenone 20 was partially hydrogenated over 10% Pd/C to deliver 29, mp 83-84°C in 80% yield. The IR spectrum: ν_{max} 1740,1700 and 1630 cm^{-1} and other spectral data were in agreement with its structure. The two carbonyl groups in 29 were now chemo-differentiated and selective Wittig olefination with the ylide derived from methyltriphenylphosphonium bromide and sodium-t-amyloxide furnished the exo-methylene bearing compound 30. The structure of 30 is fully consonant with its UV spectrum: λ_{max}^{MeOH} 236 nm, IR spectrum : ν_{max} 1700 and 880 cm^{-1}, ^1H NMR spectrum [Fig.I-7, exocyclic methylene proton resonances at δ 4.96 and 5.2] and ^{13}C NMR spectrum [Fig.I-8, exocyclic methylene carbon resonances at δ152.1 and 107.9]. Simmons-Smith cyclopropanation[29] of the exocyclic olefinic bond furnished the spirofused tetracyclic enone 31 in 50% yield. Fortunately, the cyclopropanation

Scheme I.7



Reagents & Yields : (a) H_2-10% Pd/C, ethyl acetate, 80%; (b) $Ph_3PMe^+Br^-$ - $t\text{-}C_5H_{11}O^-Na^+$, toluene, 80%; (c) CH_2I_2-Zn/Cu couple, ether, 50%; (d) H_2-PtO_2, acetic acid, 60%.

reaction could be carried out even in the presence of a sensitive enone moiety and this saved us from any protective group manoeuvre, scheme I.7.

Catalytic hydrogenation of 31 over activated PtO_2 unravelled the C_{11}-gem-dimethyl group and simultaneously reduced the double bond to give directly nor-capnellanone 32. The presence of gem-dimethyl substitution at C_{11} position provided the control element for the stereoselective reduction of the tetrasubstituted double bond to generate the less crowded cis-anti-cis stereochemistry. Since compound 32 has been previously converted to capnellene 6 in one step by Wittig olefination, our synthesis of 32 and comparison* of its spectra (IR and ^1H NMR) with that of Prof.Little's intermediate[14], completed the formal total synthesis of the (±)-capnellene 6, scheme I.7.

In the alternative approach, we employed an alkylative enone transposition[30]-dimethylcuprate addition sequence to generate C_{11}-gem-dimethylated group, scheme I.8. There is an additional advantage in this methodology as it generated an additional oxygen functionality at C_9 and renders this route amenable for adaptation to the complex capnellanols 7a-f. Consequently, bisenone 20 was treated with methylmagnesium iodide to give an intermediate allylic alcohol, which was directly oxidised with pyridinium chlorochromate[31] to give the transposed bisenone 33 in 40% yield from 20. The presence of a 3H resonance at δ 2.24 in the ^1H NMR spectrum due to the β-methyl on a α, β-unsaturated enone secured its structure, scheme I.8.

Controlled sodium borohydride reduction on 33 at -10°C proceeded with acceptable regioselectivity and the 1,4-reduction product 34 was obtained as the

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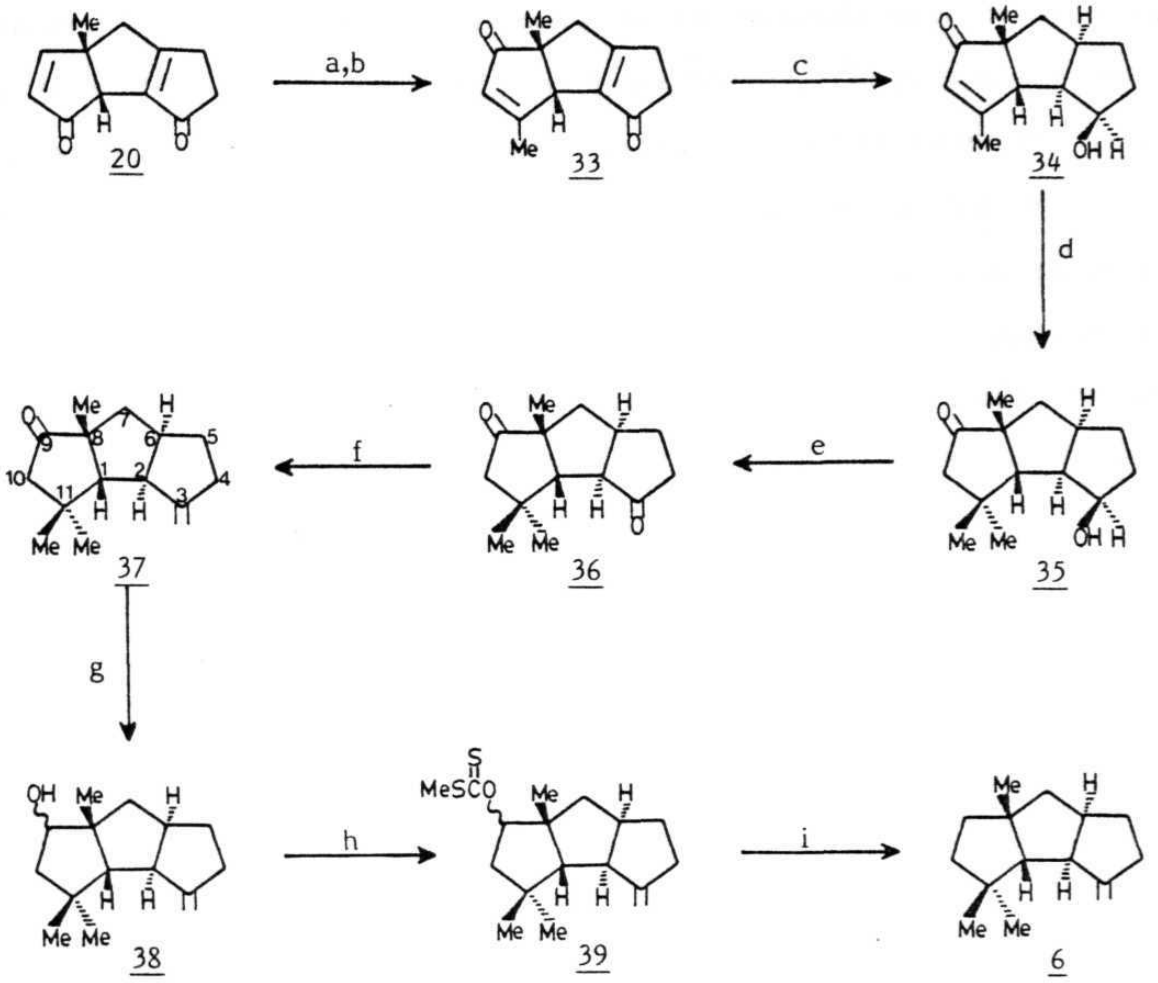
*We thank Professor R.D.Little, University of California, for supplying the comparison spectra of nor-capnellanone and capnellene.

Scheme I.8



Reagents & Yields : (a) MeMgI, ether; (b) PCC, dichloromethane, 40%; (c) $NaBH_4$, methanol, 45%; (d) $LiMe_2Cu$-BF_3-etherate, ether, 88%; (e) PCC, dichloromethane, 88%; (f) $Ph_3PMe^+Br^-$ - $t\text{-}C_5H_{11}O^-Na^+$, toluene, 90%; (g) LAH, ether, 80%; (h) NaH - THF - imidazole - CS_2 - MeI, 88%; (i) $(n\text{-}Bu)_3SnH$, toluene, 53%.

major product of the reaction. The regiochemistry of the hydride attack and structure of the hydroxy-enone 34 were confirmed from its UV spectrum:λ_{max}^{MeOH} 232 nm[characteristic of a β-methylated-2-cyclopentenone] and the ^1H NMR spectrum which retained the resonance due to the β-methyl on the enone moiety at δ 2.12. The presence of two olefinic 'C's at δ 180.9(s) and δ 127.6(d) further supported its structure.

The presence of the alkyl substitution at C_{11} once again provided the control element for the stereoselective reduction of the tetrasubstituted double bond to generate the less crowded cis-anti-cis stereochemistry. Stage was now set for the quaternisation of C_{11} position. Several attempts were made to install the second methyl group at C_{11} position through conjugate addition reactions but none of these were successful. Finally, addition of lithium dimethylcuprate to 34, in the presence of BF_3-Et_2O[32] proceeded smoothly and in good yield to deliver the gem-dimethylated compound 35 in 88% yield. The ^1H NMR spectrum [Fig.1-9, two quaternary methyl singlets at δ 1.16, 6H and 1.30, 3H] and the ^{13}C NMR spectrum [Fig.1-10, 14 signals] were in agreement with the structure of 35, scheme 1.8.

Pyridinium chlorochromate oxidation of 35 furnished the diketone 36 in good yield. Regioselective Wittig methylenation of the less hindered carbonyl group in the diketone 36 with triphenylphosphoniummethylide resulted in the formation of keto-olefin 37 in 90% yield. Finally, the deoxygenation of 37 was achieved by employing Barton's radical based deoxygenation methodology[33]. Reduction of 37 with LAH gave the hydroxy-olefin 38 and was directly converted into the S-methylthiocarbonate 39. Reduction with tri-n-butyltin hydride produced the hydrocarbon capnellene 6 which was found identical (IR and ^1H NMR) with the natural product 6, scheme I.8.

The two approaches to capnellene emanating from the common C_{12}-bisenone 14 and successfully executed by us are summarised in schemes I.7 and I.8.

I. 5. SUMMARY AND OUTLOOK

Short and stereoselective synthesis of the sesquiterpene hydrocarbon capnellene 6 by two different routes from a common triquinane precursor has been achieved. The construction of the capnellene framework outlined here is

of general applicability and has built-in flexibility. It offers encouraging prospects for pursuing the total synthesis of more complex capnellanols 7a-f. Finally, attainment of capnellene 6 in quick succession to hirsutene 4[16a] and coriolin 5[16b] further demonstrates the efficacy of our photo-thermal metathesis sequence for the construction of triquinane natural products. Indeed, with minor, tactical adjustment of alkyl substituents and functionality, it should be possible to synthesise all linearly fused triquinane natural products following this methodology[16d].

I. 6. EXPERIMENTAL

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

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

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

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

Nuclear magnetic resonance spectra: Proton magnetic resonance spectra (100MHz) were recorded on Jeol MH-100 spectrometer or Jeol FX-100 spectrometer and Carbon-13 magnetic resonance spectra (25.0 MHz) were recorded on Jeol FX-100 spectrometer. ^{1}H and ^{13}C NMR samples were made in chloroform-d solvent and chemical shifts were reported in δ scale using tetramethylsilane (Me_4Si) as the internal standard. In the ^{13}C NMR spectra, off-resonance multiplicities, when

recorded, are given in parentheses. The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. ^{13}C NMR assignments differing by only 2-3 ppm can in some cases be interchanged.

Mass spectra: Mass measurements were carried out on AEI MS-5076 mass spectrometer.

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

Chromatography: Analytical thin-layer chromatographies (TLC) were performed on (10x5 cm) glass plates coated (250 μm) with Acme's silicagel 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 vapor or UV light or by spraying sulfuric acid and heating the plates at 120°C. Column chromatography was performed using Acme's silicagel (100-200 mesh) and the column was usually eluted with ethyl acetate-hexane or ethyl acetate-benzene mixtures.

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°Cand 80°C. Dichloromethane was distilled over P_2O_5. Toluene 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 Parr hydrogenation apparatus in 250 mL pressure bottles. All solvent extracts were washed with 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, NMR spectroscopy and for crystalline solids, material having the identical melting points.

Methyl-endo-tricyclo[6.2.1.$0^{2,7}$]undeca-4,9-diene-3,6-dione (12a&b):

To an ice cooled solution of p-benzoquinone (16.2 g, 0.15 mol) in benzene (200 mL) was added at once 12 g (0.15 mol) of freshly cracked methylcyclopentadiene in benzene (10 mL). The mixture was stirred for 30 min. at ambient temperature and the solvent was removed. The solid residue on crystallisation from petroleum ether furnished 12a and 12b as yellow needles 26 g (95% of methyl isomers, 60:40 respectively), while this adduct mixture was used as such for the subsequent steps, pure 12a was obtained for characterisation purposes through repeated crystallisations from methanol as pale yellow needles, mp 115°C (lit.116-117°C)[26].

IR spectrum (KBr), ν_{max}: 2950, 1670 (carbonyl), 1600 (olefinic), 1300, 860 and 740 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ1.40 (3H,s, $\underline{H_3}C-\overset{|}{\underset{|}{C}}-$), 1.56(3H,s), 2.9(1H,d,J=8Hz), 3.4(2H,m), 5.98(2H,ABq,J_{AB}=6Hz, $\underline{HC}=\overset{|}{\underset{|}{C}}H$) and 6.53(2H,s,$\underline{HC}=\overset{|}{\underset{|}{C}}H$).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ 199.3(s), 198.7(s), 142.1(d), 141.7(d), 139.0(d), 134.9(d), 57.8(s), 55.4(t), 52.7(d), 50.9(d), 49.2(d) and 17.5(q).

Methyl-pentacyclo[5.4.0.$0^{2,6}0^{3,10}0^{5,9}$]undeca-8,11-dione (13a&b):

The above adduct mixture(20 g, 0.106 mol) in nitrogen purged ethyl acetate (750 mL) was irradiated with a Hanovia 450 W medium pressure mercury vapor lamp in a quartz immersion well through pyrex filter for 45 min. Removal of solvent and crystallization gave a mixture of pentacyclic diones 18 g (90%). The mixture was used as such for the next step. However, for characterisation purposes an analytically pure sample of pentacyclic dione 12a was prepared through repeated crystallizations of the mixture from acetone, colourless needles, mp 176°C (lit mp 175°C)[26].

IR spectrum (KBr), ν_{max}: 2950, 1760 (carbonyl), 1730 (carbonyl), 1460 and 1060 cm^{-1}.

^{1}H NMR spectrum (100 MHz, $CDCl_3$): δ 1.20(3H,s, $\underline{H_3}C-\overset{|}{\underset{|}{C}}-$), 1.95(2H, ABq, J_{AB}=11Hz) and 2.23-3.55(7H,m).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ 211.8(s), 211.1(s), 60.0(d), 55.5(d), 52.4(d), 45.9(t), 44.4(2C,d), 44.2(d), 42.9(d), 39.6(d) and 15.7(q).

Analysis for $C_{12}H_{12}O_2$ Calcd: C, 76.57; H, 6.43.
Found: C, 76.42; H, 6.45.

Methyl-cis-syn-cis-tricyclo[6.3.0.0^{2,6}]undeca-4,9-diene-3,11-dione (14&17):

The mixture of pentacyclic diones (60:40, 2.0 g, 0.01 mol) was sublimed at 130°C/0.3 mm through a quartz column [1.5 x 30 cm, connected to a vacuum line and provided with a collection flask and liquid nitrogen trap. The quartz tube was heated with a nichrome wire wound around it and was insulated with asbestos padding. The temperature was controlled by a variac and was measured by a Chromel-Alumel thermocouple on a Keithley digital multimeter. The quartz tube was preheated and equilibrated at 530°C]. The pyrolysed product from the collection flask was charged on a silica gel column (50 g). Elution with 50% ethyl acetate--benzene furnished 1.1 g (55%) of 14, which was crystallised from benzene-petroleum ether as colourless plates, mp 93-94°C.

UV spectrum λ_{max}^{MeOH}:216 nm (ε :11,650).

IR spectrum (KBr), ν_{max}: 3100, 2950, 1730 (carbonyl), 1600 (olefinic), 1470, 1350, 1200 and 840 cm^{-1}.

^{1}H NMR spectrum (100 MHz, $CDCl_3$, Fig.I-1): δ 1.30(3H,s, $\underline{H_3}C-\overset{|}{\underset{|}{C}}-$), 2.08(2H,d, J=8Hz), 2.80(1H,d,J=12Hz), 3.28(1H,dd,J_1=12Hz,J_2=6Hz), 3.60(1H,m), 5.72(1H,d, J=6Hz, -CH=C<u>H</u>-C=O), 5.84(1H,dd,J_1=6Hz,J_2=3Hz, -CH=C<u>H</u>-C=O), 7.40 (1H,d,J=6Hz, -C<u>H</u>=CH-C=O) and 7.48(1H,dd,J_1=6Hz, J_2=3Hz, -C<u>H</u>=CH-C=O).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$, Fig.I-2): δ207.7(s), 207.6(s), 170.7(d), 166.2(d), 133.3(d), 130.8(d), 60.4(d), 57.0(s), 53.1(d), 50.0(d), 38.8(t) and 27.2(q).

Analysis for $C_{12}H_{12}O_2$ Calcd: C, 76.57; H, 6.43.

Found: C, 76.67; H, 6.48.

Further elution with 60% ethyl acetate-benzene furnished 17 (800 mg, 40%) which was crystallised from benzene-petroleum ether as micro-crystals, mp 115°C.

UV spectrum λ_{max}^{MeOH}: 222 and 217 nm (ε:12,400 and 10,950).

IR spectrum (KBr), ν_{max}: 3080, 2950, 1720 (carbonyl), 1620 (olefinic), 1600, 1420, 1200, 860 and 760 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$, Fig.I-3): δ 2.08(3H,s,$\underline{H}_3C$-$\dot{C}$=$\dot{C}$), 2.10-2.40 (1H,m), 3.10-3.68(5H,m), 5.60(1H,s,-CH=C$\underline{H}$-$\dot{C}$=O), 5.88(1H,dd,J_1=8Hz,-J_2=4Hz, H_3C-$\dot{C}$=C$\underline{H}$-$\dot{C}$=O)and 7.44(1H,dd,J_1=8Hz,J_2=4Hz, -$\underline{H}$C=CH-$\dot{C}$=O).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$, Fig.I-4): δ 207.4(s), 206.2(s), 178.5(s), 165.3(d), 133.2(d), 129.7(d), 54.3(d), 53.3(d), 52.4(d), 50.2(d), 29.5(t) and 17.3(q).

Analysis for $C_{12}H_{12}O_2$ Calcd: C, 76.57; H, 6.43.

Found: C, 76.59; H, 6.43.

Photocyclisation of 14: A solution of 188 mg (1 mmol) of 14 in N_2 purged ethyl acetate (180 mL) was irradiated using Hanovia 450 W medium pressure mercury vapor lamp in a quartz immersion well with a pyrex filter for 40 min. The TLC, IR and ^1H NMR of the product after removal of the solvent was identical with the pentacyclic dione 13a.

Thermal equilibration of 8 β-methyl-tricyclo[6.3.0.$0^{2,6}$]undeca-4,9-diene-3,11-dione(14):

A solution of bisenone 14 (1g, 5.31 mmol) in benzyl benzoate (10 mL) was refluxed (316°C) for 7 min. using a salt bath. GLC analysis of the mixture indicated the presence of two compounds in the ratio of 12:1. The mixture was

diluted with dichloromethane (10mL) and charged on a silicagel column (30 g). Elution with dichloromethane removed all benzyl benzoate impurities. Further elution with 20% ethyl acetate in benzene furnished 70 mg (7%) of the cis-anti-cis-bisenone 21 which was recrystallised from ether-petroleum ether mp 67-68°C.

UV spectrum λ_{max}^{MeOH} 215 nm (ε :10,500).

IR spectrum (KBr), ν_{max}: 3080, 2950, 1720 (carbonyl), 1640 (olefinic), 1590, 1420, 1210 and 1040 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$ Fig.I-5): δ 1.24 (3H,s,$\underline{H}_3C-\overset{|}{C}-$), 1.6(1H, ABq,$J_{AB}$=14Hz), 2.16 (1H,ABq,$J_{AB}$=14Hz); 2.62(1H,d,J=2Hz), 2.9(1H,dd,-J_1=8Hz, J_2=2Hz), 3.4(1H,br m), 6.0(1H,d,J=8Hz, -CH=C$\underline{H}$-C=O), 6.1(1H,dd,J_1=8Hz, J_2=2Hz,-CH=C$\underline{H}$-C=O), 7.58(1H,d,J=6Hz, -C$\underline{H}$=CH-C=O) and7.80(1H,dd,J_1=6Hz,J_2=4Hz, -C$\underline{H}$=CH-C=O).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$ Fig.I-6): δ 209.4(s), 209.0(s), 170.7(d), 167.3(d), 130.8(d), 129.3(d), 58.9(d), 55.5(s), 52.8(d), 47.8(d), 41.2(t) and 25.3(q).

Analysis for $C_{12}H_{12}O_2$ Calcd: C, 76.57; H, 6.43.
Found: C, 77.12; H, 6.50.

Further elution with 50% ethyl acetate in benzene furnished 800 mg (80%) of the tetrasubstituted bisenone 20. Crystallisation of 20 from acetone-petroleum ether yielded colourless cubic crystals, mp 97-98°C.

UV spectrum λ_{max}^{MeOH} : 244 and 214 nm (ε : 5350 and 16150).

IR spectrum (KBr), ν_{max}: 3080, 2950, 1720 (carbonyl), 1640 (olefinic), 1590, 1430, 1200, 1040 and 780 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.48(3H,s, $\underline{H}_3C-\overset{|}{C}-$), 2.40-2.76-(6H,m) 3.16 (1H,s), 5.98(1H,d,J=8Hz, -CH=C$\underline{H}$-C=O)and 7.5(1H,d,J=8Hz,-C$\underline{H}$=CH-C=O).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ 204.7(s), 201.2(s), 183.8(s), 168.9(d), 147.6(s), 129.8(d), 57.5(s), 57.2(d), 42.6(t), 39.6(t), 25.3(t) and 25.0(q).

Analysis for $C_{12}H_{12}O_2$ Calcd: C, 76.57; H, 6.43.
Found: C, 76.22; H, 6.32.

8 β-Methyl-cis-anti-cis-tricyclo[6.3.0.0^{2,6}]undeca-3,11-dione (24):

A solution of cis-anti-cis-bisenone 21 (375 mg, 1.99 mmol) was hydrogenated over 10% Pd/C (15 mg) catalyst at 1 atm for 20 min. Catalyst was removed by filtration and the filtrate was concentrated. Crystallisation from ether-petroleum ether furnished white crystalline needles of 24 (375 mg, quantitative), mp 68-69°C.

IR spectrum (KBr), ν_{max}: 2950, 1740 (carbonyl), 1460, 1180 and 1140 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.0-2.8(13H,m) and 1.2(3H,s, $\underline{H_3}C-\overset{|}{\underset{|}{C}}-$).

^{13}C NMR spectrum (25.0MHz,$CDCl_3$): δ219.4(2C), 60.9(2C), 56.7, 48.2, 45.2, 39.9, 37.9, 34.4, 33.1, 26.8 and 23.2.

3-(Ethylene dithio)-8 β -methyl-cis-anti-cis-tricyclo[6.3.0.0^{2,6}]undeca-11-one (25):

A solution of saturated dione 24 (100 mg, 0.52 mmol), ethanedithiol (0.2 mL) and p-toluenesulphonic acid (5 mg) in dry benzene (20 mL) was refluxed with Dean-Stark water separator for 12h. The reaction mixture was poured into 10% Na_2CO_3 (20 mL) and the organic layer was washed with 10% NaOH, water and dried over Na_2SO_4 Evaporation of the solvent furnished a viscous oil, which was charged on a silica gel column (5 g). Elution with benzene furnished the thioacetal 25 (42 mg, 55%).

IR spectrum (neat), ν_{max}: 2950, 1740 (carbonyl), 1465, 1240 and 1150 cm^{-1}.

^{1}H NMR spectrum (100 MHz, $CDCl_3$): δ 1.2(3H,s, $\underline{H_3}C-\overset{|}{C}-$),1.4-2.8 (13H,m) and 3.3 (4H,m).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ221.2, 76.3, 65.9, 61.1, 51.9, 48.2, 44.5, 41.3, 40.5, 38.9, 38.8, 34.4, 29.8 and 23.2.

8 β-methyl-tricyclo[6.3.0.0^{2,6}]undeca-2,9-diene-3,11-dione (20):

Bisenone 14 (1 g, 5.31 mmol) and DBU (1 g) in dichloromethane (25mL) were refluxed for 40 h in a RB flask fitted with a reflux condensor. The reaction mixture was diluted with dichloromethane (20 mL) and washed with 30% HCl (25 mL x 3). The organic phase was washed and dried. Removal of solvent gave tetrasubstituted bisenone 20, 900 mg (90%), which was found identical (IR, NMR, GLC) with that of the thermal equilibrium product.

8 β-methyl-tricyclo[6.3.0.0^{2,6}]dodeca-2(6),11(12)-diene-3-one (30):

Tetrasubstituted bisenone 20 (500 mg, 2.65 mmol) was hydrogenated over 50 mg of 10% Pd/C catalyst in ethyl acetate (30 mL). After the consumption of approximately 1 mole equivalent of hydrogen, the catalyst was filtered and the solvent was removed. The residue was filtered through a silica gel column (20 g) to give 400 mg (80%) of the dihydro-compound 29 along with some perhydro-impurity. The sample of dihydro-compound on crystallisation from carbon tetrachloride-petroleum ether furnished colourless cubes, mp 83-84°C.

UV spectrum λ_{max}^{MeOH}: 242 nm (ε: 7650).

IR spectrum (KBr), ν_{max}: 2950, 1740 (carbonyl), 1700 (carbonyl), 1630 (olefinic) 1440, 1160, 800 and 690 cm^{-1}.

^{1}H NMR spectrum (100 MHz, $CDCl_3$): δ 1.36(3H,s, $\underline{H_3}C-\overset{|}{C}-$), 1.80-2.74 (10H,m) and 2.94(1H,br s).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ 214.2(s), 202.2(s), 186.9(s), 143.4(s), 59.1(d), 53.7(s), 45.9(t), 40.4(t), 37.9(t), 35.0(t), 27.0(q) and 25.9(t).

Mass spectrum (70 eV, m/e, relative intensity): 190(M^+,100), 162 (21), 147(30), 134(29), 106(53), 105(30), 91(29).

High resolution mass spectrum for $C_{12}H_{14}O_2$:

Calcd: m/e, 190.0994

Found: m/e, 190.0999.

Into a 25 mL three necked RB flask fitted with dry nitrogen gas inlet, septum, reflux condensor and mercury seal, methyltriphenylphosphonium bromide 1.40 g (3.95 mmol) was introduced with an addition funnel. Dry toluene (3 mL) was added and the resulting suspension was stirred vigorously. To this suspension was injected sodium t-amyloxide 3 47 mg (3.16 mmol) in dry toluene (3 mL) and stirred at ~ 40°C for 5 min. Dihydro-compound 29 (500 mg, 2.63 mmol) in dry toluene (5 mL) was introduced at once and the mixture refluxed for 3h. The reaction mixture was diluted with benzene (10 mL) and quenched with water. The organic layer was separated, washed and dried. The residue obtained after removal of the solvent was charged on a silica gel column (25 g). Elution with petroleum ether resulted in the removal of triphenylphosphine derived impurities and further elution with benzene furnished the terminal methylene compound 30 (395 mg, 80%) which was bulb-to-bulb distilled at 135°C/0.3 mm.

UV spectrum λ_{max}^{MeOH}: 236 nm (ε : 10950).

IR spectrum (neat), ν_{max} : 3100, 2950, 1700 (carbonyl) 1640 (olefinic), 1440, 1380, 1230, 1040 and 880 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$ Fig.I-7) : δ 1.24(3H,s, $\underline{H_3}C-\overset{|}{C}-$), 1.60-1.90 (2H,m), 2.20-2.80(8H,m), 3.20(1H,br s), 4.96(1H,br s, $-\overset{|}{C}=C\underline{H_2}$) and 5.20(1H,br s, $-\overset{|}{C}=C\underline{H_2}$).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$ Fig.I-8): δ 203.3, 183.3, 152.1, 148.6, 107.9, 56.6, 55.9, 46.4, 40.8, 40.4, 33.5, 27.7 and 25.7.

Mass spectrum (70 eV, m/e, relative intensity): 188 (M^+,100), 173(44), 145(21), 131(42), 117(22), 104(26), 91(24).

High resolution mass spectrum for $C_{13}H_{16}O$:

Calcd: m/e, 188.1201

Found: m/e, 188.1202.

11-Cyclopropyl-8 β-methyl-tricyclo[6.3.0.$0^{2,6}$]dodeca-2(6)-ene-3-one (31):

A mixture of zinc-copper couple[29] 1.8g (0.027 g atom) in dry ether (15mL) and a solution of methylene iodide 8.57g (0.032 mol) in dry ether (5 mL) was refluxed for 30 min with stirring. To this mixture olefin 30 (100 mg, 0.053 mmol) in dry ether (5 mL) was slowly added under reflux. After refluxing for 50 h, the ethereal layer was decanted and washed with cold 1N HCl (10 mLx3), water (10mLx3) and dried. The crude product obtained after the removal of the solvent, was charged on a silica gel column (15 g). Elution with 50% benzene-petroleum ether removed unreacted methylene iodide and further elution with benzene furnished the spiro-compound 31 (53 mg, 50%), bp 140°C/0.3 mm.

UV spectrum λ_{max}^{MeOH}: 240 nm (ε : 8720).

IR spectrum (neat), ν_{max}: 3075 (cyclopropyl), 2950, 1700 (carbonyl) 1640 (olefinic), 1430, 1380, 1240 and 1040 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.34-0.7(2H,m), 0.8-1.0(2H,m), 1.30(3H,s, $\underline{H_3}C-\overset{|}{\underset{|}{C}}-$), 1.74(4H,br s) and 2.2-2.8(7H,m).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ 204.9, 184.6, 147.8, 58.4, 57.5, 47.6, 41.8, 40.7, 35.9, 29.3, 26.9, 25.8, 21.0 and 14.9.

Mass spectrum (70 eV, m/e, relative intensity): 202(M^+,100), 187(53), 174(29), 173(53), 159(22), 145(51), 131(27), 117(21), 105(26), 91(34)

High resolution mass spectrum for $C_{14}H_{18}O$:

Calcd: m/e, 202.1357

Found: m/e, 202.1357.

8 β,11,11'-Trimethyl-cis-anti-cis-tricyclo[6.3.0.0^{2,6}]undeca-3-one (32):

The spiro-compound 31 (20 mg, 0.098 mmol) in acetic acid (3 mL) was hydrogenated over PtO_2 (5 mg, preactivated) catalyst in a Parr-hydrogenation apparatus at 3 atm pressure for 36 h. The reaction mixture was diluted with ether, filtered, washed and dried. Removal of solvent yielded a crude product mixture which was purified on a silica gel (5 g) column to give nor-capnellanone 32 (12 mg, 60%) along with another compound, probably its cis-syn-cis isomer. Comparison of the IR and ^{1}H NMR spectra of 32 with the authentic spectra[14] supplied by Prof. R.D. Little established their identity.

8 β,11-Dimethyl-tricyclo[6.3.0.0^{2,6}]undeca-2,10-diene-3,9-dione (33):

Into a 100 mL three necked RB flask fitted with dry nitrogen gas inlet, reflux condensor, pressure equalized addition funnel and mercury seal, 155 mg (6.38 mmol) of magnesium turnings were taken and dry ether (20 mL) was introduced. To this mixture methyliodide (0.5 mL, excess) was slowly added and stirring continued till all the magnesium dissolved. The Grignard reagent was cooled to -10°C and bisenone 20 (1 g, 5.31 mmol) in cold THF (10 mL) was introduced. The reaction mixture was slowly brought to room temp. and further stirred for 1h. Quenching with cold saturated NH_4Cl solution (25 mL) and extraction with ether (50 mL x 3) gave 1.1 g of crude tertiary allylic alcohol containing some unreacted bisenone 20.

The crude reaction mixture obtained above was dissolved in dry dichloromethane (20 mL) and added to a solution of pyridinium chlorochromate,[31] 1.5g in dry dichloromethane (20 mL) containing 2.0 g of activated molecular sieves (4A°). The reactants were stirred for 1.5 h and diluted with dry ether (30 mL). The resulting solution was filtered through a small florisil pad and repeatedly washed

with dichloromethane. Removal of solvent left a dark semi-solid residue which was charged on a silica gel (50 g) column. Elution with 50% ethyl acetate-benzene furnished the transposed bisenone[30] 33 (300 mg, 40% based on starting material recovery) which was bulb-to-bulb distilled at 150°C/0.4 mm.

UV spectrum λ_{max}^{MeOH}: 223 and 216 nm (: 20,551 and (15,770).

IR spectrum (neat), ν_{max} : 3075, 2950, 1700 (carbonyl), 1630 (olefinic), 1420, 1380, 1220 and 860 cm^{-1}

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.32(3H,s,$\underline{H_3}C-\dot{C}-$), 2.24(3H,s, $\underline{H_3}C-\dot{C}=\dot{C}-$), 2.4-3.0(6H,m), 3.48(1H,br s) and 5.76(1H,s, $-\dot{C}=C\underline{H}-C=O$).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ212.1(s), 202.8(s), 185.4(s), 178.9(s), 146.1(s), 127.8(d), 60.7(s), 58.6(d), 41.5(t), 40.3(t), 25.9(t), 23.2(q) and 19.3(q).

Further elution of the column with 65% ethyl acetate-benzene furnished starting bisenone 20 (300 mg).

8β,11-Dimethyl-cis-anti-cis-tricyclo[6.3.0.$0^{2,6}$]undeca-10-ene-9-one-3β-ol (34):

Sodium borohydride 150 mg (4.0 mmol) was added in small lots to a solution of transposed enone 33 (1 g, 4.95) mmol) in absolute methanol at -10°C, till the starting material was completely consumed. Acetone (10 mL) was added to the reaction mixture to destroy excess sodium borohydride and solvents were completely removed under reduced pressure. The residue was dissolved in ethyl acetate, washed and dried. Removal of the solvent gave crude material (1 g) which was charged on a silica gel (25 g) column and eluted with 30% ethyl acetate-benzene to furnish cis-anti-cis-hydroxy-enone 34 (450 mg, 44.5%) which was crystallised from benzene-petroleum ether as colourless prisms, mp 121-122°C.

UV spectrum λ_{max}^{MeOH}: 232 nm (ε : 11,680).

IR spectrum (KBr) ν_{max}: 3400 (hydroxyl), 3100, 1700 (carbonyl), 1620

(olefinic), 1450, 1020 and 860 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.2(3H,s,$\underline{H_3}C$-$\dot{C}$-), 1.24-2.0(8H,m), 2.12(3H,s,$\underline{H_3}C$-$\dot{C}$=$\dot{C}$), 2.28(1H,s), 2.95(1H,s), 4.22(1H,m,HO-$\dot{C}\underline{H}$-$\dot{C}$-) and 5.80(1H,s, (-$\dot{C}$=$\underline{C}$H-C=O).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ214.1(s), 180.9(s), 127.6(d), 73.9(d), 59.7(s), 58.3(d), 53.8(d), 44.0(t), 42.7(d), 36.0(t), 28.5(t), 22.2(q) and 18.3(q).

Further elution of the column with the same solvent gave other reduction products but these were not characterised.

8β,11,11'-Trimethyl-cis-anti-cis-tricyclo[6.3.0.$0^{2,6}$]undeca-9-one-3β-ol (35):

To a stirred solution of CuI 900 mg (4.7 mmol) in dry ether (6 mL) at -10°C, methyllithium (2 mL, 9.4 mmol) in ether was slowly added till the yellow colour persisted. To this mixture, BF_3-etherate (0.4 ml excess) was added[32] followed by the addition of the hydroxy-enone 34 (50 mg, 0.24 mmol) in dry ether (5 mL). The reaction was then brought to room temp. and stirred for 1h. The reaction was quenched with saturated NH_4Cl and NH_4OH solutions (~pH=8) and then extracted with ether (10 mL x 3). The ethereal layer was washed and dried. Removal of the solvent gave crude product (55 mg) which was purified on a silica gel (10 g) column to get the gem-dimethylated hydroxy-ketone 35 (40 mg, 88%) and was bulb-to-bulb distilled at 130°C/0.4 mm.

IR spectrum (CH_2Cl_2) ν_{max}: 3600 (hydroxyl), 2950, 1730 (carbonyl), 1440 and 1060 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$, Fig.I-9): δ 1.16[6H,s,($C\underline{H_3}$)$_2$-$\dot{C}$-], 1.30(3H,s,$\underline{H_3}C$-$\dot{C}$-), 1.4-2.6(12H,m) and 4.18(1H,m,HO-$\dot{C}\underline{H}$-$\dot{C}$-).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$, Fig.I-10): δ 225.1, 75.0, 60.9, 58.0, 53.5, 52.9, 48.8, 43.4, 36.6, 36.0, 30.8, 29.6, 26.0 and 24.9.

Analysis for $C_{14}H_{22}O_2$ Calcd: C, 75.63; H, 9.97.
Found: C, 75.12; H, 9.90.

8 β,11,11'-Trimethyl-cis-anti-cis-tricyclo[6.3.0.$0^{2,6}$]dodeca-3(12)-ene-9-one (37):

To a solution of pyridinium chlorochromate[31] (40 mg) in dry dichloromethane (10 mL) containing activated molecular sieves (4A°) was added hydroxyketone 35 (50 mg, 0.225 mmol) in dry dichloromethane (5 mL). The reaction mixture was stirred for 30 min and diluted with dry ether (10 mL). Filtration through a small florisil column and evaporation of solvent furnished the diketone 36 (44 mg, 88%), which was directly crystallised from petroleum ether as colourless needles, mp 78-79°C.

IR spectrum (neat) ν_{max}: 2950, 1730 (carbonyl), 1460, 1400, 1260, 1180 and 660 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.05(3H,s,$\underline{H_3}C-\overset{|}{C}-$), 1.09(3H,s, $\underline{H_3}C-\overset{|}{C}-$), 1.17(3H,s,$\underline{H_3}C-\overset{|}{C}-$) and 1.48-2.48(13H, m).

Into a 25 mL three necked RB flask fitted with dry nitrogen gas inlet, septum, reflux condensor and mercury seal, methyltriphenylphosphonium bromide 96 mg (0.27 mmol) was introduced with an addition funnel. The solid was suspended in dry toluene (2 mL) and sodium t-amyloxide 24 mg (0.22 mmol) in dry toluene (3 mL) was added. The yellow reaction mixture was stirred at ~40°C for 5 min and then the diketone 36 (40 mg, 0.18 mmol) in dry toluene (3 mL) was introduced at once and reactants refluxed for 2.5h. The reaction mixture was diluted with benzene (5 mL) and quenched with water.The organic layer was separated, washed and dried. The crude product obtained, after removing the solvent was chromatographed on a silica gel (25 g) column. Elution with petroleum ether removed the triphenylphosphine derived impurities and further elution with 50% benzene-petroleum ether furnished the terminal olefinic compound 37 (36 mg, 90%) which was bulb-to-bulb distilled at 125°C/0.5 mm.

IR spectrum (neat) ν_{max}: 3050, 2950, 1740 (carbonyl), 1450, 1280, 1120 and 870 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.09[6H,s,($\underline{CH_3}$)$_2$-C-], 1.12(3H,s, ($\underline{H_3}$C-C-), 1.13-2.04(8H,m), 2.08-2.38(2H,m), 2.58-2.84(1H,m), 4.74(1H,br s, -C=C$\underline{H_2}$) and 4.85(1H,br s, -C=C$\underline{H_2}$).

Capnellene (6):

Into a two necked 25 mL RB flask fitted with a rubber septum and mercury seal was placed LAH (10 mg, excess) in dry ether (5 mL). To this suspension, olefinic compound 37 (50 mg, 0.23 mmol) in dry ether (5 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 excess hydride. The reaction mixture was diluted with water and extracted with ether (10 mL x 3). The ethereal layer was washed and dried. Removal of solvent gave hydroxy-olefin 38 (40 mg, 80%, as 1:1 mixture of hydroxy-epimers).

IR spectrum (neat) ν_{max}: 3375 (hydroxyl), 2950, 1650 (olefinic), 1460, 1360, 1050 and 870 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.91(3H,s,$\underline{H_3}$C-C-), 0.95(3H,s, $\underline{H_3}$C-C-), 0.98(3H,s,$\underline{H_3}$C-C-), 0.99(3H,s,$\underline{H_3}$C-C-), 1.05(3H,s,$\underline{H_3}$C-C-), 1.13(3H,s, $\underline{H_3}$C-C-), 1.23-1.82(18H,m), 1.90-2.68(6H,m), 3.78(1H,d,J=6Hz,HO-C$\underline{H}$-C-), 3.88 (1H,d,J=6Hz,HO-C$\underline{H}$-C-), 4.72(2H,br s, -C=C$\underline{H_2}$) and 4.85(2H,br s, -C=C$\underline{H_2}$).

Hydroxy-olefin 38 (epimeric mixture, 20 mg, 0.09 mmol), NaH, (13 mg, 50% dispersion in oil, 0.27 mmol) and imidazole (2 mg) in dry THF (5 mL) was refluxed in a 25 mL three necked RB flask with stirring for 3h under nitrogen. Carbon disulfide (0.5 mL) in THF (1 mL) was then added to the reaction mixture. After refluxing for further 30 min, methyliodide (0.5 mL) was added in THF (1 mL)and refluxing continued for another 30 min. Reaction mixture was quenched

with acetic acid (0.2 mL), diluted with water and extracted with ether (10 mL x 3). The ethreal layer was washed and dried. The crude product was charged on a silica gel (5 g) column. Elution with petroleum ether removed non-polar impurities and further elution with 5% benzene-petroleum ether gave the S-methylthiocarbonate 39 (25 mg, 88%) as a mixture of epimers.

IR spectrum (neat) ν_{max}: 3075, 2950, 1660 (olefinic), 1460, 1220, 1060 and 870 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.93(3H,s,$\underline{H_3}$C-$\overset{|}{C}$-), 0.99(3H,s, $\underline{H_3}$C-$\overset{|}{C}$-), 1.07[6H,s,($C\underline{H_3}$)$_2$-$\overset{|}{C}$] 1.09(3H,s,$\underline{H_3}$C-$\overset{|}{C}$-), 1.17(3H,s,$\underline{H_3}$C-$\overset{|}{C}$-), 1.53-2.3 (20H,m), 2.40(3H,s), 2.44(3H,s), 2.45-2.78(2H,m), 4.64(2H,br s, -$\overset{|}{C}$=C$\underline{H_2}$), 4.8(2H,br s, -$\overset{|}{C}$=C$\underline{H_2}$) and 5.62(2H,ABq,J_{AB}=6Hz, (MeS-$\underset{\underset{S}{\|}}{C}$-O-$\overset{|}{C}\underline{H}$-).

Into a 25 mL three necked RB flask fitted with an argon gas inlet, reflux condensor, septum and mercury seal, was taken tri-n-butyltin hydride, 40 mg (0.13 mmol) in dry toluene (3 mL). The mixture was heated to reflux during which the S-methylthiocarbonate 39 (20 mg, 0.067 mmol) in dry toluene (2 mL) was slowly injected. After refluxing for 4h, toluene was removed under vacuum and the concentrate was charged on $AgNO_3$ impregnated silica gel (15 g) column. Elution with petroleum ether removed the organotin impurities and further elution with 10% benzene-petroleum ether furnished the hydrocarbon 6 (7 mg, 53%) which was found indentical [IR spectrum (neat) ν_{max}: 3060, 2930, 1640 (olefinic), 1460, 1380 and 870 cm^{-1}. ^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.98(3H,s,$\underline{H_3}$C-C-), 1.05(3H,s, $\underline{H_3}$C-C-), 1.14(3H,s,$\underline{H_3}$C-C-), 1.18-1.8(9H,m), 2.38-2.4(4H,m), 4.8(1H,br s, -C=C$\underline{H_2}$), 4.9(1H,br s, -C=C$\underline{H_2}$)] with the naturally occurring capnellene[10].

I. 7. Spectra

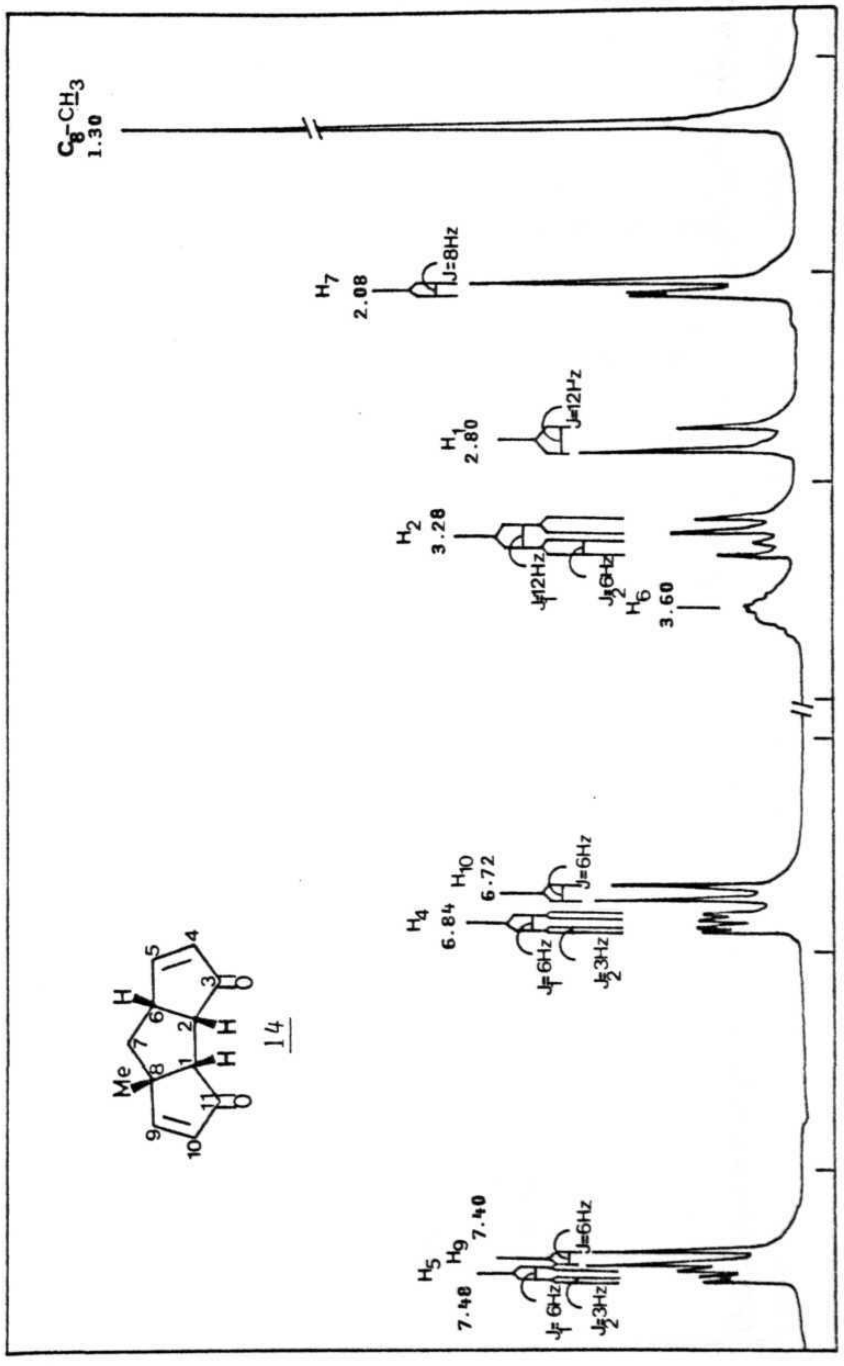


FIG.I-1 : ^1H NMR (100 MHz) spectrum of 14.

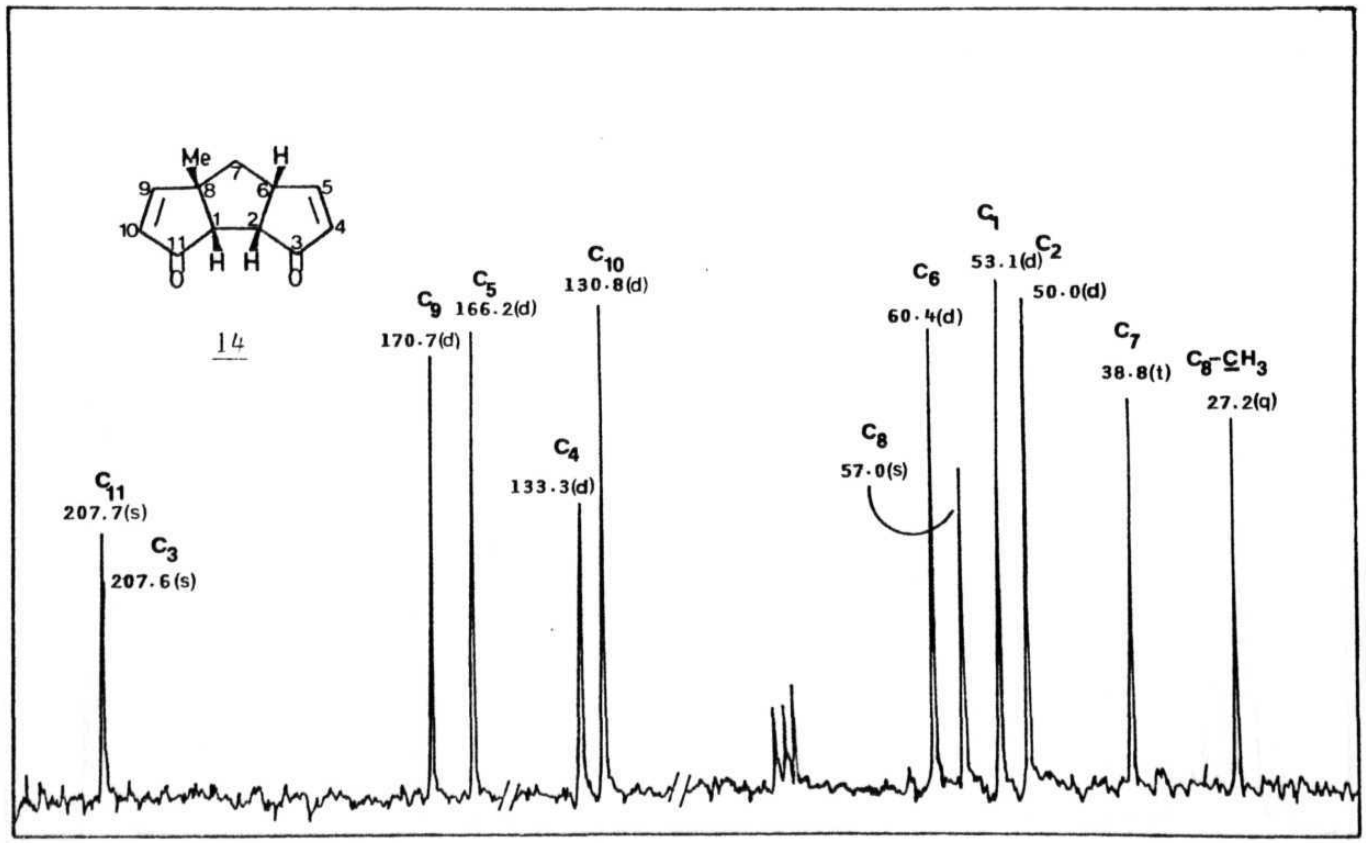


FIG.I-2 : ^{13}C NMR (25.0 MHz) spectrum of 14.

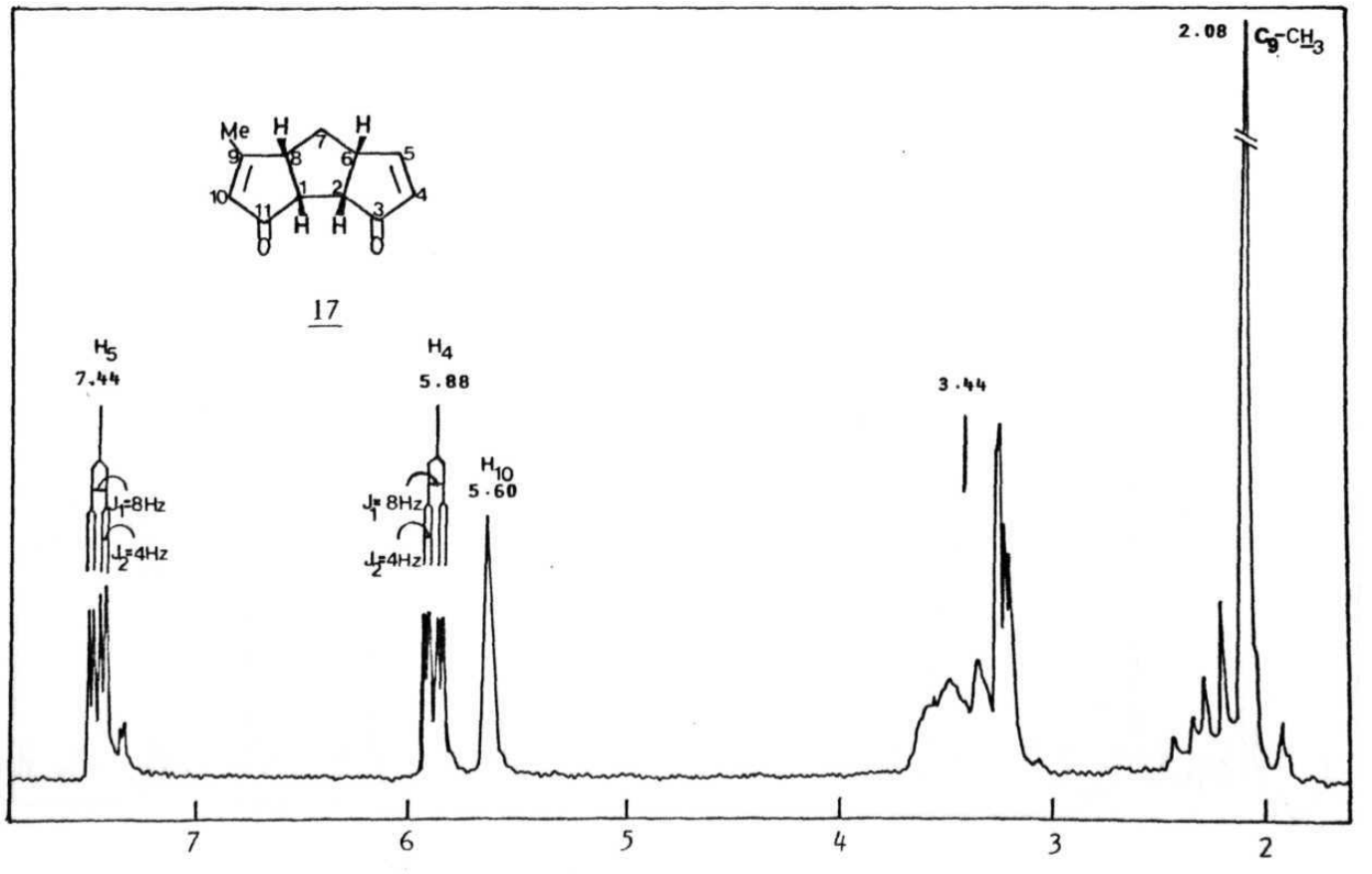


FIG.I-3 : ^{1}H NMR (100 MHz) spectrum of 17.

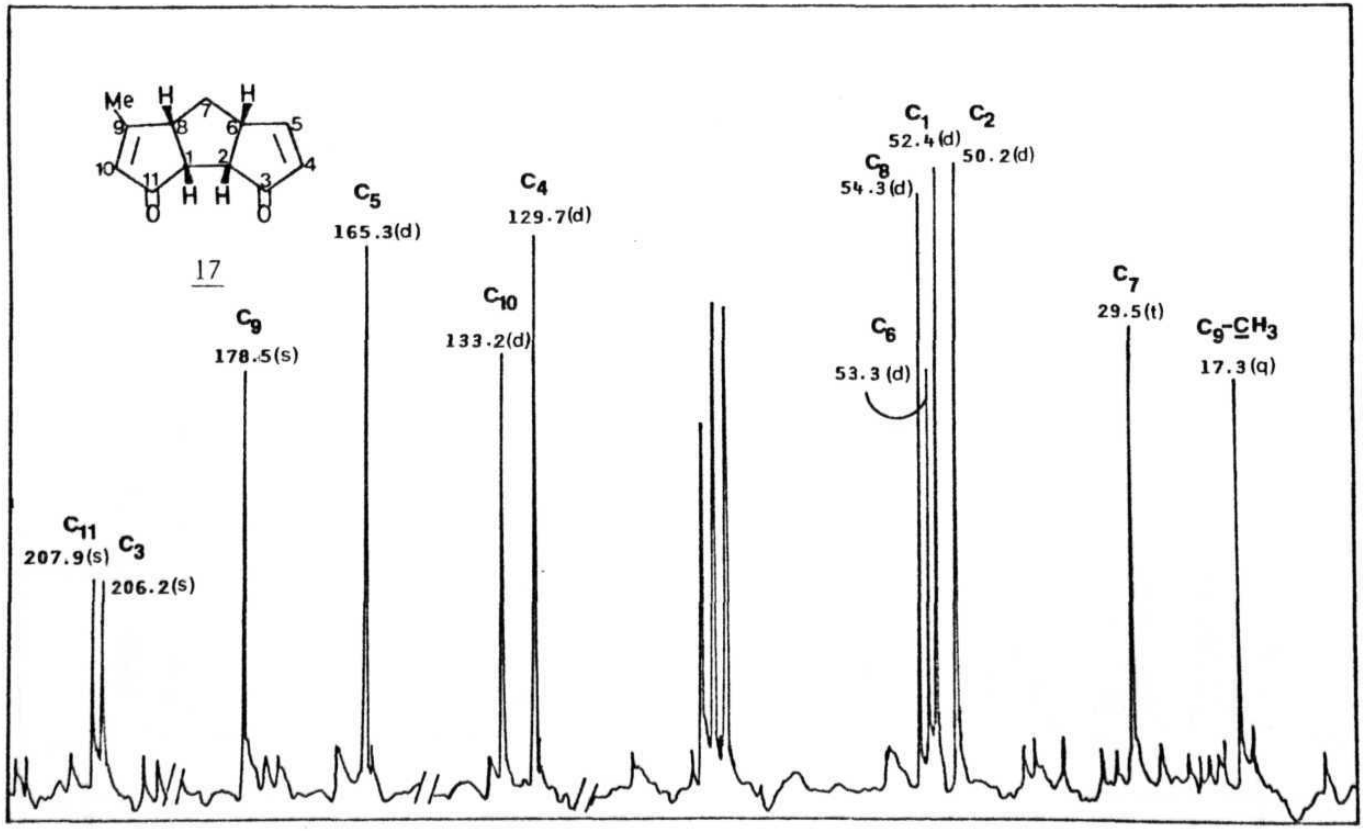


FIG.I-4 : ^{13}C NMR (25.0 MHz) spectrum of 17.

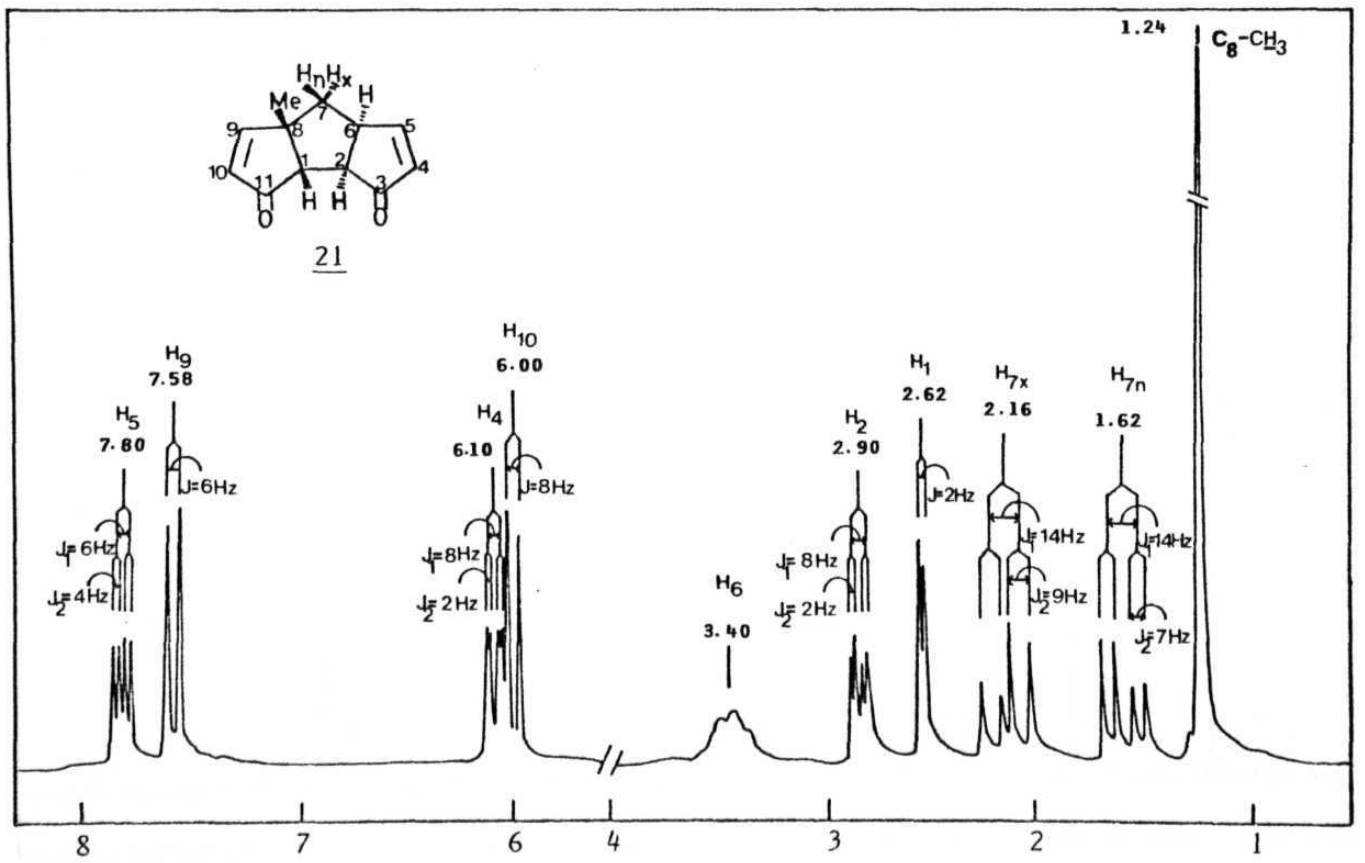


FIG.I-5 : ^{1}H NMR (100 MHz) spectrum of 21.

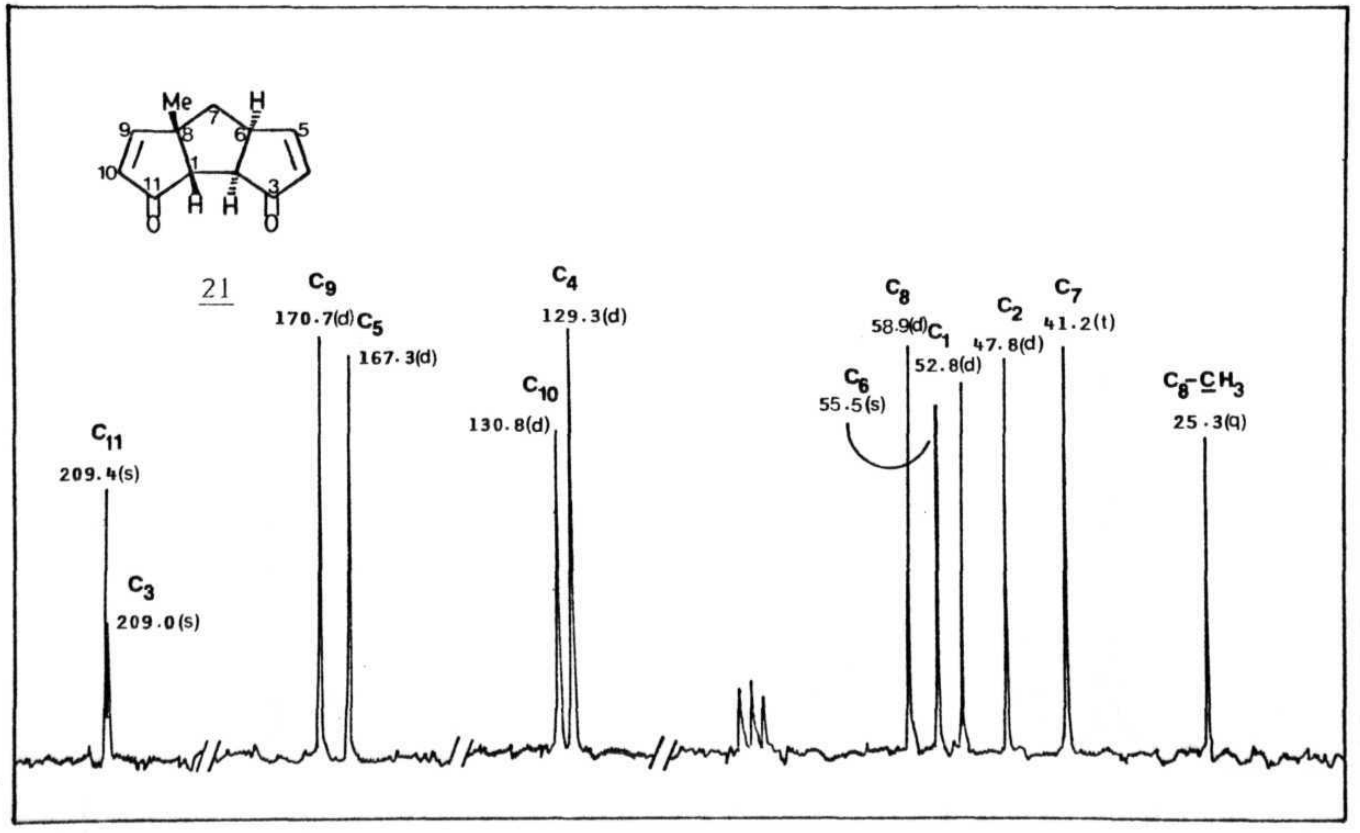


FIG.I-6 : ^{13}C NMR (25.0 MHz) spectrum of 21.

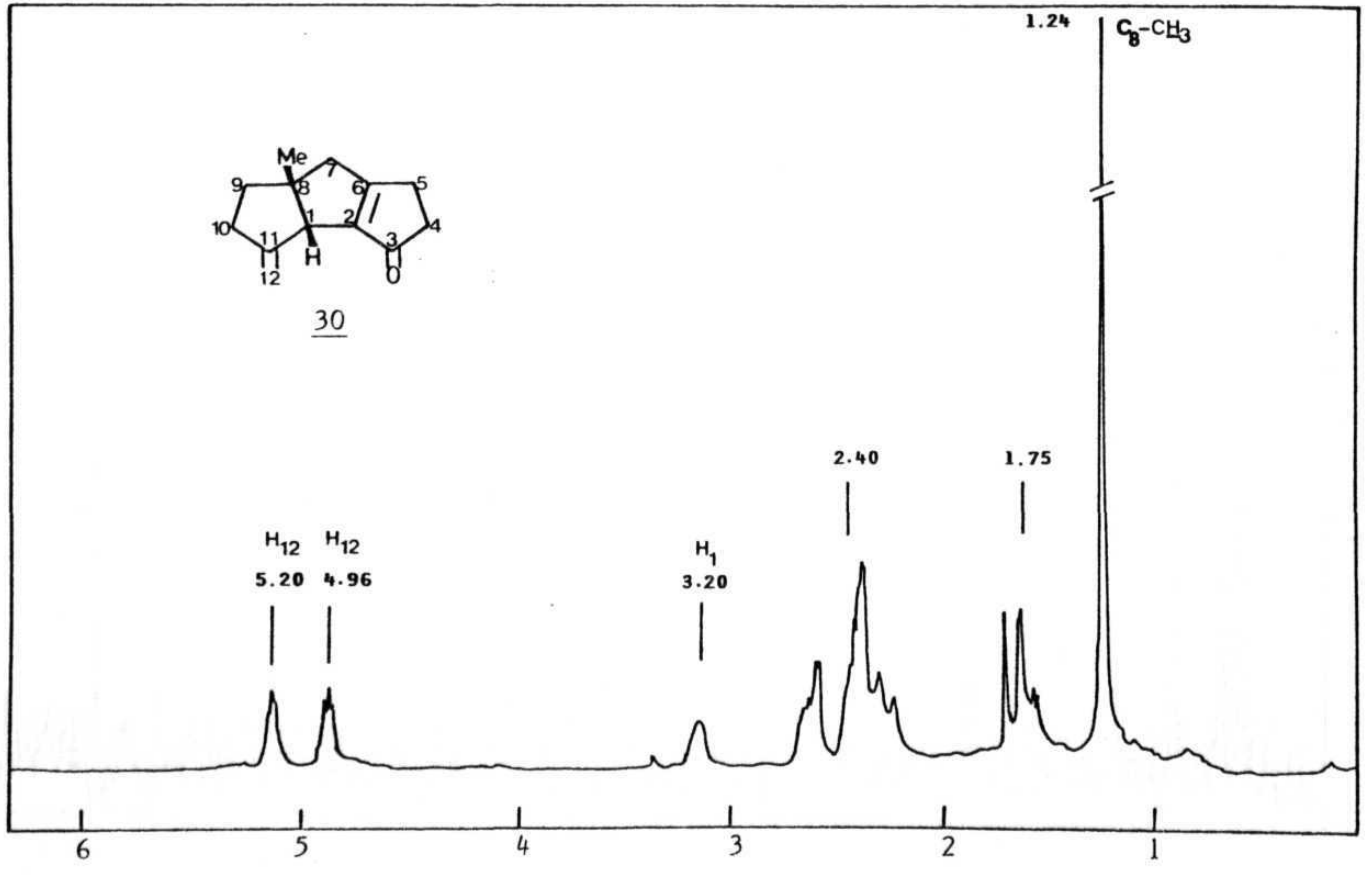


FIG.I-7 : ^{1}H NMR(100 MHz) spectrum of 30.

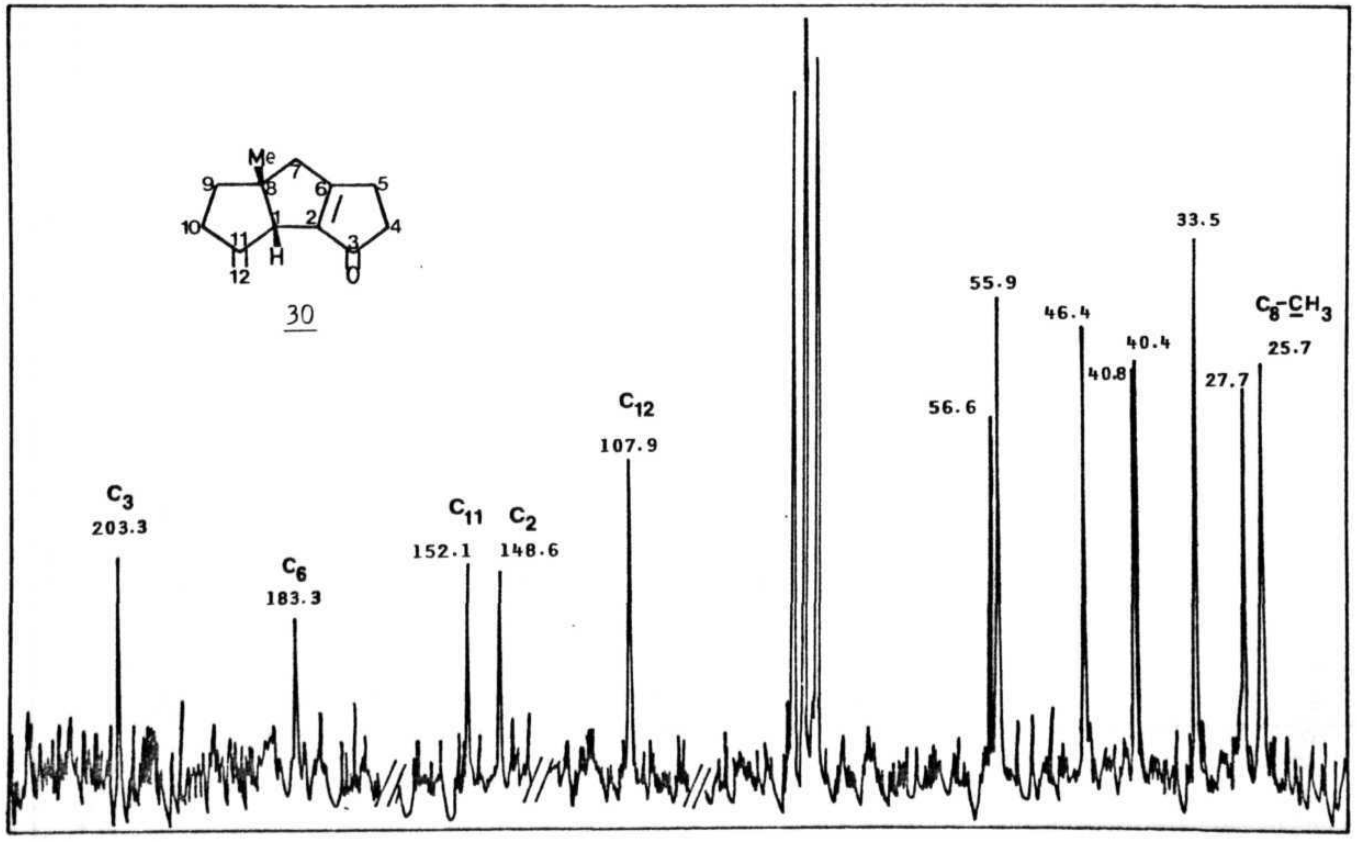


FIG.I-8 ^{13}C NMR (25.0 MHz) spectrum of 30.

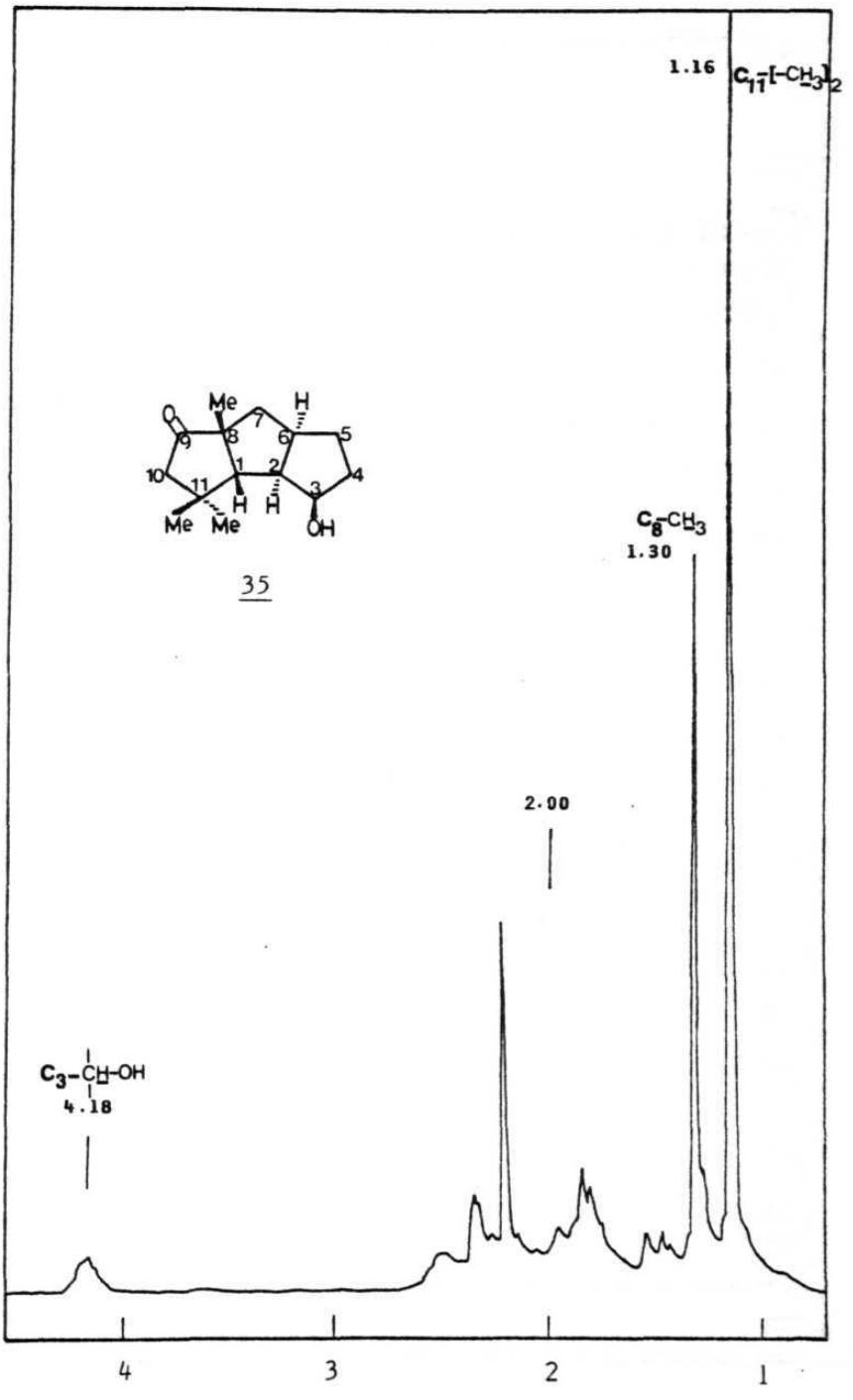


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FIG.I-9 : ^{1}H NMR (100 MHz) spectrum of 35.

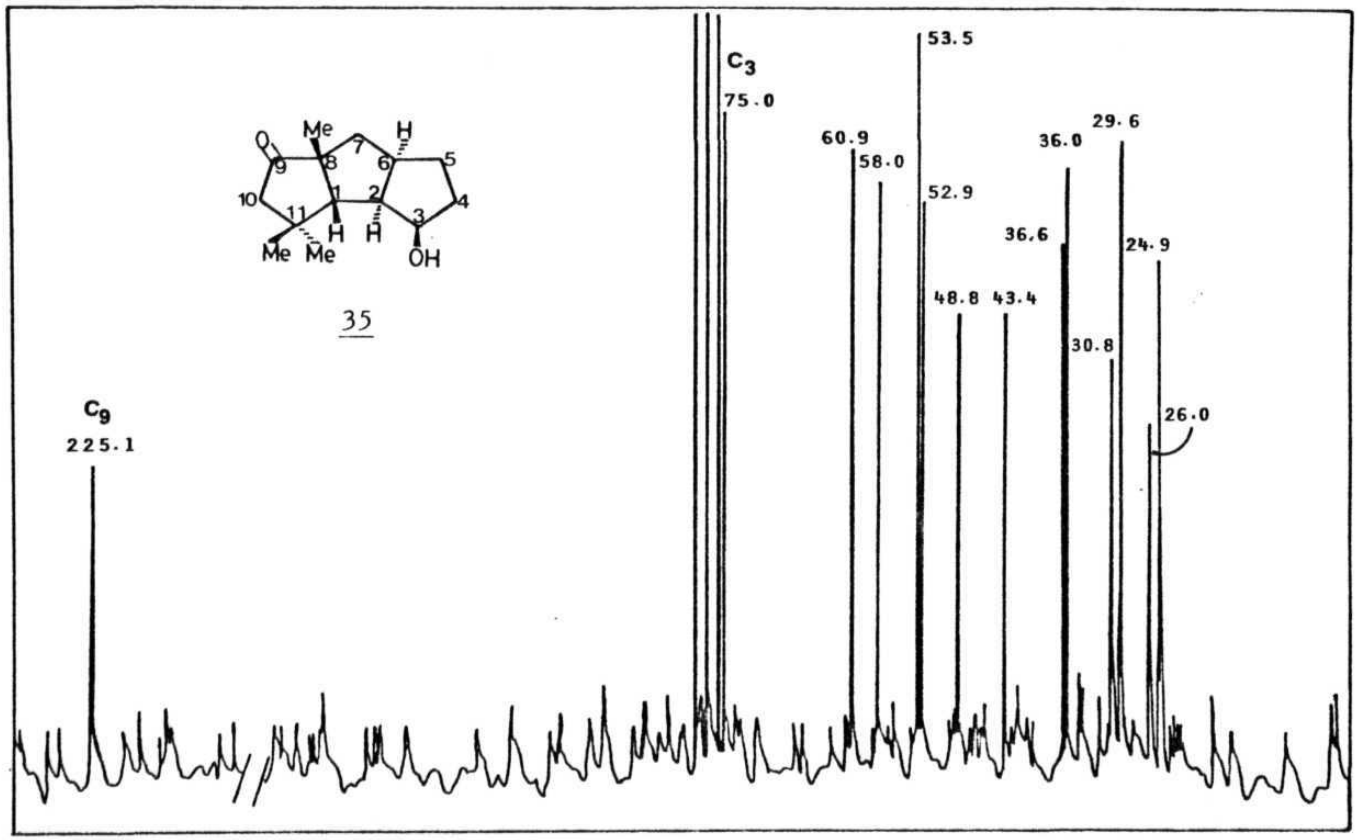

FIG.I-10 : ^{13}C NMR (25.0 MHz) spectrum of 35

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CHAPTER II

A GENERAL STEREOCONTROLLED APPROACH TO THE 5-8 FUSED SYSTEM. TOTAL SYNTHESIS OF MARINE NATURAL PRODUCT (±)-PRECAPNELLADIENE

II. 1 ABSTRACT

A new stereocontrolled approach to the synthesis of cis and trans-bicyclo[6.3.0]undecane system from readily available cis-syn-cis-triquinane bisenones 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. Thus, a tricyclo [6.3.0.$0^{2,6}$] undec-1(8)-ene (63 ,C_{11}-triquinene) emerged as the equivalent of a 5-8 fused system. The extended U-shaped geometry of 63 bestows on it exclusive reactivity on the convex face enabling complete stereochemical control. This led to the evolution of a general 5-5-5 to 5-8 strategy in which the stereochemical preferences of the former can be fully transcribed into the latter.

The choice of the tricyclo [6.3.0.$0^{2,6}$] undec-1(8)-ene (C_{11}-triquinene) route to cis-bicyclo [6.3.0] undecanes was prompted by the ready availability of functionalised cis-syn-cis-triquinane bisenones through our photo-thermal metathesis sequence. In a model study, tricyclo [6.3.0.$0^{2,6}$] undec-1(8)-enes 73 and 79 were synthesised from the corresponding triquinane enones 71 and 76, respectively, through functional group transformations indicated in schemes II.20 and

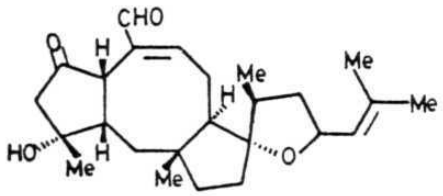
II.21. The triquinenes 73 and 79 on catalytic RuO_2-$NaIO_4$ oxidation smoothly furnished the cis-bicyclo [6.3.0] undecan-2,6-diones 74 and 81, respectively, in good yield. The bicyclic diones can be readily epimerised at the ring junction with base, thus providing an entry into both the trans and the cis fused 5-8 systems.

The 5-5-5 → 5-8 approach has been extended to the stereoselective synthesis of the biogenetically important marine natural product (±)-precapnelladiene 9. For this purpose ene-dione 71 was chosen as the starting material and converted to the endo-methyl enone 90 through chemoselective Wittig olefination and stereoselective hydrogenation. The enone 90 was next deoxygenated to the pivotal olefin 88 in two steps involving thioacetalisation and dethioacetalisation sequence. Catalytic ruthenium (IV) oxidation of the olefin 88 furnished the 5-8 diketone 87 which was transformed to the (±)-precapnelladiene 9 through a straight forward protocol.

II. 2 OBJECTIVE AND BACKGROUND

The eight membered ring is the latest entrant into the variegated assemblage of carbocyclic rings present among terpenoid natural products[1]. In the past few years, the number of terpene carbon skeleta in which a cyclooctane ring forms a part of the condensed or bridged polycyclic system have proliferated rapidly. The cyclooctane bearing carbon skeleta have now been located among C_{15}-sesqui-, C_{20}-di- and C_{25}-sesterterpenes. Presently, over fifty natural products constitute the structurally diverse and interesting family of cyclooctanoid terpenes. The 8-ring bearing natural products are fairly widely distributed in Nature, and have been isolated from terrestrial plants, marine organisms, pathogenic fungi and insects. Several of these natural products are derived through novel biosynthetic pathways and some of them exhibit promising biological activity.

The first cyclooctanoid natural product to be isolated was the sesterterpene ophiobolin A 1, isolated[2a] by the Nozoe group in 1965 from a plant pathogenic fungus. Several closely related compounds surfaced in later years[2a-c]. Incidentally, 1 was the first naturally occuring sesterterpene to have its structure fully elucidated[2a]. Other representative examples of cyclooctanoid terpenes are acetoxy crenulide 2[3] and neolemnanyl acetate 3[4] from marine sources, fusicoccin 4[5] and ophiobolin C 5[6] from phytopathogenic fungi, longipenol 6[7] and ceroplastol 7[8] from insect secretions, and taxol 8[9] from a plant source.



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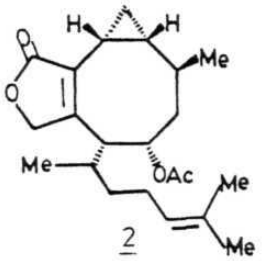

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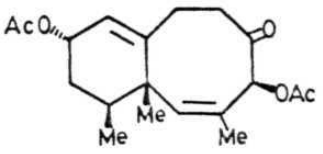

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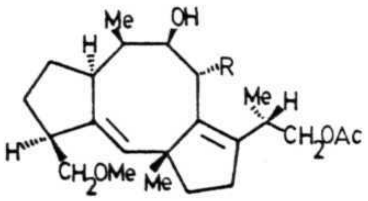

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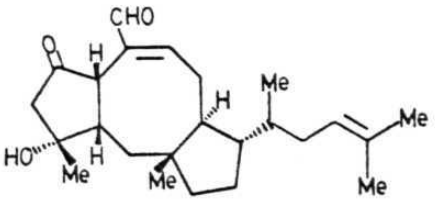

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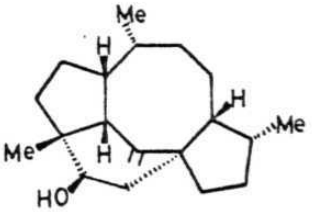

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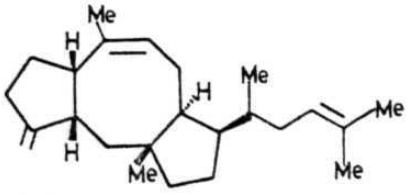

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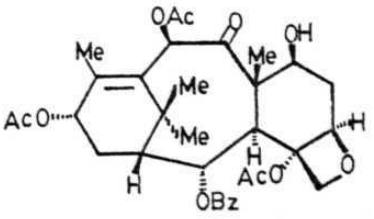

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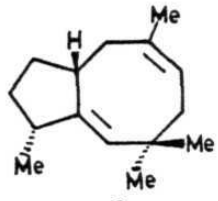
These illustrative examples highlight the range and complexity of carbocyclic skeleta built around a cyclooctane core. A complete list of known cyclooctanoid terpenes is provided at the end of this chapter as an appendix.

Among the more interesting carbocyclic variations that have been encountered in recent years embodying an eight-membered ring are the uncommon 5-8 and 5-8-5 fused ring systems. Indeed, an 8-ring shows an intriguing predilection towards partnering a 5-ring. Three closely related sesquiterpenoids of marine origin, precapnelladiene 9[10], dactylol 10[11] and poitediol 11[12] are examples of the 5-8-fused cyclopentacyclooctane nucleus. The diterpenoids basmenone 12[13] from tobacco, cycloaraneosene 13[14] from a fungus and epoxydictymene 14[15] from a brown alga are based on the more intricate 5-8-5 assembly. Sesterterpenoids ophiobolins and ceroplastols also embody the 5-8-5 system.



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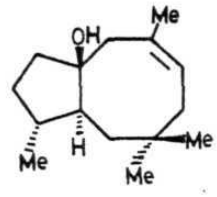

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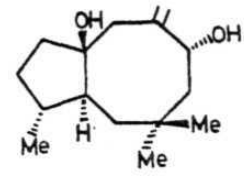

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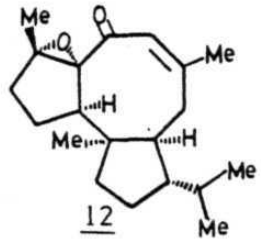

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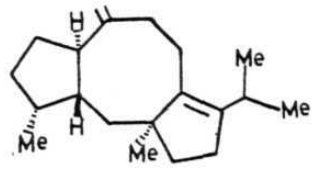

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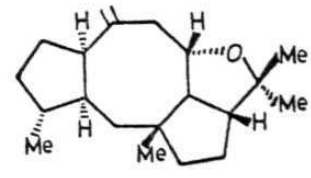


14

The cyclooctanoid terpenes bearing 5-8 and 5-8-5 ring systems are challenging targets of total synthesis due to the presence of uncommon assembly of carbocyclic rings, many stereogenic centres and complex substitution patterns. Synthetic access to them presents a combination of unique synthetic problems.

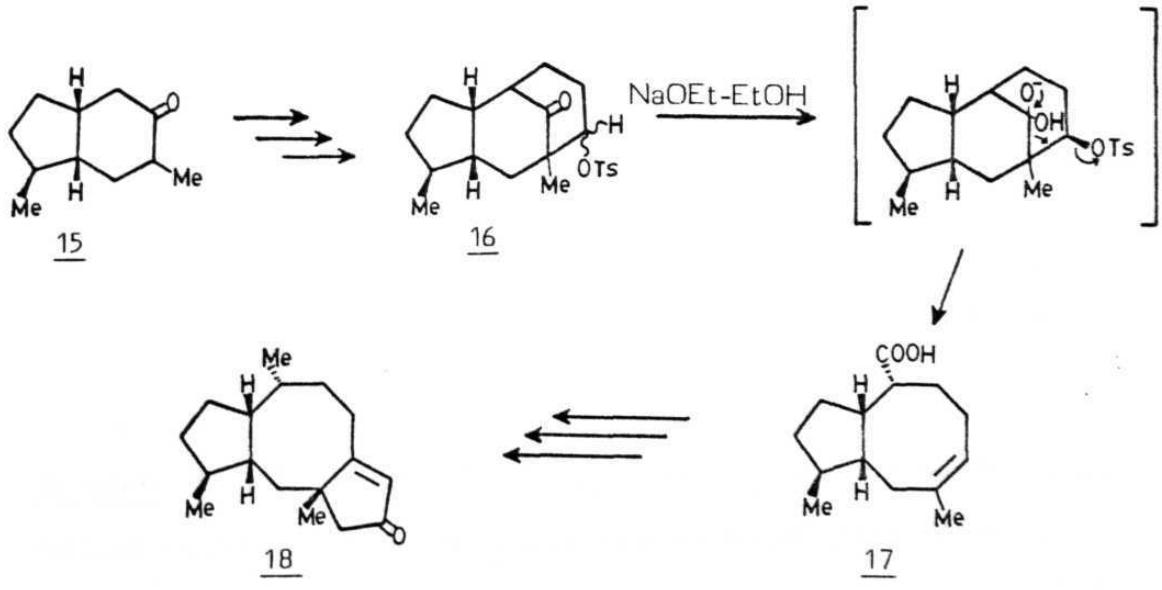
First of all, because of unfavourable entropic and enthalpic factors, traditional methods of ring formation and annulation are not applicable for the construction of cyclooctanes, and new strategies need to be developed for their synthesis. Secondly, cyclooctane rings are notorious for transannular reactions and therefore synthetic operations on them should be effected with either minimal functionality or through masked/latent functional groups. Lastly, the 8-ring and the fused systems derived from it are conformationally flexible and consequently prediction and control of stereochemistry is rendered difficult and uncertain. This is a major impediment to stereoselective syntheses as many cyclooctanoids contain remote methyl group bearing stereogenic centres[1].

Largely due to the factors enumerated above, progress towards the total synthesis of cyclooctanoid natural products has been relatively slow. Until 1984, not a single synthesis of a cyclooctanoid terpene was recorded, although results of a few model studies aimed particularly at ophiobolins, were reported[16]. However, in that year, three groups[17-19] almost simultaneously announced the total syntheses of 5-8 fused sesquiterpenes of marine origin. While Gadwood[17a] reported the total synthesis of poitediol 11, Paquette[18a] and we[19a] independently described the attainment of precapnelladiene 9. It is the detailed account of our precapnelladiene venture that forms the subject matter of this chapter.

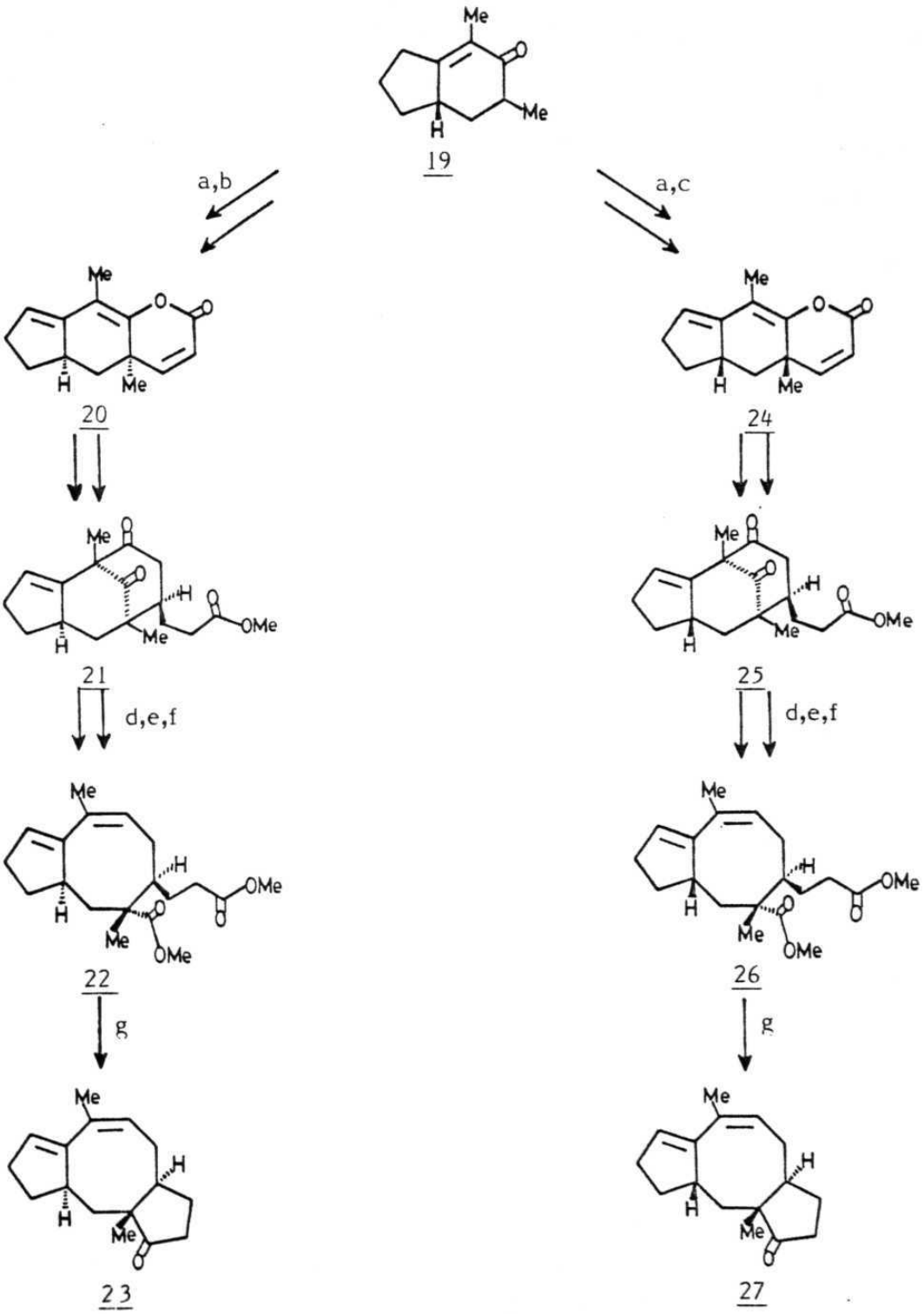
Although our precapnelladiene synthesis and related chemistry was done in 1984, the 5-8 and 5-8-5 fused cyclooctanoid natural products have continued to arouse topical interest among active synthetic chemists and much activity has been witnessed in the intervening years. For the sake of completeness and to put our own efforts in proper perspective, it would be worthwhile to present a brief, quick (mainly schematic), and up-to-date survey of the methodologies developed for the synthesis of fused cyclooctanoid carbocyclic systems. To our knowledge, the area has not been reviewed so far.

As expected, synthetic endeavours towards the 5-8 and 5-8-5 fused natural products have mainly focussed on new ways to construct the cyclooctane portion of these structures. In this context, strategies based on acyclic ring closure, fragmentation, ring expansion and cyclo-addition reactions have been explored. Early efforts in the area were mainly directed towards the construction of the 5-8-5 framework of ophiobolins and employed the fragmentation of an appropriately functionalised bicyclo [3.3.1] nonane as the key step to construct the eight membered ring. Dutta and coworkers were the first to report[16a,b] the construction of the 5-8-5 ring system in 1977. They annulated the readily available perhydroindanone 15 to the bridged tricyclic compound 16, incorporating the bicyclo [3.3.1] nonane moiety. Base catalysed fragmentation gave the bicyclo [6.3.0] undecane derivative 17, which was elaborated to the tricarbocyclic ketone 18 with well defined stereochemistry at the five chiral centres, through standard functional group alterations and a cyclopentannulation protocol, scheme II.1. Immediately after the Dutta's report, Boeckman's group described[16d] a conceptually

Scheme II.1 [16a,b]



Scheme II.2[16d]

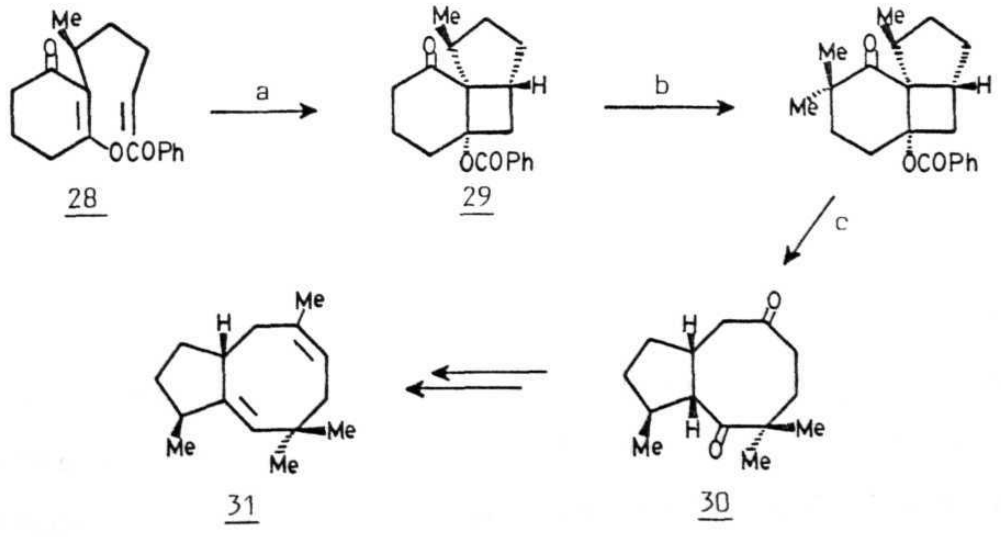


Reagents : (a) LilCA-ClCH=CHCOOCH$_3$, (b) $HClO_4$-Ac_2O, (c) NaOAc-Ac_2O, (d) Li(O-t-Bu)$_3$H, (e) $MeC_6H_6SO_2Cl$-pyridine, (f) NaOMe, (g) LiHMDS.

similar approach to assemble the carbocyclic ring system present in the sester-terpenes of the ophiobolin and ceroplastol type. The readily available bicyclic enone 19 was stereoselectively lactone annulated to either 20 or 24. Each of the lactones was transformed to the bridged compounds 21 and 25, respectively, and set for fragmentation and subsequent annulation. On regiospecific reduction and exposure to methoxide, 21 and 25 gave the 5-8 fused bicyclic diesters 22 and 26. These were then converted to the stereoisomeric tricyclic dienones 23 and 27, respectively, scheme II.2.

More recently, several groups have described access to the bicyclo [6.3.0] undecanes through de Mayo-Oppolzer fragmentation reactions[20]. Pattenden described[21] an approach to precapnelladiene, which led instead to epi-precapnelladiene 31 involving an intramolecular de Mayo reaction, scheme II.3. The enol-benzoate 28, quickly obtainable from 1,3-dimethoxybenzene, underwent facile intramolecular (2+2) cycloaddition to give the tricycle 29. Geminal dimethylation

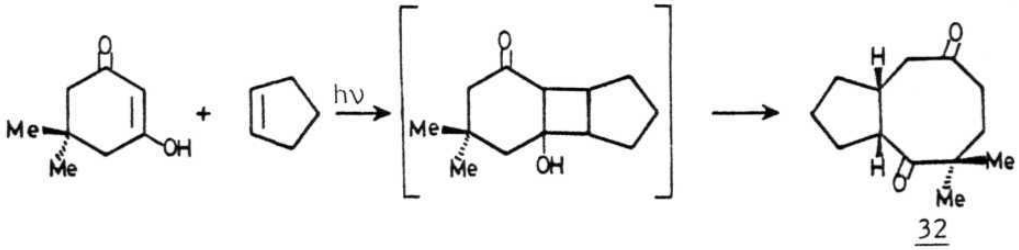
Scheme II.3[21]



Reagents: (a) h ν, Pyrex, (b) LiHMDS-MeI, (c) KOH-EtOH.

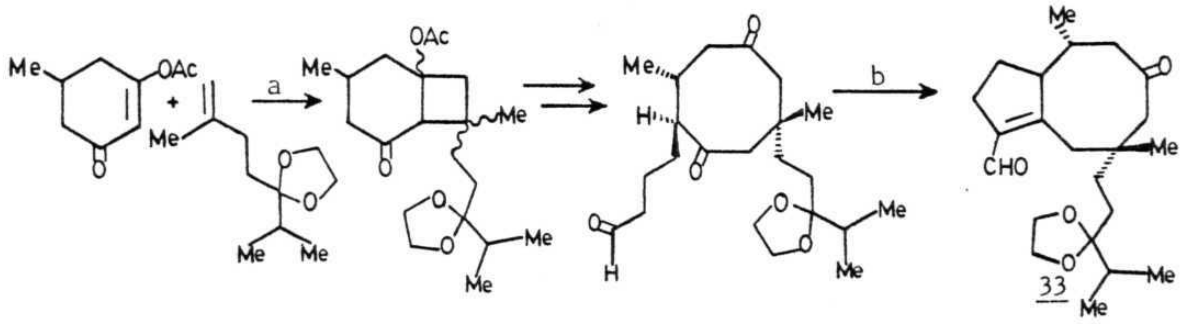
and base catalysed fragmentation revealed the 5-8 fused dione 30. A series of carefully orchestrated functional group transformations furnished epi-precapnelladiene 31. Several approaches to functionalised bicyclo [6.3.0] undecanes have also been described by Pattenden[16h,21]. Intramolecular versions of the de Mayo reaction have been employed by Weedon[16g] and Grayson[16j] to assemble the 5-8 fused diones 32 and 33 as shown in schemes II.4 and II.5, respectively.

Scheme II.4[16g]



32

Scheme II.5[16j]



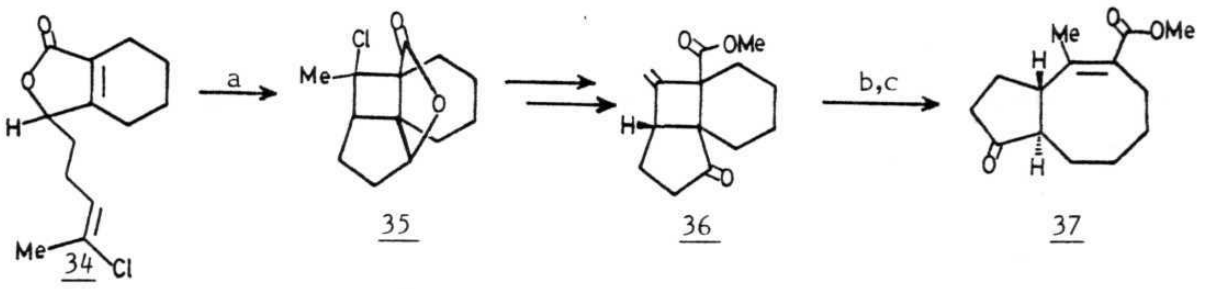
33

Reagents: (a) h ν, (b) $K^{+}tBuO^{-}$-t-BuOH.

Coates has described[16f] a closely related strategy involving an intramolecular (2+2)-photocycloaddition and reductive C-C bond fragmentation to gain entry into the 5-8 and the 5-8-5 carbocyclic frameworks. Thus, 34 on (2+2) photoclosure gave 35 which through functional group transformation was converted to the tricyclic ketoester 36. The strained cyclobutane C-C bond in 36 on reductive cleavage gave the bicyclic ketoester 37, scheme II.6. An analogous

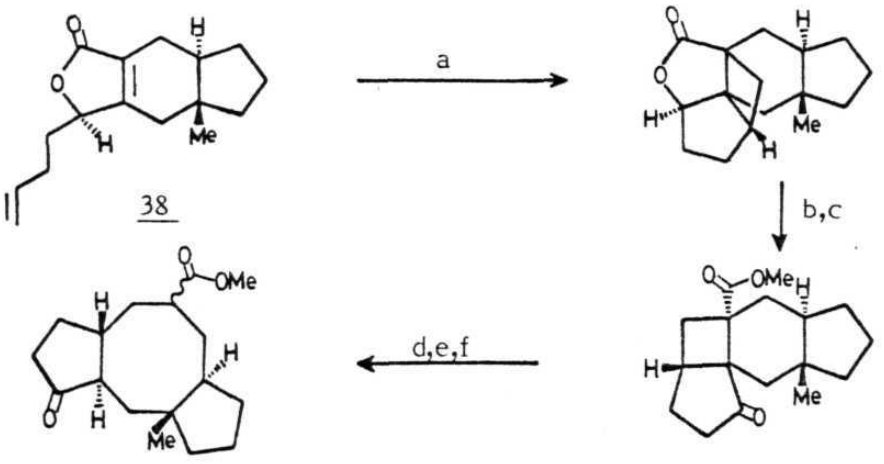
sequence emanating from the hydrindene butenolide 38 resulted in the formation of 5-8-5 ketone 39 via the steps shown in scheme II.7. In this detailed study, Coates has described[16l] the synthesis of several stereoisomeric hydrodicyclopenta-(a-d) cycloocten-1-ones.

Scheme II.6[16f]



Reagents: (a) h ν, C_6H_6, (b) Li/liq.NH_3, (c) NaOMe.

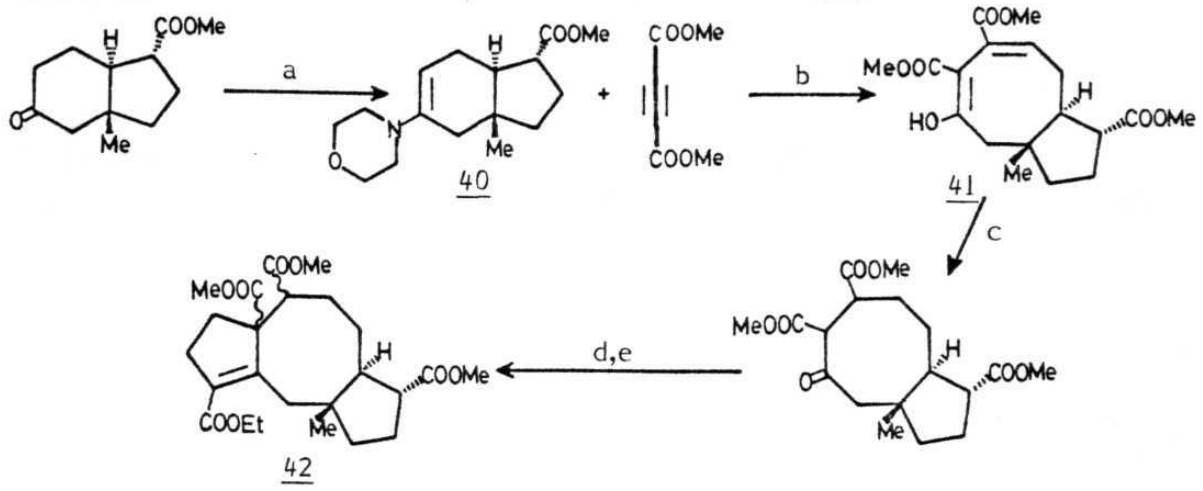
Scheme II.7[16l]



Reagents: (a) hν, p-xylene, (b) NaOH, (c) Na_2RuO_4, (d) Li/liq.NH_3, (e) CH_2N_2, (f) NaOMe.

Numerous approaches based on multi-carbon ring expansion protocols have surfaced for the construction of the eight membered ring of 5-8 and 5-8-5 fused systems. Dauben and Hart employed[16c] the (2+2) cycloaddition of acetylenic ester to enamine 40 and cyclobutene ring opening methodology for the two carbon ring expansion of a hydroindanone to furnish 41, scheme II.8. Further grafting of a five membered ring on to 41 was achieved to deliver 42.

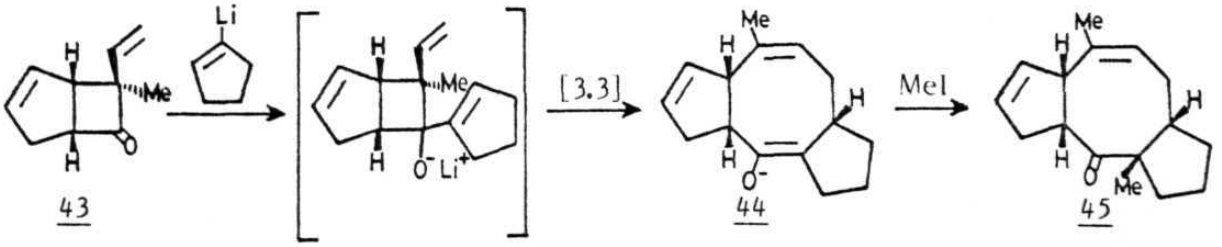
Scheme II.8[16c]



Reagents: (a) Morpholene, 4Å Molecular sieves, (b) H^+-MeOH, (c) 5% Pd-Al_2O_3, (d) NaH, (e) Carbethoxycyclopropyl triphenylphosphonium tetrafluoroborate.

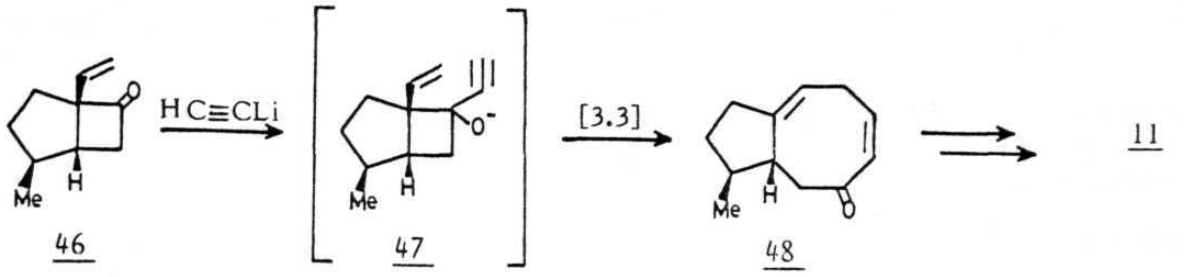
Paquette[16i,m] and Gadwood[17] have independently exploited the oxy - anionic [3.3] sigmatropic processes to construct the 5-8-5 and 5-8 systems respectively, through multiple ring expansions. Employing the dominant stereoisomer 43 obtained from the cycloaddition of 1,3-cyclopentadiene and methyl vinyl ketene, a [3.3] shift process was set up through reaction with cyclopentenyllithium. Quenching of the resulting enolate 44 furnished the tricyclic ketone 45, scheme II.9.

Scheme II.9[16i,m]



Gadwood employed[17] the vinylcyclobutanone 46, and the addition of lithium acetylide generated the oxy-Cope system 47. Facile rearrangement to the cyclooctenone 48 occurred, and it was subsequently elaborated to the sesquiterpene (±)-poitediol 11 and its 4-epimer, scheme II.10.

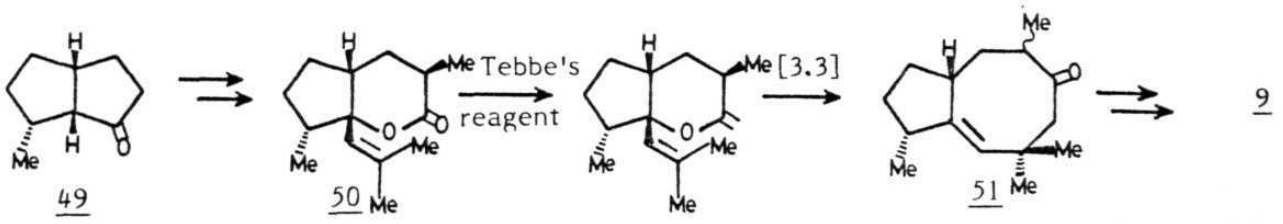
Scheme II.10[17]



46 47 48 11

Paquette has also employed[18] the [3.3]-sigmatropic process (Claisen rearrangement) in 6-alkenyl-2-methylene tetrahydropyrans to achieve the total synthesis of (±)-precapnelladiene 9. In this approach, the previously described bicyclo [3.3.0] octanone 49 was transformed into the lactone 50 in several steps. Reaction of 50 with Tebbe's reagent gave the Claisen rearrangement precursor which smoothly furnished the cyclooctanone 51. Routine functional group changes were effected to arrive at 9, scheme II.11.

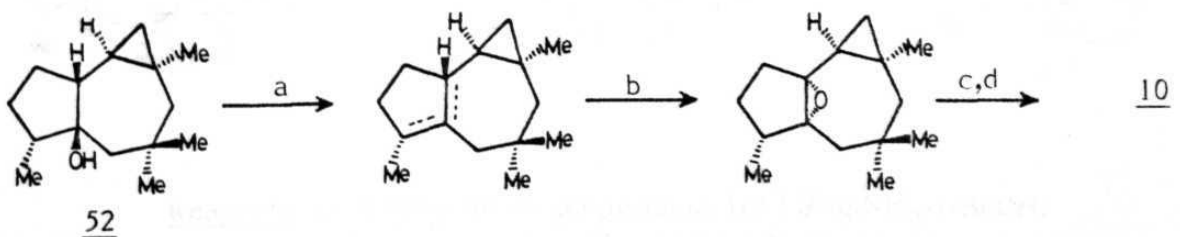
Scheme II.11[18]



49 50 51 9

A biomimetic approach involving carbonium ion mediated rearrangements and ring expansion of the bicyclo [5.1.0] octane moiety has been described[22] by Shirahama. Thus, the naturally occuring sesquiterpene africanol 52 has been

Scheme II.12[22]



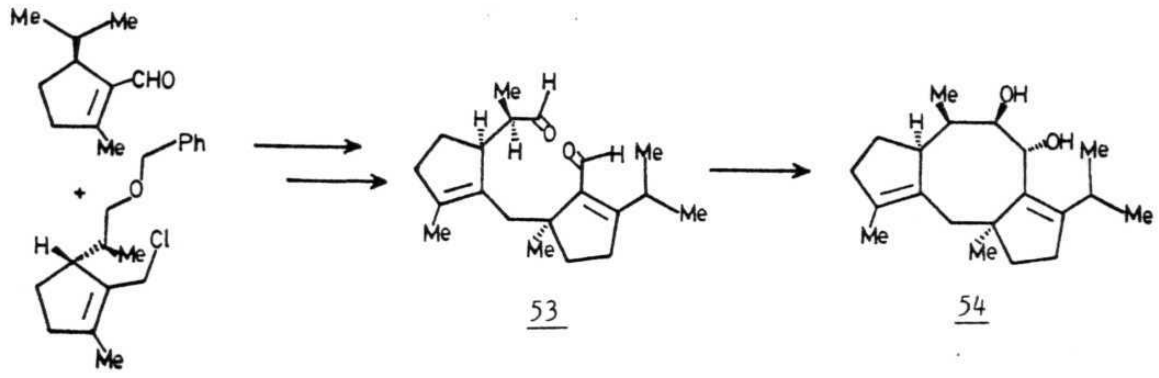
52 10

Reagents: (a) $POCl_3$-pyridine, (b) m-CPBA-CH_2Cl_2, (c) BF_3-Et_2O, (d) H_2-PtO_2.

converted into dactylol 10, as shown in the scheme II.12. Paquette has recently described[23] a synthesis of dactylol 10, essentially along similar lines.

Acyclic ring closure approach to the cyclooctanoid terpenes has been effectively pursued by Takeshita's group[16k,p]. The key step in this approach is the pinacolic coupling in the preassembled homochiral dialdehyde 53 employing low-valent titanium reagents to furnish the 5-8-5 assembly 54, scheme II.13. The approach has been successfully applied[24] for the first total synthesis of a fusicoccane

Scheme II.13[16k,p]

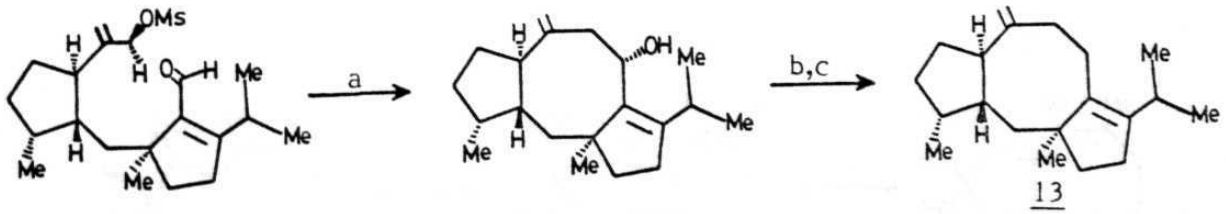


53 54

Reagent: $TiCl_4$-Zn.

diterpene cycloaraneosene 13 as shown in scheme II.14. In this case the crucial cyclisation was effected using divalent chromium species.

Scheme II.14[24]

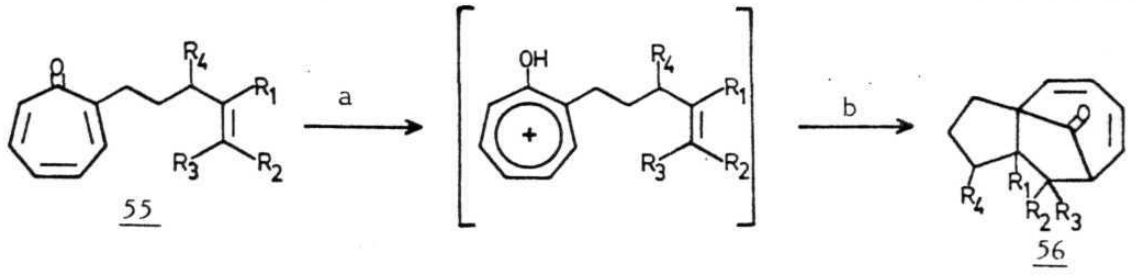


13

Reagents: (a) $CrCl_2$, (b) Ac_2O-pyridine, (c) Li/liq.NH_3-t-BuOH.

Finally, research groups of Feldman[16n] and Wender[16o,q] have very recently reported cycloaddition reactions leading to the construction of fused cyclooctane rings. Feldman has described[16n] a novel intramolecular (6π+2π)-photocycloaddition in alkenyl tropone 55 to furnish tricyclic systems 56 incorporating a 5-8 moiety. The reaction is general and several examples have been cited, scheme II.15.

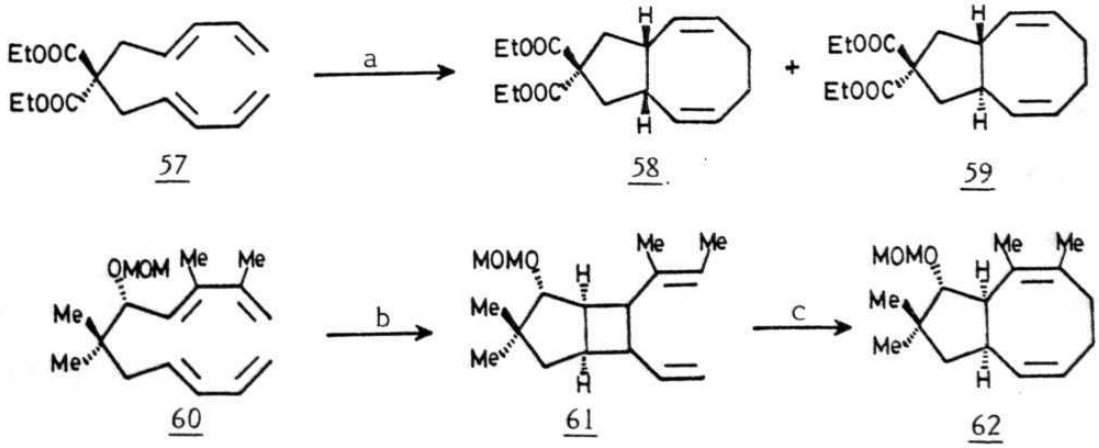
Scheme II.15[16n]



Reagents: (a) H^+-MeOH, (b) hν(350nm).

Wender has described two elegant intramolecular cycloaddition approaches to the cyclooctanoid systems, scheme II.16. The first approach[16o] involves Ni-catalysed intramolecular (4π+4π)-cycloaddition of tetraene 57 to furnish bicyclo [6.3.0] undecadienes 58 and 59, besides other minor products. The second approach[16q] involves intramolecular (2+2) photocycloaddition in tetraene 60, and the resulting divinylcyclobutane 61 undergoes [3.3]- sigmatropic rearrangement to furnish the 5-8 bicyclic 62. Wender has described several examples to support the generality of this theme.

Scheme II.16[16o,q]



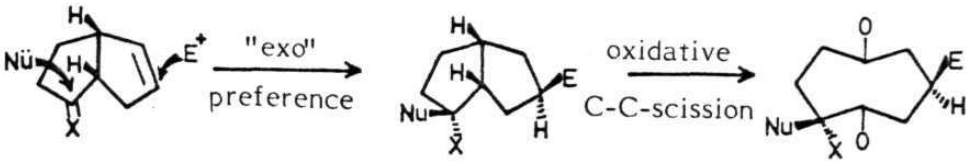
Reagents: (a) Ni^0(cat.), (b) hν(sens.), (c) Δ (130°C).

For reasons delineated earlier, the natural products based on 5-8 and 5-8-5 fused carbocyclic rings appealed to us as attractive and challenging targets of total synthesis. Towards attaining these synthetic objectives, we initiated projects in late 1983, and set for us three specific goals. To begin with, we decided to develop a general and flexible methodology for the construction of the 5-8 fused bicyclo [6.3.0] undecanes with complete substituent and stereochemical control. The second goal was to apply the methodology to a specific target molecule, and the biogenetically interesting sesquiterpene hydrocarbon precapnelladiene 9, from soft coral Capnella imbricata[10], was our choice. Finally, the 5-8 construction strategy was to be amplified to the more demanding 5-8-5 tricyclic network and natural products based on it. The evolution of our synthetic theme towards the bicyclo [6.3.0] undecanes and its successful execution leading to the first synthesis of precapnelladiene 9 is described below.

II. 3. STRATEGY AND MODEL STUDIES

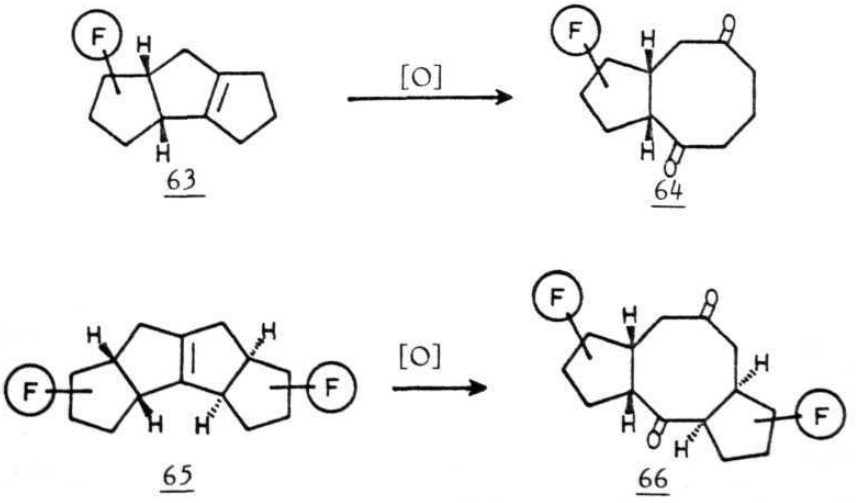
At the outset, we recognised that the main problem in constructing the bicyclo [6.3.0] undecanes resides in the annulation of the eight membered ring and control of stereochemistry in the flexible 5-8 fused system. A solution therefore lay in devising a rigid substrate which is a cyclooctane equivalent 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 bicycle would furnish the functionalised cyclooctane ring. More significantly, the spatial geometry of the cis fused bicyclo [3.3.0] octane imparts it preferential reactivity on the exo-face. Thus, the requisite stereochemistry in the eight membered ring can be present on the bicyclic frame, scheme II.17.

Scheme II.17



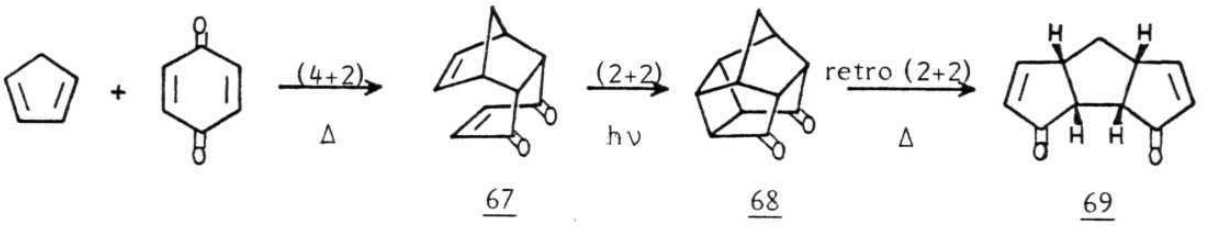
Tactical considerations in the context of bicyclo [6.3.0] undecane synthesis led us to consider the bicyclo [3.3.0] oct-1(5)-ene moiety as a masked cyclooctane-1,5-dione, and triquinene 63 emerged as the equivalent of a 5-8 system 64. The latter can be unravelled through a simple oxidative scission of the double bond. The emerging C_2 and C_6 carbonyl groups provide a convenient handle for functional group manipulations in the 8-membered ring and for ring junction epimerisation. The extended U-shaped geometry of 63 bestows on it exclusive reactivity on the convex face and its 5-5-5 fusion ensures the cis ring junction in 69. As cis-bicyclo [6.3.0] undecanes can be equilibrated with the thermodynamically more stable trans-isomer[16d,h], the dione 64 can be used to gain entry into the trans 5-8 series also. Furthermore, the 63 → 64 theme can be readily extended to the homologous C_{14}-tetraquinene 65 to provide entry into the 5-8-5 system 66, scheme II.18.

Scheme II.18



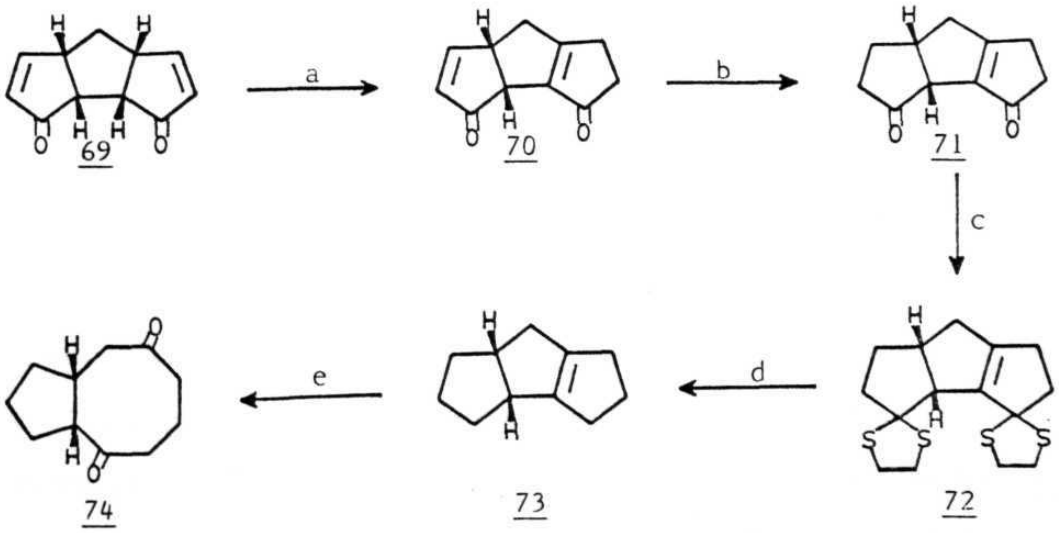
In opting for the tricyclo [6.3.0.0^{2,6}] undec-1(8)-ene (C_{11}-triquinene 63) route to the cis-bicyclo [6.3.0] undecanes, we were obviously influenced by our vantage position in having developed[25] ready access to the cis-syn-cis-triquinane bisenone 69. Indeed, 69 is available in 50-100g quantities from 1,3-cyclopentadiene and p-benzoquinone in three high yielding steps with the added flexibility of substituent control, as shown in scheme II.19. Moreover, one of the enone moieties in 69 could be easily transposed either thermally or through $RhCl_3$-isomerisation[26] to 70, having one of its double bonds in the required bridge-head position.

Scheme II.19



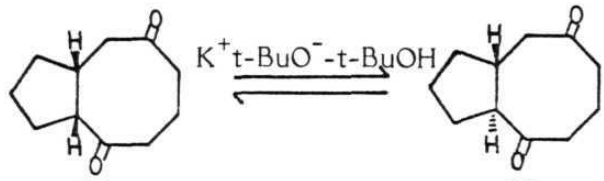
Further elaboration of 70 to the C_{11}-triquin-1(8)-ene 73 required shedding away the oxygen functionalities and oxidative cleavage to furnish the cis-bicyclo [6.3.0]

Scheme II.20



Reagents & Yields: (a) Benzylbenzoate, 305°C, 70% or $RhCl_3.3H_2O$-EtOH; (b) H_2-10% Pd/C-ethyl acetate, 100%;(c) Ethanedithiol-PTS,benzene,80%; (d) Raney Ni (W_2)-EtOH, 79%; (e) RuO_2-$NaIO_4$-CCl_4-MeCN-H_2O, 73%.

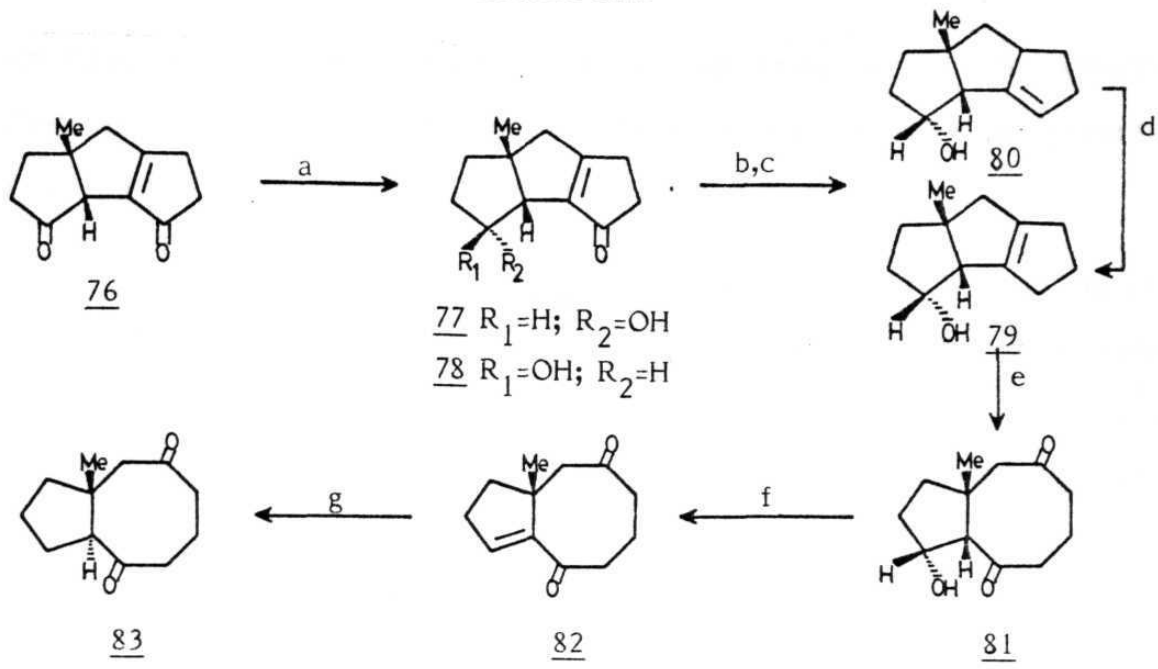
undecan-2,6-dione 74. This was accomplished in an economical sequence shown in scheme II.20. Selective catalytic hydrogenation of the disubstituted double bond in 70 furnished the ene-dione 71 which was readily transformed into the bis-thioacetal 72. Reductive dethioacetalisation gave the volatile triquinene 73, containing small traces of the fully saturated C_{11}-triquinane. This was directly oxidised with RuO_2-$NaIO_4$ according to the procedure of Sharpless[27] to furnish the cis-dione 74, mp 63-64°C. The structure of 74 was fully revealed through its IR spectrum: ν_{max} 1700 cm^{-1} and ^{13}C NMR [Fig.II-1] resonances at δ 213.9 and 212.2 due to the two cyclooctanone carbonyl groups. Thus, cis-bicyclo [6.3.0] undecan-2,6-dione could be obtained from 69 in five straight forward steps in 32% overall yield. When equilibrated with potassium t-butoxide in t-BuOH, 74 furnished a readily separable 90:10 mixture of trans-dione 75, mp 64-65°C and cis-dione 74, respectively. The ^{13}C NMR spectrum [Fig.II-2] of 75 exhibited resonances that clearly differentiated it from the cis-isomer and reaffirmed its structure.



74 75

To further extend the scope of scheme II.20 to bicyclo [6.3.0] undecanes bearing a quaternary centre and substitution in the cyclopentane ring, C_{12}-triquinane ene-dione 76 previously reported by us[28] was employed. Sodium borohydride reduction proceeded regioselectively as well as stereoselectively to furnish hydroxy-enones 77 and 78 in a ratio of 8:1. The major endo-hydroxy-enone 77 was converted into thioacetal and reduced[29] with Na/liq NH_3 to give the hydroxyolefin 79. A small amount of the isomeric hydroxy-olefin 80 was also formed in this reaction, and therefore the product from Na/liq. NH_3 reduction was briefly treated with ethanolic $RhCl_3.3H_2O$ to isomerise 80 into 79. The pure

Scheme II.21

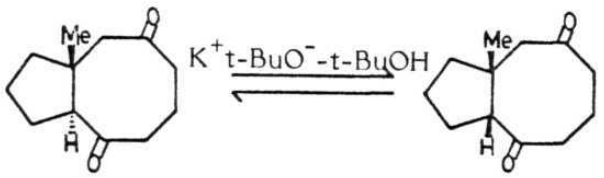


Reagents & Yields: (a) $NaBH_4$-MeOH, 80%, (b) Ethanedithiol-PTS, benzene, 79%, (c) Na-liq.NH_3, ether, 70%, (d) $RHCl_3.3H_2O$-EtOH, 95%, (e) RuO_2-$NaIO_4$-CCl_4-MeCN-H_2O, 53%, (f) PTS, benzene, 76.5%, (g) H_2-10% Pd/C, ethyl acetate, 94%.

hydroxy-olefin 79 was fully characterised on the basis of its ^1H and ^{13}C NMR spectra. While the proton spectrum was transparent in the olefinic region and featureless otherwise, the ^{13}C NMR spectrum had diagnostic Sp^2 carbon resonances at δ148.9 and 141.9 due to the bridgehead double bond. The hydroxy-olefin 79 was oxidised with RuO_4-$NaIO_4$ to the bicyclic hydroxy-dione 81. While 81 could be characterised spectroscopically, being a β-hydroxy-ketone, it showed a marked propensity towards dehydration on storage. Exposure to p-toluene sulphonic acid resulted in smooth dehydration to the enone 82 with a very useful functionality in the five membered ring. The enone formulation for 82 is fully consonant with the ν_{max} at 1680 cm^{-1} and 1600 cm^{-1} the presence of a olefinic proton signal at δ6.66 (t,J=2Hz) in the ^1H NMR spectrum. The ^{13}C NMR spectrum had complimentary signals at δ 211.6, 202.5, 150.2 and 140.4. Catalytic hydrogenation over Pd/C gave the trans-bicyclic ketone 83, whose IR spectrum : ν_{max} 1690 cm^{-1} and ^{13}C NMR [Fig.II-3] values δ 216.3 and 211.3 showed similarity

with those of 75. The formation of the trans-dione during the catalytic hydrogenation is not totally unexpected as the addition of hydrogen from the face opposite to the angular methyl group was expected.

The trans-dione 83 could be again equilibrated with base to furnish a 7:3 mixture of cis-isomer 84, mp 52-53°C and trans-isomer 83, respectively. The stereostructure of cis-dione 84 was fully in agreement with its ^{1}H and ^{13}C [Fig.II-4] NMR spectra. The change in the equilibrium concentration of cis and



83 84

trans isomers derived from 74 and 83, respectively, from 9:1 to 3:7 indicates that the energy difference between the two isomers is significantly effected due to the presence of the angular methyl group. Indeed molecular mechanics calculations[19b] have revealed that the introduction of an angular methyl group in the bicyclo[6.3.0] undecanes makes the cis fused system more stable over the trans-isomer.

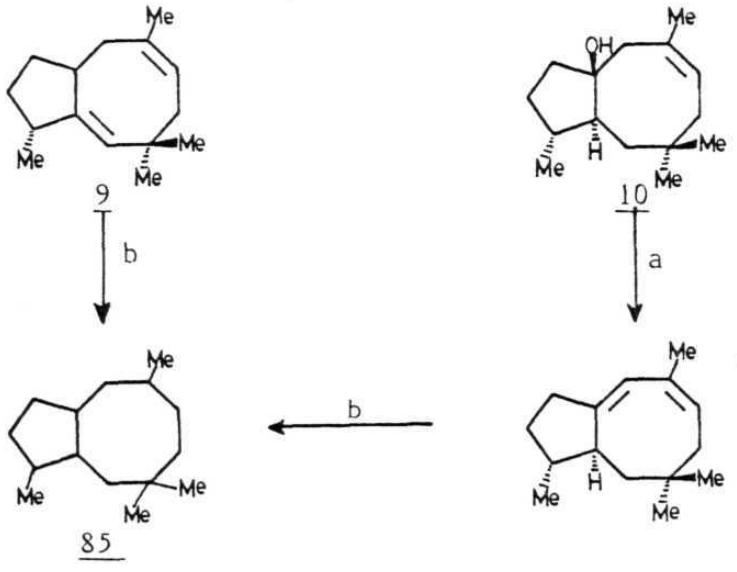
The success of the foregoing model studies impelled us to now pursue our theme towards the total synthesis of the natural product (±) precapnelladiene 9.

II. 4. SYNTHESIS OF (±)-PRECAPNELLADIENE

In 1979, Djerassi and coworkers elucidated[10] the structure of the sesquiterpene hydrocarbon precapnelladiene 9 from the soft coral Capnella imbricata. The bicyclic hydrocarbon bearing two stereogenic centres is the presumed biogenetic precursor of the polyhydroxylated triquinane sesquiterpenes

'capnellanols'[30] with which it cooccurs. Djerassi deduced the structure of 9 mainly on the basis of IR and NMR data, correlation of its reduction product 85 with that obtained from dactylol 10 as shown in scheme II.22, and the use of structure generating programme CONGEN[10]. However, there was no way of assigning the relative stereochemistry at the two stereogenic centres in 9, and this question was left open. However, later synthetic work[21] by Pattenden led to the prediction of the relative stereochemistry as indicated in 9, by a process of elimination. We assumed this to be correct and accordingly planned our synthetic strategy.

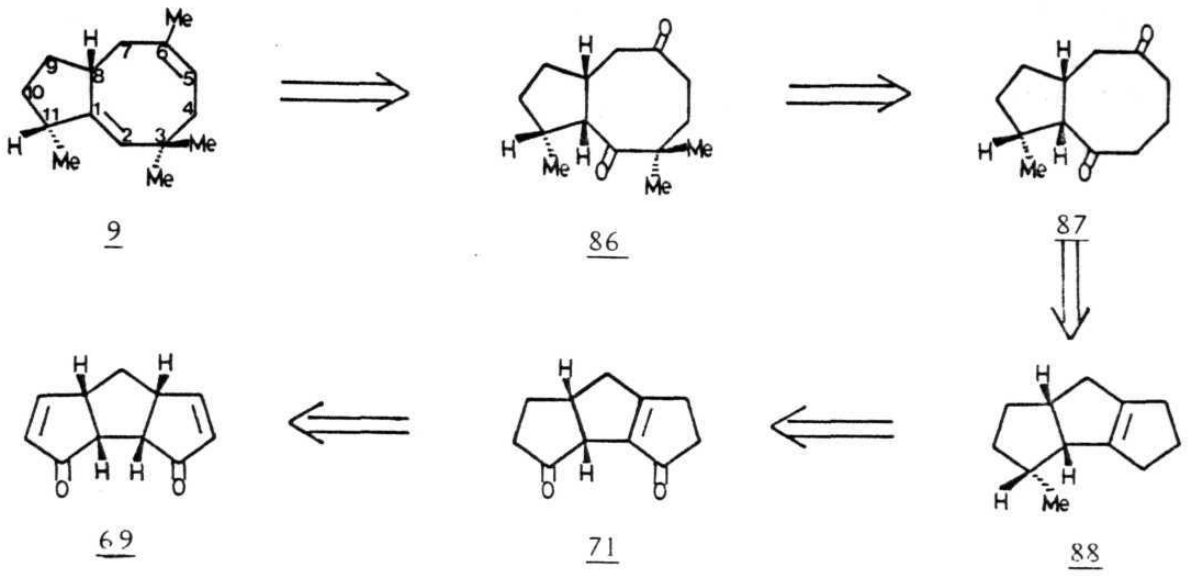
Scheme II.22



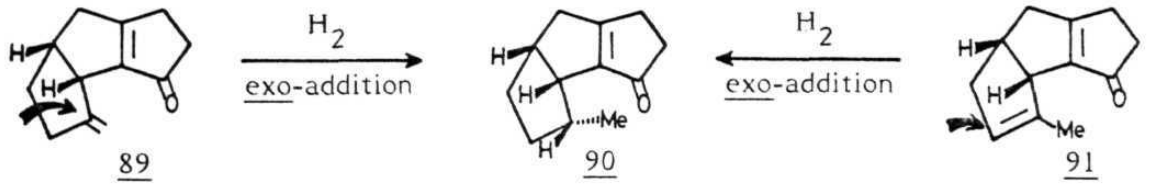
Reagents: (a) $POCl_3$, pyridine, (b) H_2-10% Pd/C, ethyl acetate.

The synthetic plan leading to 9 emerged through the retrosynthetic analysis indicated in scheme II.23 and led to the identification of the readily available bisenone 69 as the starting synthon. Successful execution of the plan required fixing the relative stereochemistry at C_8 and C_{11} stereogenic centres and building up of the methyl substitution and olefinic bonds in the eight membered ring. As the hydrogens at C_8 and C_{11} in 9 have a cis relationship, synthetic logic would

Scheme II.23

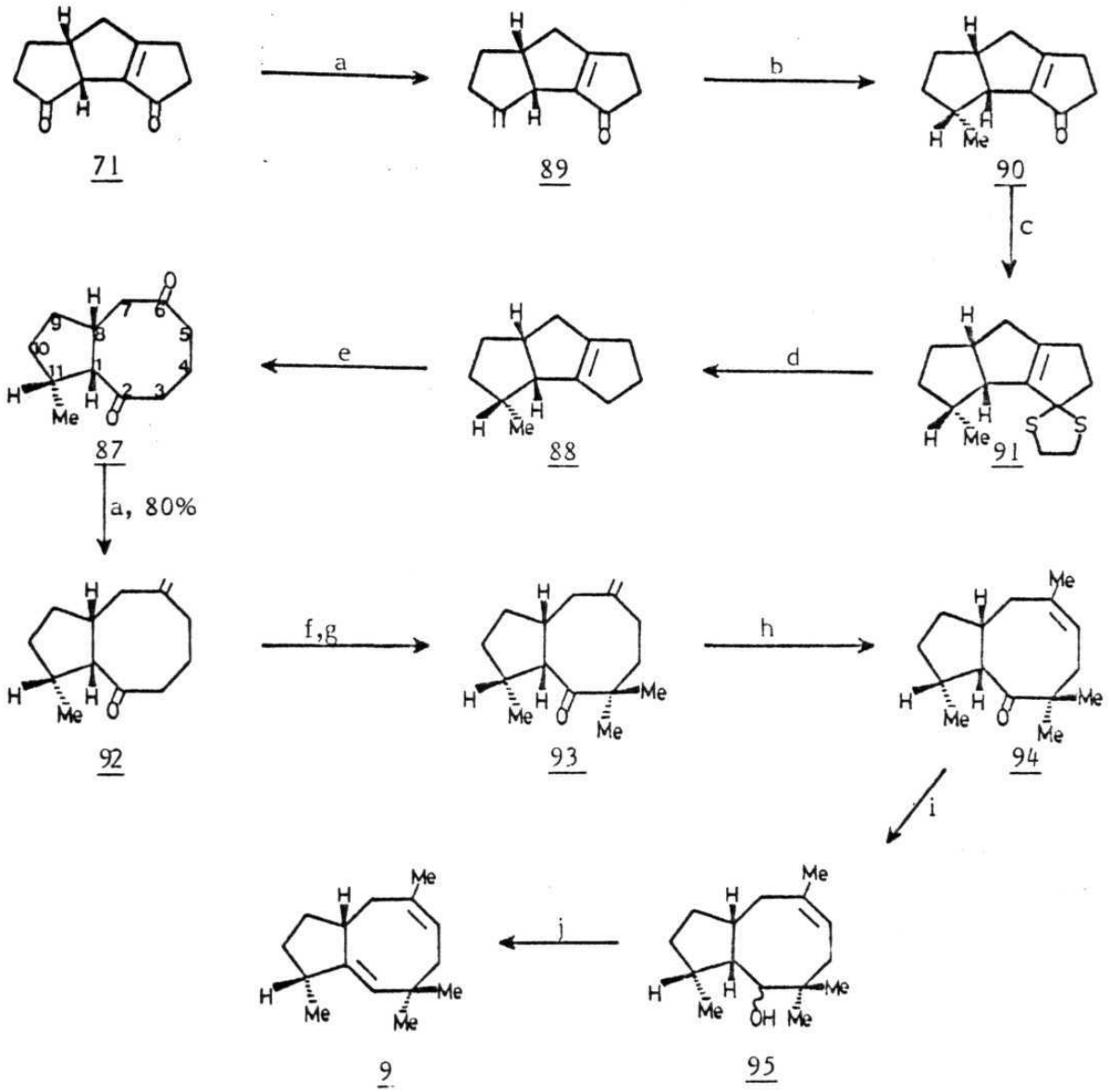


dictate that they be preset in the triquinane precursor before the unravelling process. This could be accomplished through delivery of the hydrogen from the preferred convex face of the triquinanes like 89 or 91 to give 90. The process also installs the methyl group at the desired site.



Ene-dione 71, readily available[25] as described above and having chemically differentiated carbonyl groups was selected as the starting synthon for 9. Selective Wittig olefination of the more reactive saturated carbonyl group proceeded smoothly to give 89. As planned, catalytic hydrogenation of 89 proceeded with complete stereocontrol and crystalline enone 90 mp 51-52°C, with the required endo-methyl group, was obtained in quantitative yield. The enone 90 was now reductively

Scheme II.24



Reagents & Yields: (a) $Ph_3P^+MeI^-$-t-$C_5H_{11}O^-Na^+$-toluene, 85%, (b) H_2-5% Rh/C-EtOH, 90%, (c) Ethanedithiol-PTS-benzene, 80%, (d) Na-liq.NH_3, ether, 65%, (e) RuO_2-$NaIO_4$-CCl_4-MeCN-H_2O, 80%, (f) $(Me_3Si)_2NH$-nBuLi-MeI, -78°C, tetrahydrofuran, 92%, (g) i-Pr_2NH-nBuLi-MeI, -78°C, tetrahydrofuran, 67%, (h) $RhCl_3.3H_2O$-EtOH, 80%, (i) $LiAlH_4$, ether, 80%, (j) $POCl_3$-DBU, pyridine, 70%.

deoxygenated via the thioacetalisation to 91 and desulphurisation[29] with Na/liq.NH_3 to yield the pivotal olefin 88. The tetrasubstituted olefin was slightly contaminated with its $\Delta^{1,2}$-isomer, but it was not purified further and used as such for the oxidative scission. Catalytic ruthenium dioxide oxidation of 88 employing the Sharpless conditions[27] gave the bicyclic dione 87, mp 39-40°C, whose IR spectrum exhibited a strong carbonyl absorption at 1695 cm^{-1} and ^1H and ^{13}C NMR spectra [Fig.II.5 and II-6, respectively] showed signals in the expected range, scheme II.24.

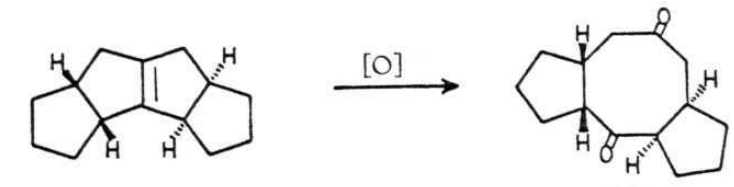
With the acquisition of the cis-bicyclic dione 87 of required stereochemistry, attention was directed towards the introduction of methyl groups and double bonds in the eight membered ring. As per our plan, the carbonyl groups were strategically located and all the required functionalities could be built around and through them. Advantage was now taken of the different steric environment prevailing around the two carbonyl groups. Chemoselective Wittig olefination of the less hindered C_6-carbonyl group furnished the keto-olefin 92, IR spectrum:ν_{max} 1695, 1640 and 890 cm^{-1}. Two successive, kinetically controlled, regioselective methylations on 92 with lithiumhexamethyldisilazide -methyliodide and lithiumdiisopropylamide-methyliodide, respectively, produced the gem-dimethylated compound 93 mp 66-67°C. The ^1H NMR spectrum [Fig.II-7] had signals at δ 1.08 (3H,s), 1.04 (3H,s) and 0.90 (3H,d,J=7Hz) and the ^{13}C NMR data [Fig.II-8] left little doubt about its formation. The stereochemical integrity at C_1 was not compromised during these alkylations. While it is not of consequence in the present context, the observation is useful in constructing other members of the 5-8 and 5-8-5 family, scheme II.24.

The C_5-C_6 double bond was now placed in its position through rhodium catalysed isomerisation[26] of the exocyclic double bond in 93 to 94. The presence of olefinic proton signal at δ 5.44 (t,J=8Hz) in 91 established its location. The final step in the precapnelladiene synthesis required conversion of the C_2-carbonyl group into the C_1-C_2 double bond and this was achieved through LAH reduction of 94

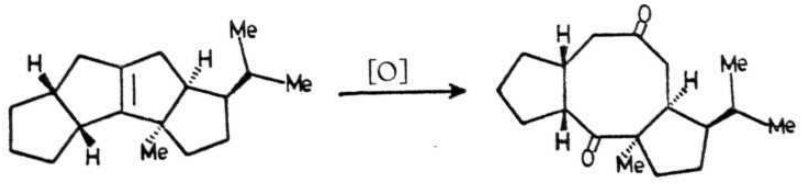
to the hydroxy compound 95 and dehydration with $POCl_3$-DBU in pyridine. The hydrocarbon obtained was spectroscopically identical (IR and ^1H NMR [Fig.II-9] with the natural product*. The synthesis of precapnelladiene was thus accomplished in 14 steps starting from cyclopentadiene and p-benzoquinone. The entire sequence is depicted in scheme II.24.

II. 5. SUMMARY AND OUTLOOK

A short, general, stereocontrolled approach to functionalised cis and trans-bicyclo [6.3.0] undecane system from the readily available cis-syn-cis-triquinane-bisenones has been developed. The 5-5-5 → 5-8 methodology has been applied to the total synthesis of sesquiterpene hydrocarbon (±)-precapnelladiene 9. The stereocontrolled synthesis of the natural product unambiguously establishes its stereochemistry. The general protocol delineated here has built-in flexibility and can be readily adapted for the synthesis of other 5-8 natural products. Furthermore, the 5-5-5 → 5-8 strategem can be further extended through a 5-5-5-5 → 5-8-5 transform to more complex cyclooctanoid di-and sesterterpenes. Concurrent efforts in our laboratory have already demonstrated[31] this possibility through the synthesis of 96 and 98 and their conversion to 97 and 99, respectively.



96 97



98 99

*We thank Professors C.Djerassi and G.Pattenden for supplying the comparison spectra.

I. 6. EXPERIMENTAL

Tricyclo[6.2.1.$0^{2,7}$]undeca-4,9,-diene-3,6-dione (67)[32]:

To an ice cold solution of freshly prepared p-benzequinone (20 g, 0.18mol)in dry benzene (50 mL) was added freshly cracked cyclopentadiene(12.3g, 0.18 mol) with gentle swirling of the flask. After the addition was complete, the reaction flask was left aside at room temperature for 2h for crystallisation. Filtration gave 28 g (88%) of the adduct 67, as pale yellow crystals, mp 76°C (lit.[32] 75.6°C).

IR spectrum (KBr) : ν_{max} : 1670 cm^{-1} (carbonyl).

Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione (68)[33]:

A solution of the adduct 67 (35 g, 0.2 mol) in ethyl acetate (800 mL) was purged with a slow stream of dry N_2 for 20 min. The solution was then irradiated with a Hanovia 450 W medium pressure mercury vapor lamp in a quartz immersion well using a pyrex filter for 2h. Evaporation of the solvent and direct crystallisation from benzene-petroleum ether furnished 31.5 g (90%), stout, white crystals of the pentacyclic dione 68, mp 243-244°C (Lit.[33] 245°C).

IR spectrum (KBr) ν_{max} : 1750 cm^{-1} (carbonyl)

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.7(2H,ABq) and 2.2-3.0(8H,m).

^{13}C NMR spectrum (22.64 MHz, $CDCl_3$): δ 211.9(s), 54.8(d), 44.7(d), 43.9(d), 40.5(t) and 38.9(d).

Cis-syn-cis-tricyclo[6.3.0.$0^{2,6}$]undeca-4,9-diene-3,11-dione (69):

Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-dione 68 (2 g, 11.5 mmol) was slowly sublimed (150°C/1 mm) through a quartz tube [1.5 x 3 cms, packed with quartz chips, connected to a vacuum line and provided with a collection

flask and liq. N_2 trap. The quartz tube was heated with a nichrome wire wound around it and was insulated with asbestos padding. The temperature was controlled by a variac and was measured by a Chromel-Alumel thermocouple on a Keithley digital multimeter. The quartz tube was preheated and equilibrated at 560°C]. The solid condensate in the receiver was collected and directly crystallised from carbon tetrachloride to furnish 1.92 g (96%) of the bisenone 69 as white silky flakes, mp 107-108°C.

UV spectrum λ_{max}^{MeOH} : 219 nm (ε:10,500).

IR spectrum (KBr) ν_{max} : 2950, 1725 (carbonyl), 1715 (carbonyl), 1695 (olefinic) and 1590 cm^{-1}.

^1H NMR spectrum (100 MHz,$CDCl_3$): δ 1.90(1H, td, J_1=14Hz,J_2=1Hz), 2.3(1H, td,J_1=14Hz,J_2=9Hz), 3.2(2H,m), 3.48(2H,m), 5.86(2H,dd,J_1=6Hz, CH=C<u>H</u>-C=O) and 7.44(2H,dd,J_1=6Hz,J_2=3Hz, C<u>H</u>=CH-C=O).

^{13}C NMR spectrum (25.0MHz,$CDCl_3$): δ 207.4(s), 165.9(d), 133.5(d), 53.1(d), 50.4(d) and 31.5(t).

Analysis for $C_{11}H_{10}O_2$ Calcd: C,75.84; H,8.10
Found: C, 75.74; H, 5.90.

Thermal equilibration of tricyclo[6.3.0.$0^{2,6}$]undeca-4,9-diene-3,11-dione (69):

A solution of bisenone 69 (1 g, 5.75 mol) in benzyl benzoate (5 mL) was maintained at 305°C in a salt bath for 3 min. GLC analysis of the mixture indicated the presence of three components in the ratio of 1:2:12. The reaction mixture was diluted with dichloromethane (10 mL) and charged on a silica gel (20g) column and chromatographed. Benzyl benzoate was eliminated by elution with dichloromethane. Further elution with 20% ethyl acetate-benzene furnished 20mg (2%) of the <u>cis</u>-<u>anti</u>-<u>cis</u>-bisenone, which was crystallised from dichloromethane-hexane, mp 99-100°C.

UV spectrum λ_{max}^{MeOH} : 222nm (ε:12,500)

IR spectrum (KBr): ν_{max} : 2950, 1715 (carbonyl), 1695 (olefinic) and 1580 cm^{-1}

^1H NMR spectrum (100MHz,$CDCl_3$): δ 1.88(2H,t,J=8Hz), 2.93(2H,d,J=6Hz), 3.45 (2H,m), 6.08(2H,dd,J_1=6Hz,J_2=3Hz, CH=C<u>H</u>-C=O) and 7.62(2H,dd,J_1=6Hz, J_2=3Hz, C<u>H</u>=CH-C=O).

^{13}C NMR spectrum (25.0MHz,$CDCl_3$): δ 209.6(s), 166.3(d), 132.2(d), 52.9(d), 48.1(d) and 34.9(t).

Further elution of the column with 40% ethyl acetate-benzene furnished 10 mg of the starting bisenone <u>69</u> identified by comparison (TLC,IR) with authentic sample and final elution of the column with ethyl acetate furnished 720 mg (72%) of the isomerised bisenone <u>70</u>, which was crystallised from carbon tetrachloride, mp 102-103°C.

UV spectrum λ_{max}^{MeOH}: 218 and 242 nm (ε : 13,100 and 5,640).

IR spectrum (KBr) ν_{max} : 2950, 1708 (carbonyl), 1695 (olefinic) and 1625 cm^{-1} (olefinic).

^1H NMR spectrum (100MHz,$CDCl_3$): δ 1.9-3.15(6H,m), 3.56(1H,m), 6.1 (1H,dd,J_1=6Hz,J_2=3Hz CH=C<u>H</u>-C=O) and 7.58(1H,dd,J_1=6Hz,J_2=3Hz, C<u>H</u>-CH-C=O)

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ205.5(s), 201.7(s), 185.1(s), 165.1(d), 143.8(s), 132.2(d), 50.4(d), 49.7(d), 40.6(t), 35.3(t) and 25.7(t)

Analysis for $C_{11}H_{10}O_2$ Calcd: C,75.84; H,5.79.
Found: C,75.49; H,5,45.

Tricyclo[6.3.0.$0^{2,6}$]undeca-1(8)-ene3,11-dione (<u>71</u>):

A solution of isomerised bisenone <u>69</u>[25] (350 mg, 2.0 mmol) was hydrogenated over 10% Pd/C catalyst (15 mg) in H_2 atmosphere (2 psi) for 15 min. Catalyst was removed by filtration and the filtrate concentrated. Crystallisation from

carbontetrachloride furnished the partially hydrogenated compound 71, (350 mg, quantitative), mp 74-76°C.

UV spectrum λ_{max}^{MeOH} : 242 nm (ε : 7,000).

IR spectrum (KBr) ν_{max} : 2950, 1735 (carbonyl), 1695 (carbonyl) and 1625 cm^{-1} (olefinic).

^1H NMR (100MHz, $CDCl_3$): δ 3.4(2H,br s) and 1.6-3.5(10H,m).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 214.5, 201.8, 187.8, 144.0, 52.2, 44.6, 40.9, 38.7, 37.5, 28.5 and 25.7.

Analysis for $C_{11}H_{12}O_2$ Calcd: C,74.98; H,6.86
Found: C,74.69; H,6.85.

3,3,11,11-Bis (ethylene dithio)-tricyclo[6.3.0.$0^{2,6}$]undeca-1(8)-ene (72):

A solution of the dihydro-compound 71 (1.5 g, 8.5 mmol), ethanedithiol (2 mL) and p-toluenesulphonic acid (50 mg) in dry benzene (100 mL) was refluxed with a Dean-Stark water separator for 30 min. The reaction mixture was diluted with benzene (30 mL), washed with $NaHCO_3$ solution, water and dried. The crude residue obtained after removal of the solvent was charged on a silica gel column (100 g). Elution with 5% benzene-petroleum ether removed the ethanedithiol impurities. Further elution with 10% benzene-petroleum ether furnished the dithioketal 72 (2.25 g, 80%).

IR spectrum (neat) ν_{max} : 2950, 1440, 1270, 960 and 660 cm^{-1}

^1H NMR spectrum (100 MHz, $CDCl_3$):δ 1.3-2.5(8H,m), 2.6-2.9(4H,m) and 3.1-3.5(8H,m).

Low resolution mass spectrum for $C_{15}H_{20}S_4$:

Calcd: m/e, 328.59

Found: m/e, 328.0

(3aβ, 9aβ) -Decahydrocyclopenta-4H ,8H-cyclooctan-4,8-dione (74):

Into a 250 mL round bottom flask were taken Raney Nickel (20 g, W_2), and dithioketal 72 (2.0 g, 6.09 mmol) in absolute ethanol (200 mL). The mixture was refluxed for 72 h and filtered. The filtrate was diluted with water (100 mL) and extracted with pentane (3x50 mL). The crude oily material obtained after removal of the solvent was charged on a silica gel column (10 g). Elution with pentane furnished the hydrocarbon 73 (600 mg, 79%).

IR spectrum (neat) ν_{max} : 2950 and 1440 cm^{-1}, which was contaminated with some fully saturated hydrocarbon.

The above hydrocarbon mixture 73 (600 mg) was dissolved in a mixture of carbontetrachloride (5 mL), acetonitrile (5 mL) and water (7 mL). To this mixture sodium periodate (1.5 g) and ruthenium dioxide (10 mg) were added[26]. After stirring for 30 min, the reaction mixture was diluted and extracted with dichloromethane (3x20 mL). The organic layer was washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (30 g) and elution with petroleum ether removed the saturated hydrocarbon impurities. Further elution with ethyl acetate-benzene furnished the dione 74 (400 mg, 73%) mp 63-64°C.

IR spectrum (KBr) ν_{max} : 2950, 1700 (carbonyl), 1440 and 1240 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ1.3-2.9(15H,m) and 3.1(1H,dd,J_1=16Hz, J_2=8Hz).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.II-1): δ 213.9, 212.9, 63.6, 44.5, 43.1, 42.3, 39.8, 32.6, 25.2, 22.8 and 22.5.

Analysis for $C_{11}H_{16}O_2$ Calcd: C,73.30; H,8.95.
Found: C,73.25; H,9.07.

(3aα,9aβ) -Decahydrocyclopenta-4H,8H-cyclooctan-4,8-dione (75):

Into a 25 mL three necked round bottom flask fitted with dry nitrogen

gas inlet, rubber septum and mercury seal were taken freshly sublimed t-BuOK (10 mg) and dry t-BuOH (3 mL). After stirring for 5 min the cis-diketone 74, (60 mg, 0.33 mmol) in dry THF (2 mL) was added through a syringe. The reaction mixture was stirred for 1h at room temperature and then quenched with saturated NH_4Cl solution. The mixture was extracted with ether (3x10 mL) and the combined organic layer washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (10 g). Careful elution with 10% ethyl acetate-benzene furnished the starting diketone 74 (5 mg, 8%). Further elution with the same solvent furnished the trans-diketone 75 (46 mg, 76%) which was crystallised from ether-petroleum ether, mp 64-65°C (lit.[16h] 64.5°C).

IR spectrum (KBr) ν_{max} : 2950, 1700 (carbonyl), 1440 and 1240 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.16-3.1(16H,m).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.II-2): δ 214.4, 211.7, 56.2, 46.4, 44.4, 43.2, 43.1, 34.1, 29.4, 22.6 and 21.3.

The IR, ^1H NMR and ^{13}C NMR data were fully in agreement with the reported values[16h].

6 β-Methyl-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene-11-one-3-ols (77 & 78):

To a solution of 76[28] (1.6 g, 8.42 mmol) in dry methanol (150 mL) was added sodium borohydride 2.0 g (excess) in 200 mg lots at -10°C. Addition of sodium borohydride was stopped after the consumption of all starting material. Acetone (10 mL) was added to quench the excess borohydride. After 10 min methanol was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave crude product (1.6 g) which was charged on a silica gel column (50 g). Elution with 25% ethyl acetate-benzene removed less polar impurities. Further elution with 50% ethyl

acetate-benzene furnished the hydroxy-enones 77 and 78 (1.4 g, 86%) as a mixture of hydroxy-epimers (8:1), which was bulb-to-bulb distilled at 160°C/0.3 mm. The mixture of hydroxy-epimers was more conveniently separated in the next step.

UV spectrum λ_{max}^{MeOH}: 238 nm (ε : 10,580).

IR spectrum (neat) ν_{max} : 3450 (hydroxyl), 2950, 1680 (carbonyl), 1630 (olefinic) and 1380 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$, as a mixture of epimers): δ 1.06(6H,s, $\underline{H_3}C$-C-), 1.2-1.9(9H,m), 2.2-2.74(13 H,m), 3.14(2H,br s) and 4.2(2H,m, HO-C<u>H</u>-C).

Analysis for $C_{12}H_{16}O_2$ Calcd: C,74.97; H,8.39
Found: C,75.04; H,8.25.

6 β-Methyl-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene-3 α-ol (79):

A mixture of hydroxy-enone 77 and 78 (800 mg, 4.2 mmol), ethanedithiol (1 mL) and p-toluenesulphonic acid (20 mg) in dry benzene (50 mL) was refluxed with a Dean-Stark water separator for 30 min. The reaction mixture was diluted with benzene (30 mL), washed with $NaHCO_3$ solution and dried. The crude residue obtained after removal of the solvent was charged on a silica gel column (50 g)

Elution with 50% benzene-petroleum ether removed the ethanedithiol impurities. Further elution with benzene furnished the endo-hydroxy-thioketal, 800mg (76%).

IR spectrum (neat) ν_{max} : 3450 (hydroxyl), 2950, 1660 (olefinic), 1440, 1000 and 820 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$: δ1.06(3H,s $\underline{H_3}C$-C-), 1.4-1.9(4H,m), 2.0(1H,s), 2.06-2.3(4H,m), 2.4-2.6(1H,m), 2.88(2H,t,J=8Hz), 3.26(4H,s, (-S-CH_2-CH_2-S-) and 4.16(1H, br s, HO-C<u>H</u>-C-).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 150.9, 144.7, 73.6, 71.0, 60.9, 55.8, 49.4, 46.7, 41.2, 40.5, 38.5, 35.5, 29.9 and 28.8.

Analysis for $C_{14}H_{20}OS_2$ Calcd: C,62.64; H,7.51

Found: C,62.83; H,7.74.

Continued elution with benzene gave the minor exo-hydroxy-thioketal 100 mg (10%).

IR spectrum (neat) ν_{max}: 3450 (hydroxyl), 2950, 1660 (olefinic), 1440, 1020 and 820 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.0(3H,s H_3C-C-), 1.24-1.64(4H,m), 1.68-2.08(4H,m), 2.2(1H,br s), 2.44(1H,s), 2.64(2H,t,J=8Hz), 3.14(4H,s, (-S-CH_2-CH_2-S-) and 4.08(1H, m, HO-CH-C-).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 147.7, 145.7, 77.3, 71.1, 62.0, 55.5, 51.1, 45.6, 40.4, 40.1, 38.6, 34.2, 29.8 and 28.2.

Into a two necked 250 mL round bottom flask fitted with a guard tube and stopper was taken liquid NH_3 (100 mL). To this freshly cut sodium metal, 300 mg (13.0 mg atom) was added piece by piece. The resulting blue solution was stirred for 5 min and the thioketal, 950 mg (3.8 mmol) in dry ether (50 mL) was slowly added to it. The reaction mixture was quenched with NH_4Cl solution after all ammonia had evaporated. The reaction mixture was diluted and extracted with ether (3x50 mL), washed and dried. The crude material obtained after removing the solvent was loaded on a small silica gel column (20 g). Elution with 50% benzene-petroleum ether gave a mixture of double bond isomers 79 and 80 (475mg, 70%)as revealed by the presence of additional ^1H NMR signal at δ 5.5. The mixture of isomers 79 and 80 (475 mg, 2.7 mmol) and $RhCl_3.3H_2O$ (50 mg) in absolute ethanol (30 mL) were refluxed for 4 h in a 50 mL round bottomed flask.

The reaction mixture was passed through a small alumina (10 g) column, removal of the solvent furnished the pure hydroxy-olefin 79 (450 mg, 95%) as a single isomer, which was bulb-to-bulb distilled at 120°C/0.4 min.

IR spectrum (neat) ν_{max} : 3350 (hydroxyl), 2950, 1440 and 1040 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.1(3H,s $\underline{H_3}C$-C-), 1.18-1.28(2H,m), 1.46(2H,s), 1.5-1.7(2H,m), 1.9-2.2(7H,m), 2.4(1H,d,J=7Hz) and 4.18(1H,m, HO-C$\underline{H}$-C).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 148.9, 141.9, 74.9, 60.7, 55.2, 46.2, 38.5, 35.3, 29.8(2c), 29.6 and 27.9.

Analysis for $C_{12}H_{18}O$ Calcd: C,80.85; H,10.18
Found: C,80.59; H,10.21.

(3a β,9aβ)-Decahydro-3a-methyl-cyclopenta-5H,9H-cyclooctan-5,9-dione-1-ol (81):

Hydroxy-olefin 79 (320 mg, 1.8 mmol) was dissolved in a mixture of carbotetrachloride (2 mL), acetonitrile (2 mL) and water (3 mL). To this mixture sodium periodate (900 mg) and ruthenium dioxide (8 mg) were added. After stirring for 5 min, the reaction mixture was diluted and extracted with dichloromethane (3 x 20 mL). The organic layer was washed and dried. The crude material obtained after removal of the solvent was loaded on a silica gel column (50 g) and elution with 30% ethyl acetate-benzene furnished the hydroxy-dione 81 (200 mg, 53%).

IR spectrum (neat) ν_{max} : 3450 (hydroxyl), 2950, 1680 (carbonyl), 1450 and 1080 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.08(3H,s, $\underline{H_3}C$-C-), 1.2-2.8(13H,m), 3.0(1H,d,J=6Hz) and 4.5(1H,m, HO-C$\underline{H}$-C).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 215.4, 210.8, 75.8, 63.2, 51.9,

45.6, 45.1, 44.1, 38.5, 32.5, 28.2 and 21.7.

(3a β)-2,3,3a,4,6,7,8-Octahydro-3a-methyl-cyclopenta-5H,9H-cyclooctan-5,9-dione (82):

The above hydroxy-dione 81 (200 mg, 0.952 mmol) in dry benzene (15 mL) and p-toluenesulphonic acid (10 mg) were refluxed for 1h in a 25 mL round bottom flask. The reaction mixture was diluted with benzene (20 mL) washed with $NaHCO_3$ solution, water and dried. The product 82 (140 mg, 76.5%) obtained after removal of the solvent was bulb-to-bulb distilled at 140°C/0.3 mm.

IR spectrum (neat) ν_{max} : 3050, 2950, 1680 (carbonyl), 1600 (olefinic), 1440, 1300 and 1240 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.24(3H,s, $\underline{H_3}C$-C-), 1.6-2.08-(4H,m), 2.2-2.76(8H,m) and 6.66(1H,t,J=4Hz, -C<u>H</u>=C-C=O).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 211.6, 202.5, 150.2, 140.4, 54.9, 47.9, 41.7, 41.3, 40.9, 29.1, 26.0 and 22.0.

Analysis for $C_{12}H_{16}O_2$ Calcd: C, 74.97; H, 8.39.
Found: C, 74.83; H, 8.60.

(3aα ,9a,β)-Decahydro-9a-methyl-cyclopenta-4H,8H-cyclooctan-4,8-dione (83):

The enedione 82 (100 mg, 0.52 mmol) in ethyl acetate (20 mL) and 10% Pd/C (10 mg) were taken in 250 mL Parr-hydrogenation flask. After shaking the reaction mixture in H_2 atmosphere (10 psi) for 10 min the catalyst was filtered and the filtrate was concentrated. The product was bulb-to-bulb distilled at 140°C/0.4 mm to get pure trans-dione 83 (95 mg, 94%).

IR spectrum (neat): ν_{max} : 2950, 1690 (carbonyl), 1450, 1200 and 1040 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.9(3H,s, $\underline{H_3}C$-C-), 1.16-2.44 (14H,m) and 2.68(1H,m).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.II-3): δ 216.3, 211.3, 57.7, 49.8, 45.6, 44.9, 39.9, 33.8, 28.5, 27.1, 22.1 and 21.5.

Analysis for $C_{12}H_{16}O_2$ Calcd: C, 74.19; H, 9.34.
Found: C, 74.18; H, 9.42.

(3aβ,9aβ) -Decahydro-9a-methyl-cyclopenta-4H,8H-cyclooctan-4,8-dione (84):

Into a 25 mL three necked round bottom flask fitted with dry nitrogen gas inlet, rubber septum and mercury seal, were taken freshly sublimed t-BuOK (10 mg) and dry t-BuOH (3 mL). After stirring for 5 min. the trans-dione 83 (60 mg, 0.3 mmol) in dry THF (2 mL) was added through a syringe. The reaction mixture was stirred for 1 h at room temperature and then quenched with saturated NH_4Cl. The mixture was extracted with ether (3x10 mL) and the combined organic layer was washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (10 g). Careful elution with 10% ethyl acetate-benzene furnished the starting trans-dione 83 (18 mg, 30%). Further elution with the same solvent furnished the cis-dione 84 (32 mg, 53%) and was crystallised from ether-petroleum ether, mp 52-53°C.

IR spectrum (neat) ν_{max}: 2950, 1700 (carbonyl), 1440, 1200 and 860 cm^{-1}. cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.8(3H,s, H_3C-C-), 1.4-2.9(14H,m) and 3.1(1H,dd,J_1=12Hz,J_2=8Hz).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.II-4): δ 212.2, 210.8, 56.4, 52.2, 45.6(2C), 45.1, 43.5, 27.5, 20.5, 20.0 and 19.2.

Analysis for $C_{12}H_{18}O_2$ Calcd: C,74.19; H,9.34.
Found: C,74.21; H,9.36.

Tricyclo[6.3.0.$0^{2,6}$]dodeca-1(8),3(12)-diene-11-one (89):

Into a 50 mL three necked round bottom flask fitted with dry nitrogen

inlet, septum, reflux condensor and mercury seal, methyltriphenylphosphonium bromide, 1.7 g (4.77 mmol) was introduced with an addition funnel and the solid was suspended in dry toluene (10 mL). To this suspension was added sodium t-amyloxide, 420 mg (3.81 mmol) in dry toluene (10 mL). The resulting yellow reaction mixture was stirred at ~ 40°C for 5 min and then the enedione 71 (560 mg, 3.18 mmol) in dry toluene 5 mL) was introduced at once. The reaction mixture was refluxed for 3.5 h and then diluted with benzene (20 mL) and brine (15 mL). The organic layer was separated, washed and dried. Removal of solvent gave an oily residue which was charged on a silica gel (50 g) column. Elution with petroleum ether removed the triphenylphosphine derived impurities. Further elution with benzene furnished the terminal olefinic compound 89 (475 mg, 85%) which was bulb-to-bulb distilled at 110°C/0.4 mm.

UV spectrum λ_{max}^{MeOH} : 238 nm (ε : 14,970).

IR spectrum (neat) ν_{max} : 3075, 2950, 1700 (carbonyl), 1660 (olefinic), 1640 (olefinic), 1440 and 890 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.2-1.4(1H,m), 1.7-2.8(9H,m), 3.0-3.4(1H,m), 3.4-3.6(1H,m), 4.75(1H,br s, C=C$\underline{H}_2$) and 5.1(1H,br s, C=C$\underline{H}_2$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 203.1, 185.0, 151.8, 148.7, 107.5, 48.2, 47.7, 41.0, 38.5, 33.6, 33.3 and 25.4.

Analysis for $C_{12}H_{14}O$ Calcd: C,82.72; H,8.10.
Found: C,82.50; H, 8.24.

3α-Methyl-tricyclo[6.3.0.$0^{2,6}$]undeca-1(8)-ene-11-one (90):

The exo-methylene compound 89 (475 mg, 2.72 mmol) was taken in ethanol (25 mL) and hydrogenated in a Parr-hydrogenation apparatus over 5% Rh/C catalyst (50 mg) at 2 psi pressure. After the consumption of approximately 1 mole of hydrogen, the catalyst was filtered and the solvent was removed.

The residue was filtered through a silica gel (20 g) column to give 440 mg (90%) of endo-methyl compound 90 and was crystallised from petroleum ether to furnish colourless cubes, mp 51-52°C.

UV spectrum λ_{max}^{MeOH} : 240 nm (ε : 15,560).

IR spectrum (KBr) ν_{max}: 2950, 1700 (carbonyl), 1640 (olefinic), 1420, and 1380 cm^{-1}.

^1H NMR (100MHz, $CDCl_3$): δ 0.92(3H,d,J=8Hz, $\underline{H_3}C$-CH), 1.36-1.72(4H,m), 2.04 (1H,br s), 2.2 (1H,br s), 2.48(1H,br s), 2.56-2.8(3H,m) and 3.0-3.4(2H,m).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 203.9, 187.8, 148.5, 47.9, 47.8, 40.9, 40.4, 38.0, 33.9, 33.7, 25.5 and 16.9.

Analysis for $C_{12}H_{16}O$ Calcd: C,81.77; H,9.15.

Found: C,81.57; H,9.17.

3α-Methyl-11,11-ethylenedithio-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene (91):

A solution of the enone 90 (200 mg, 1.14 mmol), ethanedithiol (0.5 mL) and p-toluenesulphonic acid (10 g) in dry benzene (30 mL) was refluxed with a Dean-Stark water separator for 30 min. The reaction mixture was diluted with benzene (30 mL), washed with aq. $NaHCO_3$ water and dried. The crude residue obtained after removal of the solvent was charged on a silica gel (20 g) column. Elution with 20% benzene-petroleum ether removed the ethanedithiol impurities. Further elution with 50% benzene-petroleum ether furnished the thioketal 91 (230 mg, 80%).

IR spectrum (neat) ν_{max} : 2950, 1660 (olefinic), 1450 and 810 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.90(3H,d,J=8Hz, $\underline{H_3}C$-CH-), 1.2-2.5 (10H,m), 2.76-3.1(3H,m) and 3.2-3.32(4H,m).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 158.8, 147.2, 72.2, 51.5, 50.3,

49.6, 40.6, 39.6, 39.2, 37.2, 36.4, 31.2, 28.7 and 17.3.

(3aβ,9aα)-Decahydro- 3α-methyl-cyclopenta-4H,8H-cyclooctan-4,8-dione (87):

Into a two necked 100 mL RB flask, fitted with a guard tube and stopper, was taken liquid NH_3 (50 mL). To this freshly cut sodium metal, 200 mg (8.7 mg atom) was added piece by piece. The resulting blue solution was stirred for 5 min and the thioacetal 91 (580 mg, 2.3 mmol) in dry ether (10 mL) was slowly added to it. The reaction mixture was quenched with saturated NH_4Cl solution after all the ammonia had evaporated. The reaction mixture was diluted and extracted with n-pentane (3x30 mL), washed and dried over anhydrous Na_2SO_4. The crude material obtained after removing the solvent was loaded on a small silica gel column (5 g). Elution with n-pentane gave 88 (245 mg, 65%), IR spectrum (neat, mixture of isomers): ν_{max} 3050, 2950, 1460 and 1120 cm^{-1}, contaminated with traces of $\Delta^{1(2)}$ double bond isomer. The above hydrocarbon mixture 88 (245 mg, 1.5 mmol) was dissolved in a mixture of carbontetrachloride, acetonitrile and water (each 5 mL). To this mixture sodium periodate (800 mg) and ruthenium dioxide (12 mg) were added. After stirring for 30 min. the reaction mixture was diluted and extracted with dichloromethane (3 x 10 mL). The organic layer was washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (30 g) and elution with 10% ethyl acetate-benzene furnished the dione 87 (235 mg, 80%), mp 39-40°C.

IR spectrum (neat) ν_{max}: 2950, 1695 (carbonyl), 1460, 1310 and 1180 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$, Fig.II-5): δ 0.90(3H,d,J=7Hz, $\underline{H_3}C$-CH), 1.6-2.6(14H,m) and 3.10(1H, t,J=6Hz).

^{13}C NMR spectrum 25.0MHz, $CDCl_3$, Fig.II-6): δ 215.2, 213.9, 56.1, 47.3, 44.9, 43.9(2C), 39.5, 31.5, 30.9, 23.1 and 15.9.

Mass spectrum (70eV, m/e, relative intensity): 194(M^+,80), 166(38), 139(21), 124(21), 113(50), 111(55), 109(39), 84(28), 81(100), 80(49), 67(25), 55(24).

High resolution mass spectrum for $C_{12}H_{18}O_2$:

Calcd: m/e 194.1306.

Found: m/e 194.1307.

(3a β,9a β)-Decahydro-3 α-methyl-8-methylene-cyclopenta-4H-cyclooctan-4-one (92):

Into a 25 mL three necked round bottomed flask fitted with dry nitrogen inlet, septum, reflux condensor and mercury seal, methyltriphenylphosphonium bromide, 415 mg (1.15 mmol) was introduced with an addition funnel and the solid was suspended in dry toluene (5 mL). To this suspension, was added sodium t-amyloxide, 101 mg (0.92 mmol) in dry toluene (5 mL). The resulting yellow reaction mixture was stirred at ~ 40°C for 5 min and then the dione 87 (150 mg, 0.77 mmol) in dry toluene (5 mL) was introduced at once. The reaction mixture was refluxed for 2.5 h and then diluted with benzene (10 mL) and brine (15 mL). The organic layer was separated, washed and dried. Removal of the solvent gave an oily residue which was charged on a silica gel column (30 g). Elution with petroleum ether removed triphenylphosphine derived impurities. Further elution with 50% benzene-petroleum ether furnished the exo-methylene compound 92 (120 mg, 81%).

IR spectrum (neat) ν_{max} : 3075, 2950, 1695 (carbonyl), 1640 (olefinic), 1460, 1390 and 890 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.86(3H,d,J=7Hz, $\underline{H_3}C$-CH), 1.24-2.5 (14H,m), 3.24(1H,t, J=6Hz), 4.72(1H,br s, C=C$\underline{H_2}$) and 4.88(1H,br s, C=C$\underline{H_2}$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 215.4, 148.5, 114.3, 55.1, 48.3,

47.8, 39.3, 38.7, 37.7, 31.8, 30.8, 25.6 and 15.9.

Analysis for $C_{13}H_{20}O$ Calcd: C,81.20; H,10.48.
Found: C,81.48; H,10.59.

(3aβ,9aβ)-Decahydro-3α,5,5-trimethyl-8-methylene-cyclopenta-4H-cyclooctan-4-one (93):

Into a 25 mL three necked round bottom fitted with dry nitrogen gas inlet, septum and mercury seal, n-BuLi 1.2 ML (0.4 mmol) in hexane was introduced. It was cooled to -78°C and hexamethyldisilazane (0.2 mL) was added. The mixture was stirred for 20 min, then THF (2 mL) was added to dissolve the solid material formed. After 10 min the keto-olefin 92 (50 mg, 0.26 mmol) in THF (1 mL) was slowly added and was stirred for 20 min. Then methyliodide (0.2 mL, excess) was added to quench the enolate. The reaction mixture was slowly brought to room temperature and stirred for 3h. The reaction mixture was then worked up by adding saturated NH_4Cl solution to it, diluted and extracted with ether (3 x 20 mL). The organic layer was washed and dried. The crude material obtained after removing the solvent was charged on a silica gel column (30 g). Elution with 10% ethyl acetate-benzene furnished monoalkylated compound, 50 mg (92%) mp 45-46°C.

IR spectrum (neat) ν_{max} : 3075, 2950, 1700 (carbonyl), 1640 (olefinic), 1460 and 890 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.88(3H,d,J=8Hz, $\underline{H_3}C$-CH), 1.0(3H,d,J=8Hz, $\underline{H_3}C$-CH), 1.52-2.52(13H,m), 3.2(1H,t,J=6Hz), 4.7(1H,br s, C=C$\underline{H_2}$) and 4.84(1H,br s, C=C$\underline{H_2}$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 217.9, 148.6, 114.4, 51.7, 50.9, 48.6, 39.5, 38.2, 38.0, 34.7, 31.8, 30.5, 17.8 and 16.2.

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

Found: C,81.58; H,10.83.

Into a 25 mL three necked round bottom flask fitted with dry nitrogen gas inlet, septum and mercury seal, diisopropylamine (0.2 mL) in THF (1 mL) was introduced. This mixture was cooled to -78°C, then n-BuLi (1 mL, 0.3 mmol) in hexane was slowly added to it. After 30 min monoalkylated compound, (50 mg, 0.24 mmol) in THF (1 m L) was slowly introduced and stirring continued for another 25 min. The enolate was quenched with methyliodide (0.2 mL) at the same temperature and the reaction mixture was slowly warmed to room temperature. After 1h, saturated NH_4Cl solution was added and the reaction mixture was extracted with ether (3x20 mL). The organic layer was washed and dried. The crude product obtained after the removal of solvent was charged on a silica gel column (20 g). Elution with 5% ethyl acetate-benzene furnished the gem-dimethylated product 93 (22 mg, 67% based on the recovery of starting material), mp 66-67°C.

IR spectrum (KBr) ν_{max} : 3075, 2950, 1600 (carbonyl), 1635 (olefinic), 1460 and 880 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$, Fig.II-7): δ 0.90(3H,d,J=7Hz, $\underline{H_3}C$-CH), 1.04(3H,s, $\underline{H_3}C$-C-), 1.08(3H,s, $\underline{H_3}C$-C-), 1.5-1.88(6H,m), 2.0-2.42(6H,m), 3.34 (1H,t,J=6Hz), 4.68(1H, br s, C=C$\underline{H_2}$) and 4.84(1H,br s, C=CH_2).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.II-8): δ 218.4, 148.5, 114.5, 51.6, 49.0, 48.3, 40.6, 40.0, 37.9, 35.2, 31.9, 30.5, 27.2, 21.4 and 16.3.

Analysis for $C_{15}H_{24}O$ Calcd: C,81.76; H,10.98.

Found: C,81.56; H,10.99.

Further elution of the column with 10% ethyl acetate-benzene resulted in the recovery of the starting material (20 mg).

(3a β ,9a β)-1,2,3,3a,5,6,9,9a-Octahydro-3 α ,5,5,8-tetramethyl-cyclopenta-4H-cyclo-octan-4-one (94):

A solution of gem-dimethylated compound 93 (25 mg, 0.11 mmol) and $RhCl_3.3H_2O$, 12 mg (0.05 mmol) in absolute ethanol (2 mL) was heated to reflux in a 5 mL round bottomed flask fitted with reflux condensor for 6 h. The reaction mixture was passed through a short alumina column. The crude product obtained after removal of the solvent was charged on a silica gel column (5 g). Elution with 10% ethyl acetate in benzene furnished the isomerised keto-olefin 94 (20mg, 80%) which was bulb-to-bulb distilled at 110°C/0.5 mm.

IR spectrum (neat) ν_{max} : 3050, 2950, 1695 (carbonyl), 1660 (olefinic), and 1460 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.86(3H,d,J=7Hz, $\underline{H_3}C$-CH), 1.08 (3H,s, $\underline{H_3}C$-C-), 1.2(3H,s, $\underline{H_3}C$-C-), 1.76(3H,s, $\underline{H_3}C$-C=C),1.6-2.3(10H,m), 3.24 (1H, t ,J=6Hz) and 5.44(1H,t,J=8Hz, $\underline{H}C$=C).

Mass spectrum (70 eV, m/e, relative intensity): 220(M^+,12), 205(46), 165(100), 164(46), 149(22), 138(90), 122(47), 121(30), 109(79), 95(49), 82(28), 81(37), 79(22), 67(28).

High resolution mass spectrum for $C_{15}H_{24}O$:

Calcd: m/e 220.1827

Found: m/e 220.1817

(3aβ,9aβ)-1,2,3,3a,5,6,9,9a-Octahydro-3 α ,5,5,8-tetramethyl-cyclopentacyclooctan-4-ol (95):

Into a two necked 20 mL round bottom flask fitted with a rubber septum and mercury seal was placed LAH, 5 mg (excess) in dry ether (5 mL). To this suspension, keto-olefin 94 (20 mg, 0.09 mmol) in dry ether (5 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 excess hydride. The reaction mixture was diluted with water and extracted with ether (3x10 mL). The ethereal layer was washed and dried. Removal of solvent gave hydroxyolefin 95 (16 mg, 80%).

IR spectrum (neat)ν_{max} : 3550 (hydroxyl), 2950, 1460 and 1030 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.84(3H,s, $\underline{H_3}C$-C-), 0.98(3H,d,J=8Hz, $\underline{H_3}C$-CH), 1.02(3H,s, $\underline{H_3}C$-C-), 1.74(3H,s,$\underline{H_3}C$-C=C)1.2-2.0(10H,m), 2.2-3.0(2H,m), 3.48(1H,d,J=2Hz) and 5.36 (1H,t,J=8Hz, $\underline{H}C$=C-).

Mass spectrum (70 eV, m/e, relative intensity): 222(M^+,83), 204(71), 189(100), 175(21), 161(75), 153(23), 152(25), 151(51), 149(26), 148(53), 147(28), 136(25), 135(28), 133(87), 122(68), 121(34), 119(28), 111(47),109(42), 107(61), 105(39), 93(45), 91(29), 81(77), 79(37).

High resolution mass spectrum for $C_{15}H_{26}O$:

Calcd: m/e 222.1983

Found: m/e 222.1981.

(±)-Precapnelladiene 1:

The hydroxy-olefin 95 (15 mg, 0.06 mmol) in dry pyridine (0.5 mL) was placed in a 5 mL round bottomed flask fitted with a drying tube. To this stirred solution, phosphorousoxychloride (0.2 mL) was added at 0-5°C, and the mixture was stirred for 4 1/2 days at room temperature (30°C). DBU (0.1 mL) was added to the reaction mixture and then stirred at 60°C for 2 h. The reaction mixture was diluted with pentane (5 mL) and slowly quenched with water (2 mL) to hydrolyse the excess phosphorousoxychloride. The reaction mixture was extracted with pentane (3x5 mL) and washed with dil. HCl (20%, 3x5 mL) and brine. Removal of solvent gave crude diene 9, 12 mg which was charged on a $AgNO_3$ impreg-

nated silica gel (5 g) column. Elution with pentane removed all oily impurities. Further elution with 50% benzene-pentane furnished pure diene 9 (9 mg, 70%).

IR spectrum (neat) ν_{max} : 2950, 1440, 1370, 1360 and 850 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$, Fig.II-9): δ 0.97[6H,s,-C-($C\underline{H}_3$)$_2$], 1.07(3H,d,J=6Hz, $\underline{H}_3C$-CH), 1.64(3H,s,$\underline{H}_3C$-C=C), 1.08-1.9(6H,m), 2.14-2.54(2H,m), 2.7-3.08(1H,m), 3.34-3.64(1H,m), 5.0(1H,br s, $\underline{H}C$=C-), 5.34(1H,t,J=8Hz, $\underline{H}C$=C-).

The IR and ^1H NMR spectra of 9 were found to be exactly identical with those of naturally occurring precapnelladiene[10].

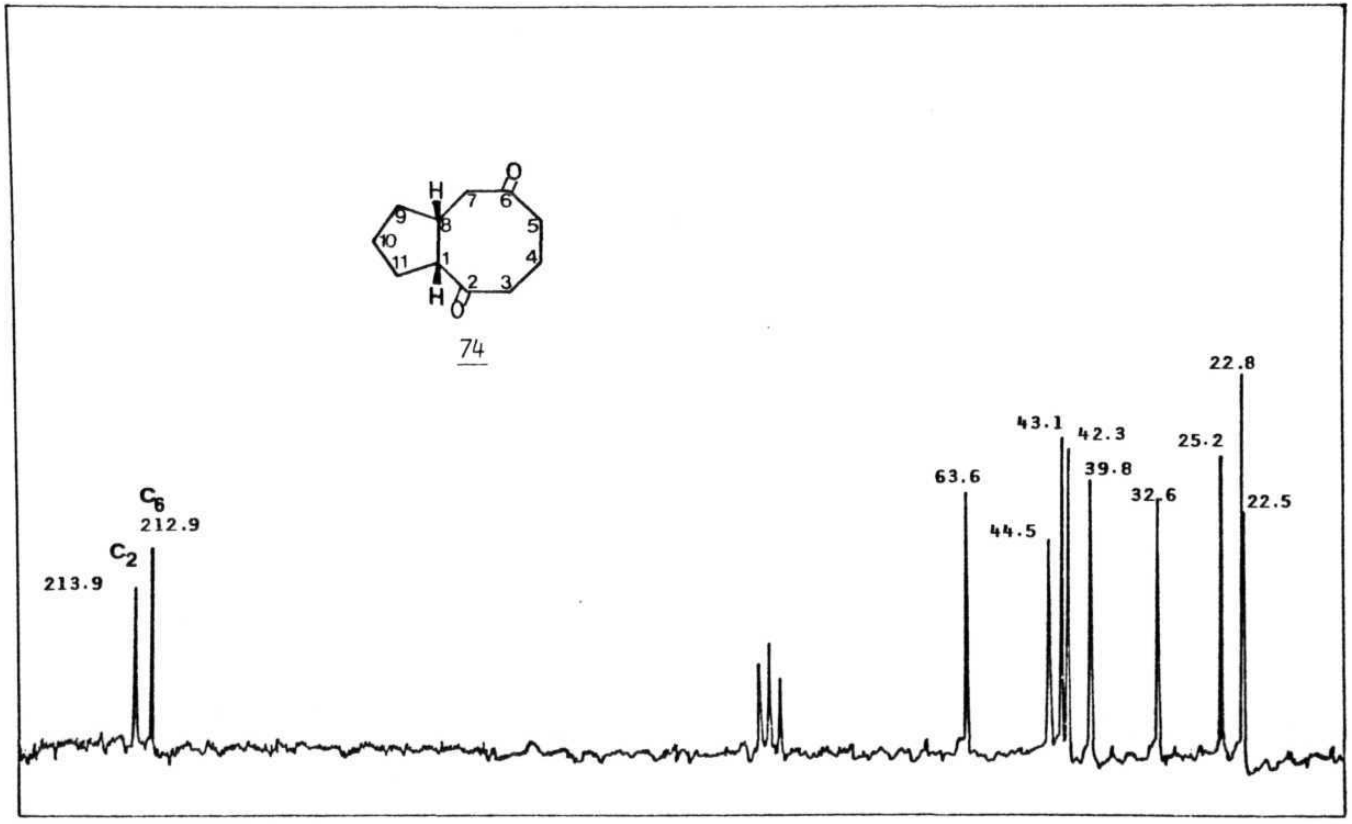


FIG.II-1 : ^{13}C NMR (25.0 MHz) spectrum of 74.

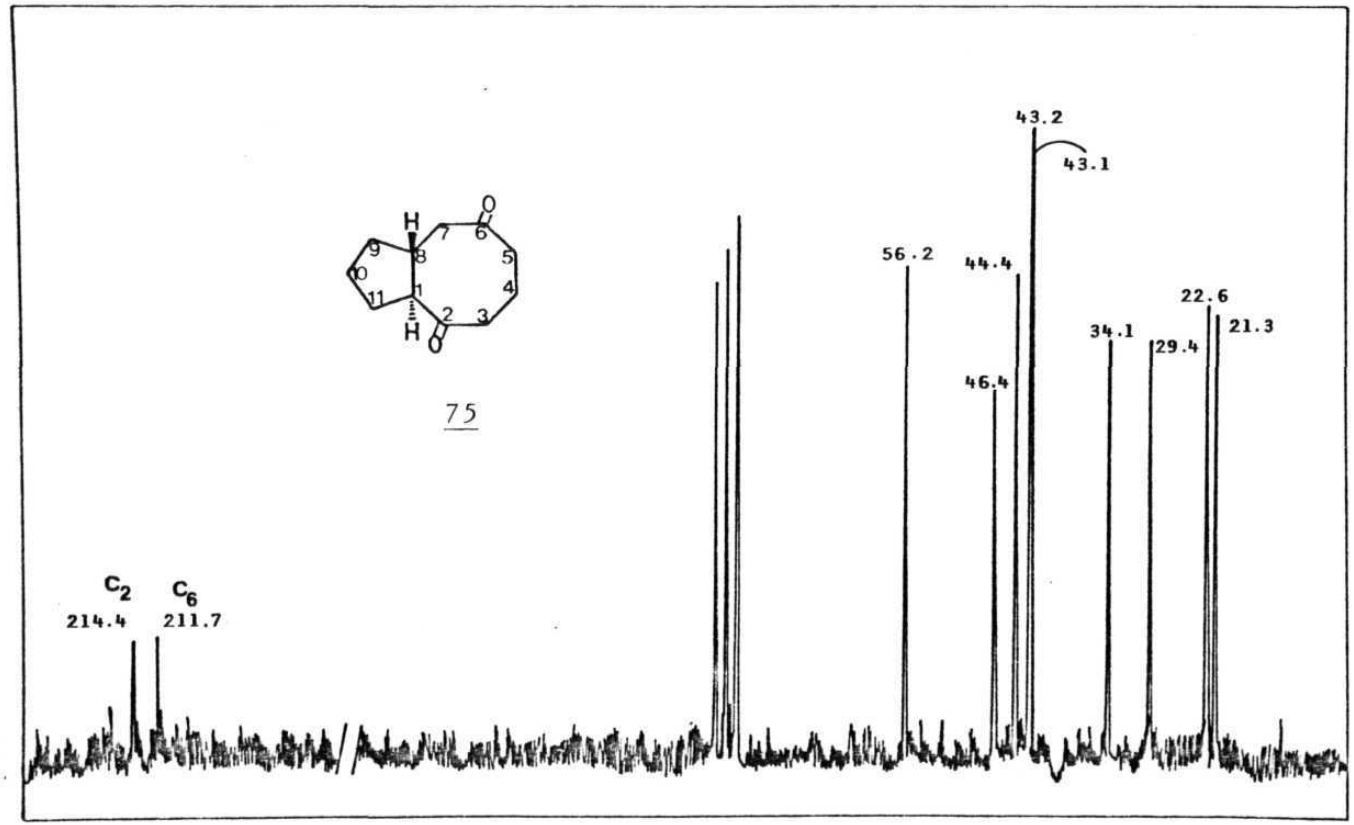


FIG.II-2 : ^{13}C NMR (25.0 MHz) spectrum of 75.

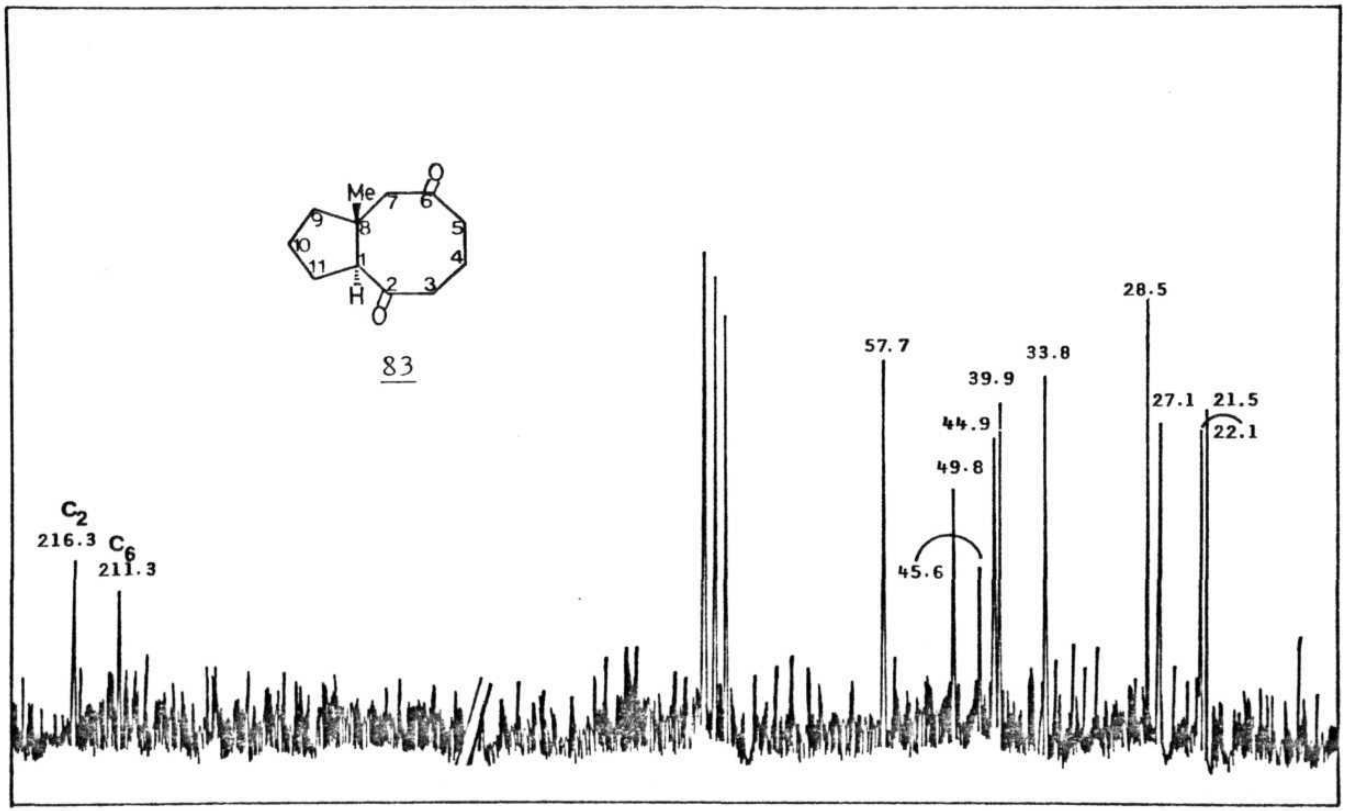


FIG.II-3 : ^{13}C NMR (25.0 MHz) spectrum of 83.

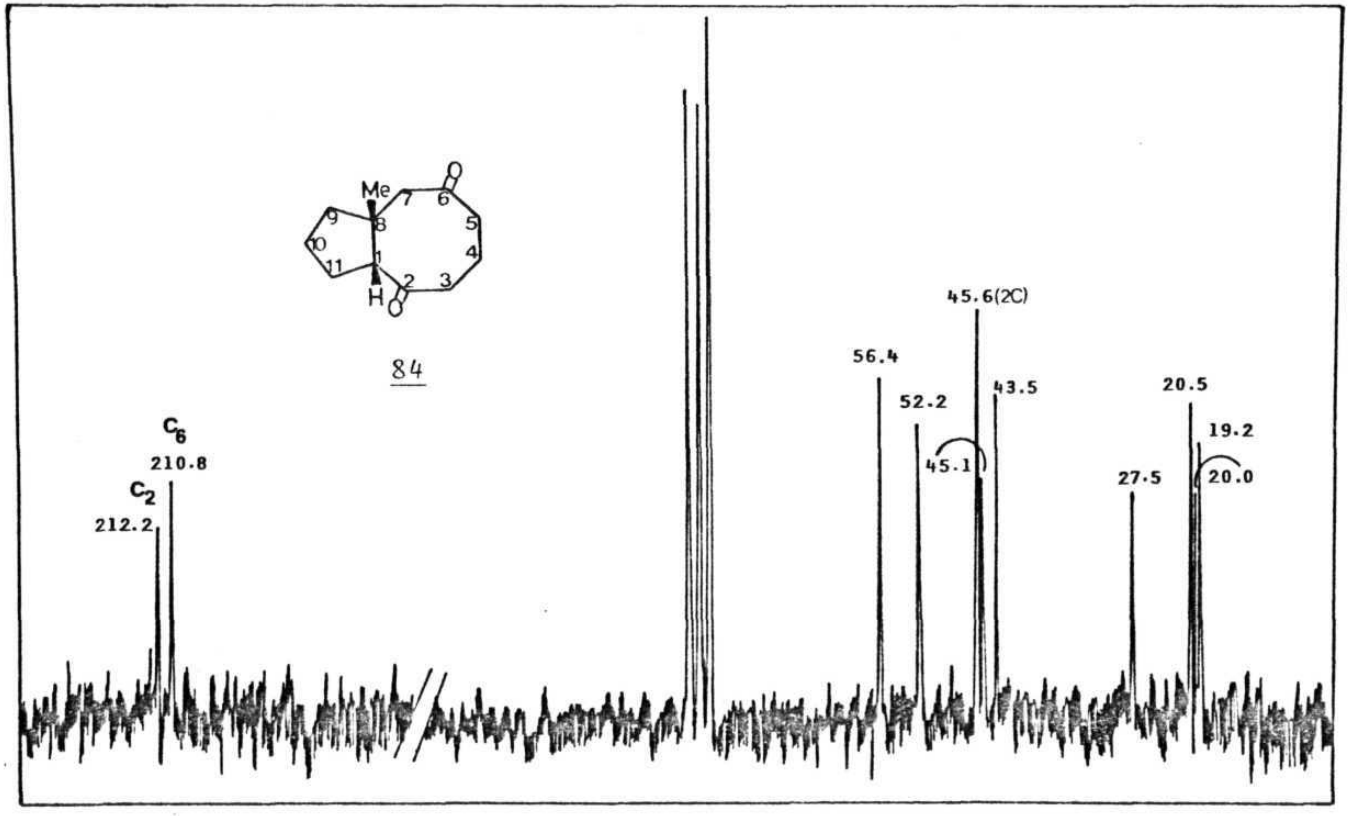


FIG.II-4 : ^{13}C NMR (25.0 MHz) spectrum of 84.

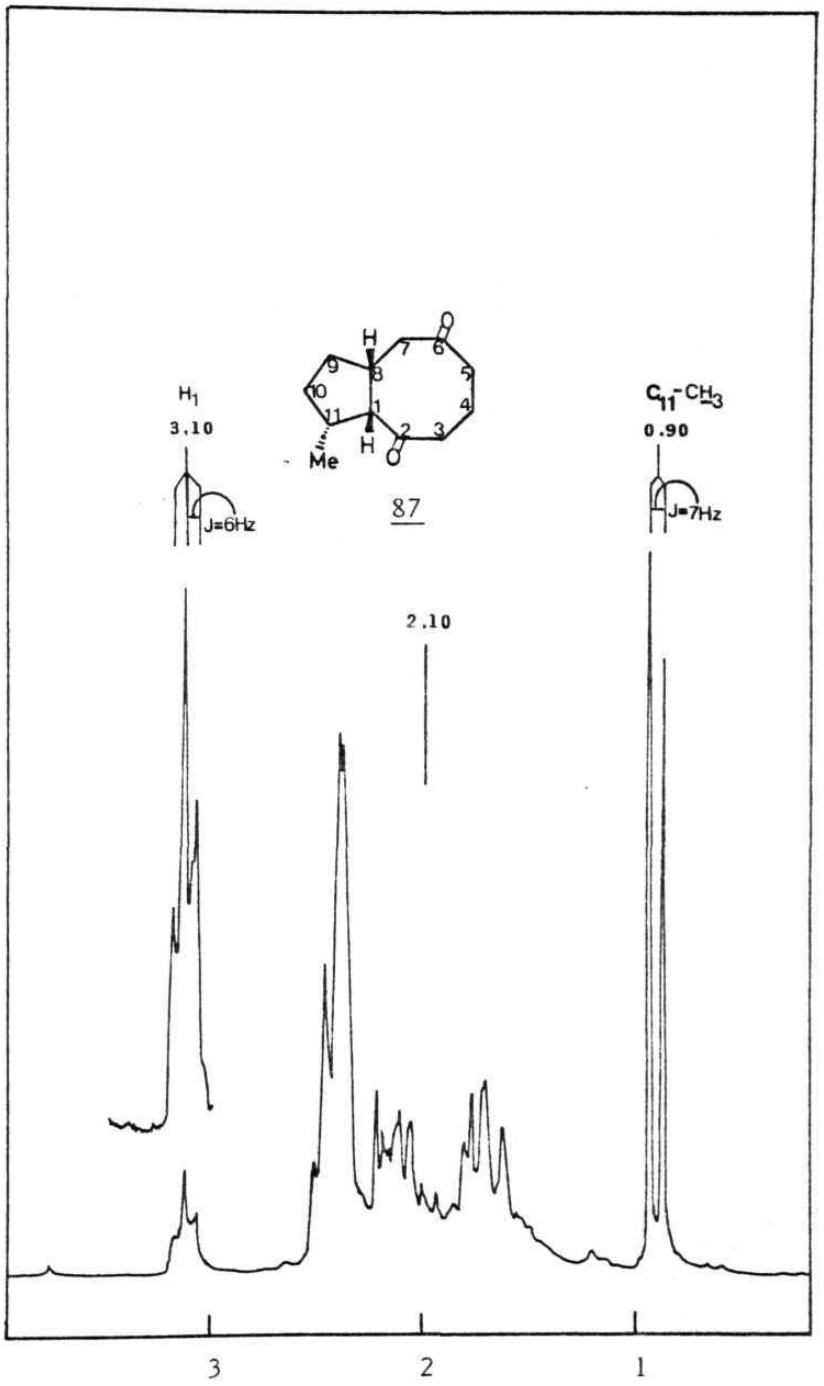


FIG.II-5 : ^{1}H NMR (100 MHz) spectrum of 87.

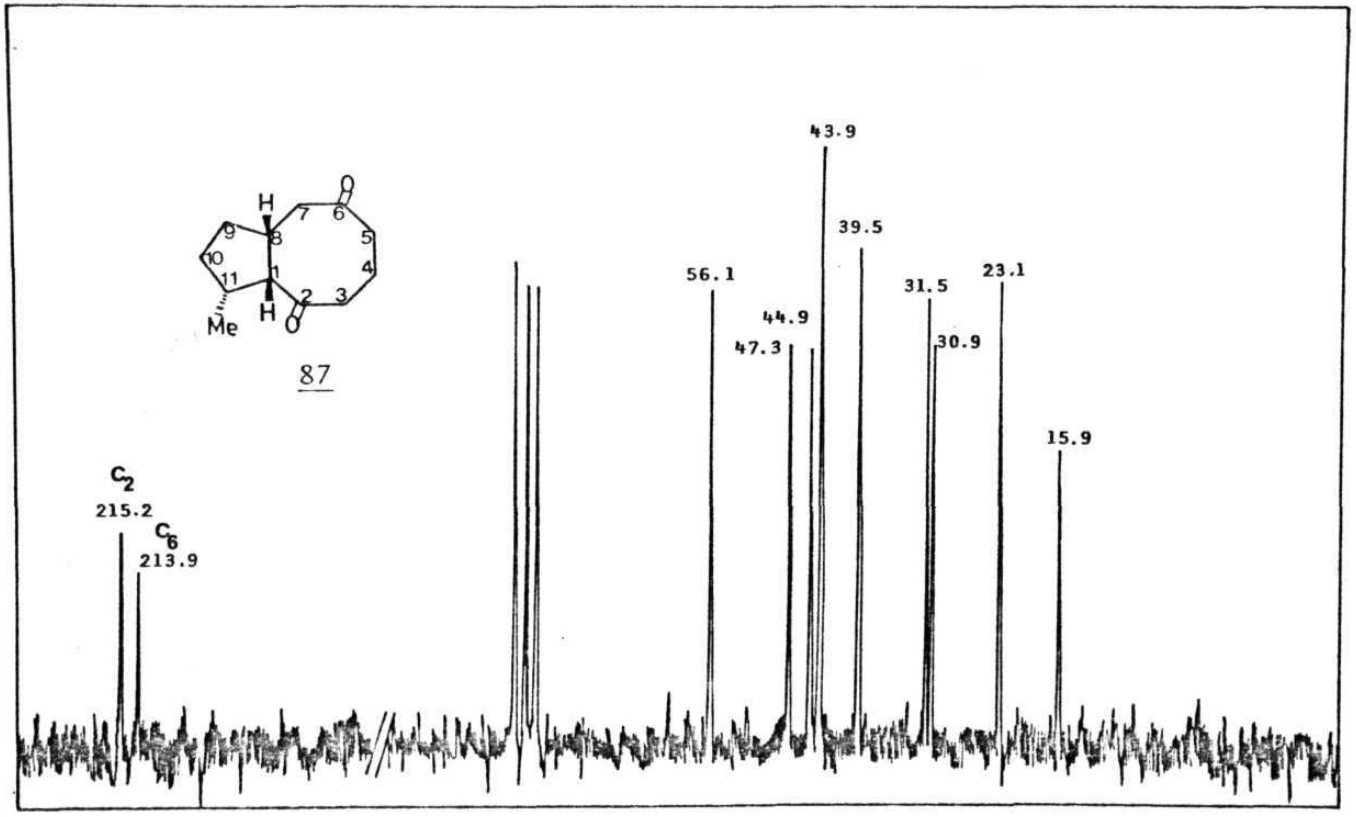


FIG.II-6 : ^{13}C NMR (25.0 MHz) spectrum of 87.

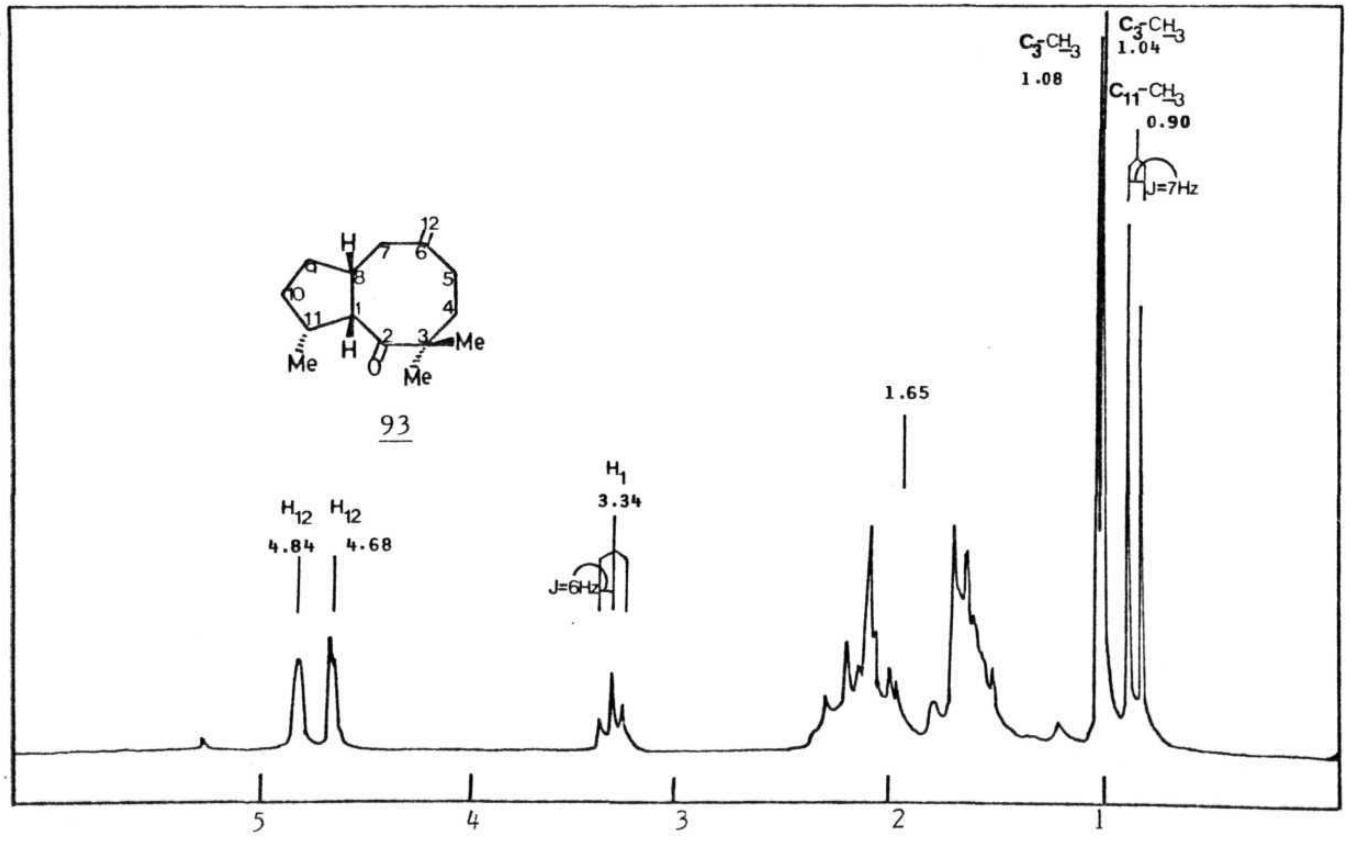


FIG.II-7 : ^{1}H NMR (100 MHz) spectrum of 93.

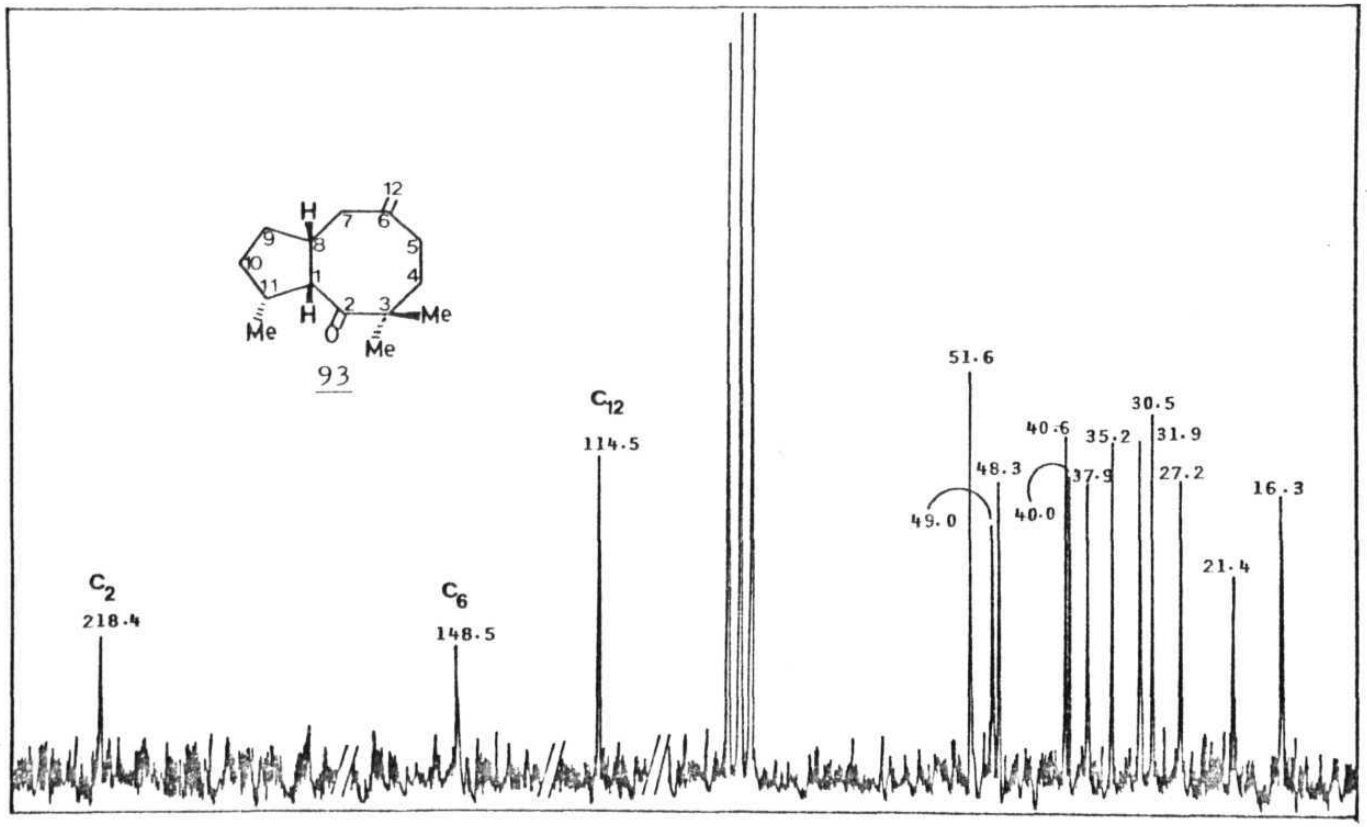


FIG.II-8 : ^{13}C NMR (25.0 MHz) spectrum of 93.

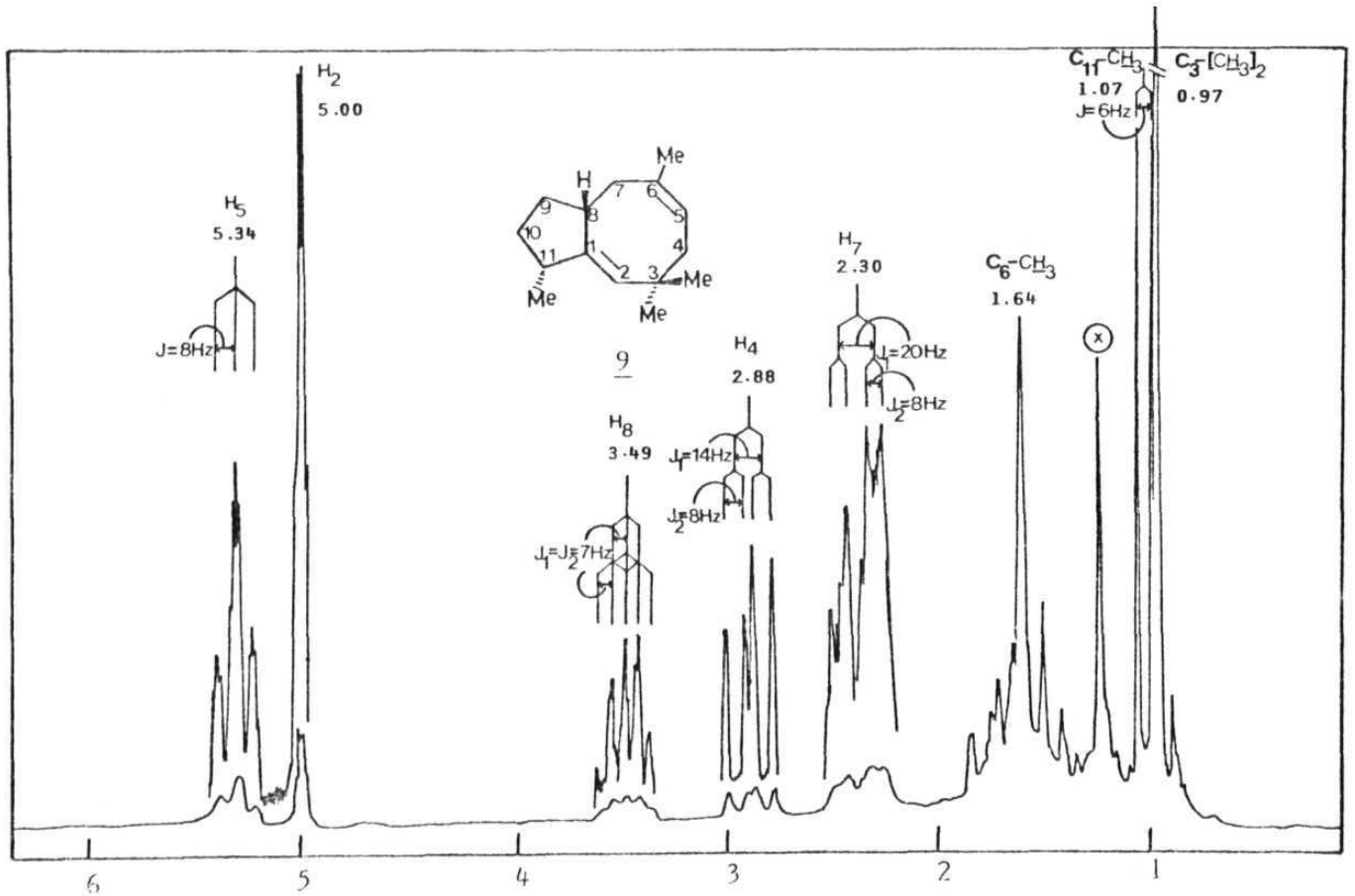


FIG.II-9 : ^{1}H NMR (100 MHz) spectrum of 9.

II. 8. REFERENCES

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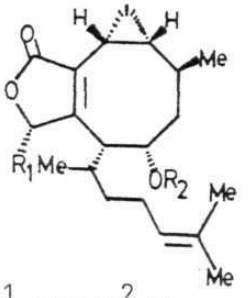
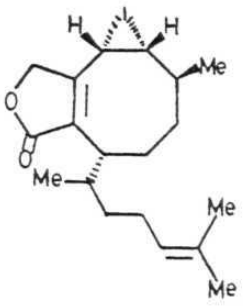
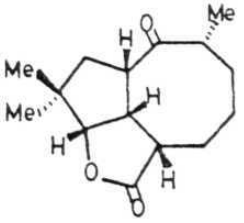
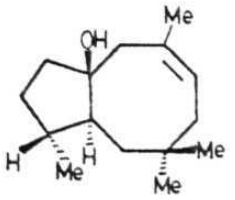
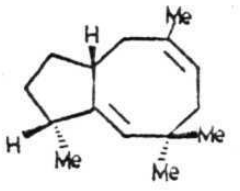
APPENDIX : A COMPILATION OF KNOWN CYCLOOCTANOID TERPENES

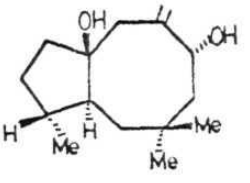
S.No.	Name	Molecular formula	Structure	Origin	Ref.
1	Crenulide	$C_{20}H_{30}O_4$	 R^1=OH; R^2=H	*Aplysia vaccaria* (Sea hare)	1
2	Acetoxy crenulide	$C_{22}H_{32}O_4$	R^1=H; R^2=Ac	*Dictyota crenulata* (Brown alga)	2
3	Pachylactone	$C_{20}H_{30}O_2$		*Pachydictyon coriaceum*	3
4	Asteriscanolide	$C_{15}H_{22}O_3$		*Asteriscus aquaticus* (Compositae)	4
5	Dactylol	$C_{15}H_{26}O$		*Aplysia dactylomela* (Sea hare)	5

6 Precapnelladiene $C_{15}H_{24}$



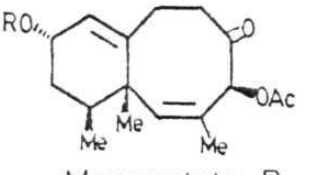
Capnella imbricata (Soft coral) 6

7 Poitediol $C_{15}H_{26}O_2$



Laurencia poitei (Sea weed) 7

8 Neolemnanyl acetate

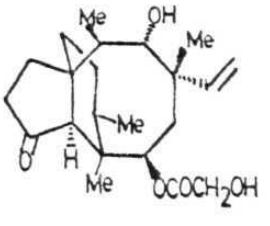


Lemnalia africana (Soft coral) 8

$C_{17}H_{24}O_4$ Monoacetate, R = H

$C_{19}H_{26}O_5$ Diacetate, R = Ac

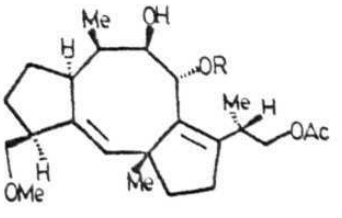
9 Pleuromutlin $C_{22}H_{34}O_5$



Bacidiomycetes (Fungus) 9

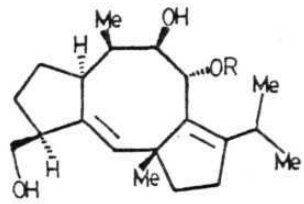
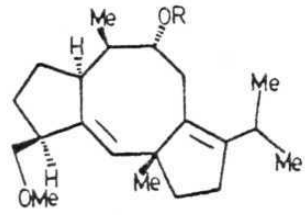
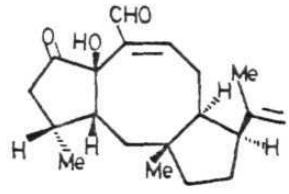
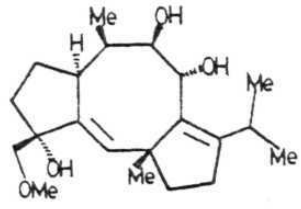
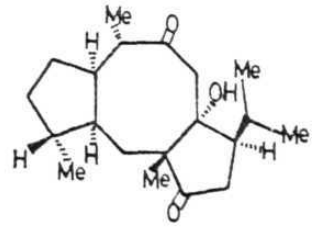
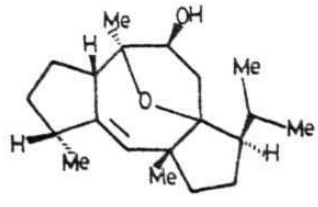
FUSICOCCANE TYPE

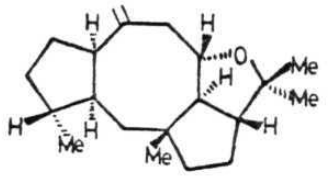
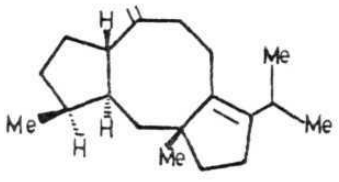
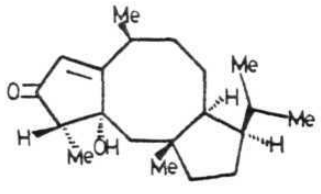
10 Fusicoccin-A aglycone $C_{22}H_{35}O_5$



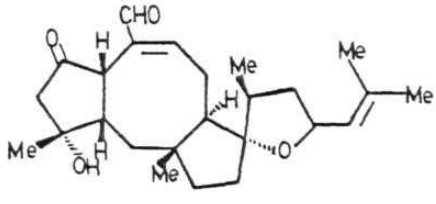
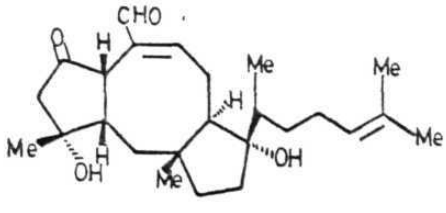
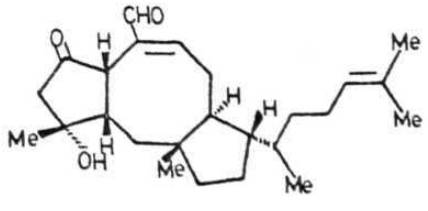
Fusicoccum amygdali (Phytopathogenic fungus) 10

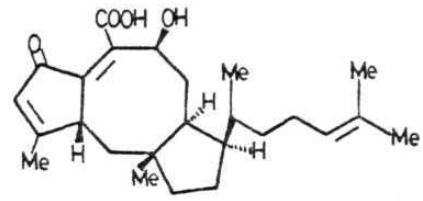
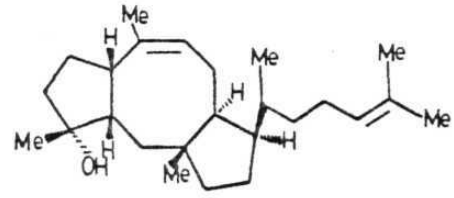
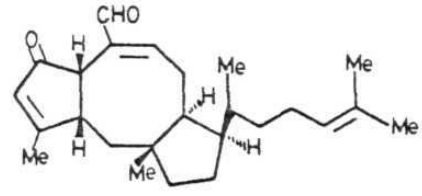
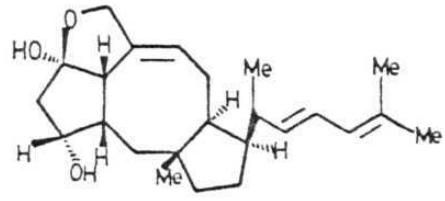
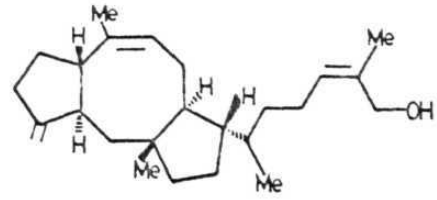
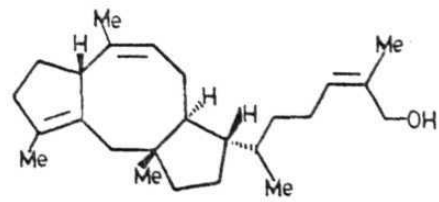
R = Sugar

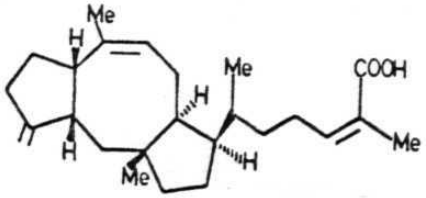
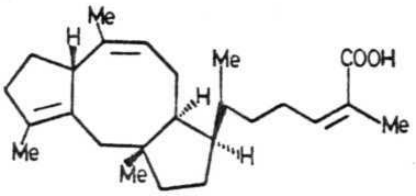
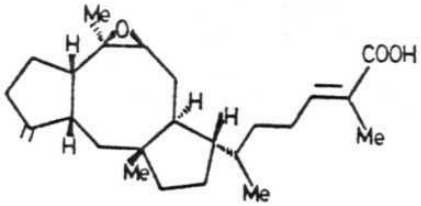
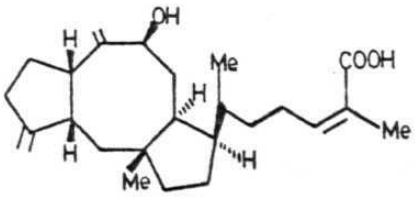
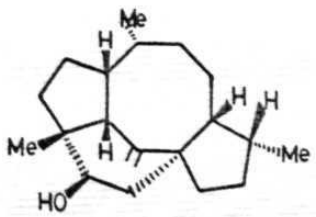
11	Fusicoccin-H aglycone	$C_{20}H_{31}O_3$	 R = Glucose	*Fusicoccum amygdali* (Phytopathogenic fungus)	11
12	Fusicoccin-J aglycone	$C_{20}H_{33}O_2$	 R = Sugar	,,	12
13	Fusicoccin-Cotylenen type	$C_{20}H_{28}O_3$		*Cercospora traversiana* (Fungus)	13
14	Cotylenol	$C_{20}H_{34}O_4$		,,	14
15	Roseadione	$C_{20}H_{32}O_3$		*Hypoestes rosea* (Acanthaceae)	15
16	Roseanolone	$C_{20}H_{32}O_2$			16

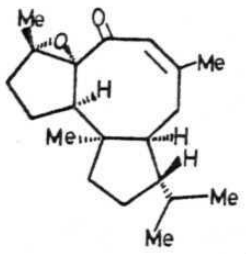
17	Epoxydictyomene	$C_{20}H_{32}O$		*Dictyota dichotoma* (Brown alga)	17
18	Cycloaraneosene	$C_{20}H_{32}$		*Sorderia araneosa* Cain (Metabolite)	18
19	Anadensin	$C_{20}H_{32}O_2$		*Anastrepla orcadensis* (Liverwort)	19

OPHIOBOLANE TYPE

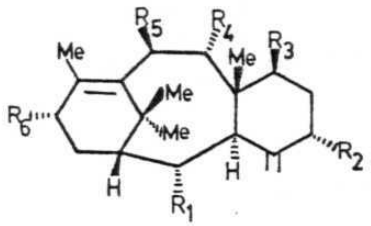
20	Ophiobolin-A	$C_{25}H_{36}O_4$		*Cochliobolus miyabeanus* & *Helminthosporium oryzae* (Phytopathogenic fungus)	20
21	Ophiobolin-B	$C_{25}H_{38}O_4$		*Cochliobolus miyabeanus*, *Helminthosporium oryzae* & *Helminthosporium zizianiae* (Phytopathogenic fungus)	20c, 21
22	Ophiobolin-C	$C_{25}H_{38}O_3$		*Cochliobolus heterostrophus* & *Helminthosporium zizianiae* (Phytopathogenic fungus)	20c, 21b

23	Ophiobolin-D (Cephalonic acid)	$C_{25}H_{36}O_4$		*Cephalosporium caerulens* (Helvolic acid - producing microorganism)	20c, 22
24	Ophiobolin-F	$C_{25}H_{42}O$		*Cochliobolus heterostrophus* (Phytopathogenic fungus)	23
25	Ophiobolin-G	$C_{25}H_{36}O_2$		*Aspergillus ustus*	24
26	Ophiobolin-H	$C_{25}H_{38}O_3$		,,	24
27	Ceroplastol-I	$C_{25}H_{40}O$		*Ceroplastes albolineatus* (Insect wax)	25
28	Ceroplastol-II	,,		,,	25c, 26a

29	Ceroplasteric acid	$C_{25}H_{38}O_2$		*Ceroplastes albolineatus* (Insect wax)	25
30	Albolic acid	$C_{25}H_{38}O_2$		,,	26b
31	Ceralbic acid-I	$C_{25}H_{38}O_3$		,,	25b
32	Ceralbic acid-II	,,		,,	25b
33	Longipenol	$C_{20}H_{32}O$		*Longipeditermes longipes*	27

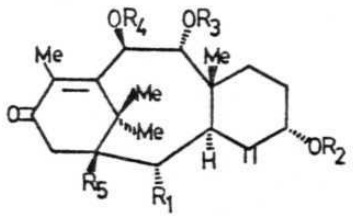
34	Basmenone	$C_{20}H_{30}O_2$		Greek tabocco	**28**

TAXANE TYPE

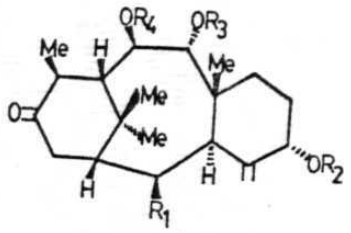


35	Taxa-4(20)-11-diene, 2 α, 5α , 7α , 10β -tetraol, 5 α, 7 β, 10β -tri-OAc, 2-(α -methyl butyroyl)	$C_{31}H_{46}O_8$	R^1=O ; R^2=R^3=R^5=OAc; R^4=R^6=H	*Taxus baccata* (Heartwood of yew)	**2**
36	Taxa-4(20)-11-diene, 2 α, 5α , 7β , 9α,10 β -pentaol, 7 β, 9 α,10β -tri-OAc,2-(α-methyl-butyroyl)	$C_{30}H_{44}O_9$	R^1=O ; R^2=OH; R^3=R^4=OAc; R^6=H	,,	,,
37	Taxa-4(20)-11-diene, 2α , 5α , 7 β, 9α , 10β -pentaol,5α , 7 β, 9α 10 β, tetra-OAc, 2-(α -methyl butyroyl)	$C_{32}H_{46}O_{10}$	R^1=O ; R^2=R^3=R^4=OAc; R^5=OH; R^6=H	,,	,,
38	Taxa-4(20)-11-diene, 5 α, 7α , 9α , 10β , 13 α-pentaol-penta-OAc	$C_{30}H_{42}O_{10}$	R^1=H; R^2=R^3=R^4=R^5=R^6=OAc	,,	,,
39	Taxa-4(20)-11-diene, 2 α, 5α , 7β , 9 α,10 β 13 α-Hexaol-Hexa-OAc	$C_{32}H_{44}O_{12}$	R^1=R^2=R^3=R^4=R^5=R^6=OAc	,,	,,

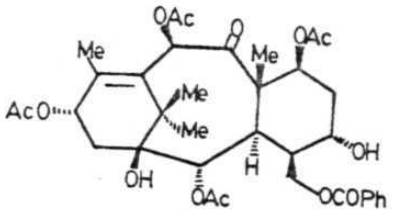
40	Taxa-4(20)-11-diene, 2α, 5α, 9α, 10β,13α -pentaol-penta-OAc	$C_{30}H_{42}O_{10}$	R^1=R^2=R^4=R^5=R^6=OAc; R^3=H	*Taxus baccata* (Heartwood of yew)	29
41	Taxa-4(20)-11-diene, 5α, 9α, 10β, 13α-tetraol	$C_{20}H_{32}O_4$	R^1=R^3=H; R^2=R^4=R^5=R^6=OH	,,	30
42	Texa-4(20)-11-diene, 5α, 9α, 10β, 13α-tetraol-9,10-di-OAc	$C_{24}H_{36}O_6$	R^1=R^3=H; R^2=R^6=OH; R^4=R^5=OAc	,,	29
43	Taxusin	$C_{28}H_{40}O_8$	R^1=R^3=H; R^2=R^4=R^5=R^6=OAc	,,	,,

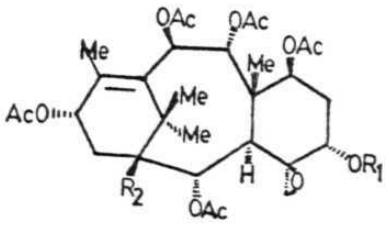


44	Taxicin-I, O-cinnamoyl	$C_{29}H_{36}O_7$	R^1=R^5=OH; R^2=CO-CH:CHPh; R^3=R^4=H	*Taxus cuspidata* (Yew tree)	31
45	Taxicin-II, O-cinnamoyl	$C_{29}H_{36}O_6$	R_1=OH; R^2=CO-CH:CHPh; R^3=R^4=R^5=H	,,	32
46	Taxinine-A	$C_{26}H_{36}O_8$	R^1=OAc; R^2=R^5=H; R^3=R^4=Ac	,,	33
47	Taxinine-B	$C_{35}H_{42}O_9$	R^1=OAc; R^2=CO-CH:CHPh; R^3=R^4=Ac; R^5=H	,,	33, 34
48	Taxinine-H	$C_{28}H_{38}O_9$	R^1=OAc; R^2=R^3=R^4=Ac; R^5=H	,,	33
49	Taxinine-I	$C_{36}H_{47}O_9$	R^1=OAc; R^2=CO-CH(NMe_2)Ph; R^3=R^4=Ac; R^5=H	,,	33b
50	Taxinine	$C_{34}H_{47}O_7$	R^1=R^5=H; R^2=$COCH_2CH(NMe_2)Ph$; R^3=R^4=Ac	,,	,,

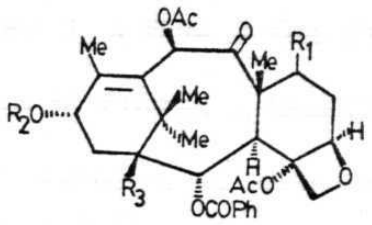


51	Taxinine-K	$C_{24}H_{30}O_6$	R^1=R^2=H; R^3=R^4=Ac	*Taxus cuspidata*	33
52	Taxinine-L	$C_{28}H_{34}O_9$	R^1=OAc; R^2=R^3=R^4=Ac	,,	,,

53	Baccatin	$C_{33}H_{42}O_{13}$		*Taxus baccata*	35



54	Baccatin-I	$C_{32}H_{44}O_{13}$	R^1=Ac; R^2=H	*Taxus baccata*	36
55	Baccatin-I-5-de-Ac	$C_{30}H_{44}O_{12}$	R^1=R^2=H	,,	,,
56	Baccatin-I-1-OH	$C_{32}H_{46}O_{14}$	R^1=Ac; R^2=OH	,,	,,



57	Baccatin-V	$C_{31}H_{38}O_{11}$	R^1=α-OH; R^2=H; R^3=OH	*Taxus baccata*	37
58	Baccatin-III	,,	R^1=β-OH; R^2=H; R^3=OH	,,	38
59	Taxol	$C_{33}H_{40}O_{12}$	R^1=β-OH; R^2=Ac; R^3=OH	,,	,,
		$C_{47}H_{51}O_{14}$	R^1=β-OH; R^3=OH R^2=CO-CH(OH)-CH(Ph)-NHCOPh	,,	39
60	Cephalomannine	$C_{44}H_{53}O_{13}$	R^1=β-OH; R^3=H R^2=CO-CH(OH)-CH(Ph)-NH-C(CH_3):$CHCH_3$	,,	38

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CHAPTER III

SYNTHETIC STUDIES TOWARDS THE ABD RING SYSTEM OF LONGIPENOL

III. 1. ABSTRACT

A novel approach for the synthesis of diterpene longipenol 1 has been conceived. Efforts towards the construction of the ABD ring system of 1 are described in this chapter. The key element of this approach has been the application of the general 5-5-5 → 5-8 methodology to the synthesis of the AB ring system of 1 to which ring D can be appended.

Thus, readily available ene-dione 12 was subjected to the modified Wittig (Wadsworth - Emmons) reaction to deliver the ester-enone 13 which on thioacetalisation and dethioacetalisation sequence furnished the triquinene esters 19a,b as an epimeric mixture. These olefinic-esters 19a,b on ruthenium dioxide oxidation furnished the exo-and endo-substituted 5-8 diketones 21 and 20, respectively, scheme III.4. Claisen-type cyclisation reaction to construct the D ring was attempted on 20, after protecting the C_6-carbonyl group, using lithiumhexamethyldisilazide. However, cyclisation through enol-oxygen resulted in the formation of undesired enol-lactone 24.

In order to circumvent this problem, the oxidation level of the reaction site was altered from ester to an alcohol to set up an intramolecular

displacement reaction. The olefinic-esters 19a,b were converted to mesylates 28a,b which on treatment with ruthenium dioxide, furnished exo- and endo-diketo-mesylates 30 and 29, respectively. When the endo-diketo-mesylate 29 was treated with Li-HMDS, once again the undesired enol-ether 31 was obtained, scheme III.7.

Eventually, we opted for the intramolecular Mukaiyama reaction to construct the D ring. For this purpose the olefinic esters 19a,b were converted to the aldehydes 37a,b via reduction with LAH and oxidation with PCC, respectively. The aldehyde functionality was protected as the dimethyl-acetal and subjected to ruthenium dioxide oxidation to deliver the exo- and endo-5-8-diketo-acetals 33 and 32, respectively, scheme III.9. The stereo-chemistry of the diketo-acetal 32 was established through an unambiguous synthesis of the endo-diketo-acetal 32, scheme III.10.

Having obtained the diketo-acetals 32 and 33 of secured stereochemistry, Mukaiyama reaction was initially attempted on the compound of more abundant exo series. To effect the cyclisation at C_3-site, the C_6-carbonyl group in 33 was also protected as the bis-dimethylacetal 40. $TiCl_4$ mediated cyclisation reaction on the trimethylsilyl enol ether derived from the bis-acetal 40, resulted in the formation of ring D and tricyclic dione 41 was obtained. The same set of reactions were now attempted in the endo series also and bis-dimethylacetal 34 was prepared, scheme III.11. Reaction of 35 with $TiCl_4$ led only to the diketo-aldehyde 43 and no cyclisation product was detected.

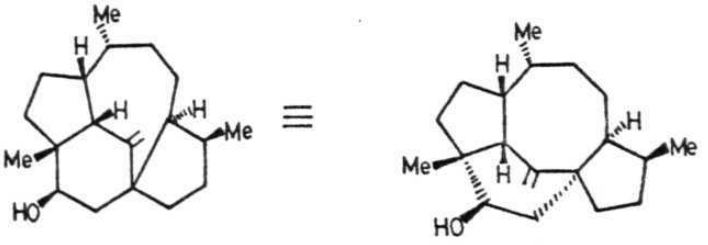
III. 2 OBJECTIVE AND BACKGROUND

In the past few years, several C_{15}-sesqui-, C_{20}-di- and C_{25}-sester-terpene natural products embodying an eight membered ring have been isolated and characterised from terrestrial plants, marine organisms, phytopathogenic

fungi and insects. A complete list of these natural products has been compiled in the appendix to the chapter II of this thesis. Approaches pursued by various groups towards the total synthesis of 5-8 and 5-8-5 fused natural products have also been summarised as the background material in the previous chapter.

The generality of our 5-5-5 → 5-8 route (chapter II) and the successful accomplishment of the total synthesis of the marine natural product precapnelladiene[1] prompted us to further extend this methodology for the construction of other complex natural products having 5-8 fused carbocyclic framework.

In 1984, Prestwich, Tempesta and Turner reported[2] the isolation of a novel tetracyclic diterpene longipenol 1 from the termite soldier Longipeditermes longipes from the Malaysian rain forests. The structure and stereochemistry of 1 was established through ^{13}C NMR and 2D-^{1}H NMR (COSY,



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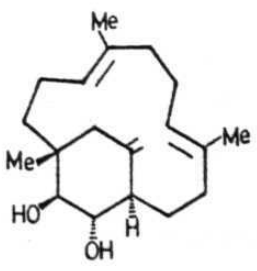

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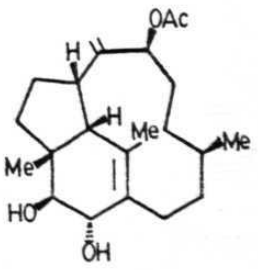
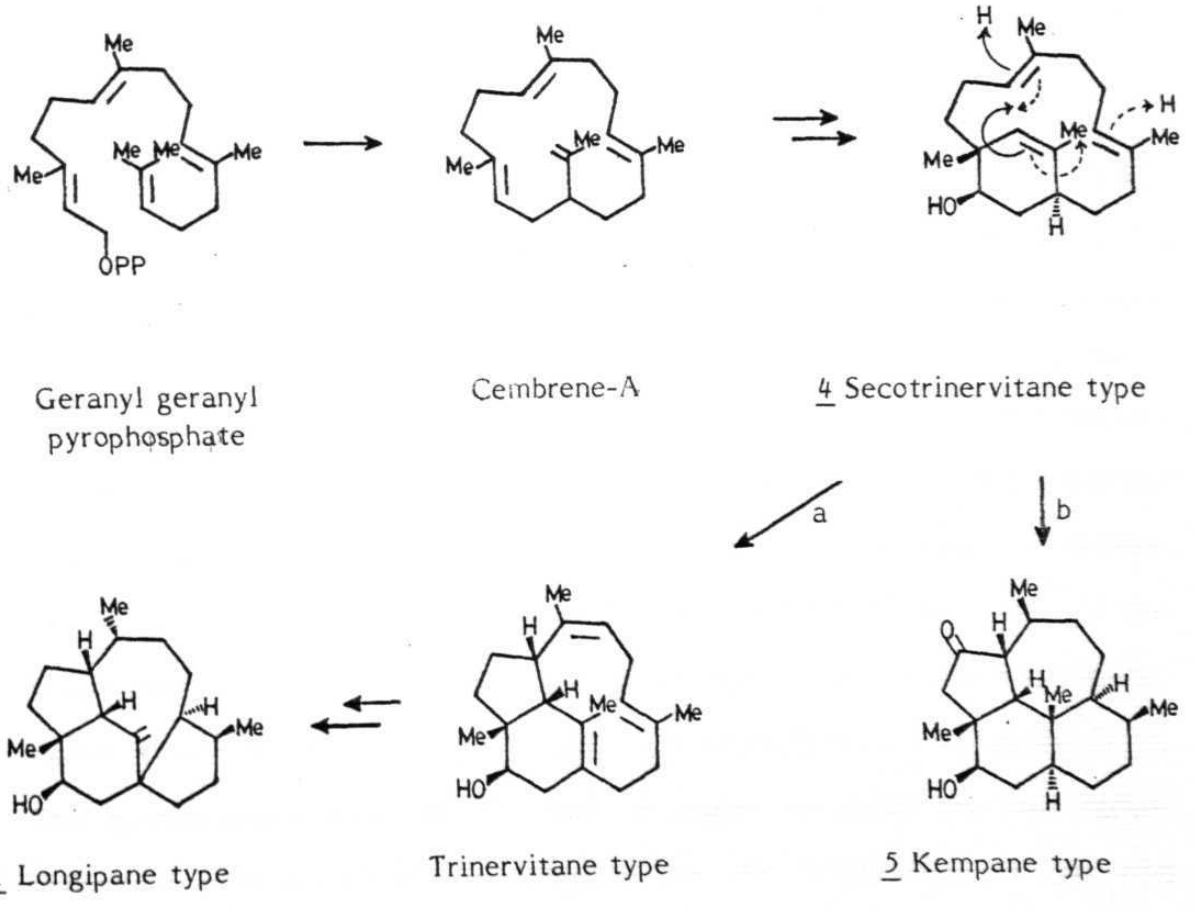


3

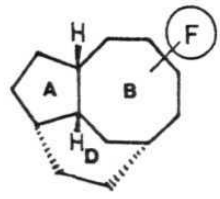
NOSY) studies. The absolute configuration depicted in 1 was assigned on the basis of biogenetic analogy with related termite diterpenes[2,5]. Interestingly, longipenol 1 cooccurs in the termite soldier's defensive secretions, with biogenetically related diterpenes 2[3] and 3[4] having the secotrinervitane and trinervitane skeleton, respectively. It is reasonable to suggest that the novel tetracyclic diterpene 1 is biogenetically derived from a secotrinervitane precursor 4[5] as shown in scheme III.1 and represents a novel deviation from the more common cyclisation to the tetracyclic kempane skeleton 5.

Longipenol 1 appealed to us as an attractive and challenging target

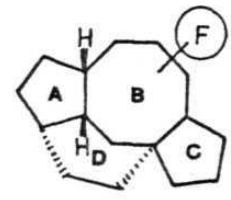
Scheme III. 1[2,5]



of total synthesis, particularly because of its tetracarbocyclic cage-like structure. No synthetic efforts towards 1 have so far appeared in literature. To begin with, we essentially embarked on an exercise in carbocyclic ring construction and aimed at the generation of the functionalised ABD ring system 6 to which the ring C could be appended to give the ABCD framework 7. Our efforts towards this end are detailed in this chapter.



6

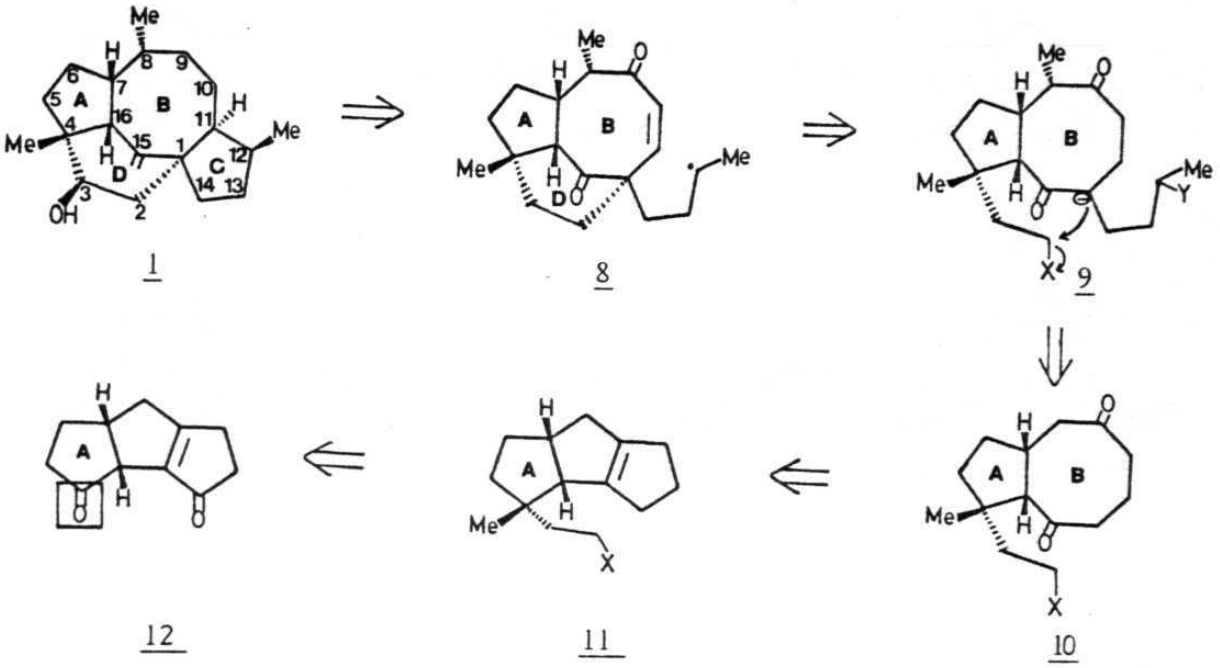


7

III. 3. STRATEGY

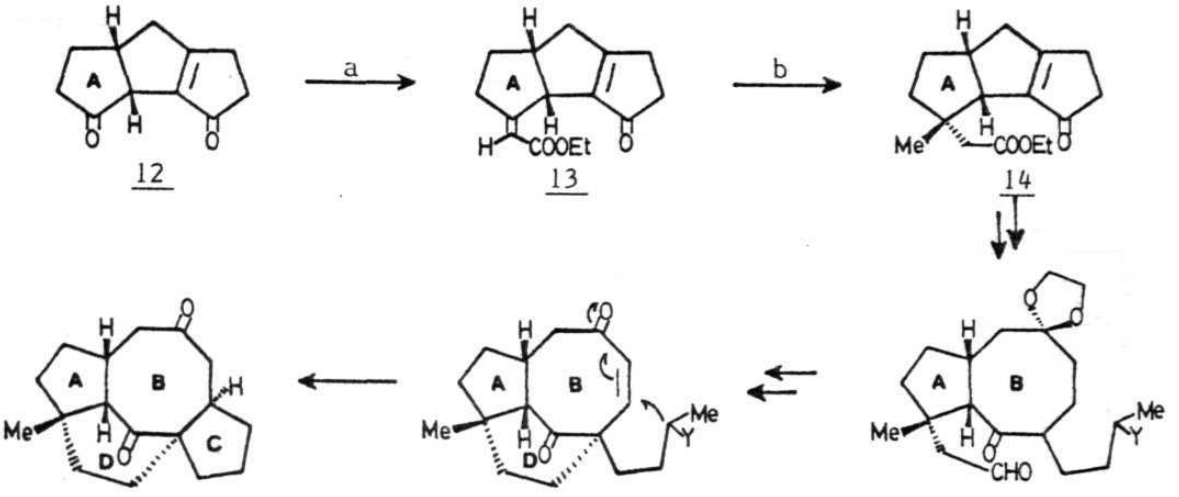
Recognition of the presence of a 5-8 fused moiety in the tetracarbocyclic frame of longipenol 1 was a motivating factor for undertaking this project. Therefore, the ABCD framework was sought to be created around the AB moiety, which in turn could be obtained from the appropriate 5-5-5 fused precursor 11. Retrosynthetic analysis indicated in scheme III.2 showed the way. In order to implement the synthetic protocol to 1, delineated by this retrosynthetic analysis, it was necessary to devise solutions for several key steps. The first of these included stereoselective quaternisation of the boxed carbonyl in 12 to correctly set the stereochemistry at the three contiguous stereogenic centres (C_4, C_7 and C_{16}) of longipenol 1 as shown in 11. The quaternisation operation was also envisaged to install the two carbon side-chain with appropriate functionality for the construction of the ring

Scheme III.2



D (see 9). The other important operation was the generation of the quaternary centre at C_1 and the construction of the ring C. The solutions that we had in mind for the above mentioned key steps are indicated in scheme III.3. The saturated carbonyl group in 12 was expected to undergo modified Wittig olefination[6] to furnish 13. The C_4-quaternary centre was to be created now through the conjugate addition of Yamamoto's reagent ($MeCu.BF_3$)[7]. The addition in view of the past precedence[1], was anticipated from the convex face to deliver 14 having desired relative stereochemistry at the three centres. After functional group adjustments and cyclooctane revelation step, rings C and D could be appended via an intramolecular aldol reaction (or variant) 15 → 16 and intramolecular radical addition[8] to the enone moiety 16 → 17, respectively.

Scheme III.3



Reagents: (a) $(EtO)_2$-P(O)-CHCOOEt-Na^+; (b) $LiMe_2Cu$, BF_3-Et_2O

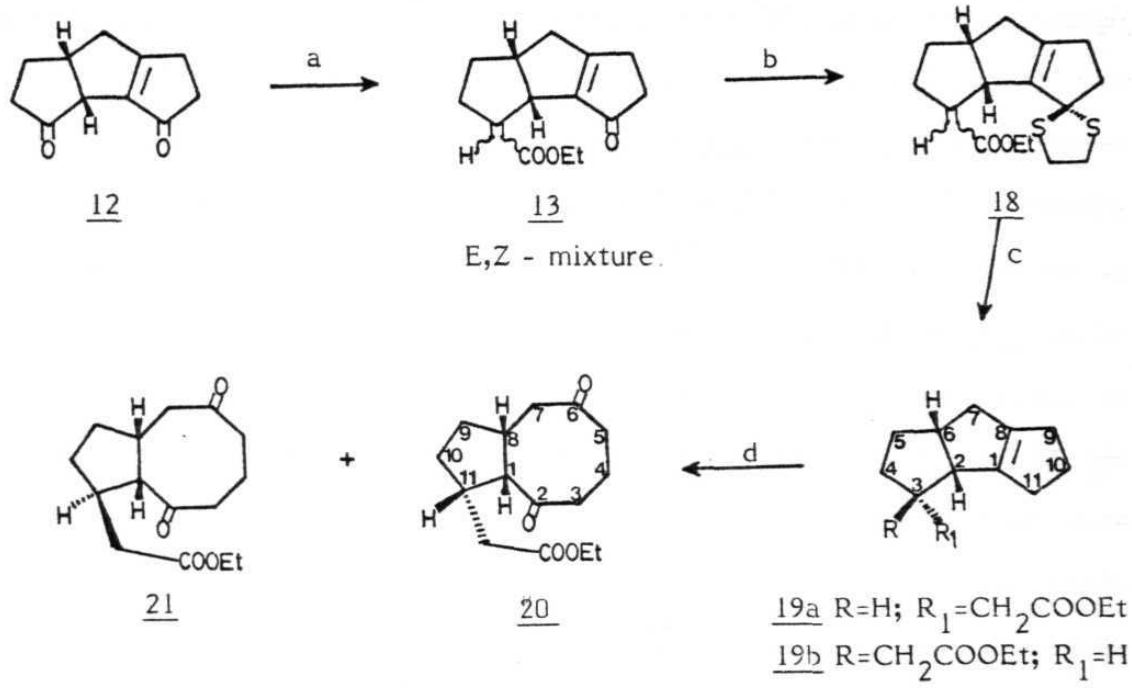
Schemes III.2 and III.3 provided a reasonable outline of the strategy for embarking on the total synthesis of longipenol 1. Further tactical refinements of this methodology were still needed and difficulties along the way were anticipated, but it was time now to make a beginning. Detailed below are the results of this endeavour.

III. 4. SYNTHETIC STUDIES

As mentioned in the schemes III.2 and III.3, the readily available triquinane based ene-dione 12[9] was chosen as the starting material. Chemoselective Wadsworth - Emmons modification[6] of the Wittig reaction, using triethylphosphonoacetate on 12 furnished the unsaturated ester 13, as a (1:5) mixture of E, Z isomers, in 75% yield. Although the E,Z mixture could be

resolved on a silica gel column for characterisation purposes (vide experimental), in practice it was not essential to separate them and the mixture was carried on to the next step.

Scheme III.4



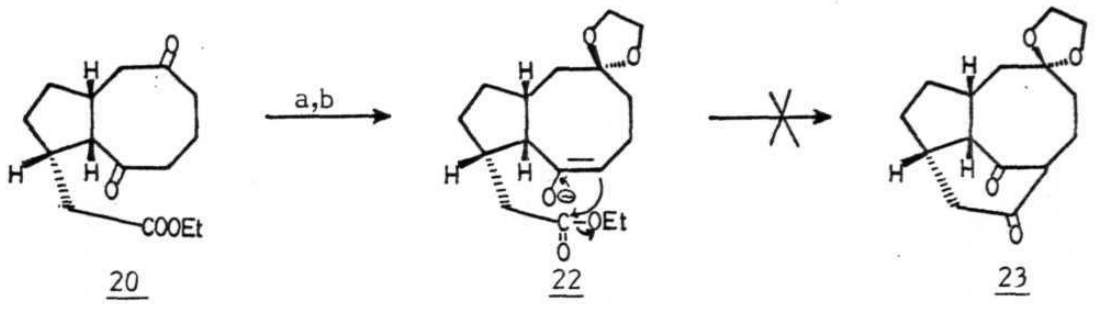
Reagents & Yields: (a) $(EtO)_2$ P(O)CH_2COOEt, NaH, THF, 75%; (b) Ethanedithiol, PTS, benzene, 80%; (c) Na-liq.NH_3, ether, 55%; (d) RuO_2-$NaIO_4$, CCl_4-CH_3CN-H_2O, 77%.

Thioacetalisation of 13 with ethanedithiol in the presence of PTS yielded the thioacetal 18 which on treatment with Na-liq.NH_3[10] delivered a 1:4 diastereoisomeric mixture (^{1}H NMR) of olefinic esters 19a and 19b, respectively, in 55% yield. The esters 19a and 19b defied separation and therefore

it was not possible to make stereochemical assignment to them. Their stereochemistry was deduced through transformations described later in this sequel. Catalytic ruthenium dioxide oxidation[11] of 19a,b furnished a mixture of exo- and endo-5-8 fused diketo-esters in a ratio of 1:4, scheme III.4. The epimeric crystalline diketones 20, mp 60°C and 21, mp 65-66°C could be readily separated on silica gel chromatography and characterised on the basis of their spectral data. The structure of the endo-diketo-ester 20 was confirmed through its ^{13}C NMR (Fig.III-1) resonances at δ 215.0, 213.0 and 173.9 due to two keto-carbonyl and one ester carbonyl groups. The exo-isomer 21 had the corresponding ^{13}C NMR (Fig.III-2) resonances at δ 213.9, 212.2 and 172.2. Although, the major product during the liq.NH_3 reduction[12] of the α,β-unsaturated moiety in 18 was expected to be the thermodynamically more stable exo-isomer 21, it was still necessary to unambiguously secure the stereochemistry of 20 and 21. Initial indications about the relative stereochemistry of 20 and 21 was provided from the incisive analysis of their ^{1}H and ^{13}C NMR data and comparison with the data on related compounds available in our laboratory. However, the rigorous evidence for this stereochemical assignment was achieved through the conversion of 19a,b into the 5-8-diketo-acetals 33 and 32, scheme III.9. The minor isomer 32 was found to be identical with the endo-5-8-diketo-acetal synthesised independently, by an unambiguous route as shown in scheme III.10. These transformations are discussed further, later in this chapter. Consequently, 20 (minor) and 21 (major) were formulated as endo- and exo-isomers, respectively.

At this stage we attempted a Claisen-type of condensation reaction on 20 to construct the D ring (22 → 23, scheme III.5). In order to carry out the condensation at the required site, the C_6-carbonyl group of 20 was protected as the cyclic acetal and the kinetic enolate 22 was generated using

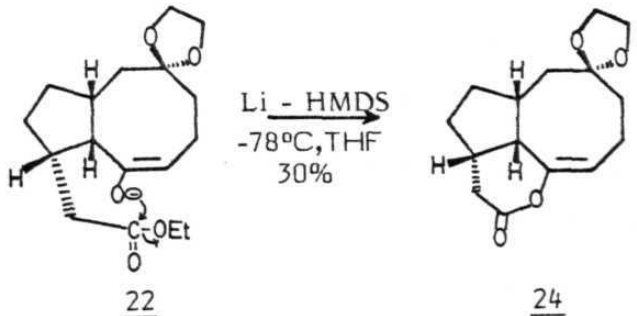
Scheme III.5



20 22 23

Reagents: (a) Ethanediol, PTS, benzene; (b) Li-HMDS, THF.

Li-HMDS. However, reaction did not proceed as anticipated to 23 but instead furnished enol-lactone 24. Apparently the enolate 22 exhibits marked preference for O-attack on the ester carbonyl group. The structure of 24 was



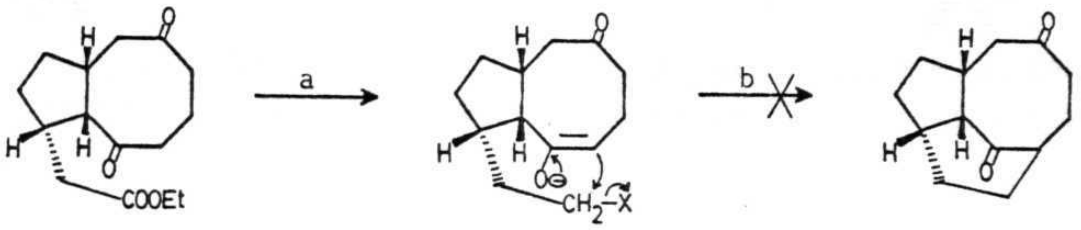
22 24

revealed from its IR spectrum (ν_{max}: 1770 cm^{-1} due to lactone moiety) and ^1H NMR resonance at δ 5.6 (1H,t,J=8Hz, due to cyclooctene proton).

In order to effect the cyclisation in the required way to generate the D ring, we explored the alternate strategy of employing an intramolecular

displacement reaction (25 → 26), scheme III.6. This necessitated change in the oxidation level of the reaction site from an ester to $-CH_2-X$ moiety.

Scheme III.6

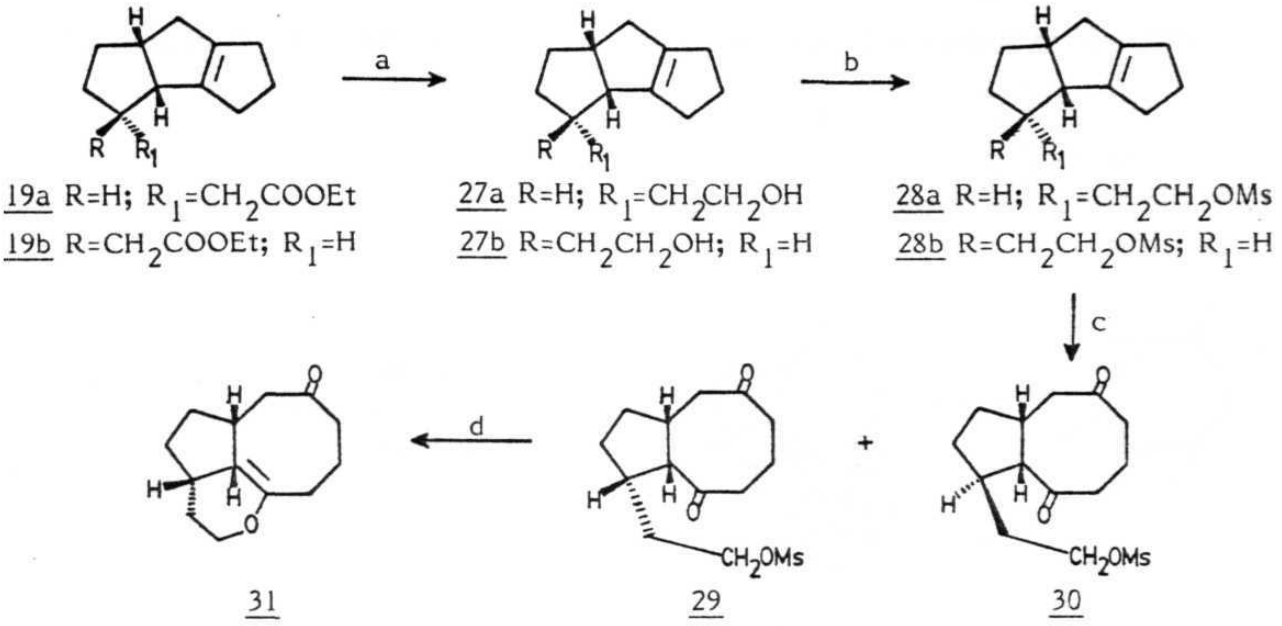


20 25 26

(a) $-COOEt \rightarrow -CH_2-X$; (b) Base

For this purpose the olefinic-esters 19a,b were converted to the hydroxy compounds 27a,b through LAH reduction and further to the mesylates 28a,b. The olefinic-mesylates 28a,b were subjected to ruthenium dioxide oxidation to deliver the endo- and exo-diketo-mesylates in 1:4 ratio, scheme III.7. The keto-mesylates 29 and 30 were amenable to chromatographic separation. The structure of the endo-isomer 29 was confirmed from its ^1H NMR resonances at δ 2.96(3H,s, CH_3-SO_2-O-), 3.3(1H,t,J=6Hz, C_1-exo-proton, characteristic of endo-substitution) and 4.14(2H,t,J=6Hz, $-CH_2-O-SO_2-$) and ^{13}C NMR spectrum (Fig.III-3, δ 215.7 and 213.2 due to cyclooctane dione moiety). The exo-diketo-mesylate 30 had similar ^1H and ^{13}C NMR (Fig.III-4) spectra with that of the endo-isomer 29, but lacked the presence of the deshielded C_1-exo-proton. The displacement reaction was now attempted on 29 by generating

Scheme III.7



19a R=H; R_1=CH_2COOEt 27a R=H; R_1=CH_2CH_2OH 28a R=H; R_1=CH_2CH_2OMs

19b R=CH_2COOEt; R_1=H 27b R=CH_2CH_2OH; R_1=H 28b R=CH_2CH_2OMs; R_1=H

31 29 30

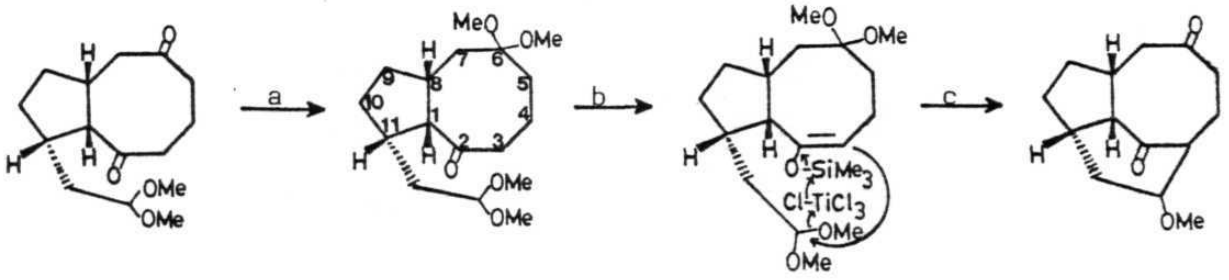
Reagents & Yields: (a) LAH, ether, 90%; (b) Me-$C_6H_4SO_2Cl$, pyridine, 62%; (c) RuO_2-$NaIO_4$, CCl_4-CH_3CN-H_2O, 72%; (d) $(Me_3Si)_2NH$, n-BuLi, THF, -78°C → 0°C, 23%.

the enolate anion using Li-HMDS as base. Once again exclusive displacement by the enolate oxygen was encountered and the tricyclic enol ether 31 was obtained. The structure of the 31 was indicated by its spectral data (vide experimental). Change in base, solvent and reaction conditions had no effect on the mode of this cyclisation.

In order to circumvent these problems a directed aldol cyclisation strategy was designed using the well known Mukaiyama reaction[13]. According

to this plan, the ester functionality in 20 was sought to be converted to a protected aldehyde as in 32. The C_6-carbonyl group of the 32 was also to be protected in order to regioselectively generate the trimethylsilyl enol

Scheme III.8



32 34 35 36

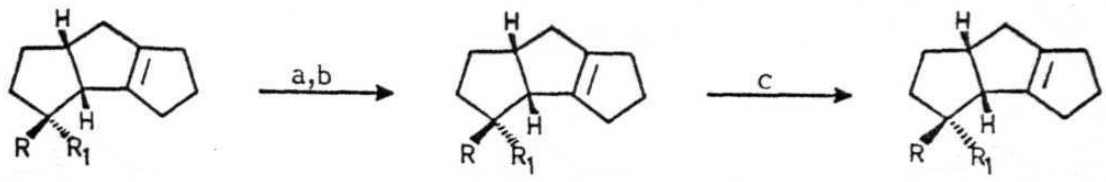
Reagents: (a) MeOH, PPTS, Trimethylorthoformate; (b) $(Me_3Si)_2NH$, nBuLi, THF, Me_3SiCl; (c) $TiCl_4$, dichloromethane.

ether 35 from 34. $TiCl_4$-mediated cyclisation of 35 was expected to give the tricyclic compound 36 as shown in scheme III.8.

To put the scheme III.8 into practice, the olefinic-esters 19a,b were converted to aldehydes 37a,b via LAH reduction and PCC oxidation[14]. The aldehydes 37a,b were protected as dimethylacetals 38a,b and ruthenium dioxide oxidation gave a separable mixture of exo- and endo-diketo-acetals 33 and 32 (4:1), respectively, in 70% yield (scheme III.9).

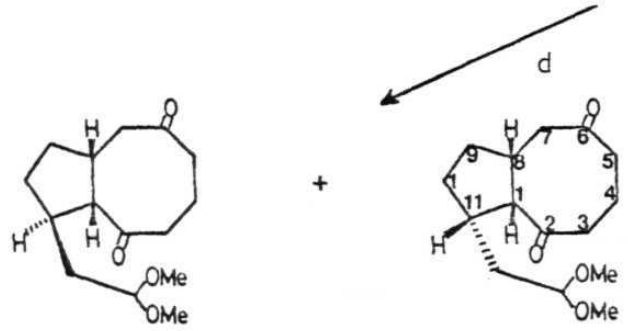
The ^1H NMR and ^{13}C NMR spectra of 32 and 33 are displayed in

Scheme III.9



19a R=H; R_1=CH_2COOEt 37a R=H; R_1=CH_2CHO 38a R=H; R_1=$CH_2CH(OMe)_2$

19b R=CH_2COOEt; R_1=H 37b R=CH_2CHO; R_1=H 38b R=$CH_2CH(OMe)_2$; R_1=H



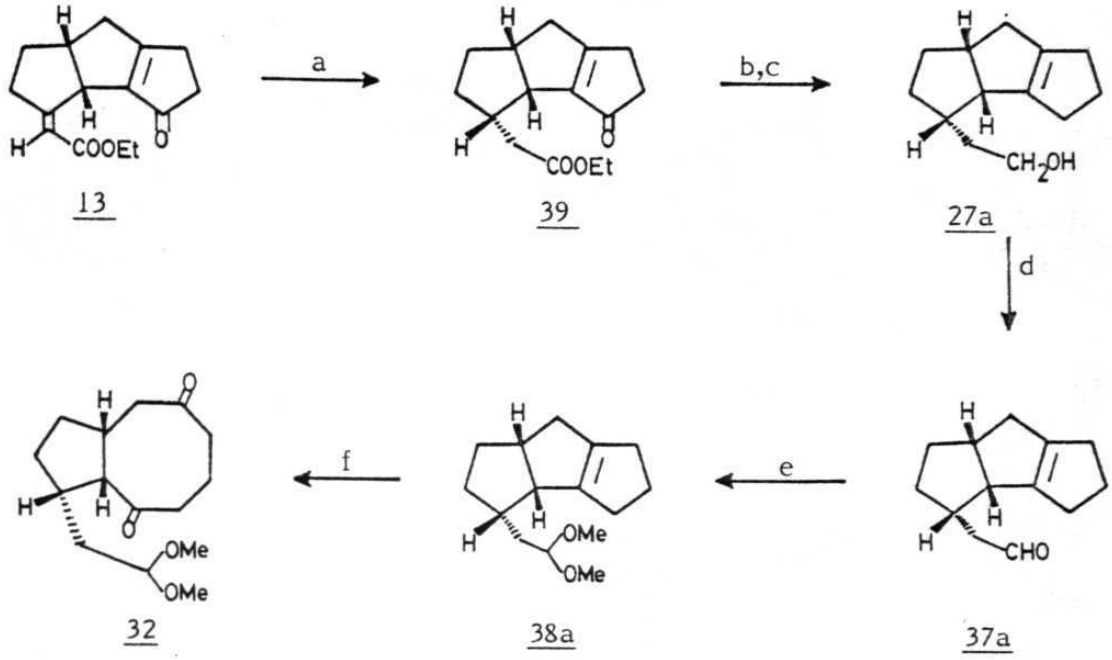
33 32

Reagents & Yields: (a) LAH, ether, 90%; (b) PCC, Molecular seives, 4A°, dichloromethane, 70%; (c) MeOH, PPTS, Trimethylorthoformate, 80%; (d) RuO_2-$NaIO_4$, CCl_4-CH_3CN-H_2O, 70%.

Fig.III-5, III-6, III-7 and III-8 and were in full agreement with the assigned structures. Their stereochemistry was confirmed through an unambiguous synthesis of 32 as shown in scheme III.10.

Catalytic hydrogenation of the ester 13 using Lindlar's catalyst furnished the endo-ester 39 in low yield along with other reduction products. The α,β-unsaturated ester moiety in 13 was expected to undergo hydrogenation

Scheme III.10



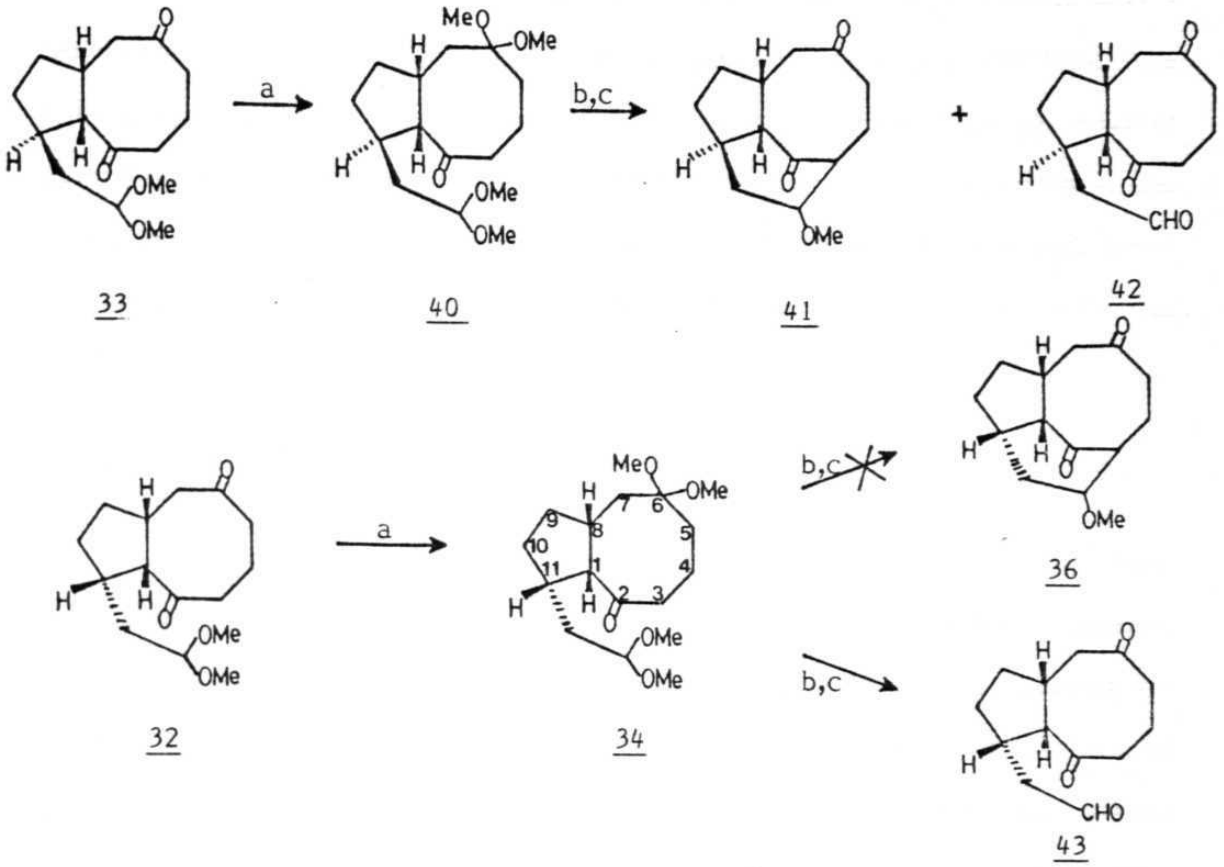
Reagents & Yields: (a) H_2-Lindlar's catalyst, ethyl acetate, 30%; (b) Ethanedithiol, PTS, benzene, 75%; (c) Na-liq.NH_3, ether, 60%; (d) PCC, Molecular seives, 4A°, dichloromethane, 80%; (e) MeOH, PPTS, Trimethylorthoformate, 70%; (f) RuO_2-$NaIO_4$, CCl_4-CH_3CN-H_2O, 75%.

preferentially from the convex face to deliver the endo-product 39[1,12]. The ester 39 was further transformed to the 5-8 bicyclic dione derivative 32 (scheme III.10) by employing the same sequence as shown in scheme III.9.

With the availability of 32 and 33 of established stereochemistry, we attempted to set up the Mukaiyama reaction[13]. First attempt was made on the more abundant isomer 33. In order to effect the C-C bond formation through C_3, the C_6-carbonyl group of 33 was protected as dimethylacetal

using PPTS in benzene and 40, was readily obtained. The trimethylsilyl enol

Scheme III.11



Reagents & Yields: (a) MeOH, PPTS, Trimethylorthoformate, 75%; (b) $(Me_3Si)_2NH$, nBuLi, THF, TMSCl; (c) $TiCl_4$, dichloromethane, 70%.

ether derived from 40, on treatment with $TiCl_4$ furnished the tricyclic compound 41 in 35% yield along with some acetal hydrolysed product 42, scheme III.11. The structure of the tricyclic compound 41 was revealed from its ^1H NMR (Fig.III-9) resonances at δ3.26(3H,s) and 3.68(1H,t,J=8Hz) due to $-OCH_3$ and $-CH-OCH_3$ protons, respectively and ^{13}C NMR (Fig.III-10) signals at δ215.9, 214.8,

and 81.9. Having effected the key cyclisation on the major but unwanted exo-isomer 33, we attempted the cyclisation of the required endo-isomer 32. Consequently, 32 was transformed into the bis-dimethylacetal 34 and the derived trimethylsilyl enol ether was reacted with $TiCl_4$, scheme III.11. However, no cyclisation product could be isolated from this reaction. The only isolable product from the reaction was the diketo-aldehyde 43. Several attempts were made to cyclise 32 using different reaction conditions and Lewis acid catalysts but the required cyclisation could not be effected. Since the tricyclic compound 36 of correct stereochemistry could not be obtained, further efforts in this area were terminated.

III. 5. SUMMARY AND OUTLOOK

An approach towards the synthesis of diterpene longipenol 1 has been conceived with immediate focus on the construction of the ABD ring system. The 5-5-5 → 5-8 methodology was employed to obtain the key precursors for further elaboration. Several 5-8-diketones bearing the AB ring portion of longipenol with well defined stereochemistry were synthesised and efforts were made to append the D-ring on to them. In only one case, it was possible to obtain the tricyclic ABD ring bearing compound 41 but with undesired stereochemistry. However, we still believe that our basic strategy (scheme III.3) is a sound one and perhaps a different methodology for ring D construction is needed. This could pave the way for further efforts towards 1.

III. 6 EXPERIMENTAL

(2 β,6 β)-3(Carboethoxymethylene)-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene-11-one(13):

Into a 100 mL three necked RB flask fitted with dry nitrogen gas inlet, reflux condensor, pressure equilized addition funnel and mercury seal, NaH (1.50 g, 31 mmol, 50% oil dispersion) was taken and dry THF (25 mL) was introduced. To this stirred suspension triethylphosphonoacetate (8 mL, 40 mmol) in dry THF (20mL) was slowly added. After 20 min, the ene-dione 12 (4.6 g,26.1 mmol) in dry THF (20 mL) was added at once and stirring continued for 1 h. The reaction mixture was worked up after adding water to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ether (3x20 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The crude product obtained after removal of the solvent was charged on a silica gel (20 g) column. Elution with petroleum ether removed the oil impurities. Further elution with 40% ethyl acetate-petroleum ether furnished the minor isomer (800 mg, 12.5%).

UV spectrum: λ_{max}^{MeOH}: 206 (ε =11,320) and 227 (ε = 14,470).

IR spectrum (neat) ν_{max} :3050, 2950, 1710 (ester carbonyl), 1690 (enone carbonyl), 1650 (olefinic), 1630 (olefinic), 1200 and 1030 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$) : δ 1.30(3H,t,J=8Hz, -$COOCH_2\underline{CH_3}$) 1.4-3.0(10H,m), 3.0-3.3(1H,m), 3.6-3.8(1H,m), 4.1(2H,q,J=8Hz, -$COO\underline{CH_2}CH_3$), and 6.2(1H,d,J= 2Hz, -C=$\underline{CH}$COOEt).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$) : δ 202.4, 185.6, 166.7, 164.9, 147.1, 114.4, 59.3, 50.5, 46.3, 40.8, 37.9, 32.6, 31.5, 25.4 and 14.1.

Analysis for $C_{15}H_{18}O_3$ Calcd: C, 73.14; H, 7.37

Found: C, 72.93; H, 7.98.

Continued elution with 50% ethylacetate - petroleum ether yielded the major product (4.0g, 6.25%).

UV spectrum: λ_{max}^{MeOH}: 203(ε =12,260) and 225 (ε = 15,660).

IR spectrum (neat), ν_{max}: 3050, 2950, 1700 (carbonyl), 1660(olefinic), 1630 (olefinic), 1440, 1200 and 1030 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$: δ 1.31(3H,t,J=8Hz, $-COOCH_2\underline{CH_3}$) 1.4-3.0(10H,m), 3.28(1H,t,J=10Hz, 4.23(2H,m, $-COO\underline{CH_2}CH_3$), 4.76(1H,br s, C_2-proton) and 5.81(1H,d,J=2Hz, $-C=\underline{CH}COOEt$).

Analysis for $C_{15}H_{18}O_3$ Calcd: C,73.14; H,7.37

Found: C,72.90; H,6.99.

(2 β ,6 β)-3-(Carboethoxymethylene)-11,11-ethylenedithio-tricyclo[6.3.0.$0^{2,6}$] undeca-1(8)-one(18):

A solution of the ester-enone 13 (2.0g, 8.3 mmol), ethanedithiol (3mL) and p-totuenesulphonic acid (50 mg) in dry benzene (60 mL) was refluxed with a Dean-Stark water separator for 20 min. The reaction mixture was diluted with benzene (20 mL), washed with $NaHCO_3$ solution, water and dried. The crude residue obtained after removal of the solvent was charged on a silica gel column (20 g). Elution with 5% ethyl acetate - petroleum ether removed the ethanedithiol impurities. Further elution with 20% ethyl acetate petroleum ether furnished the thioketal 18 (2.1 g, 80%).

UV spectrum : λ_{max}^{MeOH}: 209 (ε = 19,430)

IR spectrum (neat) ,ν_{max}: 2950, 1710 (carbonyl), 1660(olefinic), 1200 and 1040 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$: δ 1.28(3H,t,J=8Hz, $-COOCH_2\underline{CH_3}$) 1.4-3.0(11H,m), 3.0-3.28(4H,m), 4.08(2H,q,J=8Hz, $-COO\underline{CH_2}CH_3$), 4.7(1H,br s, C_2-proton) and 5.7(1H,br s, $-C=\underline{CH}COOEt$).

(2β,6β)-3[(2-carboethoxy)ethyl]-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene(19a,b):

Into a two necked 500 mL RB flask fitted with a guard tube and stopper was taken liq. NH_3(250 mL). To this freshly cut sodium metal (2.4g, 0.104 g atom) was added piece by piece. The resulting blue solution was stirred for 5 min and the thioketal 18 (2.1g, 6.2 mmol) in dry ether (50 mL) was slowly added to it. The reaction mixture was quenched with NH_4Cl solution after all ammonia had evaporated. The reaction mixture was diluted and extracted with ether (3x50 mL), washed and dried. The crude material obtained after removing the solvent was loaded on a small silica gel (10 g) column. Elution with 20% ethyl acetate - petroleum ether gave a mixture of epimers 19a,b at C_3-carbon (800mg, 55%).

IR spectrum (neat), ν_{max}: 2950, 1720 (carbonyl), 1440, 1150 and 1020 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.0(3H,t,J=8Hz, $-COOCH_2\underline{CH_3}$), 1.4-2.6(16H,m), 2.6-3.2(1H,m) and 4.1(2H,q,J=8Hz, $-COO\underline{CH_2}CH_3$).

Analysis for $C_{15}H_{22}O_2$ Calcd: C,76.88; H,9.46
Found: C,76.40; H,9.52.

(3a β,9aβ)-1-(2-Carboethoxy)ethyl-decahydro-5H,9H- cyclopentacycloocta-5,9-diones(20&21):

The olefinic-esters 19a,b (400 mg, 1.7mmol) were dissolved in a mixture of carbontetrachloride (2mL), Acetonitrile (2mL) and water (3 mL).Sodium periodate (1.5g) and ruthenium dioxide (10mg) were added to it. After stirring for 15 min, the reaction mixture was diluted and extracted with dichloromethane (50 mL). The organic layer was washed with water and dried over Na_2SO_4. The crude material obtained after removal of the solvent was charged on a silica gel (15 g) column. Careful elution with 40% ethyl acetate-hexane furnished the minor endo-diketo-ester 20, mp 60°C (80 mg, 17.5%).

IR spectrum (neat), ν_{max}: 2950, 1730 (ester carbonyl), 1690 (carbonyl), 1440, 1310 and 1030 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.2(3H,t,J=8Hz, $-COOCH_2\underline{CH_3}$), 1.4-2.8(16H,m), 3.44(1H,br s, C_1-proton) and 4.04(2H,q,J=8Hz, $-COO\underline{CH_2}CH_3$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.III-1): δ 215.0, 213.0, 173.9, 60.2, 51.5, 46.9, 45.3, 43.5, 43.1, 40.7, 35.9, 29.9(2C), 22.7 and 19.3.

Analysis for $C_{15}H_{22}O_4$ Calcd: C,67.64; H,8.33

Found: C,67.44; H,8.40.

Further elution with the same solvent system furnished the major exo-diketo-ester 21, mp 65-66°C (320mg, 70%).

IR spectrum (KBr), ν_{max}: 2950, 1730 (ester carbonyl), 1690 (carbonyl), 1460, 1320, 1200 and 1020 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.22(3H,t,J=8Hz, $-COOCH_2\underline{CH_3}$), 1.4-3.0(17H,m) and 4.06(2H,q,J=8Hz, $-COO\underline{CH_2}CH_3$).

^{13}C NMR spectrum (25.0MHz,$CDCl_3$, Fig.III-2): δ 213.9, 212.2, 172.2, 60.9, 57.9, 45.3, 45.2, 43.6, 41.7, 39.5, 37.8, 33.1, 31.7, 22.8 and 19.3.

Analysis for $C_{15}H_{22}O_4$ Calcd: C,67.64; H,8.33

Found: C,67.52; H,8.60.

(3aβ,9aβ)-1β-(2-Carboethoxy)ethyl-5,5-dimethyleneketal-decahydro-9H-cyclopentacycloocta-9-one(22):

The minor endo-diketo-ester 20 (10mg, 0.038 mmol), ethanediol (0.1 mL) and PPTS (3mg) in dry benzene (2 mL) were refluxed with a Dean-Stark water separator for 30 min. Benzene was removed under reduced pressure and the resulting crude material was dissolved in ether (5 mL). The ethereal layer was washed with water, brine and dried over Na_2SO_4. The crude material obtained after removing the solvent was filtered through a small silica gel column to get the ketal 22 (9mg, 77%).

IR spectrum (neat), ν_{max}: 2950, 1730 (carbonyl), 1700 (carbonyl) and 1120 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ1.23(3H,t,J=8Hz, $-COOCH_2\underline{CH_3}$), 1.3-2.8(17H,m), 3.56(1H,t,J=6Hz, C_1-proton), 3.9[4H,s,$-O-(\underline{CH_2})_2-O-$] and 4.1 (2H,q,J=8Hz, $-COO\underline{CH_2}CH_3$).

Into a three necked RB flask fitted with dry nitrogen gas inlet, rubber septum and mercury seal, nBuLi (0.028 mL) in hexane was introduced. The flask was cooled to -78°C and hexamethyldisilazane (0.02 mL) was added. The mixture was stirred for 20 min then THF (0.5 mL) was added to dissolve the solid material formed. After 15 min the endo-monoketal 22 (9 mg, 0.029 mmol) in THF (0.5 mL) was slowly added and was allowed to stir for 1h. Then the reaction mixture was worked up by adding water to it. The organic layer separated and the aqueous layer was extracted with ether (5 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The crude material obtained after removal of the solvent was filtered through a small silica gel column to get the enol-lactone 24 (3mg, 30%).

IR spectrum (neat), ν_{max}: 2950, 1770 (lactone) and 1120 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.2-2.5(12H,m), 3.2-3.6(1H,m), 3.92[4H,s,$-O-(\underline{CH_2})_2-O-$], 4.2(2H,q,J=8Hz) and 5.62(1H,t,J=8Hz, $-\underline{CH}=C-O-$).

(2 β,6 β)-3-(2-hydroxyl)ethyl-tricyclo(6.3.0.0^{2,6}]undeca-1(8)-ene(27a,b):

Into a two necked 100mL RB flask fitted with a rubber septum and mercury seal, LAH (150 mg, excess) and dry ether (10mL) were introduced. To this suspension, epimeric ester mixture 19a,b (1.0g, 4.27 mmol) in dry ether (50 mL) was slowly added through a syringe. The reaction mixture was stirred for 45 min. A few drops of ethyl acetate were added to destroy the

excess hydride. The reaction mixture was diluted with water and extracted with ether (3x25 mL). The ethereal layer was washed and dried. Removal of solvent gave hydroxy-olefins 27a,b (750 mg, 90%).

IR spectrum (neat), ν_{max}: 3300 (hydroxyl), 2950, 1460, 1065 and 1040 cm^{-1}

^1H NMR spectrum (100 MHz, $CDCl_3$): δ1.2-2.6(16H,m), 2.6-3.4(2H,m) and 3.64(2H,t,J=6Hz, $-CH_2\underline{CH_2}OH$).

Analysis for $C_{13}H_{20}O$ Calcd: C,81.20; H,10.48
Found: C,80.93; H,10.40

(2β,6β-3-(2-O-mesyl)ethyl-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene(28a,b):

To an ice cold solution of hydroxy-olefins 27a,b (500 mg, 2.6 mmol) in pyridine (5 mL) was added freshly distilled methanesulfonyl chloride (0.3mL). After stirring it for 2h, the reaction mixture was diluted with petroleum ether and water was added dropwise. The organic layer was separated and the aqueous layer was extracted with ether (3x10mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The crude material obtained after removal of the solvent was charged on a small alumina column (5g). Elution with 20% ethylacetate - hexane furnished the mesylates 28a,b (500mg, 62.5%).

IR spectrum (neat), ν_{max}: 2950, 1460, 1360, 1180 and 960 cm^{-1}.

(3aβ,9aβ)-1-(2-O-mesyl)ethyl-decahydro-5H,9H-cyclopentacycloocta-5,9-diones (29&30):

The mesylate mixture 28a,b (500 mg, 1.85 mmol) was dissolved in a mixture of carbontetrachloride (2mL), acetonitrile (2mL) and water (3mL). Sodium periodate (1.8 g) and ruthenium dioxide (5mg) were added to it. After

stirring for 5 min. the reaction mixture was diluted and extracted with dichloromethane (30 mL). The organic layer was washed with water and dried. The crude material obtained after removal of the solvent was charged on a neutral alumina column (10g). Careful elution with 40% ethyl acetate - hexane furnished the minor endo-diketo-mesylate 29 (70 mg, 12.7%).

IR spectrum (neat), ν_{max}: 2950, 1700(carbonyl), 1460, 1360, 1180 and 920 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.6-2.68(16H,m), 2.96(3H,s, $-OSO_2-\underline{CH_3}$), 3.3(1H,t,J=6Hz, C_1-proton) and 4.14(2H,t,J=6Hz, $-\underline{CH_2}O-SO_2-$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.III-3): δ 215.7, 213.2, 69.9, 53.9, 46.9, 45.3, 43.5, 42.9, 41.5, 37.1, 30.5, 29.5, 29.4 and 22.5.

Continued elution with the same solvent system furnished the major exo-diketo-mesylate 30 (280mg, 60%).

IR spectrum (neat), ν_{max}: 2950, 1695 (carbonyl), 1450, 1350, 1180 and 920 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.2-2.9(17H,m), 3.0(3H,s, $O-SO_2-\underline{CH_3}$) and 4.0-4.36(2H,m,$-\underline{CH_2}-O-SO_2-$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.III-4): δ 214.2, 212.9, 65.2, 60.0, 45.8, 43.6, 42.6, 40.0, 37.1, 36.5, 34.6, 32.7, 30.6 and 22.9.

(5β,8β)-2-Oxa-tricyclo(6.5.1.$0^{5,14}$)-tetradeca-1(14)-ene-10-one(31):

Into a three necked RB flask fitted with dry nitrogen gas inlet, rubber septum and mercury seal, nBuLi (0.14mL) in hexane was introduced. The flask was cooled to -78°C and hexamethyldisilazane (0.1mL, excess) was added. The mixture was stirred for 20 min then THF (1 mL) was added to dissolve the solid material formed. After 15 min. the endo-diketo -mesylate

29 (50 mg, 0.16 mmol) in THF (2mL) was slowly added and was allowed to stir for 30 min. Then the reaction mixture was worked up by adding water to it. The organic layer separated and the aqueous layer was extracted with ether (3x5mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The crude material obtained after removal of the solvent was charged on a silica gel column (2g). Elution with 20% ethyl acetate-hexane furnished the tricyclic compound 31 (8mg, 23%).

IR spectrum (neat), ν_{max}: 2950, 1700 (carbonyl), 1440 and 1100 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.2-3.0(15H,m) and 3.5-4.32 (3H,m).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 215.5, 173.0, 145.4, 66.1, 55.2, 39.8, 39.0, 37.5, 33.7, 30.6, 30.0, 29.2 and 19.7.

(2 β,6 β)-3-(2-ethanal)-tricyclo[6.3.0.$0^{2,6}$]undeca-1(8)-ene(37a,b):

To a solution of pyridinium chlorochromate[14] (750 mg) in dry dichloromethane (30mL) containing activated molecular seives (4A^{o}) was added a mixture hydroxy-olefins 27a,b (500mg, 2.6 mmol). The reaction mixture was stirred for 25 min. and diluted with ether (20 mL). Filtration through a small florisil column and evaporation of solvent furnished the aldehydes 37a,b (350mg, 70%).

IR spectrum (neat), ν_{max}: 2950, 2775 (aldehyde), 1720 (carbonyl), 1450 and 1030 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.0-2.7(16H,m), 2.8-3.3(1H,m) and 9.77(1H,t,J=2Hz, -CHO).

(2β ,6 β)-3-(2-ethanaldimethylacetal)-tricyclo[6.3.0.$0^{2,6}$]undeca-1(8)-ene(38a,b):

A mixture of the aldehydes 37a,b (500mg, 2.63 mmol), trimethyl

orthoformate (1mL), PPTS (150 mg) in dry methanol was refluxed for 1h. Methanol was removed under reduced pressure. The crude material was dissolved in ether (30 mL), washed with water, brine and then dried over Na_2SO_4. The crude material obtained after removal of the solvent was bulb-to-bulb distilled at 140°C/0.5 mm to furnish the dimethylacetals 38a,b (500mg, 80%).

IR spectrum (neat), ν_{max}: 2950, 1450, 1130 and 1050 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.0-2.6(16H,m), 2.9-3.4(1H,m, C_2-proton), 3.2[6H,s,-CH(OCH_3)$_2$]and 4.2-4.4[1H,m,-CH(OCH_3)$_2$].

Analysis for $C_{15}H_{24}O_2$ Calcd: C,76.22; H,10.40
Found: C,76.03; H,10.15

(3aβ,9aβ)-1-(2-ethanaldimethylacetal)-decahydro-5H,9H-cyclopentacycloocta-5,9-diones (32&33):

The dimethylacetal mixture 38a,b (1g, 4.28 mmol) was dissolved in a mixture of carbontetrachloride (2mL), acetonitrile (2mL) and water (3mL). To this mixture sodium periodate (2g) and ruthenium dioxide (10mg) were added. After stirring for 10 min, the reaction mixture was diluted and extracted with dichloromethane (50 mL). The organic layer was washed with water and dried. The crude material obtained after removing the solvent was loaded on a silica gel column (20 g). Careful elution with 50% ethyl acetate - petroleum ether furnished the minor endo-diketone 32 (150 mg, 13%).

IR spectrum (neat), ν_{max}: 2950, 1700 (carbonyl), 1460, 1130, 1060 and 920 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$, Fig.III-5): δ1.4-2.5(16H,m), 3.12-(3H,s,-OCH_3), 3.18(3H,s,-OCH_3) and 4.1[1H,t,J=8Hz,-CH(OCH_3)$_2$].

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.III-6): δ215.8, 213.9, 104.8,

54.1, 53.8, 52.5, 46.7, 45.4, 43.6, 43.1,40.5, 33.8, 30.0, 25.6 and 22.7.

Analysis for $C_{15}H_{24}O_4$ Calcd: C,67.13; H,9.02

Found: C,66.80; H, 8.97 .

Continued elution with the same solvent system furnished the major exo-diketo-acetal 33 (650 mg, 57.5%).

IR spectrum (neat), ν_{max}: 2950, 1700 (carbonyl), 1450, 1130 and 1050 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$, Fig.III-7): δ 1.0-3.0(16H,m), 3.08(3H,s,-OC<u>H</u>$_3$), 3.12(3H,s,-OC<u>H</u>$_3$), 3.0-3.2(1H,m,C_1-proton and 4.12[1H,t,J=8Hz, -C<u>H</u>$(OCH_3)_2$].

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$, Fig.III-8): δ 214.5, 213.5, 103.9, 59.3, 52.5, 52.4, 44.8, 43.8, 42.8, 40.7, 38.1, 36.8, 33.1, 31.6 and 22.6.

Analysis for $C_{15}H_{24}O_4$ Calcd: C,67.13; H,9.02

Found: C,67.01; H,9.00.

(2β ,6β)-3(Carboethoxymethylene)-tricyclo[6.3.0.$0^{2,6}$]undeca-1(8)-ene-11-one(39):

The ester-enone 13 (500 mg, 2.03 mmol) was hydrogenated over Lindlar's catalyst (20 mg) in ethyl acetate (10 mL). After the consumption of the starting material, the reaction mixture was filtered and the solvent was removed. The concentrate obtained after removal of the ethyl acetate was loaded on a silica gel column (10 g). Elution with 30% ethyl acetate-hexane removed all the perhydro-compounds (350mg). Further elution with 40% ethylacetate - hexane furnished the required endo-dihydro-compound 39 (150 mg, 30%).

IR spectrum (neat), ν_{max}: 2950, 1730 (ester carbonyl), 1700 (enone carbonyl), 1640 (olefinic), 1460, 1400, 1180 and 1040 cm^{-1}.

^{1}H NMR spectrum (100MHz, $CDCl_3$): δ 1.14(3H,t,J=8Hz), -$COOCH_2\underline{CH_3}$) 1.4-3.0(14H,m), 3.3(1H,br s, C_2-proton) and 4.1(2H,q,J=8Hz, -$COO\underline{CH_2}CH_3$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 203.8, 189.0, 173.5, 147.9, 59.8, 47.0, 46.9, 40.8, 40.4, 39.9, 36.8, 33.8, 30.6, 25.5 and 14.1.

Analysis for $C_{15}H_{20}O_3$ Calcd: C,72.55; H,8.12

Found: C,72.32; H,8.02.

(2 β,6β)-3β(2-Hydroxyl)ethyl-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene(27a):

To a solution of the endo-ester-enone 39 (70 mg, 0.28 mmol) in benzene (10 mL) was added p-toluenesulphonic acid (5 mg), and ethanedithiol (0.3 mL), and the mixture was refluxed with a Dean-Stark water separator for 25 min. The reaction mixture was diluted with benzene (15 mL), washed with $NaHCO_3$ solution and dried. The crude residue obtained after removal of the solvent was charged on a silica gel column (5g). Elution with 10% ethyl acetate - hexane removed the ethanedithiol impurities. Further elution with 20% ethyl acetate-hexane furnished the thioacetal (70mg, 75%).

IR spectrum (neat), ν_{max}: 2950, 1730 (ester carbonyl), 1420, 1160 and 1040 cm^{-1}.

^{1}H NMR spectrum (100MHz, $CDCl_3$): δ 1.2(3H,t,J=8Hz, -$COOCH_2\underline{CH_3}$), 1.3-2.9(14H,m), 3.1(1H,br,s, C_2-proton), 3.3[4H,d,J=2Hz, -S-$(CH_2)_2$-S-]and 4.1-(2H,q,J=8Hz, -$COO\underline{CH_2}CH_3$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 174.0, 151.9, 140.5, 71.3, 59.8, 50.9, 49.3, 48.7, 40.4, 39.6, 38.5, 38.4, 35.7, 33.5, 30.9, 29.3 and 14.2.

Into a two necked 50 mL RB flask fitted with a guard tube and stopper was taken liq. NH_3 (15 mL). To this freshly cut sodium metal (110mg, 4.7 mg atom) was added piece by piece. The resulting blue solution was stirred for

5 min and the thioacetal (70 mg, 0.21 mmol) in dry ether (5 mL) was slowly added to it. After evaporating the ammonia, the reaction mixture was quenched with NH_4Cl solution. The reaction mixture was diluted and extracted with ether (3x10 mL), washed and dried. The crude material resulted after the removal of the solvent was loaded on a small silica gel column. Elution with 10% ethyl acetate-petroleum ether removed all sulfur impurities. Further elution with 20% ethyl acetate-petroleum ether furnished the hydroxy-olefin 27a (25mg, 60%).

IR Spectrum (neat), ν_{max}: 3350 (hydroxyl), 1460, 1060 and 1030 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.0-2.6(16H,m), 2.6-3.4(2H,m), and 3.64(2H,t,J=7Hz, $-C\underline{H}_2OH$).

Analysis for $C_{12}H_{20}O$ Calcd: C,81.20; H,10.48
Found: C,80.79; H,9.98.

(2 β,6 β)-3 β(2-ethanal)-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene(37a):

The hydroxy-olefin 27a (25mg, 0.13 mmol) in dichloromethane (5 mL) was added to a solution of pyridinium chlorochromate (35mg) in dry dichloromethane (3mL) containing activated molecular seives (4A°). The reaction mixture was stirred for 25 min and diluted with ether (5 mL). Filtration through a small florisil column and evaporation of the solvent furnished the aldehyde 37a (20mg, 80%).

IR Spectrum (neat), ν_{max}: 2950, 2475 (aldehyde), 1730 (carbonyl), 1450 and 1020 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 0.9-2.7(16H,m), 2.7-3.3(1H,m), and 9.77(1H,t,J=2Hz, $-C\underline{H}O$).

(2 β,6 β)-3 β(2-ethanaldimethylacetal)-tricyclo[6.3.0.0^{2,6}]undeca-1(8)-ene(38a):

To a solution of the aldehyde 37a (20mg, 0.10 mmol) in dry methanol (5mL), was added trimethylorthoformate (0.2 mL) and PPTS (5mg). The reaction mixture was refluxed for 1h and the methanol was removed under reduced pressure. The crude material was dissolved in ether (10 mL), washed with water, brine and dried over Na_2SO_4. After evaporating the solvent, the concentrate was filtered through a small silica gel column to furnish dimethylacetal 38a (18mg, 70%).

IR spectrum (neat), ν_{max}: 2950, 1460 and 1020 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.2-2.6(16H,m), 2.6-3.0(1H,m), 3.3[6H,s, -CH-(OC$\underline{H}_3$)$_2$] and 4.4[1H,t,J=7Hz, -C$\underline{H}$-(OCH$_3$)$_2$].

(3a β,9a β)-1 β(2-ethanaldimethylacetal)-decahydro-5H,9H-cyclopentacycloocta-5,9-dione (32):

The olefinic-acetal 38a (18mg, 0.076 mmol) was dissolved in a mixture of carbontetrachloride (0.5 mL), acetonitrile (0.5 mL) and water (0.8 mL). To this mixture sodium periodate (80 mg) and ruthenium dioxide (2 mg) were added. After stirring for 10 min, the reaction mixture was diluted and extracted with dichloromethane (5 mL). The organic layer was washed with water and dried. The crude material obtained after removal of the solvent was passed through a small silica gel column and the resulting diketo-acetal 32 (12 mg, 75%) was found identical (IR, ^1H NMR) with the minor endo-diketo-acetal 32 obtained from the mixture of olefinic-acetals 38a,b.

(3a β,9a β)-1 α(2-ethanaldimethylacetal)-decahydro-9H-cyclopentacycloocta-5,5-dimethylacetal-9-one (40):

The major exo-diketo-acetal 33 (250 mg, 0.932 mmol), trimethylorthoformate (0.5 mL) and PPTS (80 mg) were refluxed in dry methanol (25mL) for

1 h. Methanol was removed under reduced pressure and the resulting crude material was dissolved in ether (50 mL). The ethereal layer was washed with water, brine and dried over Na_2SO_4. The crude material obtained after removing the solvent was filtered through a small silica gel column to get bis-acetal 40 (220mg, 75%).

IR spectrum (neat), ν_{max}: 2950, 1700 (carbonyl), 1460, 1130 and 1060 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.0-2.6(17H,m), 3.0(3H,s, $-OC\underline{H}_3$), 3.04(3H,s,$-OC\underline{H}_3$), 3.12((3H,s,$-OC\underline{H}_3$), 3.16(3H,s,$-OC\underline{H}_3$), and 4.1[1H,dd, J_1=8Hz,J_2=4Hz, $-C\underline{H}(OCH_3)_2$].

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 216.0, 104.4, 102.5, 58.7, 52.9, 51.9, 47.5, 47.4, 47.0, 40.4, 38.4, 38.1, 35.0, 34.8, 33.0, 31.9 and 18.3.

(1 β, 4α,12 β)-2-methoxy-tricyclo[5.4.2.$0^{4,12}$]-trideca-10,13-dione(41):

Into a three necked RB flask fitted with dry nitrogen gas inlet, rubber septum and mercury seal, n-BuLi (0.15 mL) in hexane was introduced. It was cooled to -78°C and hexamethyldisilayane (0.1 mL) was added. The mixture was stirred for 20 min, then THF (1 mL) was added to dissolve the solid material formed. After 10 min the bis-acetal 40 (30 mg, 0.095 mmol) in THF (2 mL) was slowly added and was stirred for 20 min. Then freshly distilled trimethylsilyl chloride (0.1 mL) was added to quench the enolate. After 30 min, $NaHCO_3$ solution was added to the reaction mixture and it was extracted with ether (3x5 mL). The organic layer was washed and dried. The silyl enol ether obtained after removing the solvent was dissolved in dry dichloromethane (5 mL) and was taken into another three necked RB flask fitted with dry nitrogen set up. The reaction mixture was cooled to -78°C and $TiCl_4$ (0.1 mL) in dry dichloromethane (1 mL) was introduced. After stirring it for 30 min at -78°C and

1h at 0°C, the reaction mixture was quenched with $NaHCO_3$ solution. The organic layer was diluted and extracted with dichloromethane (3x5 mL). The crude material obtained after removing the solvent was charged on a small silica gel column. Careful elution with 60% ethyl acetate - petroleum ether furnished the cyclised diketone 41 (8 mg, 35.5%).

IR spectrum (neat), ν_{max}: 2950, 1700 (carbonyl), 1460, 1280 and 1100 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$, Fig.III-9): δ 1.0-2.9(16H,m), 3.26(3H,s, -OC<u>H</u>$_3$) and 3.68(1H,t,J=8Hz, -C<u>H</u>-OCH$_3$).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$, Fig.III-10): δ 215.9, 214.8, 81.9, 58.6, 56.3, 54.4, 45.8, 43.2, 36.7, 35.9, 33.1, 29.6(2C) and 27.8.

Analysis for $C_{14}H_{20}O_3$ Calcd: C,71.16; H,8.53
Found: C,71.42; H,8.40.

Further elution with 70% ethyl acetate - petroleum ether yielded the diketoaldehyde 42 (10 mg, 47%)

IR spectrum (neat), ν_{max}: 2950, 2775 (aldehyde), 1700 (carbonyl), 1460 and 1280 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.8-3.6(16H,m), 3.6-3.9 (1H,m) and 9.49(1H,d,J=2Hz, -C<u>H</u>O).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 214.2, 213.1, 201.8, 58.7, 49.2, 44.7, 43.7, 42.7, 40.3, 34.1, 32.5, 30.5 and 22.8.

(3aβ,9aβ)-1β (2-ethanaldimethylacetal)-decahydro-9H-cyclopentacycloocta-5,5-dimethylacetal-9-one(34):

The minor <u>endo</u>-diketo-acetal 32 (50 mg, 0.186 mmol) trimethyl-

orthoformate (0.5 mL) and PPTS were refluxed in dry methanol (3 mL) for 45 min. The crude material obtained, after removing the methanol under reduced pressure was dissolved in ether (15 mL). The ethereal layer was washed with water, brine and dried over Na_2SO_4. The crude material obtained after removing the solvent was filtered through small silica gel column to furnish the bis-acetal 34 (48 mg, 80%).

IR spectrum (neat), ν_{max}: 2950, 1700 (carbonyl), 1460, 1130 and 1040 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$); δ 1.0-2.6(16H,m), 3.08(3H,s, $-OC\underline{H}_3$), 3.16(3H,s, $-OC\underline{H}_3$), 3.24(3H,s, $-OC\underline{H}_3$), 3.28(3H,s, $-OC\underline{H}_3$), 3.2-3.4 (1H,m,C_1-proton) and 4.2[1H,t,J=8Hz, $-C\underline{H}-(OCH_3)_2$].

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 216.6, 104.7, 103.0, 55.8, 53.6, 52.5, 48.0, 47.7(2C), 41.2, 39.3, 35.5, 34.1, 32.2, 31.2, 29.6 and 18.9.

(3aβ,9aβ)-1β(2-ethanal)-decahydro-5H,9H-cyclopentacycloocta-5,9-dione(43):

Into a three necked RB flask fitted with dry N_2 gas inlet, rubber septum and mercury seal, n-BuLi (0.16 mL) in hexane was introduced. It was cooled to -78°C and hexamethyldisilazane (0.1 mL) was added. The mixture was stirred for 20 min, then THF (1 mL) was added to dissolve the solid material formed. After 10 min, the bis-acetal 34 (35 mg, 0.11 mmol) in THF (2mL) was slowly added and was stirred for 20 min. Then freshly distilled trimethylsilyl chloride (0.1 mL) was added to quench the enolate. After 30 min, $NaHCO_3$ solution was added to the reaction mixture and it was extracted with ether (3x5 mL). The organic layer was washed and dried. The silyl enol ether obtained after removing the solvent was dissolved in dry dichloromethane (6 mL) and was taken into another three necked RB flask fitted with dry N_2 set up. The reaction mixture was cooled to -78°C and $TiCl_4$(0.1 mL) in dry

dichloromethane (1 mL) was introduced. After stirring for 1 h at -78°C and 1 h at 0°C, the reaction mixture was quenched with $NaHCO_3$ solution. The organic layer was diluted and extracted with dichloromethane (3x5 mL). The crude material obtained after removal of the solvent was charged on a small silica gel column. Careful elution with 60% ethyl acetate-hexane furnished the diketo-aldehyde 43 (15mg, 60%).

IR spectrum (neat), ν_{max}: 2950, 2775 (aldehyde), 1700 (carbonyl), 1460, 1200 and 1030 cm^{-1}.

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.2-3.0(16H,m), 3.15-3.45 (1H,m) and 9.7(1H,br,s, -CHO).

III. 7. SPECTRA

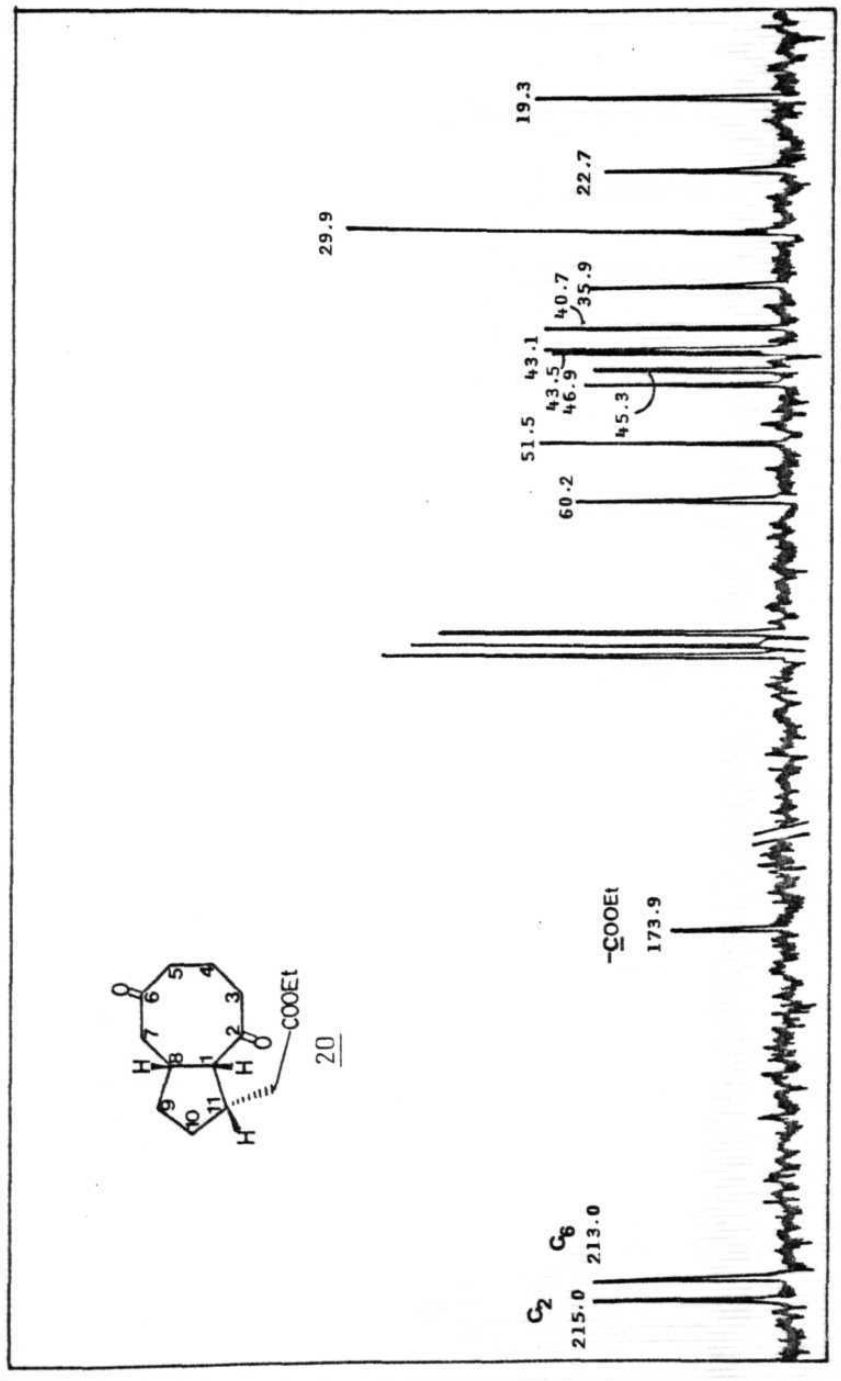


FIG.III-1 : ^{13}C NMR (25.0 MHz) spectrum of 20.

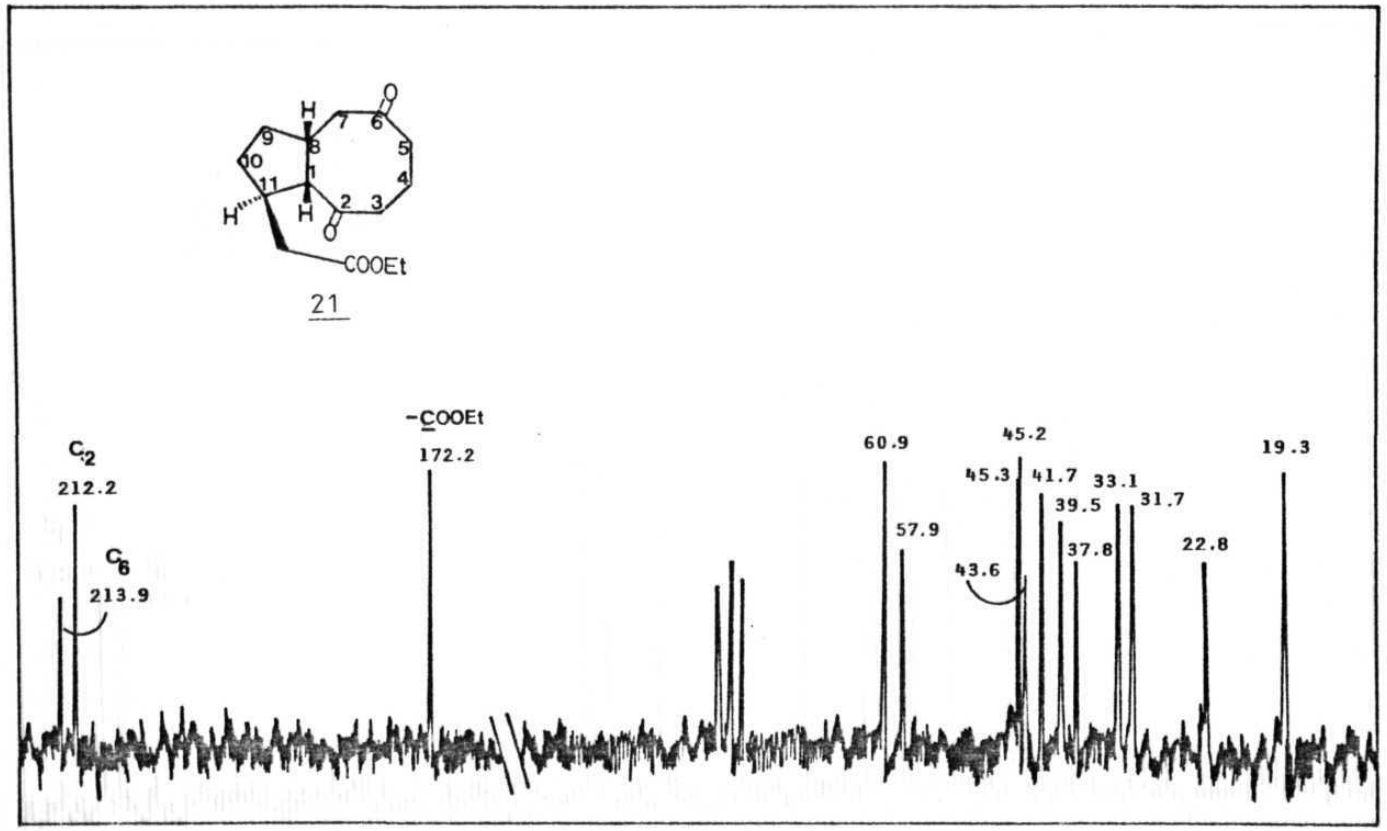


FIG.III-2 : ^{13}C NMR (25.0 MHz) spectrum of 21.

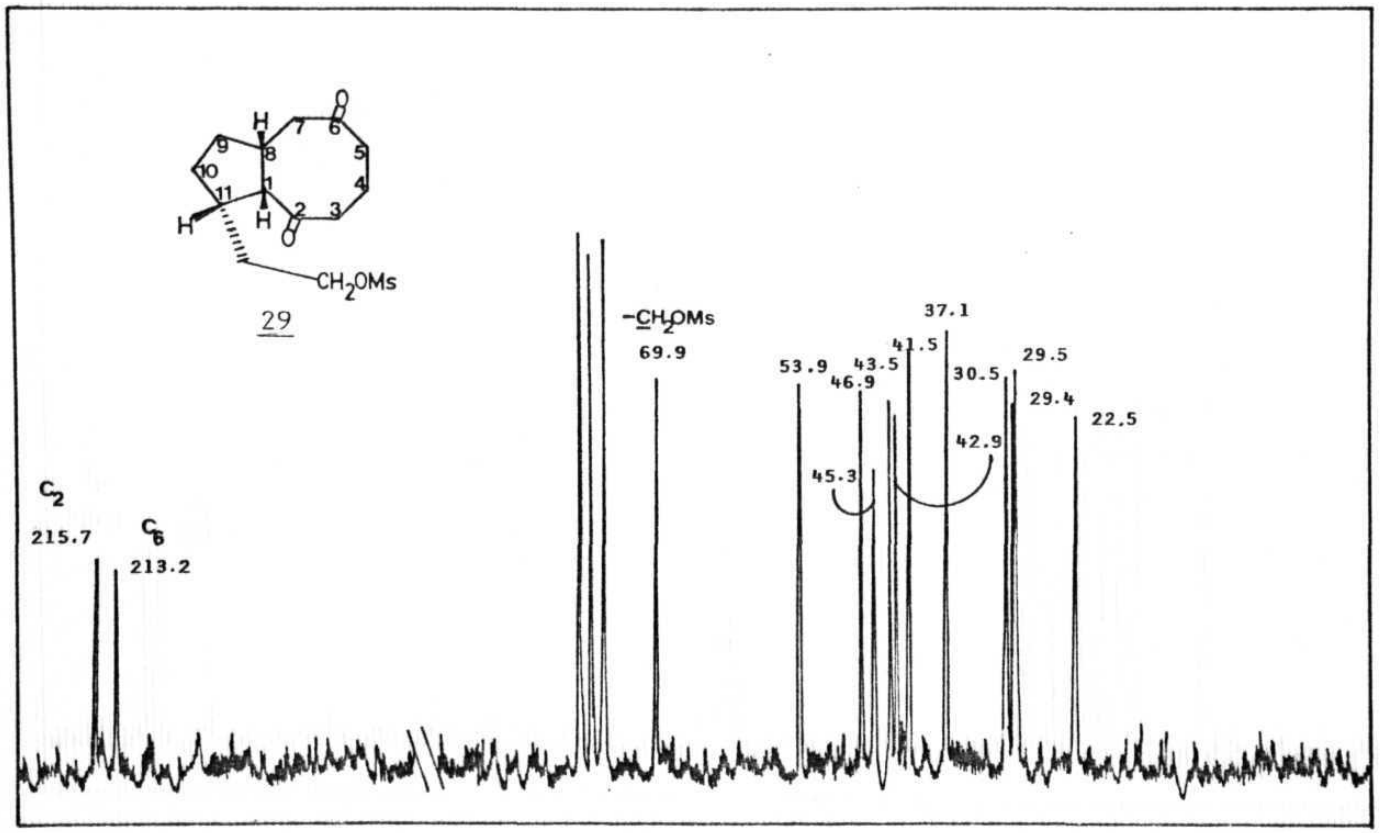


FIG.III-3 : ^{13}C NMR (25.0 MHz) spectrum of 29.

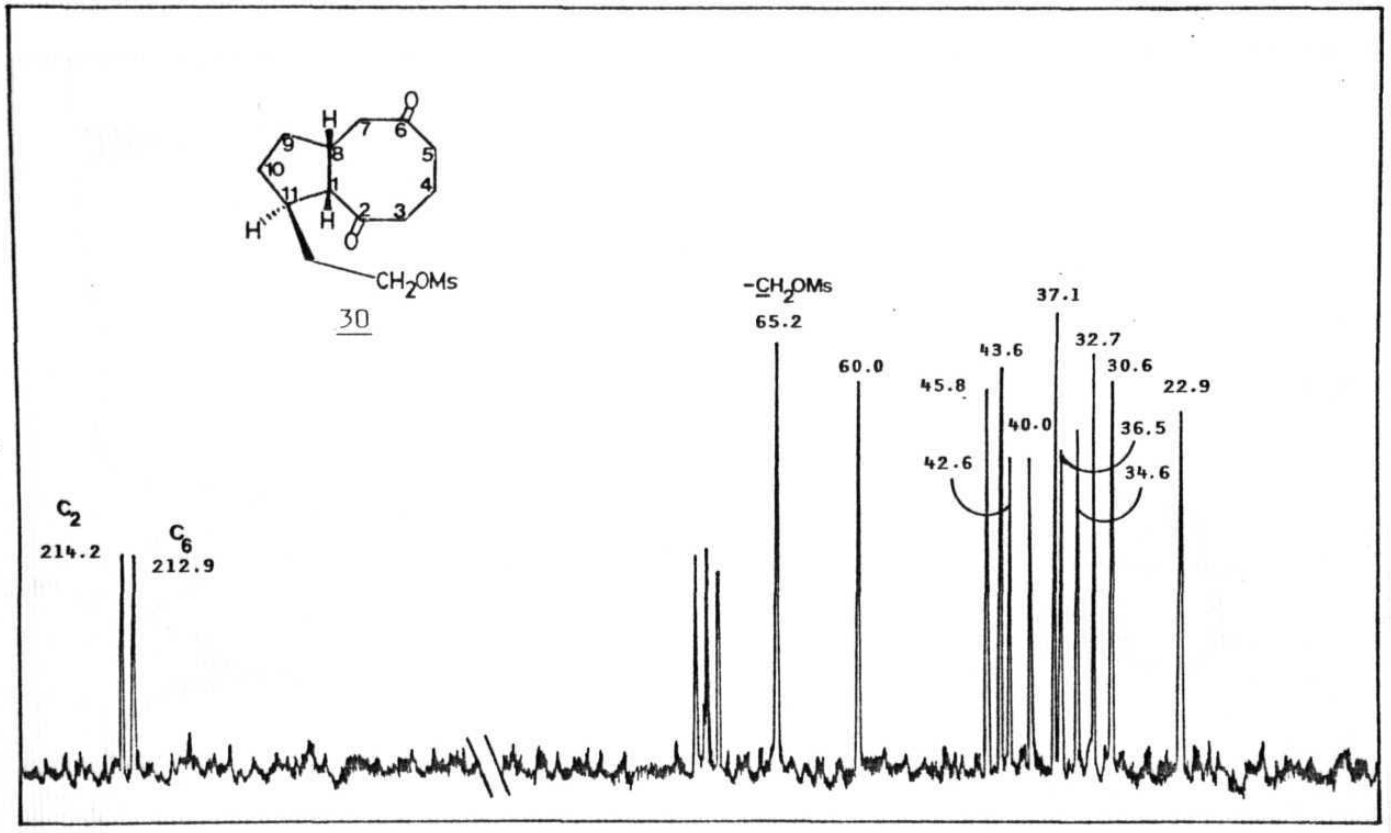


FIG.III-4 : ^{13}C NMR (25.0 MHz) spectrum of 30.

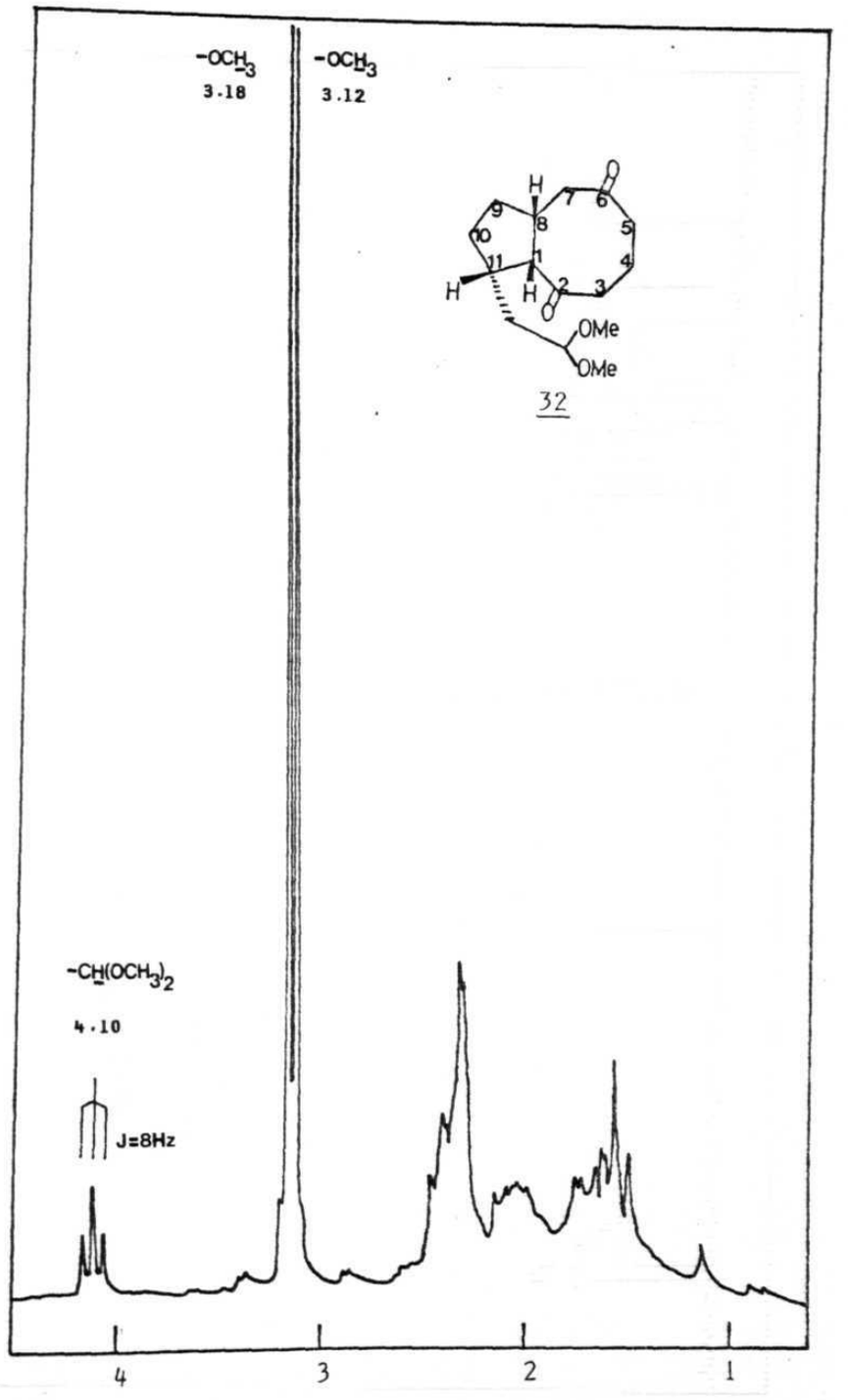


FIG.III-5 : ^{1}H NMR (100 MHz) spectrum of 32.

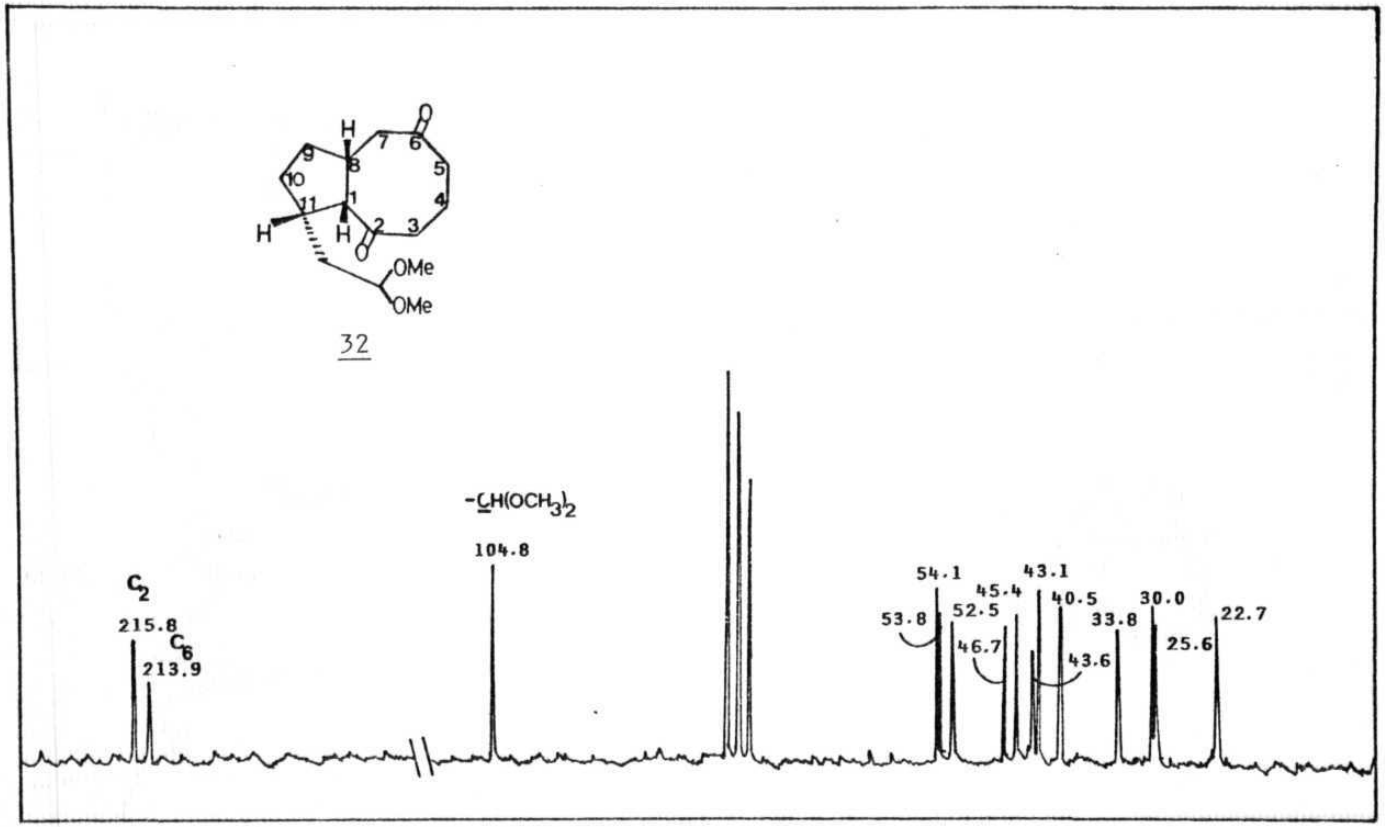
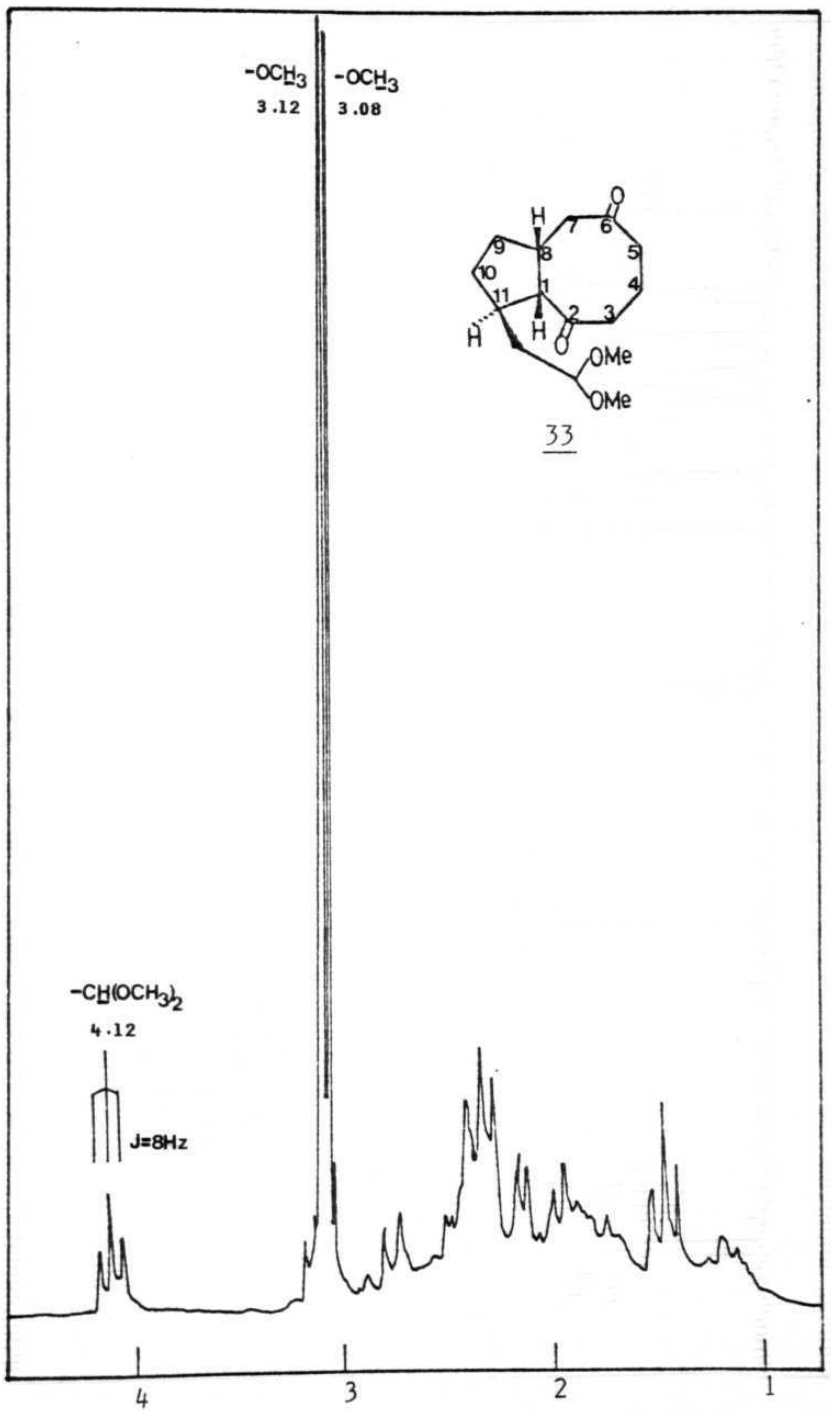


FIG.III-6 : ^{13}C NMR (25.0 MHz) spectrum of 32.



33

FIG.III-7 : ^{1}H NMR (100 MHz) spectrum of 33.

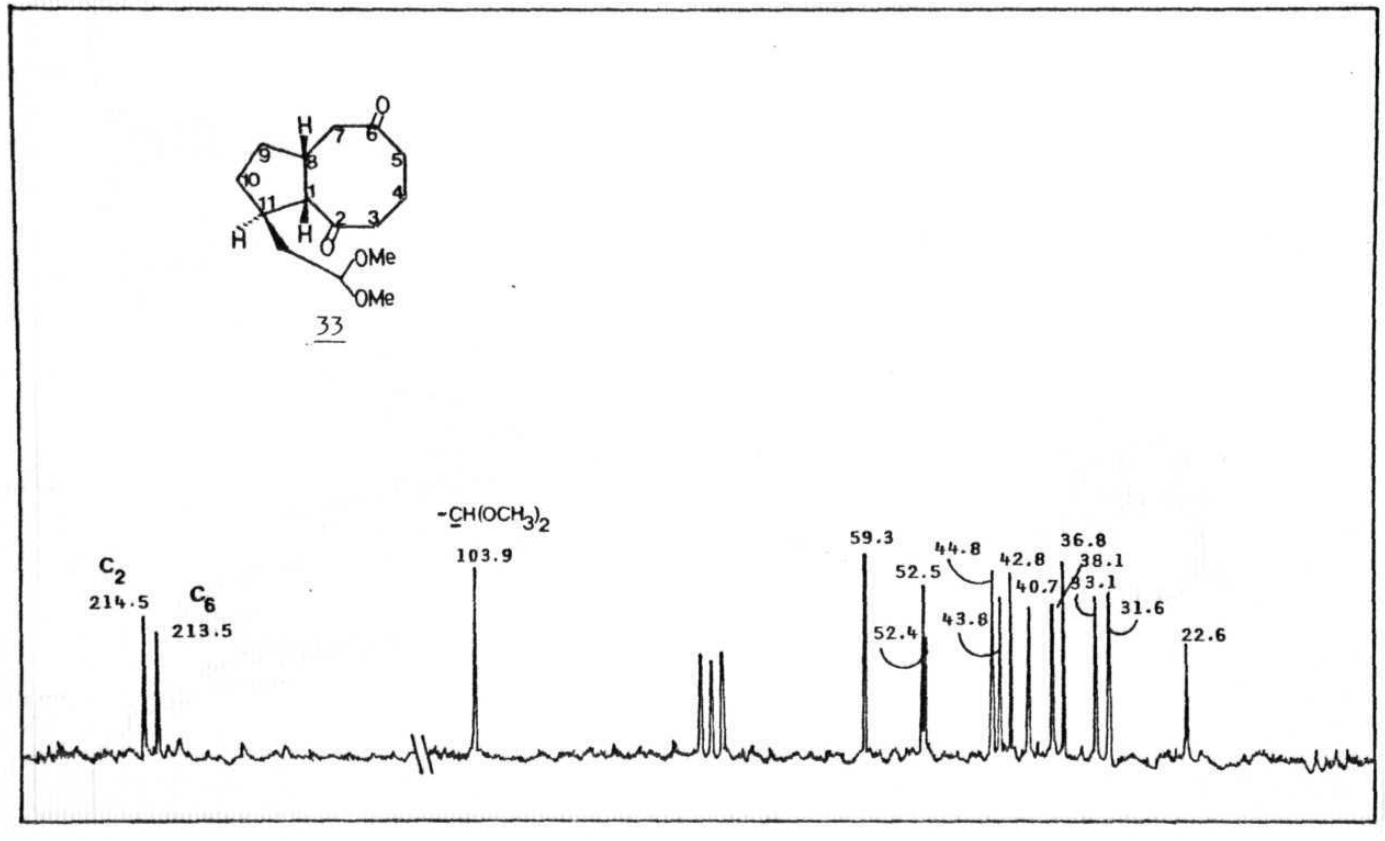
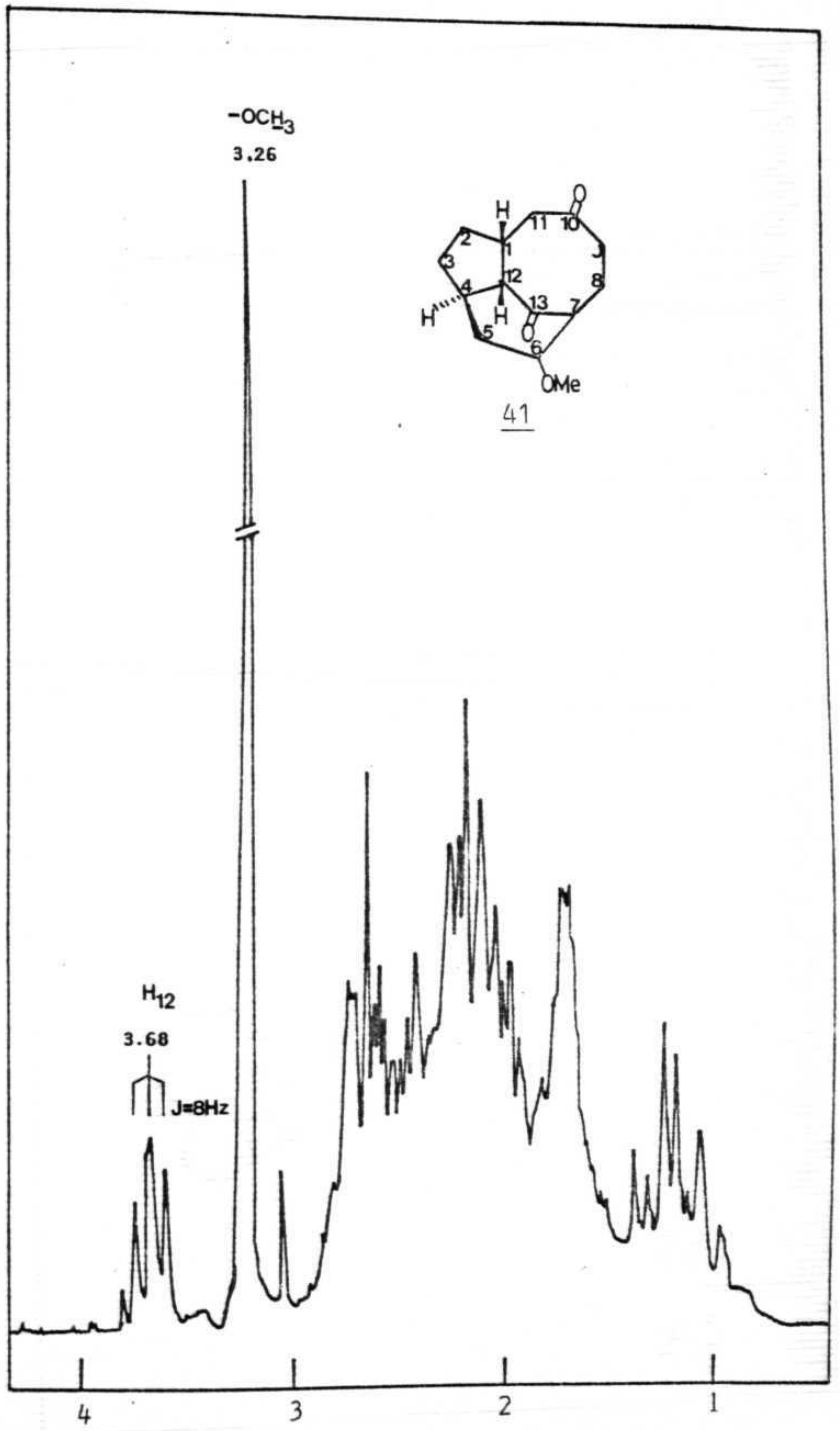


FIG.III-8 : ^{13}C NMR (25.0 MHz) spectrum of 33.



41

FIG.III-9 : ^{1}H NMR (100 MHz) spectrum of 41.

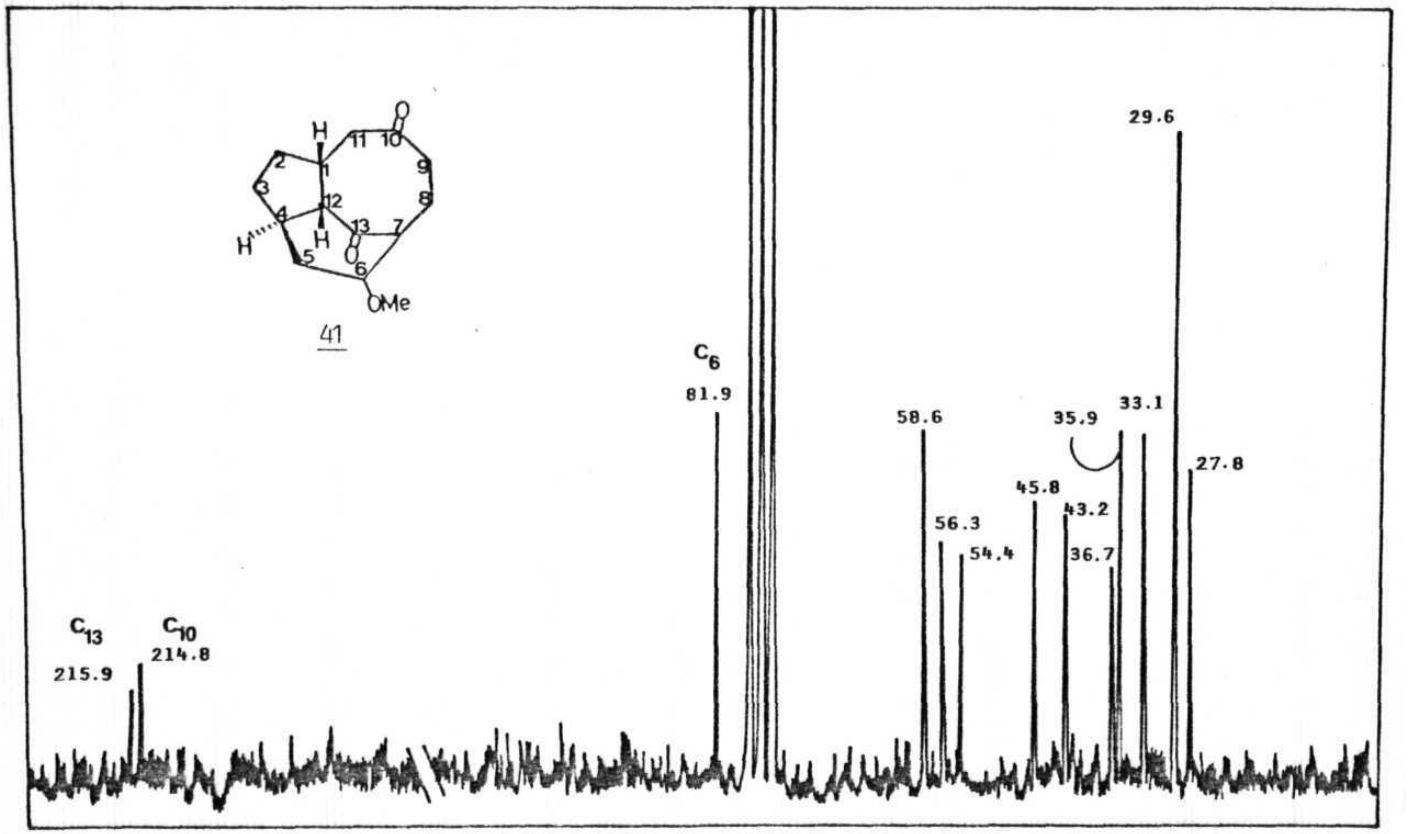


FIG.III-10 : ^{13}C NMR (25.0 MHz) spectrum of 41.

III. 8. REFERENCES

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CHAPTER IV

SYNTHETIC STUDIES TOWARDS THE CONSTRUCTION OF THE PERHYDRO-as-INDACENE MOIETY OF IKARUGAMYCIN

IV. 1 ABSTRACT

A novel approach for the rapid construction of the 5-6-5-tricarbocyclic ring systems is delineated. The key element in this approach is the photo-thermal metathesis of readily available Diels-Alder adducts to furnish the perhydro-as-indacene moiety. Thus, Diels-Alder adduct 11 obtained from 1,3-cyclohexadiene and p-benzoquinone was photocyclised to the pentacyclic dione 12. Thermal cyclobutane fragmentation of 12 under FVP conditions furnished the 5-6-5-fused tricyclic bisenone 13 in 8% yield.

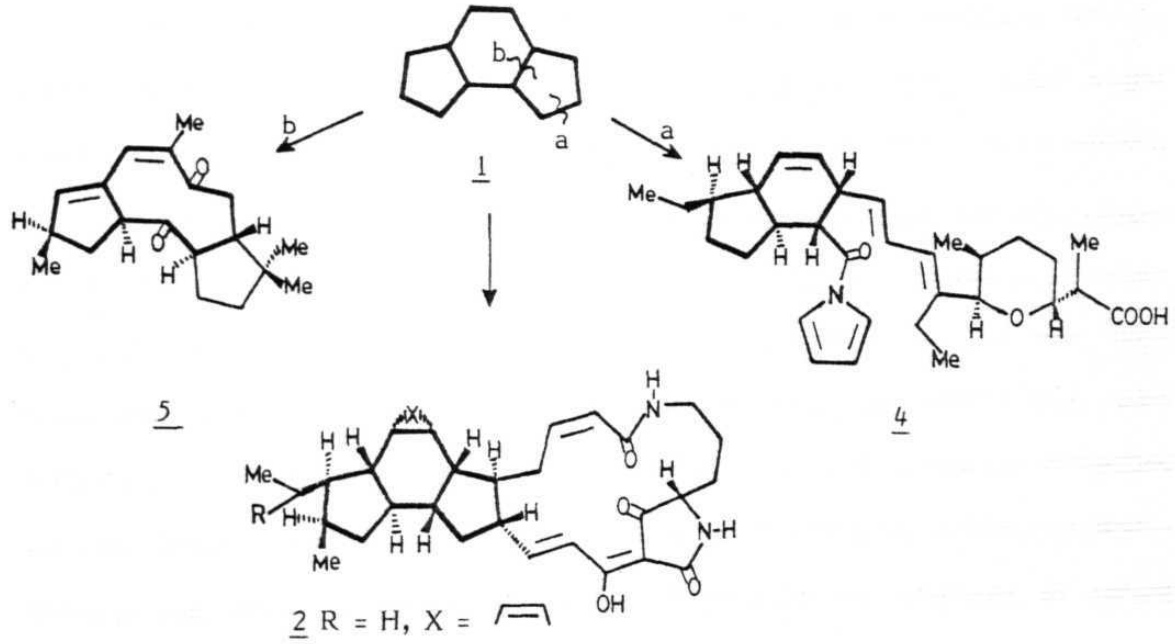
Based on this theme, attempts were made to design the carbocyclic framework of ikarugamycin 2. Towards this end, the Diels-Alder adduct 16 obtained from 1,3-cyclohexadiene and 2-methyl-p-benzoquinone was chosen as the starting material and photocyclised to the pentacyclic dione 17. Subsequent cyclobutane fragmentation of the dione 17 furnished the cis-syn-cis-bisenone 18 in ~ 15% yield. Conjugate additon of ethylmagnesium bromide in presence of Cu(I) gave the dialkylated diketone 21. Regio-and stereoselective sodium borohydride reduction produced the lactol 22. Acid catalysed dehydration of 22 furnished a mixture of cis-syn-cis and trans-anti-cis-perhydro-as-indacene derivatives 24 and 25, respectively. Stereochemistry to 24 and 25 has been assigned on the basis of past precedences, deuterium exchange reaction and other data. While the stereochemistry at the ring junctions and the ethyl group could be fixed as required for ikarugamycin 2, the C_2-methyl group

had the epimeric stereochemistry. Further tactical adjustments are needed to correctly install the C_2-methyl group.

VI. 2 OBJECTIVE AND BACKGROUND:

Nature has a special penchant for the creation of diverse carbocyclic frameworks and the presence of myriad carbocyclic skeleta among natural products, specially terpenes, bear testimony to its expertise. Thus, it is surprising that the perhydro-as-indacene framework 1, representing 5-6-5 ring fusion, has not been encountered among terpenes*. However, carbocyclic moiety 1 has recently been located in the structurally novel antibiotics ikarugamycin 2[1] and capsimycin 3[2].

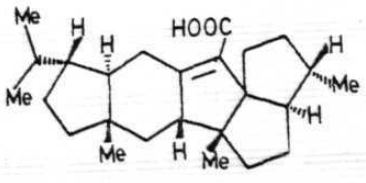
Scheme IV.1



2 R = H, X = 

3 R = OCH_3, X = O

*The closest example is of sesterterpene retigeranic acid i which has part of its carbocyclic skeleton made-up of perhydro-as-indacene moiety.[5]



RETIGERANIC ACID i

In addition, secoperhydro-as-indacene fragments, formally derived from 1 as shown in scheme IV.1, are present in many biologically important natural products of current interest, e.g. indanomycin (x-14547A, 4)[3] and jatrophatrione 5[4].

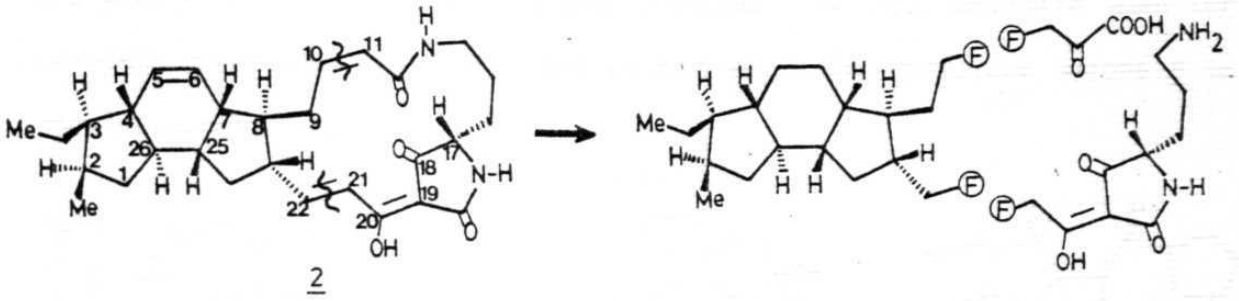
Ikarugamycin was first isolated in 1972 by Jomon et. al.[1a] from a culture broth of Streptomyces phaeochromogens var ikaruganensis Sakai. Extensive degradative studies, elegantly carried out in the laboratories of Hirata[1b,c], led to the determination of its structure and absolute configuration as depicted in 2. Its biological properties include strong specific anti-protozoal activity, in vitro antiamoebic activity and activity against Gram-positive bacteria. More recently, a closely related compound capsimycin 3 has been isolated from Streptomyces sp No. C_{49-87} and its structure has been elucidated on the basis of spectral and X-ray diffraction studies[2]. Capsimycin exhibits marked inhibitory activity against several phytopathogenic fungi e.g., Phytophthora capsici (Leaf blight disease of cucumber) and Pythium debaryanum (Damping off disease of cucumber).

Structurally, 2 and 3 are unique among natural products and are composed of distinctly recognisable carbocyclic (left segment) and heterocyclic (right segment) entities. While the carbocyclic portion is made up of the rare, non-terpenoid, trans-anti-cis-decahydro-as-indacene system, the heterocyclic part consists of a macrocyclic lactam with an enoyltetramic acid residue embedded with it. These structural features and the associated biological activity of ikarugamycin has drawn considerable attention from synthetic chemists in recent years.

As a target of total synthesis, 2 poses a synthetic challenge of considerable magnitude. Besides a network of functionalities, there are nine stereogenic centres, eight of which are contiguous and reside on the carbocyclic segment. Retrosynthetic logic indicates that the carbocyclic and enoyltetramic acid moieties be assembled separately with complimentary functionalities and

then joined together across the C_{10}-C_{11} and C_{21}-C_{22} olefinic bonds as shown in scheme IV.2. Synthetic approaches towards ikarugamycin 2 reported so far[6a-d]

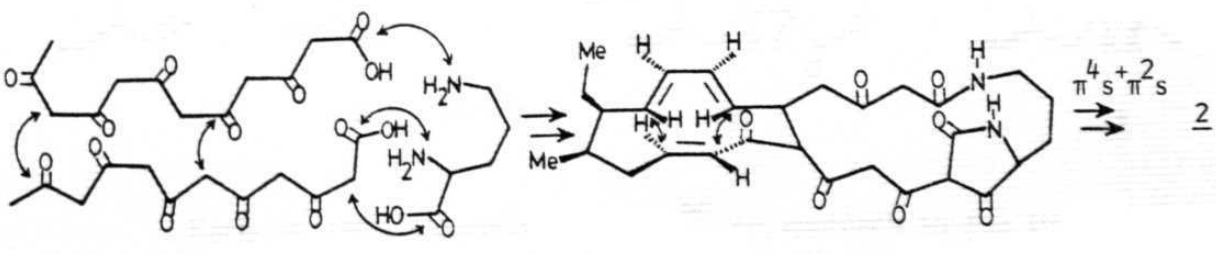
Scheme IV.2



2

have focussed on the construction of the carbocyclic decahydro-as-indacene segment, with one exception[6d] which describes the synthesis of the 3-acetyltetramic acid moiety. The inspiration for the initial approaches towards the synthesis of tricarbocyclic fragment of ikarugamycin was provided by the biogenetic hypothesis of Ito and Hirata[1c]. In a brilliant proposal, they conceived the formation of 2 from two hexa-acetate chains and the aminoacid L-ornithine as shown in scheme IV.3. The key ring forming step was an intramolecular Diels-Alder reaction within a macrocyclic triene 6 to generate the trans-anti-cis-decahydro-as-indacene moiety.

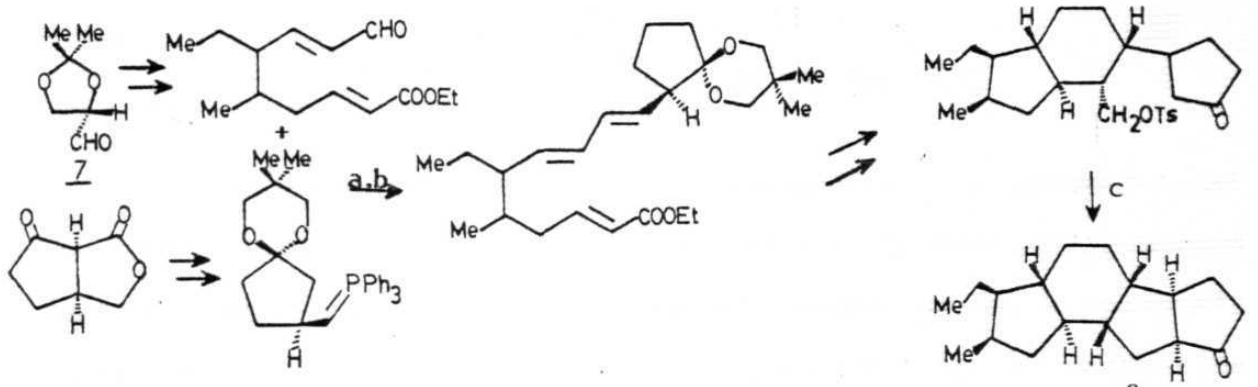
Scheme IV.3



6

Following the lead provided by the biogenetic hypothesis, Boeckman et.al.[6a] and Kurth et.al.[6b] outlined stereocontrolled approaches to the carbocyclic segment of ikarugamycin employing the intramolecular Diels-Alder reaction as the pivotal step. The Boeckman theme, reported[6a] in 1983, emanated from the (s)-(-)-glyceraldehyde acetonide 7 and terminated in the tetracyclic ketone 8 as shown in scheme IV.4.

Scheme IV.4[6a]

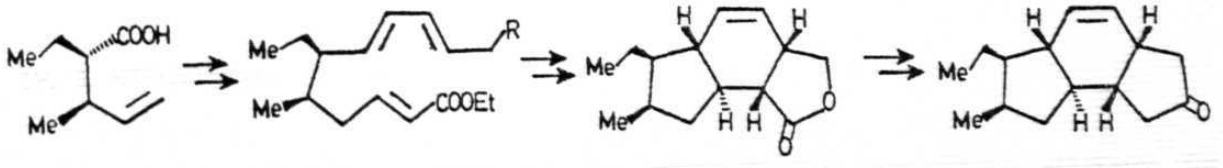


8

Reagents: (a) -50°C → 0°C, 2h; (b) Cat.I_2; (c) t-BuO^-K^+, BuOH, benzene.

The Kurth route[6b] from the readily available (E)-crotyl butanoate to the tricyclic ketone 9 appeared in 1984 and is outlined in scheme IV.5. In both these approaches, the 5-6 bicyclic system is first constructed via the Diels-Alder strategy and the third ring is appended subsequently.

Scheme IV.5[6b]



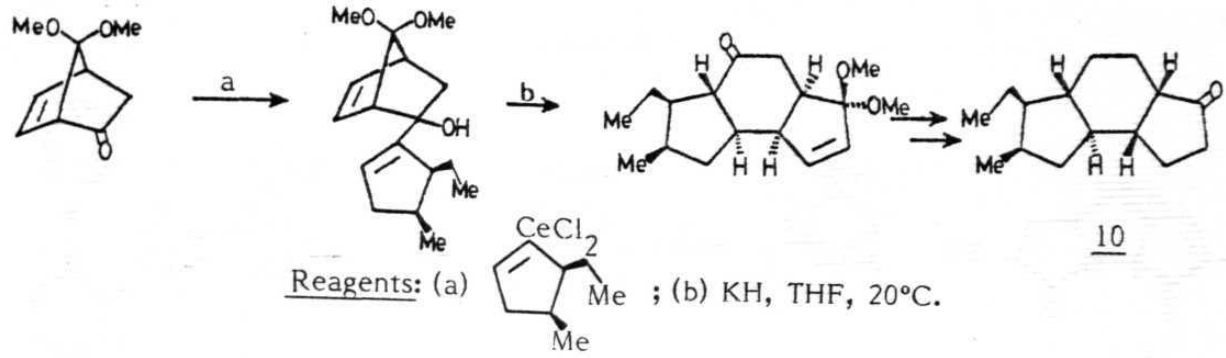
R = OTBDMS

9

Early in 1987, Paquette described[6c] an approach to the tricyclic decahydro-as-indacenone 10 from 7,7-dimethoxy-5-norbornen-2-one in which an anionic oxy-Cope rearrangement figured as key step, scheme IV.6. An interesting feature

of this approach is the high diastereoselective bias in the addition of the dichlorocerium reagent to the 7,7-dimethoxy-5-norbornen-2-one.

Scheme IV.6[6c]



Reagents: (a) $CeCl_2$ Me Me ; (b) KH, THF, 20°C.

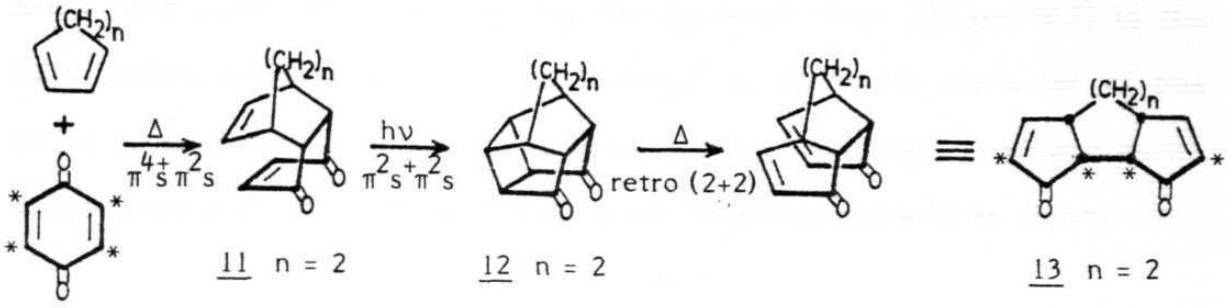
Like many others, we[7] also found ikarugamycin 2, an appealing target for total synthesis and were particularly attracted to its decahydro-as-indacene based left segment. In its 5-6-5 fused carbocyclic system, we saw an opportunity to extend the scope of our short, general, photo-thermal metathesis route to the 5-5-5 fused system. At the time of the inception of the project only two rationally designed routes to the 5-6-5 ring system were known, both of which employed the intramolecular Diels-Alder strategy in fairly long sequences of reactions. Thus, there was clearly a need for the development of new and concise way to the 5-6-5 fused system. In this chapter of the thesis, we outline a short (3 steps), photo-thermal metathesis approach[8] to the perhydro-as-indacene ring system and describe efforts directed towards the left segment of ikarugamycin 2.

IV. 3. STRATEGY:

A generalised version of our photo-thermal metathesis strategy for the construction of tricarbocyclic systems is shown in scheme IV.7[8]. According to it, deployment of 1,3-cyclohexadiene (n=2) and p-benzoquinone as starting materials would lead to the 5-6-5 bisenone 13 (n=2) in only three steps involving heat

and light as reagents. Formation of 13 from its caged precursor 12 ensures cis-syn-cis stereochemistry at the ring junctions. The approach has remarkable flexibility with regard to the installation of substituents on the carbocyclic framework.

Scheme IV.7



11 n = 2 12 n = 2 13 n = 2

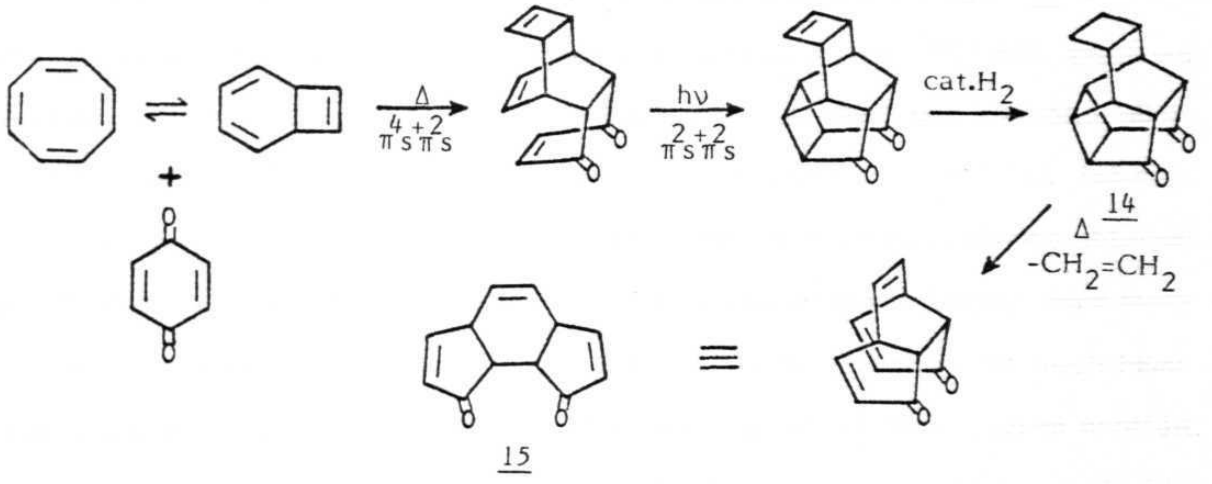
For example, the bottom six carbon atoms (heavy lined) in 13 are derived from p-benzoquinone and any substitution at the starred (*) positions in 13 can be achieved by having it at the complementary position of the starting p-benzoquinone. Similarly, substituents on the rest of 13 can be installed by employing an appropriately substituted 1,3-cyclohexadiene. In addition, the two enone functionalities in 13 provide a convenient means of introducing substituents at the position marked with arrows through the conjugate addition-enolate capture protocol. A perusal of the carbocyclic fragment of ikarugamycin 2 depicted in scheme IV.2 reveals that alkyl residues are present at the sites marked with arrow in 13.

Since the carbocyclic segment of 2 has as many as eight stereogenic centres, the synthetic strategy must provide for their creation in an orderly manner. Fortunately, the cis-syn-cis-bisenone 13 has a facially biased topology which enables it to react stereoselectively from the exo (convex face) side. Thus alkyl residues can be incorporated in the bisenone 13 in a stereoselective manner. Also, the strategic location of the carbonyl groups in the bisenone 13 can be exploited to generate the required trans-anti-cis stereochemistry at the ring junction from

the cis-syn-cis present, through epimerisation at one of the centres α to the carbonyl. There is precedence for this expectation in the known greater stability of trans-bicyclo[4.3.0]nonan-2-one over its cis-isomer[9].

The tricarbocyclic portion of ikarugamycin 2 has an isolated disubstituted double bond in the six membered ring. Our projected route (scheme IV.7) to the 5-6-5 system does not provide much leverage for the ready placement of this double bond. We therefore, kept in mind the option of eventually employing cyclo-octatetraene as the diene in the photo-thermal metathesis sequence as shown in

Scheme IV.8



scheme IV.8. Here the last step (14 → 15) was envisaged to undergo two regioselective cyclobutane fragmentations with the elimination of ethylene. The resulting 5-6-5 tricyclic compound 15 has the cyclohexene double bond in position and retains the two enone moieties.

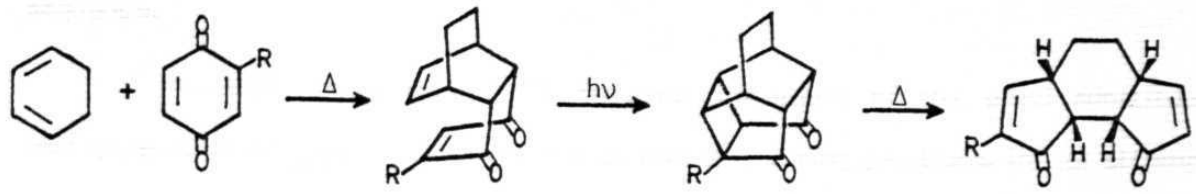
The foregoing strategic analysis identified the methodology for the rapid generation of the functionalised 5-6-5-tricarbocyclic system and for establishing the substitution pattern in a stereoselective manner. The time was now ripe to give practical shape to the ideas enumerated above.

IV. 4 SYNTHESIS OF 5-6-5 TRICARBOCYCLIC SYSTEM

As emphasized above, the first major stride towards the projected construction of the left segment of ikarugamycin 2 had to be the successful implementation of the scheme IV.7 leading to the key 5-6-5 bisenone system. Readily available[10] Diels-Alder adduct 11 of 1,3-cyclohexadiene and p-benzoquinone undergoes smooth photochemical (2+2)-cycloaddition to furnish the previously described[11] pentacyclic caged dione 12 in good yield. Sublimation of 12 through a quartz tube kept at 600°C ± 10°C, 1mm, employing a home made FVP set-up gave the cyclobutane fragmentation product 13, mp 104-105°C, in 8% yield along with some p-benzoquinone and hydroquinone. The structure of tricyclic bisenone 13 was revealed through its spectral characteristics. In particular, its ^{1}H NMR spectrum showed olefinic proton signals at δ 7.42(dd,J_1=6Hz, J_2=3Hz) and 6.22(dd,J_1=6Hz, J_2=2Hz) and the ^{13}C NMR spectrum had six resonances at δ 209.3(s), 163.9(d), 133.7(d), 45.3(d), 40.9(d), 22.4(t) in accordance with its symmetry. Having obtained the desired 5-6-5 bisenone 13, albeit in meagre yield, several attempts were made to enhance its yield through variation in FVP conditions. However, not much headway could be made. The low yield of 13 in the FVP of 12 is in marked contrast to the behaviour of the lower homologue of 12 which gives almost quantitative yield of the 5-6-5-bisenone. The reasons for this dramatic alteration in yield are not fully apparent but possibly reside in the strain energy difference between the two precursor pentacyclic diones[12].

Synthesis of the substituted bisenone 18 was attempted next, as it had the methyl group in the required position (scheme IV.9) and it was expected that its two non-equivalent enone moities would be amenable to chemo-differentiation. Reaction between 1,3-cyclohexadiene and 2-methyl-p-benzoquinone readily furnished the tricyclic endo-adduct 16 mp 88-89°C, in 80% yield. Irradiation of

Scheme IV.9



11 R = H
16 R = Me

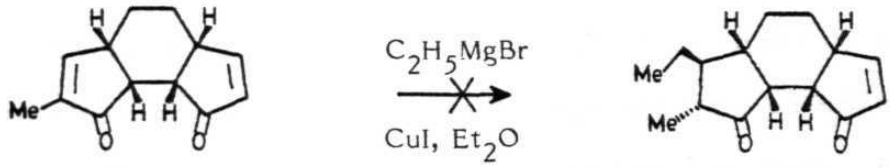
12 R = H
17 R = Me

13 R = H
18 R = Me

16 from a 450W Hanovia mercury vapor lamp through a pyrex filter led to the expected (2+2)-photoclosure and the pentacyclic dione 17 was obtained in 85% yield. The IR absorption at 1740 cm^{-1} and ^1H NMR singlet at δ 1.2(3H) fully supported the caged structure of 17. Thermal cyclobutane cleavage in 17 was achieved at 600°C ± 10°C, 0.8 mm, employing FVP conditions. The methyl substituted tricyclic bisenone 18, mp 77-78°C, was obtained in ~ 15% yield along with some 2-methylhydroquinone and 2-methyl-p-benzoquinone. The IR spectrum (ν_{max}: 1720 and 1620 cm^{-1}) of 18 indicated the presence of 2-cyclopentenone substructure. The ^1H NMR spectrum (Fig. IV-1) of bisenone 18 showed the presence of two characteristic β -proton resonances at δ 7.4(dd,J_1=6Hz, J_2=2Hz) and 7.0(br,s) of the 2-cyclopentenone moiety along with vinylic methyl resonance at δ 1.8. The ^{13}C NMR spectrum (Fig.IV-2) revealed striking similarity to 13 and related quinanes and exhibited resonances at δ 209.5(2C), 164.4, 157.7, 141.1, 133.2, 45.4, 45.1, 39.5, 38.4, 22.9, 21.9 and 9.86. The assignment of cis-syn-cis stereochemistry to 18 follows from its genesis from the caged precursor 17 and from reactions described later in this sequel. While the yield in the FVP reaction was once again

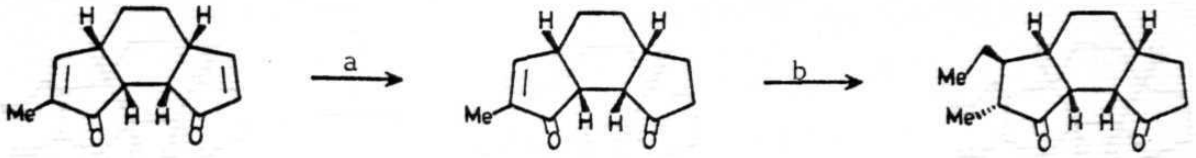
not quite satisfactory due to competing retro (2+2) and (4+2) reactions, it was still acceptable due to the fact that readily available/commercial starting materials are used and only heat, light and heat are employed as reagents in the three step sequence.

Further elaboration of 18 required placement of the ethyl substituent and generation of trans stereochemistry at one of the ring junctions. Initial attempts to carry out regioselective 1,4-addition of the ethyl magnesium bromide in the presence of CuI to give 19 led to an intractable mixture of products. Therefore, it became necessary to differentiate between the two enone moieties.



18 19

Selective catalytic hydrogenation of the disubstituted double bond in 18 gave the ene-dione 20. Conjugate addition of ethylmagnesium bromide in the presence of CuI furnished 21 as a single stereoisomer as indicated by its ^1H NMR signals at δ 0.94(3H,t,J=7Hz) and 1.12(3H,d,J=7Hz) and its 15 line ^{13}C NMR spectrum (vide experimental). The stereochemistry at the two newly created stereogenic centres follows from the expected preferred addition of the ethyl group and proton to the folded 20 from the convex face. It was recognised at this stage that while the ethyl group had the correct stereochemical disposition, the methyl group bearing



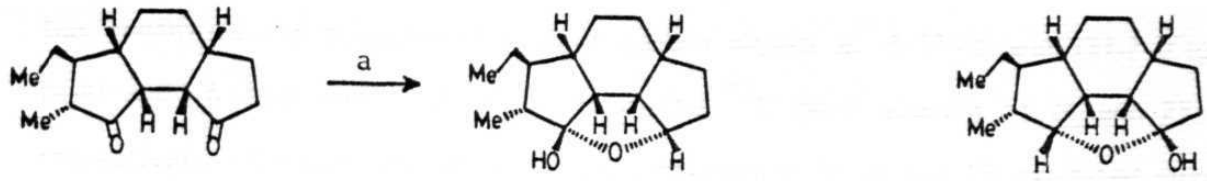
18 20 21

Reagents & Yields : (a) H_2 - 10% Pd/C, ethyl acetate, 80%; (b) C_2H_5MgBr, CuI, Et_2O, 60%.

carbon centre needed to be epimerised. It was our expectation, rather an optimistic one, that this could be achieved in subsequent steps.

At this stage, the two carbonyl groups of 21 needed to be chemodifferentiated and this was accomplished through carefully controlled sodium borohydride reduction. The resulting reduction product was readily formulated as the hemi-acetal 22 on the basis of a single proton resonance at δ 4.64-4.9(m) in the ^1H NMR spectrum and resonances at δ 119.4 and 86.9 due to $>C<^{-O-}_{-O-}$ and -C-O- functionalities, respectively, in the ^{13}C NMR spectrum. The alternative formulation 23 for the lactol was ruled out on the basis of the multiplicity of the ^1H NMR signal at δ 4.64-4.9 and subsequent reactions of 22. The formation of 22 was reassuring in the sense that the cis-syn-cis stereochemistry at the ring junctions was intact.

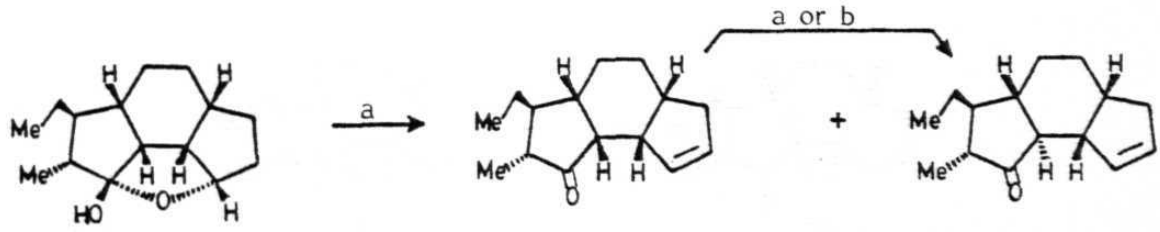
The hemi-acetal 22 was now subjected to acid catalysed dehydration in refluxing benzene in the presence of catalytic amount of p-toluenesulphonic acid. When the reaction was terminated after 1 h two tricyclic products 24



21 22 23

Reagents & Yields : (a) $NaBH_4$, MeOH, 70%.

(40%) and 25 (30%) could be isolated. Careful monitoring of the reaction revealed that 24 was formed initially but on prolonged exposure converted into 25. In a separate experiment, it was shown that pure 24 in refluxing benzene-p-toluene-sulphonic acid was completely transformed to 25 (60%). The structures of 24 and 25 were deduced as follows:



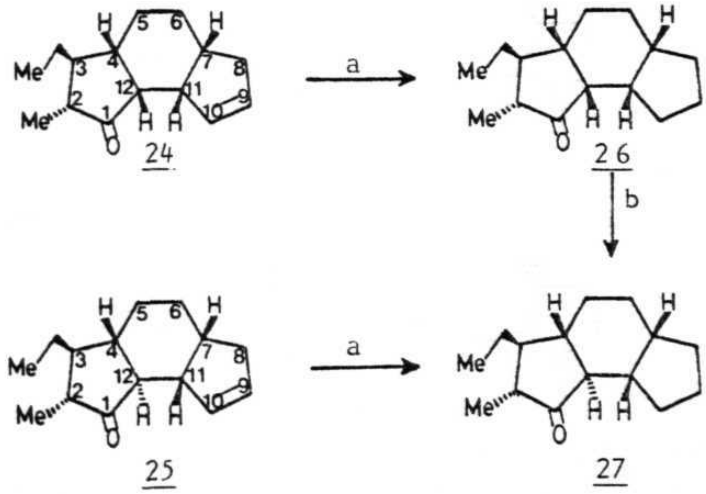
22 24 25

Reagents & Yields : (a) PTS - benzene, 70%; (b) NaOMe, MeOH, THF, 50%.

Both, 24 and 25 exhibited cyclopentanone absorption band at 1740 cm^{-1}

in their IR spectra and their ^{1}H NMR spectra (Fig.IV-3 and IV-5 respectively) showed the presence of two olefinic protons besides other expected signals. This has confirmed the presence of olefinic carbon signals at δ 133.0 and 131.2 (Fig.-IV-4) and δ 136.0 and 120.8 (Fig.IV-6) in the ^{13}C NMR spectra of 24 and 25, respectively. However, the olefinic proton resonances in 24 and 25 exhibited significant and quite unexpected chemical shift differences. While 24 had its olefinic proton resonances centred at δ 5.24 and 5.60, 25 had the corresponding signals at δ 5.73 and 6.20. It was therefore essential to establish that one was dealing with stereoisomers and not double bond isomers. This was established in a straight forward manner as shown in scheme IV.10. Catalytic hydrogenation of 24 and

Scheme IV.10



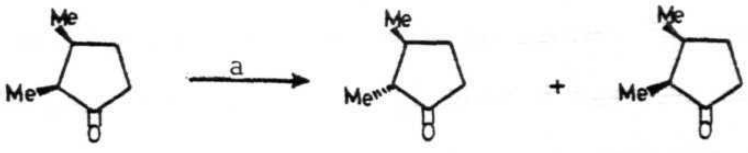
24 26 25 27

Reagents & Yields : (a) H_2 - 10% Pd/C, ethyl acetate, 90%; (b) PTS - benzene, 60%.

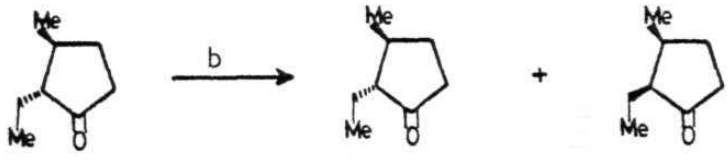
25 gave the dihydro-compounds 26 and 27, respectively, which were not identical. Furthermore, 26 could be epimerised to 27 thereby showing that enones 24 and 25 were stereoisomers.

When enone 25 was equilibrated in presence of NaOMe in MeOD, upto two deuterium atoms were incorporated. The ^{1}H NMR spectrum of the deuterated product was nearly identical with its precursor but the tertiary methyl group now appeared as a singlet δ 1.16 and there was diminution in the signal intensity in the δ 2.0-2.5 region. This indicated that both C_2 and C_{12} centres were involved in the conversion of 24 to 25 and led to their stereochemical assignment. There

Table IV.1

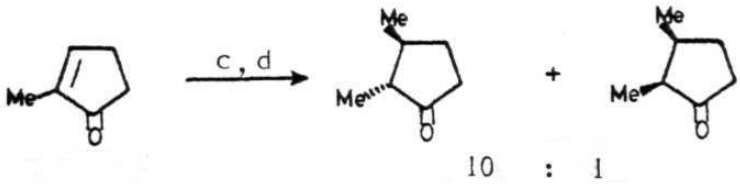


cis : trans (commercial) — 93 : 7 — Ref. **13**

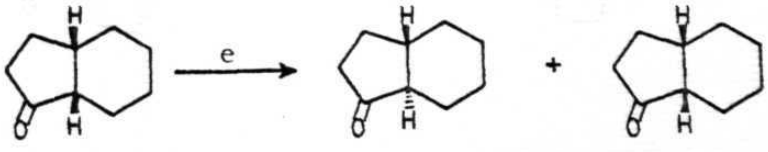


9 : 1 — 7 : 1 — Ref. **14**

cis : trans



10 : 1 — Ref. **15**



1 : 1 — Ref. **9**

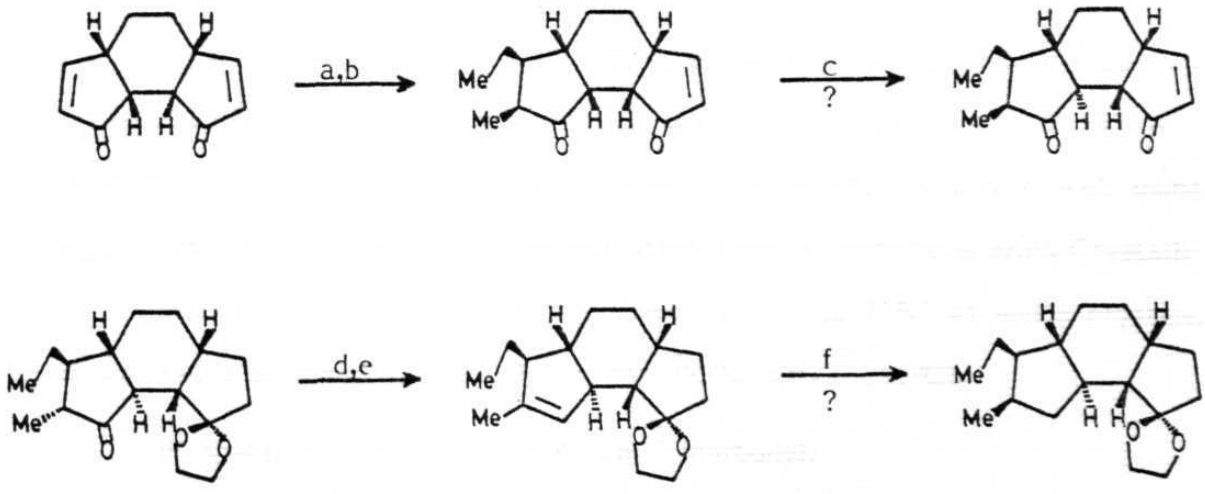
is ample precedence in literature to support this assignment. Some relevant examples are summarised in table IV.1. The 2,3-dialkylated cyclopentanones as well

as the 5-6 fused bicyclic systems display marked preference for the thermodynamically more stable trans arrangement. At this stage, further efforts were abandoned pending the solution of the problem of establishing the cis relationship of C_2 and C_3 alkyl substituents.

IV. 5 SUMMARY AND OUTLOOK

A photo-thermal metathesis route to the decahydro-as-indacene bisenones has been established. The generation of 13 and 18 in only three steps from abundantly available starting materials, make them useful synthons for natural product synthesis. Efforts have been made to convert 18 into the carbocyclic segment of the antibiotic ikarugamycin 2. While it has been possible to generate the required trans-anti-cis stereochemistry in the tricyclic system 25 and also install

Scheme IV.11



Reagents : C_2H_5MgBr, CuI; (b) MeI; (c) Base; (d) p-Me-$C_6H_4SO_2NHNH_2$; (e) n-BuLi; (f) Cat.H_2.

the alkyl substituents at C_2 and C_3, the stereochemistry at C_2 has posed problems. Therefore alternate solutions to control C_2 stereochemistry need to be devised. Some of these possibilities are indicated in scheme IV.11. Once this problem is overcome, the overall theme outlined here can be fruitfully applied to the synthesis of 2.

IV. 6. EXPERIMENTAL

Tricyclo[6.2.2.0^{2,7}]dodeca-4,9-diene-3,6-dione (11)[10]:

Freshly sublimed p-benzoquinone (2g, 18.5 mmol) and 1,3-cyclohexadiene (3.5 g, 43.7 mmol) in benzene (20 mL) were refluxed for 5 h. Benzene was removed under reduced pressure and the adduct 11 was crystallised from petroleum ether (2g, 58%),mp 85-86°C (Lit.[10] 86°C).

IR spectrum (KBr), ν_{max}: 1665 cm^{-1} (carbonyl).

Pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodeca-9,12-dione (12)[11]:

A solution of the adduct 11 (2g, 10.6 mmol) in ethyl acetate (120 mL) was purged with nitrogen gas. The solution was then irradiated with a 450 W Hanovia medium pressure mercury vapor lamp in a quartz immersion well using a Vycor filter for 7h. Removal of solvent gave a white amorphous solid. Crystallisation from benzene-petroleum ether furnished 12 (1.5 g, 75%) as white crystals, which was twice sublimed at 160°C/1 mm, mp 255°C (Lit.[11] 256°C).

IR spectrum (KBr), ν_{max}: 1745 cm^{-1} (carbonyl)

^{1}H NMR spectrum (60 MHz, $CDCl_3$): δ 1.8(4H,m) and 2.0-3.0(8H,m).

^{13}C NMR spectrum (22.64 MHz, $CDCl_3$): δ 211.4(s), 48.2(d), 47.5(d), 35.6(d), 31.5(d) and 16.7(t).

Tricyclo[7.3.0.0^{2,6}]dodeca-4,10-diene-3,12-dione (13):

Pentacyclic dione 12 (1g, 5.32 mmol) was slowly sublimed (140°C/1mm) through a quartz tube at 600°C ± 15°, as described in earlier chapters. The yellow condensate in the liquid N_2 trap was dissolved in dichloromethane. Removal of solvent gave 400 mg (70%) of a yellow solid and was identified as benzoquinone by comparison (mp, IR spectrum) with an authentic sample. The condensate in the delivery tube was charged on a small silica gel (5 g) column and chromatographed. Elution with 40% ethyl acetate-benzene furnished 80 mg (8 %) of the bisenone 13, which was crystallised from dichloromethane-petroleum ether as colorless plates, mp 104-105°C.

UV spectrum, λ_{max}^{MeOH}: 218 nm (ε : 15,200)

IR spectrum (KBr), ν_{max}: 1700 (carbonyl) and 1585 cm^{-1} (cyclopentenone).

^1H NMR spectrum (100MHz, $CDCl_3$): δ 1.0-2.0[4H,m, $(-CH_2-)_2$], 2.84 (2H,dd,J_1=6Hz, J_2=2Hz), 2.9-3.3(2H,m), 6.22(2H,dd,J_1=6Hz, J_2=2Hz, -CH=CH-C=O) and 7.42(2H,dd,J_1=6Hz, J_2=3Hz, -CH=CH-C=O).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 209.3(s), 163.9(d), 133.7(d), 45.3(d), 40.9(d), 22.4(t).

Analysis for $C_{12}H_{12}O_2$ Calcd: C,76.57; H,6.43
Found: C,75.80; H,6.56.

4-Methyl-tricyclo[6.2.2.0^{2,7}]dodeca-4,9-diene-2,6-dione (16)[10]:

A solution of freshly prepared 2-methyl-p-benzoquinone (5 g, 0.04 mol) and 1,3-cyclohexadiene (3.2 g, 0.04 mol) in benzene (30 mL) was refluxed for 16 h. Benzene was removed under reduced pressure and the adduct 16 (6.56 g, 80%) was crystallised from petroleum ether, mp 88-89°C.

IR spectrum (KBr), ν_{max}: 3050, 2950, 1670 (carbonyl), 1200, 720 and 670 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.36(2H,d,J=8Hz), 1.72(2H,d, J=8Hz), 1.96(3H,d,J=2Hz, C=C-C<u>H</u>$_3$), 3.0(2H, s), 3.2(2H,br s), 6.18(2H,t,J=4Hz, C<u>H</u>=CH-) and 6.54(1H,s,-C<u>H</u>=C-CH_3).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ 198.9(s), 198.2(s), 151.0(s), 139.0(d), 133.2(d), 132.7(d), 49.4(d), 48.8(d), 35.1(d), 34.8(d), 24.4(2C,t) and 16.2(q).

Analysis for $C_{13}H_{14}O_2$ Calcd: C, 77.20; H, 6.98

Found: C, 77.29; H, 6.94.

1-Methyl-pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodeca-9,12-diene (17)[11]:

A solution of the adduct <u>16</u> (6 g, 0.03 mol) in ethyl acetate (125mL) was purged with a slow stream of purified N_2 for 10 min. The solution was then irradiated with a 450W Hanovia medium pressure mercury vapor lamp in a quartz immersion well using a Vycor filter for 8h. Removal of the solvent gave the crude solid material, which upon distillation furnished the pentacyclic dione <u>17</u> (5.1 g, 85%).

IR spectrum (KBr), ν_{max}: 2950, 1740 (carbonyl) and 1030 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.20(3H,s,-C-C<u>H</u>$_3$), 1.24(1H,s), 1,8(3H,m), 2.08(2H,br s), 2.5(3H,m), 2.76(1H,m) and 3.08(1H,m).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ211.9, 211.2, 53.4, 51.6, 47.6, 47.3, 40.7, 32.3, 30.6, 30.1, 16.3, 15.9 and 15.3.

Analysis for $C_{13}H_{14}O_2$ Calcd: C, 77.20; H, 6.98

Found: C, 77.26; H, 7.03.

4-Methyl-<u>cis</u>-<u>syn</u>-<u>cis</u>-tricyclo[7.3.0.0^{2,6}]dodeca-4,10-diene-3,12-dione (18):

Pentacyclic dione <u>17</u> (10 g, 0.05 mol) was slowly sublimed (140°C/0.8mm

through a quartz tube at 600°C (±10°C), as described earlier. The yellow condensate in the liq.N_2 trap was dissolved in dichloromethane. Removal of solvent gave a yellow solid (1.6 g) and was identified as methyl-p-benzoquinone by comparison (mp, IR spectrum) with an authentic sample. The condensate in the delivery tube was charged on a silica gel (80 g) column and chromatographed. Elution with 20% ethylacetate-benzene furnished the methyl-hydroquinone (2 g). Further elution with 50% ethyl acetate-benzene yielded the bisenone 18 (1,5 g, 15%) which was crystallised from dichloromethane-petroleum ether as colourless cubes, mp 77-78°C.

UV spectrum λ_{max}^{MeOH}: 219.6 nm (ε :14,583).

IR spectrum (KBr), ν_{max}: 2950, 1720 (carbonyl), 1620 (olefinic), 1580, 1420, 1030 and 880 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$, Fig.IV-1): δ1.28(2H,m), 1.7(2H,m), 1.8(3H, t, J=1Hz, -CH=C(CH3)-C=O), 2.9(2H, br s), 3.1(2H, m), 6.2(1H, dd, J_1=6Hz, J_2= 2Hz, -CH=CH-C=O), 7.0(1H, br s, -CH=C-C=O) and 7.40(1H,dd,J_1=6Hz, J_2=2Hz, -CH=CH-C=O).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$, Fig.IV-2): δ 209.5(2C), 164.4, 157.7, 141.1, 133.2, 45.4, 45.1, 39.5, 38.4, 22.2, 21.9 and 9.86.

Analysis for $C_{13}H_{14}O_2$ Calcd: C,77.20; H,6.98

Found: C,77.23; H,6.95.

4-Methyl-cis-syn-cis-tricyclo[7.3.0.0^{2,6}]dodeca-4-ene-3,12-dione (20):

A solution of the bisenone 18 (1 g, 5 mmol) was hydrogenated over 10% Pd/C catalyst (20mg) in H_2 atm. for 10 min. Catalyst was removed by filtration and filtrate concentrated. The crude product was charged on a silica gel (15 g) column. Elution with 25% ethyl acetate - benzene removed the perhydro-impurities. Further elution with 30% ethyl acetate-benzene furnished the partially hydrogenated compound 20 (800 mg, 80%).

UV spectrum λ_{max}^{MeOH}: 228.6 nm (ε : 8119)

IR spectrum (neat), ν_{max} : 2950, 1740 (carbonyl), 1700 (carbonyl), 1640 (olefinic), 1430, 1160 and 920 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.6-0.9(1H,m), 1.0-1.6(4H,m), 1.6(3H,s,-C=C-C=O), 1.9-2.4(5H,m), 2.8(1H,t,J=6Hz), 3.0(1H,br s) and 6.9(1H,s, CH=C-C=O).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$); δ221.1(s), 210.2(s), 158.6(d), 140.5(s), 47.5(d), 45.3(d), 38.9(t), 37.6(t), 36.1(t), 30.1(t), 25.1(d), 23.2(d) and 9.98(q).

Analysis for $C_{13}H_{16}O_2$ Calcd: C,76.24; H,7.91

Found: C,76.44; H,7.90.

4 α-Methyl-5 β-ethyl-cis-syn-cis-tricyclo[7.3.0.0^{2,6}]dodeca-3,12-dione(21):

Into a stirred solution of ethylmagnesium bromide [prepared from magnesium turnings (480 mg, 20 mmol) and ethylbromide (0.5 ml, excess)] in dry ether (20 mL) at 0°C was added cuprous iodide (1 g, 10 mmol) at once. After stirring this reaction mixture for 10 min, the ene-dione 20 (1 g, 5 mmol) in dry ether (10 mL) was slowly added. Then the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with NH_4OH and NH_4Cl ($p^H \sim 9$) and then extracted with ether (3 x 30 mL). The crude product obtained after removal of the solvent was charged on a silica gel (10 g) column. Elution with 20% ethyl acetate - benzene removed the less polar impurities. Further elution with 30% ethyl acetate furnished the diketone 21 (680 mg, 60%) as a single isomer, bp 160°C/0.4 mm.

IR spectrum (neat), ν_{max}: 2950, 1740 (carbonyl) 1360 and 1150 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.94(3H,t,J=7Hz,-CH-CH_2-CH_3), 1.12(3H,d,J=7Hz, -CH-CH_3), 1.2-2.1(10H,m), 2.1-2.3(4H,m) and 2.6(2H,d,J=7Hz).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$): δ 220.8, 219.5, 49.3, 48.9, 47.6, 46.6, 37.8, 35.8, 35.3, 27.2, 25.4, 25.1, 24.8, 13.7 and 10.9.

Analysis for $C_{15}H_{22}O_2$ Calcd: C,79.58; H,10.19

Found: C,79.88; H,9.98

Sodium borohydride reduction of the diketone (21):

To a solution of 21 (600 mg, 2.5 mmol) in dry methanol (50 mL) was added sodium borohydride (500 mg, excess) in 10 mg lots at -10°C. Addition of sodium borohydride was stopped after the consumption of all starting material. Acetone (5 mL) was added to quench the excess borohydride. After 10 min methanol was removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave crude product which was filtered through small silica gel (5 g) column to furnish the lactol 22 (420 mg, 70%).

IR spectrum (neat), ν_{max}: 3750 (hydroxyl), 2950, 1460, 1280 and 1040 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.84(3H,t,J=7Hz,-CH-CH_2-$\underline{CH_3}$), 0.96(3H,d,J=7Hz,-CH-$\underline{CH_3}$), 1.14-2.1(16H,m), 2.4-2.9(3H,m) and 4.64-4.9(1H,m).

^{13}C NMR spectrum (25.0MHz, $CDCl_3$): δ 119.4, 86.9, 46.9, 46.4(2C), 44.4, 36.6, 35.3, 34.3, 30.4, 23.7, 22.9(2C), 10.8 and 10.4.

Low resolution mass spectrum for $C_{15}H_{24}O_2$

Calcd: m/e, 236.18

Found: m/e, 236.0.

4α-Methyl-5β-ethyl-trans-anti-cis-tricyclo[7.3.0.0^{2,6}]dodeca-11-ene-3-one (25):

To a solution of the lactol 22 (100 mg, 0.46 mmol) in dry benzene (10mL) was added p-toluenesulphonic acid (10 mg). The mixture was heated at 60°C for 1h and saturated sodium bicarbonate solution (2 mL) was added to it. The organic layer was separated and the aqueous layer was extracted with benzene (3 x 10 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The crude product obtained after removal of the solvent was charged on a small silica gel (5 g) column. Elution with 30% benzene-petroleum ether furnished the keto-olefin 25 (37 mg, 40%).

IR spectrum (neat), ν_{max}: 2950, 1740 (carbonyl), 1430, 1360, 1010 and 700 cm^{-1}.

^1H NMR spectrum (400 MHz, $CDCl_3$, Fig.IV-5): δ 0.96(3H,t,J=7Hz, -CH-CH_2-CH_3), 1.11(3H,d,J=7Hz,-CH-CH_3), 1.2-1.3(3H,m), 1.45-1.52(2H,m), 1.52-1.60(1H,m), 1.62-1.69(1H,m), 1.71-1.77(1H,m), 2.29-2.37(1H,m), 2.42-2.47(1H,m), 5.73(1H,d,J=7Hz, -CH=CH-) and 6.2(1H,d,J=7Hz, -CH=CH-).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$, Fig.IV-6): δ 220.0, 136.0, 120.8, 57.7, 50.1, 48.9, 44.4, 43.7, 38.6, 35.1, 27.2, 27.1,24.6, 15.7 and 11.8.

Analysis for $C_{15}H_{22}O$ Calcd: C,82.55; H,10.34

Found: C,82.51; H,10.16.

Further elution with 40% benzene-petroleum ether gave the keto-olefin 24 (28 mg, 30%).

IR spectrum (neat), ν_{max}: 2950, 1730(carbonyl), 1450, 1370, 1210 and 1010 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$, Fig. IV-3): δ 0.92(3H, t, J=7Hz, -CH-CH_2-CH_3), 1.08(3H,d,J=7Hz, -CH-CH_3), 1.16-2.08(1H,m), 2.3-2.64(2H,m), 3.04-3.36(1H,m), 5.24(1H,m,-CH=CH-) and 5.6(1H,m, -CH=CH-).

^{13}C NMR spectrum (25.0 MHz, $CDCl_3$, Fig.IV-4): δ 223.9, 133.0, 131.2,

50.5, 50.0, 46.9, 45.1, 40.9, 39.2, 33.6, 28.3, 24.5, 22.1, 12.6 and 10.7.

When the reaction was continued for an additional 2 h period, only keto-olefin 25 was formed in 60% yield.

Acid catalysed equilibration of (24):

To a solution of the cis-syn-cis-keto-olefin 24 (10 mg, 0.046 mmol) in dry benzene (1 mL) was added p-toluenesulphonic acid (1 mg). The mixture was heated at 60°C for 1 h and saturated sodium bicarbonate solution (0.5 mL) was added to it. The organic layer was separated and the aqueous layer was extracted with benzene (3 x 2 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The crude product obtained after removal of the solvent was bulb-to-bulb distilled at 140°C/0.8mm to furnish trans-anti-cis-keto-olefin 25 (6 mg, 60%). The TLC, IR and ^1H NMR spectra of this product were found identical with that of the product isolated from the dehydration of the lactol 22.

Base catalysed equilibration of (24):

Into a 10 mL three necked round bottomed flask fitted with dry N_2 gas inlet, rubber septum and mercury seal, were taken freshly prepared sodium methoxide (5 mg) and dry methanol (1 mL). After stirring for 5 min the cis-syn-cis-keto-olefin 24 (10 mg, 0.046 mmol) in dry THF (0.5 ml) was added through a syringe. The reaction mixture was stirred for 1 h at room temperature and then quenched with saturated NH_4Cl. The mixture was extracted with ether (3 x 5 mL) and the combined organic layer was washed and dried. The crude material was bulb-to-bulb distilled at 140°C/0.8mm to yield the keto-olefin 25, (5 mg, 50%), whose spectral data (IR and ^1H NMR) was identical with that of the authentic sample of 25.

Deuterium exchange studies on (25):

Into a 10 mL three necked round bottom flask fitted with dry N_2 gas

inlet, rubber septum and mercury seal, were taken freshly prepared sodium methoxide (5 mg) and MeOD. To this mixture the trans-anti-cis-keto-olefin 25 (10 mg 0.046 mmol) in dry THF (0.5 mL) was added through a syringe. The reaction mixture was stirred for 1 h at room temperature and then quenched with D_2O. The mixture was extracted with ether (3 x 5 mL) and the combined organic layer was dried over Na_2SO_4. The crude material obtained after removal of the solvent was filtered through a small silica gel (1 g) column. Elution with 30% benzene-petroleum ether furnished the deuterated keto-olefin (5 mg, 50%).

IR spectrum (neat), ν_{max}: 3075, 2950, 1740 (carbonyl), 1450 and 1220 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 1.0(3H,t,J=6Hz,-CH-CH_2-CH_3), 1.16(3H,s,-CD-CH_3), 1.2-2.5(12H,m), 5.7(1H,d,J=7Hz,-CH=CH-) and 6.2(1H,d,J=7Hz).

4α-Methyl-5β-ethyl-trans-anti-cis-tricyclo[7.3.0.0^{2,6}]dodeca-3-one (27):

The keto-olefin 25 (10 mg, 0.046 mmol) in ethyl acetate (3 mL) and 10% Pd/C (2 mg) were taken in a Parr-hydrogenation flask. After shaking the reaction mixture in H_2 atmosphere (10 psi) for 10 min. the catalyst was filtered and the filtrate was concentrated. The product was bulb-to-bulb distilled at 140°C/0.6mm to get pure saturated ketone 27 (9 mg, 90%).

IR spectrum (neat), ν_{max}: 2950, 1730 (carbonyl), 1440, 1360, 1160 and 1000 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$); δ 1.0(3H,t,J=7Hz,-CH-CH_2-CH_3), 1.24(3H,d,J=7Hz) and 1.30-2.30(18H,m).

4α-Methyl-5β-ethyl-cis-syn-cis-tricyclo[7.3.0.0^{2,6}]dodeca-3-one (26):

The keto-olefin 24 (10 mg, 0.046 mmol) in ethyl acetate (3 mL) was hydrogenated over 10% Pd/C (2 mg) catalyst at 10 psi for 10 min. Catalyst was

removed by filtration and the filtrate concentrated. The product was bulb-to-bulb distilled at 145°C/0.6 mm to get the ketone 26 (9 mg, 90%).

IR spectrum (neat), ν_{max}: 2950, 1740 (carbonyl), 1460 and 1160 cm^{-1}.

^1H NMR spectrum (100 MHz, $CDCl_3$): δ 0.96(3H,t,J=7Hz,-CH-CH_2-$\underline{CH_3}$), 1.14(3H,d,J=7Hz,-CH-$\underline{CH_3}$) and 1.20-2.7(18H,m).

Acid catalysed equilibration of (26):

To a solution of the ketone 26 (10 mg, 0.045 mmol) in dry benzene (1mL)was added p-toluenesulphonic acid (1 mg). The mixture was heated to 60-70°C for 1 h and saturated sodium bicarbonate solution (0.5 mL) was added to it. The organic layer was separated and the aqueous layer was extracted with benzene (3 x 5 mL). The combined organic layer was washed with water and dried. The crude product obtained after removal of the solvent was bulb-to-bulb distilled at 140°C/0.6mm to furnish the equilibrated product (6 mg, 60%), whose spectral data (IR and ^1H NMR) was found identical with that of the saturated ketone 27.

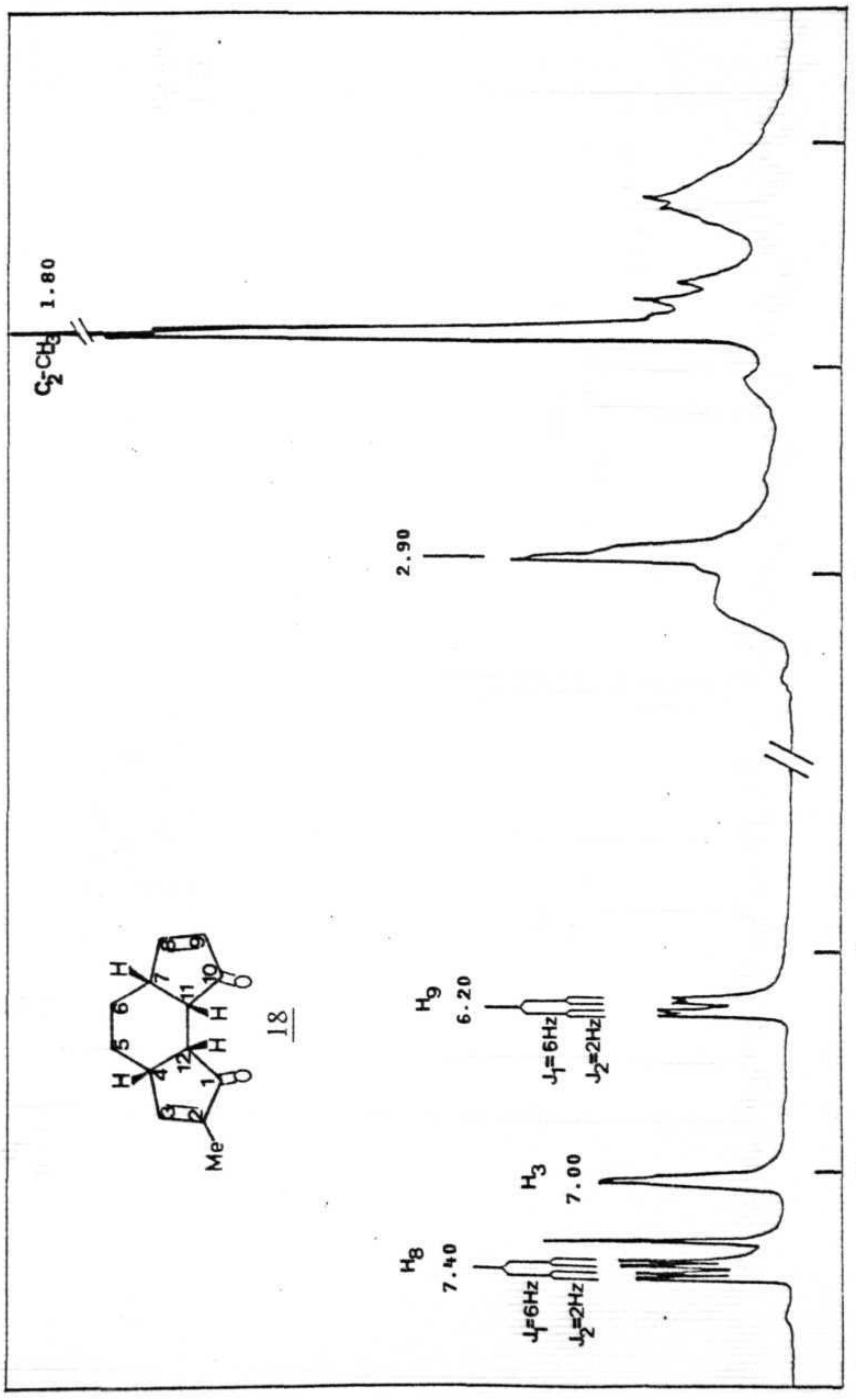


FIG. IV-1 : ^{1}H NMR (100 MHz) spectrum of 18.

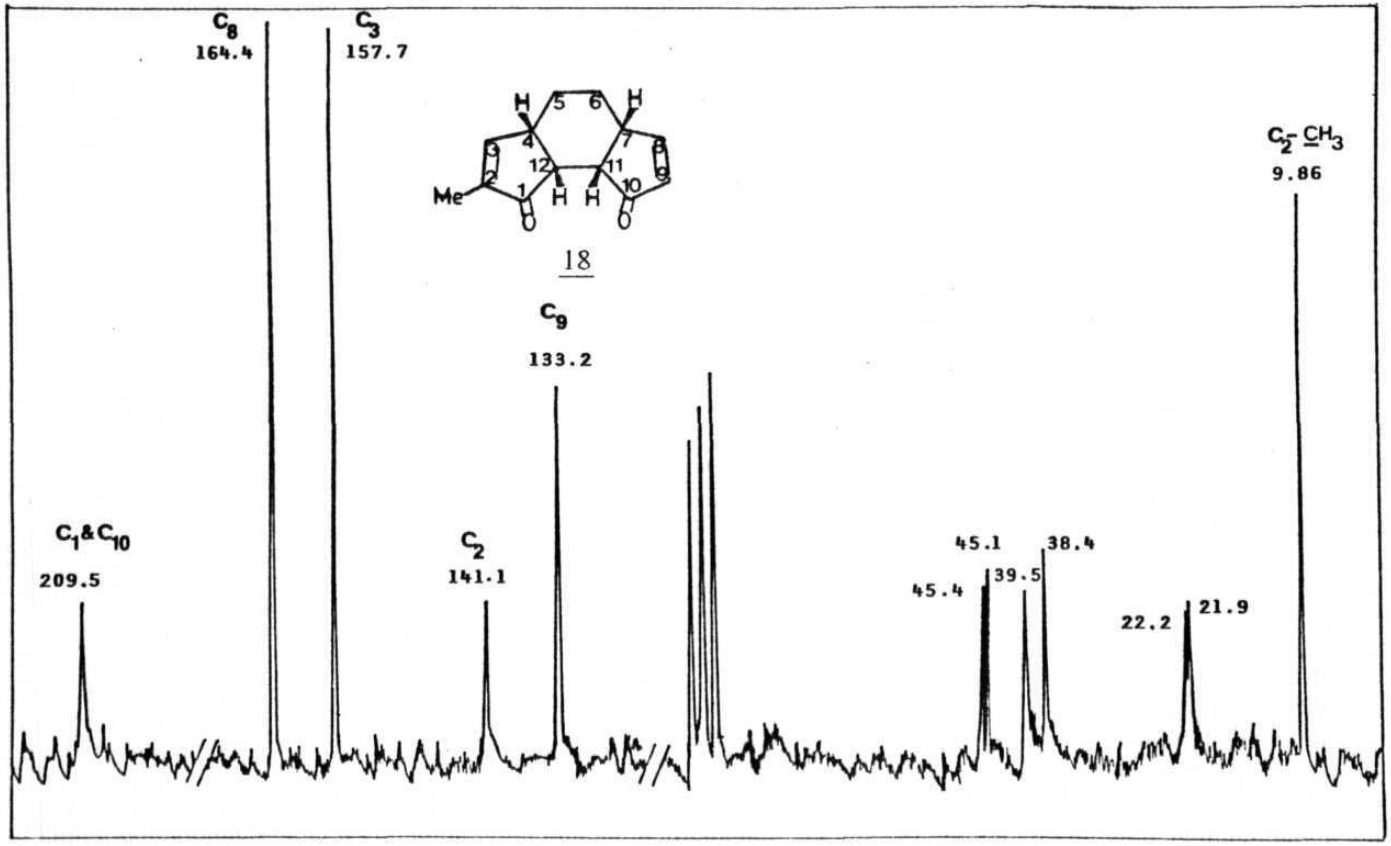
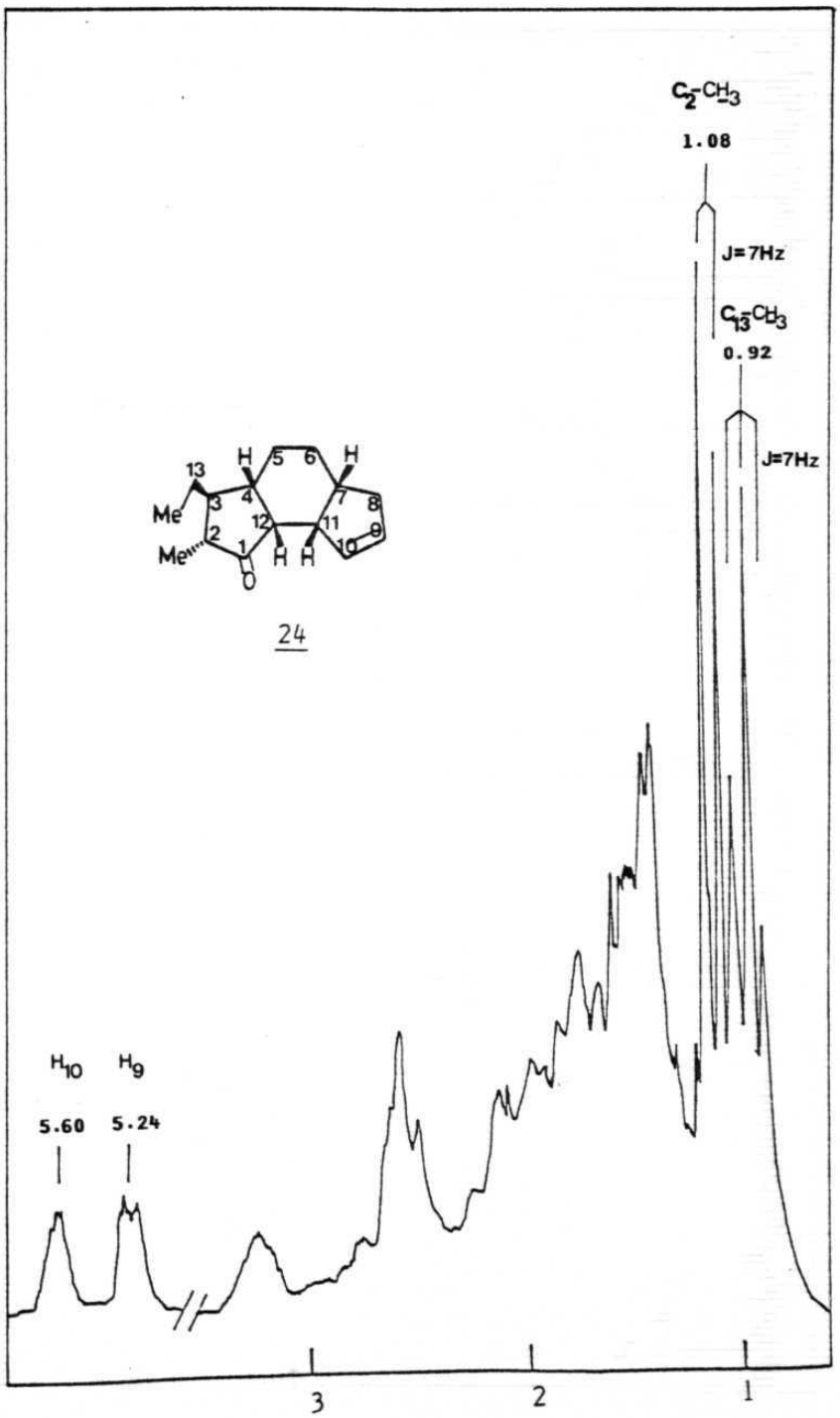


FIG. IV-2 : ^{13}C NMR (25.0 MHz) spectrum of 18.



24

FIG. IV-3 : ^{1}H NMR (100 MHz) spectrum of 24.

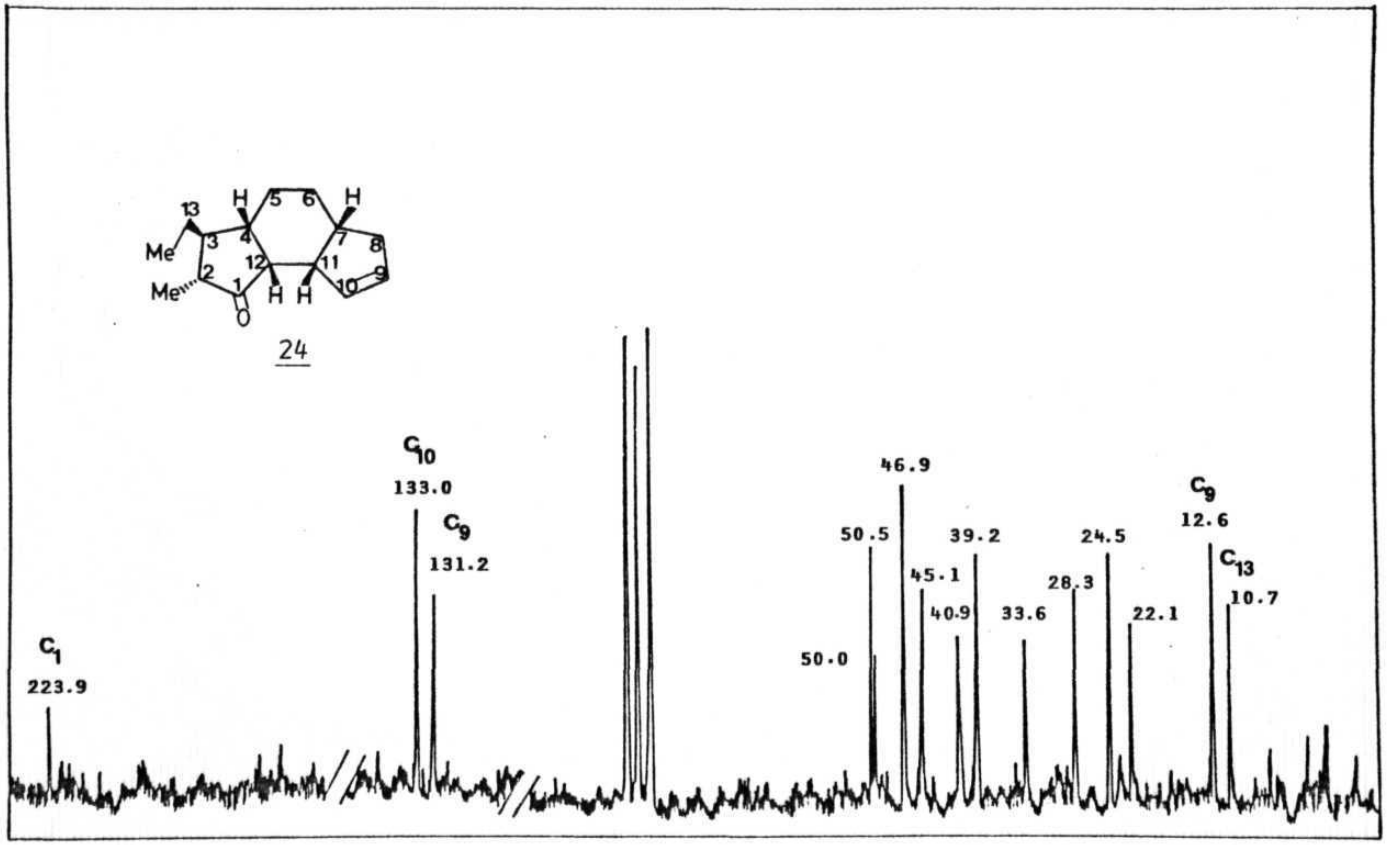
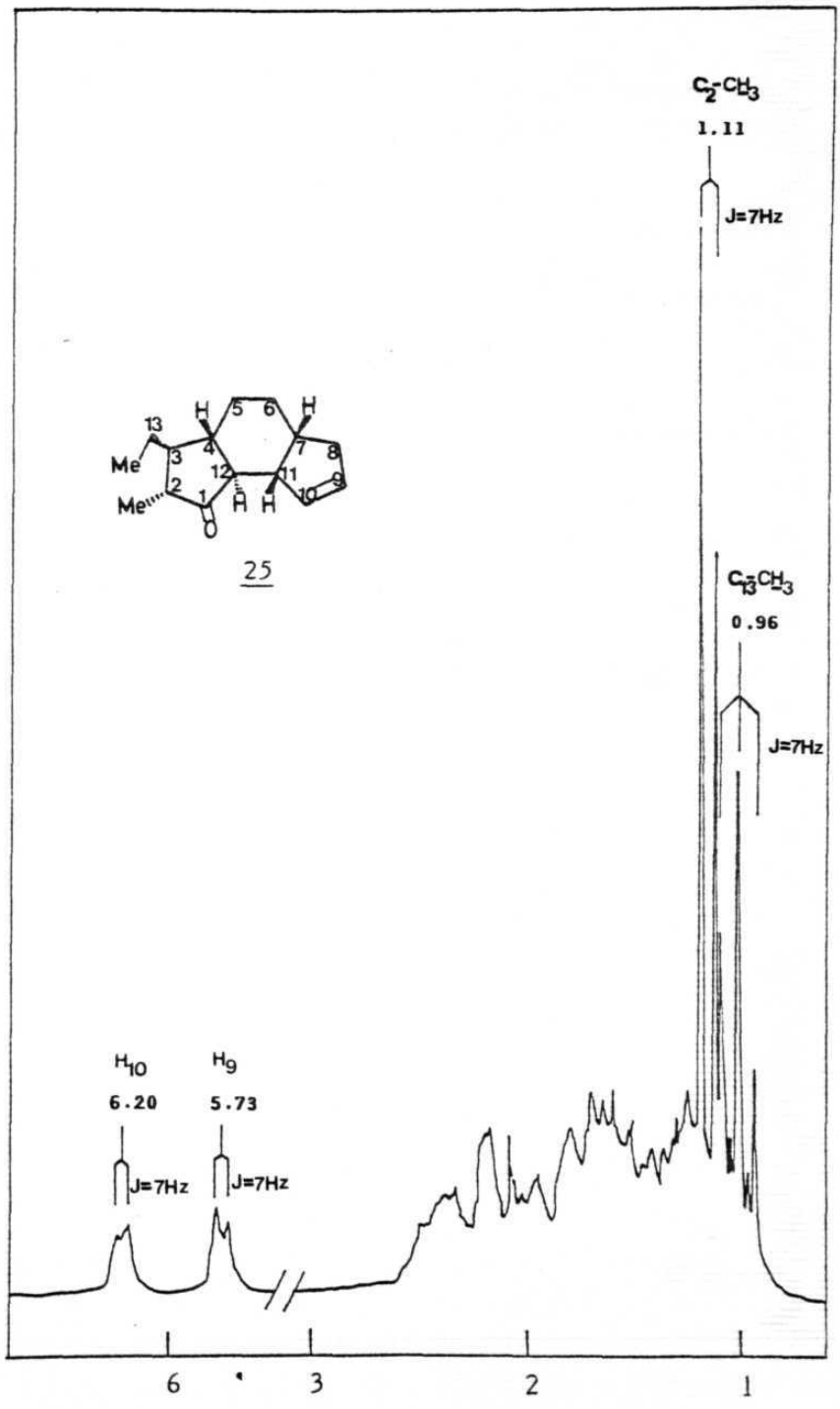


FIG. IV-4 : ^{13}C NMR (25.0 MHz) spectrum of 24.



25

FIG. IV-5 : ^{1}H NMR (100 MHz) spectrum of 25.

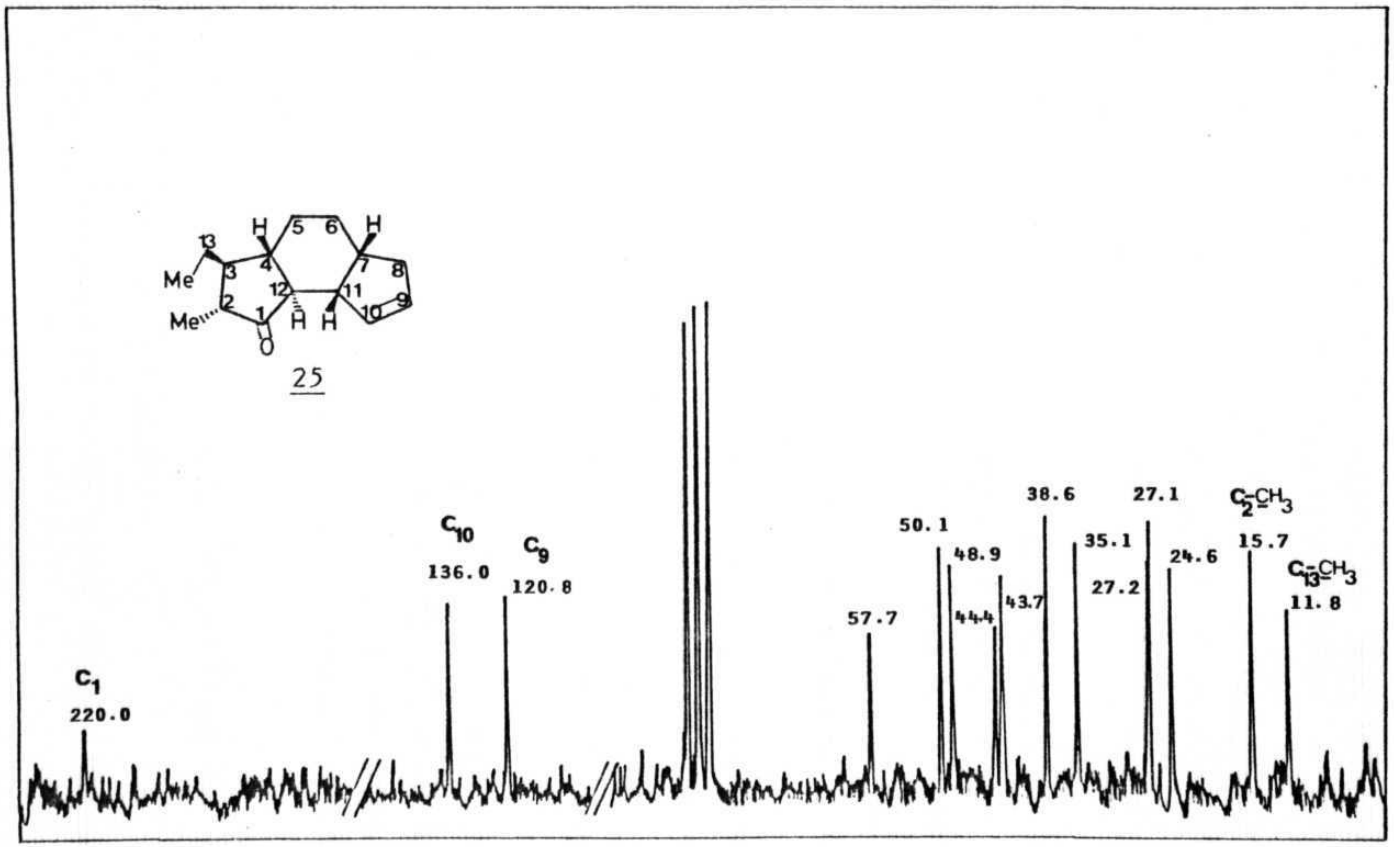


FIG. IV-6 : ^{13}C NMR (25.0 MHz) spectrum of 25.

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VITAE

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