NEW STRATEGIES FOR NATURAL PRODUCTS SYNTHESIS BASED ON TRICYCLO[5.2.1.$0^{2,6}$]DECANE RING SYSTEM

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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CERTIFICATE

Certified that the work embodied in this thesis entitled **"New Strategies For Natural Products Synthesis Based on Tricyclo[5.2.1.$0^{2,6}$]decane Ring System"** has been carried out by Mr. M. Praveen under my supervision and that the same has not been submitted elsewhere for a degree.

Goverdhan Mehta

(Thesis Supervisor)

Dean

School of Chemistry

Acknowledgments

It is with great pleasure that I thank Professor Goverdhan Mehta for his inspiring guidance and critical comments throughout my research tenure.

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

ABBREVIATIONS

Ac	:	acetyl
Ac_2C	:	acetic anhydride
AIBN	:	azobisisobutyronitrile
Bu	:	butyl
DCM	:	dichloromethane
DIBAL-H	:	diisobutyl aluminum hydride
Et	:	ethyl
HMPA	:	hexamethylphosphoramide
LAH	:	lithium aluminum hydride
Me	:	methyl
Ms	:	methanesulphonyl
PCC	:	pyridinium chlorochromate
PDC	:	pyridinium dichromate
py	:	pyridine
p-TSA	:	p-toluene sulfonic acid
r.t.	:	room temperature
THF	:	tetrahydrofuran
TsCl	:	p-toluene sulfonyl chloride

PREFACE

Natural products have always provided inspiration, challenge and opportunity to practicing synthetic organic chemists. As new and diverse range of structural types are unravelled from Nature, synthetic chemists are required to generate newer, shorter and conceptually novel strategies for their synthesis. Indeed, this complementary relationship between the structural elucidation of natural products and the urge to synthesize them has been at the vanguard of developments in synthetic organic chemistry. Among the various types of natural products, those possessing diverse carbocyclic ring systems hold special appeal to synthetic chemists as varied strategies need to be devised for carbocyclic ring construction with concomitant functionalization and installation of stereogenic centres. Natural products based on fused 6-5 carbocyclic ring systems are numerous and their synthesis attracted our attention and we have ventured to devise a short stereoselective approach to this ring system. These endeavours have culminated in the synthesis of three different types of natural products bearing the hydrindane system and form the main subject matter of this thesis.

The thesis entitled **"New strategies for Natural products synthesis based on Tricyclo[5.2.1.$0^{2,6}$]decane ring**

system" consists of two parts, I) Total synthesis of hydrindane based natural products, II) Diastereoselectivities in nucleophilic additions to tricyclo[5.2.1.$0^{2,6}$]decan-10-ones and potential application to natural products synthesis. Each part of the thesis is further subdivided into 1) Abstract, 2) Introduction, 3) Results and discussion, 4) Summary, 5) Experimental, 6) Spectra and 7) References.

The first part describes a new and general approach for the synthesis of cis-hydrindanes employing a highly stereoselective Haller-Bauer cleavage of readily available tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-diones and elaboration, mainly through functional group manipulation, of some of the cis-hydrindanes into a few important and interesting natural products, namely (±)-coronafacic acid, (±)-pumiliotoxin C and primnoeid sesquiterpenoid skeleton. This part also mentions the synthesis of chiral cis-hydrindane from chiral tricyclo[5.2.1.$0^{2,6}$]decane derivative obtained from the corresponding racemic tricyclic derivatives via enzymatic resolution method.

The second part of the thesis is concerned with the diastereoselective studies in nucleophilic additions to tricyclo[5.2.1.$0^{2,6}$]decanone systems and the (Z)-Vinyl alcohol obtained as a major product during the diastereoselective addition of the vinyl grignard to

tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one has been elaborated to 5,6,5 fused system, an important building block for many natural products, via an oxy-Cope protocol.

Part I

Total Synthesis of Hydrindane Based Natural Products

I.1. ABSTRACT

A new and general approach for the construction of functionalized cis-hydrindanes employing hydroxide mediated Haller-Bauer cleavage of abundantly available tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-diones has been developed. The efficacy of this approach has been demonstrated through the synthesis of a diverse range of cis-hydrindanes 22, 29-34 from the corresponding tricyclo[5.2.1.$0^{2,6}$]decan-10-ones 9-13.

We have further elaborated the most readily available tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 9 to three important and interesting natural products, namely (±)-coronafacic acid 40, (±)-pumiliotoxin C 41 and primnoeid-type sesquiterpene skeleton 67.

Our approach to coronafacic acid 40 emnated from tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 9 via cis-hydrindanone 22. Allylic oxidation of 27 after protecting the carbonyl group furnished enone 47. The enone 47 was further subjected to Wittig ethylidation and regio- and stereoselective hydrogenation to give 49. The ketal ester 49 on hydrolysis furnished (±)-coronafacic acid 40, which was found to be identical with the natural product.

To achieve a synthesis of pumiliotoxin C 41 cis-

hydrindanone 23 was considered to be the most appropriate precursor. The ester functionality in 25, having correct stereochemistry at the three contiguous centers for the synthesis of 41, was first transformed to a methyl group via the bromide 60. The methyl substituted hydrindanone 57 was elaborated in a 4 step sequence to pumiliotoxin C 41 through the intermediacy of bicyclic lactam 62.

For the synthesis of primnoeid skeleton, the cis-hydrindanone 23 was employed. Allylic oxidation of 25 after protecting the carbonyl group gave ester ketone 72. The ester ketone 72 on methyllithium addition gave diol 73, which on dehydration furnished the aromatic ketone 74. The ketone 74 smoothly underwent partial hydrogenation to 75. gem-Dialkylation on 75 delivered the Primnoeid skeleton 67.

We have further investigated the kinetic resolution of several of the tricyclo[5.2.1.$0^{2,6}$]decanes having a hydroxyl functionality at C_3 by employing, a) PLE catalyzed hydrolysis of the derived acetates 83-85 and b) transesterification of the alcohols 14, 81 and 82. The results have been moderately successful in providing access to chiral tricyclo[5.2.1.$0^{2,6}$]decane derivatives, The chiral alcohol (+)-14 has been elaborated in three steps into chiral cis-hydrindanone (+)-22 through Haller-Bauer methodology.

I.2. INTRODUCTION:

The investigations into the chemistry of "natural products" have not only been an essential element in man's endeavour to unravel the mysteries of the living world, but at the same time these studies have constantly refreshed and enriched the very fabric of organic chemistry itself, imparting new ideas and stimulating new directions in which the subject may grow. Natural product chemistry has undergone an explosive growth during the latter half of the current century. This has been brought about by a number of factors; one of which has been the isolation and characterization of growing number of products from natural sources[1] as a result of availability of newer techniques of isolation and purification. Further, the advent of new spectral tools, particularly ^{1}H, ^{13}C NMR (1D and 2D) and X-ray crystallography have made the structure determination a fairly routine exercise. The observation that a very large number of natural products, though scarce from natural resources, possess wide ranging biological activity has stimulated synthetic chemists interest in these compounds. Natural products also serve as lead compounds for preparing an array of synthetic analogues for biological screening. Thus, a combination of potential applications and intellectual challenge associated with their syntheses have brought natural products into the centre stage of

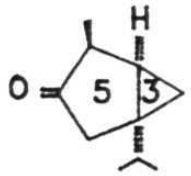
contemporary organic chemistry research.

Over the past quarter of a century, the accomplishments in the syntheses of natural products have been most impressive. The total synthesis of vitamin B_{12}[2a], gibberellins[2b], palytoxin[2c], avermectin[2d] and taxol[2e] are some of the representative examples of major accomplishments. Several recent monographs[3] document many of the notable achievements in the total synthesis of natural products.

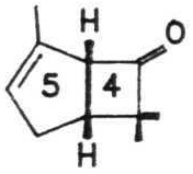
The most fascinating feature of natural products from synthetic chemist's perspective is the breathtaking structural diversity present in them in terms of number and size of rings, extent and range of functionalization and number of stereogenic centres. Of particular interest is the wide occurrence of carbocyclic ring systems composed of different combination of ring sizes 3 to 14. For example, five membered rings are encountered among natural products fused to rings of all sizes and compounds based on 5-3, 5-4, 5-5, 5-6, 5-7, 5-8, 5-9 and 5-11 fused systems have been isolated and examples are shown in the Chart 1.[4] Such carbocyclic networks are generally found among terpenes.

Natural products based entirely on the hydrindane (bicyclic 6,5 fused ring system) skeleton or embodying this system or its equivalent as the core unit in their structure

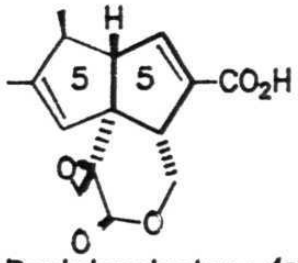
Chart 1



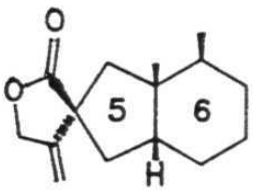
Thujone [4a]



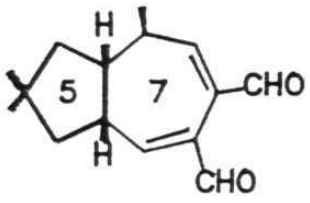
Filifolone [4b]



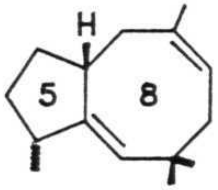
Pentalenolactone [4c]



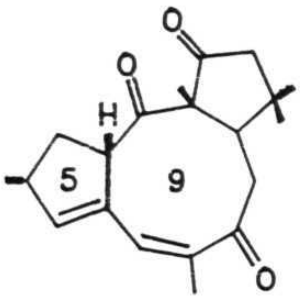
Bakkenolide [4d]



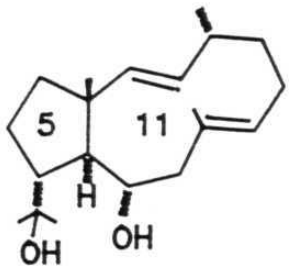
Velleral [4e]



Precapnelladiene [4f]



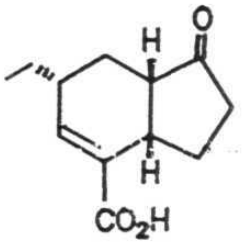
Jatrophatrione [4g]



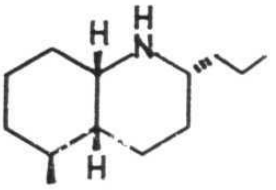
Dolabelladiene–diol [4h]

have been widely encountered among alkaloids, terpenes, steroids etc., **Chart 2**[5], and have evoked considerable synthetic interest in recent years.

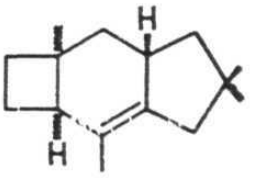
Chart 2



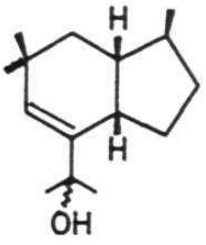
Coronafacic acid [5a]



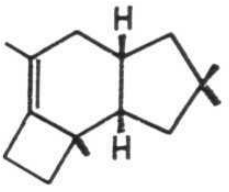
Pumiliotoxin [5b]



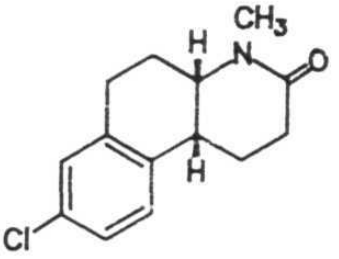
Sterpurene [5c]



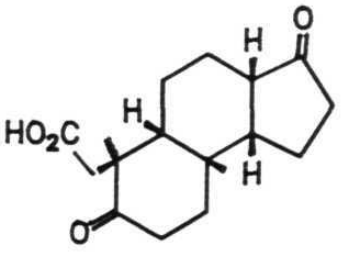
Brasilane Type [5d]



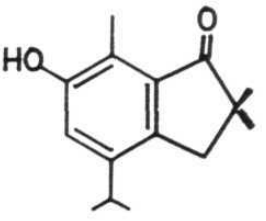
Protoilludine [5e]



LY 191704 [5f]



Barbacenane acid [5g]



Primnoeide Type [5h]

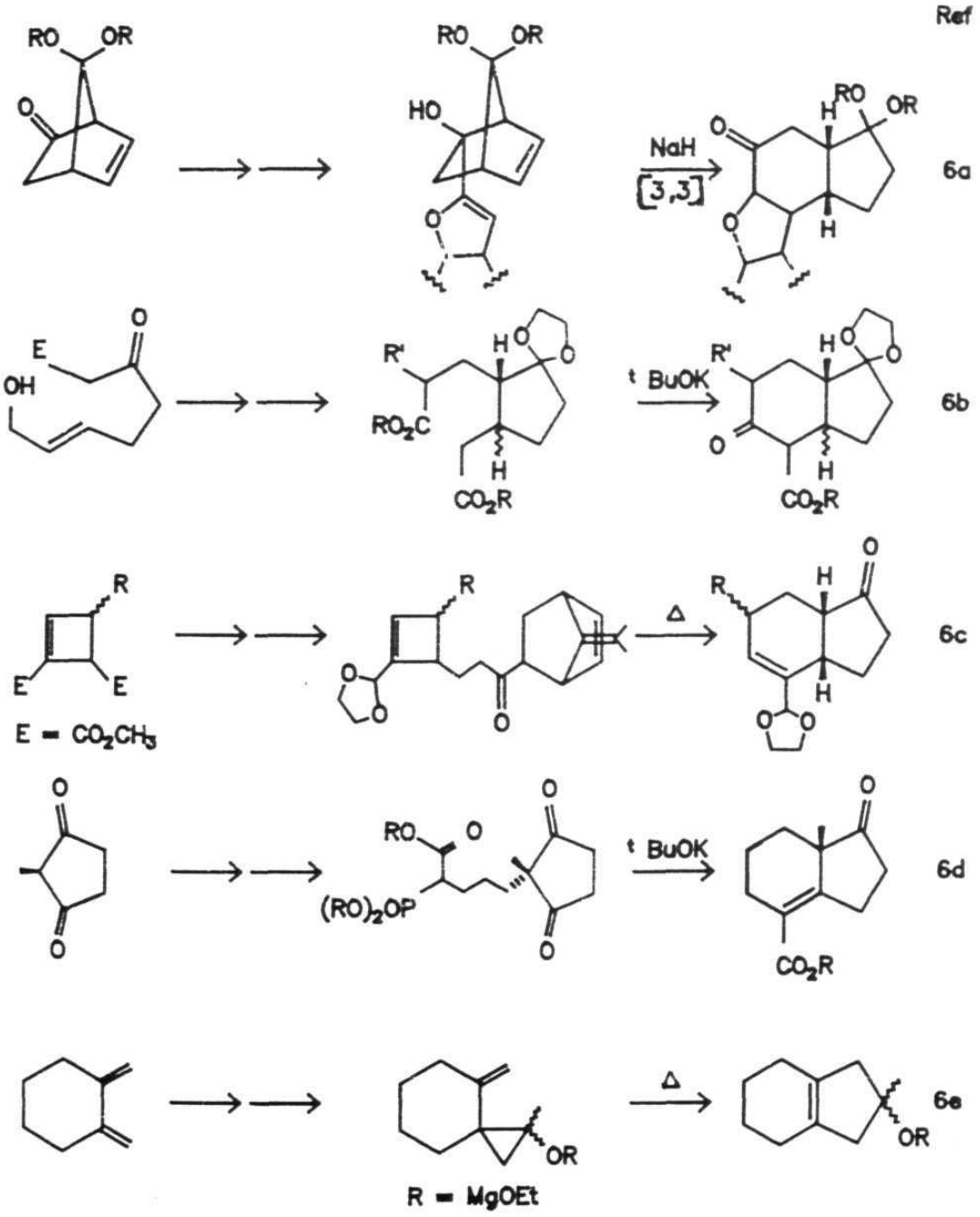
Both, cis and trans fused hydrindane moieties are present among the natural products. Many of these compounds also exhibit biological activity and are endowed with diverse functionalization and stereochemical patterns which further enhanced their synthetic appeal.

Several synthetic routes have been developed for the construction of the hydrindane ring system. Many of them are directed towards a specific target molecule. A selection of some of the approaches, both classical and modern ones, is displayed in Scheme 1.[6] We have not included here the classical indanone synthesis employing aromatic precursor. In general, these approaches lead to a mixture of cis and trans-hydrindane products. Synthetic methodologies that can stereoselectively deliver only cis-hydrindanes are very few.

We became interested in the total synthesis of some of the cis-hydrindane based natural products depicted in Chart 2. As methods for accessing cis-hydrindane ring system were not readily available in the literature, we decided to first develop a new, reliable, general and stereoselective route to this system. We also expected that such a route would generate enough functionality on the cis-hydrindane core to enable further manipulations en route to the natural products.

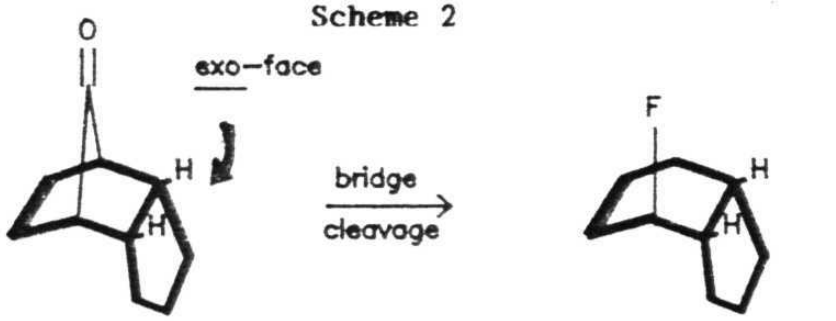
Our search for a general methodology for the generation

Scheme 1


Ref
RO
OR
O
HO
NaH
[3,3]
H
6a
E
OH
R'
RO2C
t BuOK
CO2R
6b
R
E = CO2CH3
Δ
6c
(RO)2OP
6d
OR
R = MgOEt
6e

of cis-hydrindanes led us to the endo-tricyclo[5.2.1.$0^{2,6}$]decan-10-one ring system 1, which appeared to us to be a repository of the cis 6-5 fused system (see heavy lines). Removal of the bridge, exploiting the reactive carbonyl functionality could unravel the cis-hydrindane framework 2 with adequate functionalization, Scheme 2.

Scheme 2



1 2 F = Functionality

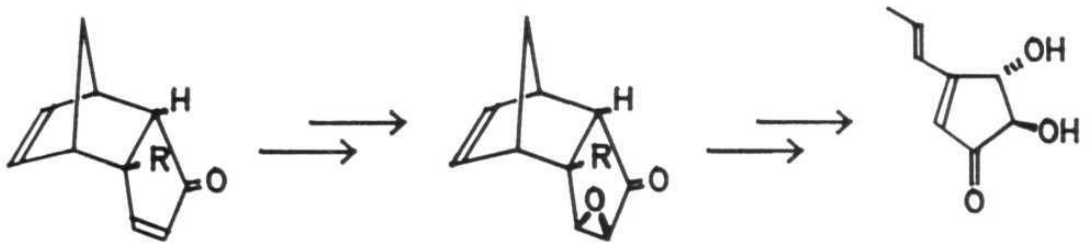
The advantage of employing the tricyclo[5.2.1.$0^{2,6}$]decan-10-one system lay in its ready accessibility in quantity and in a more embellished form in just a few steps. Further, the endo form 1 ensures that on the removal of the carbon bridge only the cis-hydrindane framework will be generated in a stereoselective manner. Another key advantage with the framework 1 is that its folded-shape enables stereoselective operations on it. Thus, chemical manipulations on 1 would result in the approach of the reagents/adducts on to the exo (convex) face only.

It may be mentioned here that the tricyclodecane ring system 1 has been employed previously in natural product

synthesis, but these efforts have been mainly directed towards:

- extraction of functionalized cyclopentene moiety via thermally (FVP) induced (4+2)-cycloreversion protocol. A typical example culminating in the synthesis of a cyclopentanoid natural product is shown in **Scheme 3**.[7] Several conceptually similar synthetic approaches have been reported in the literature.[8]

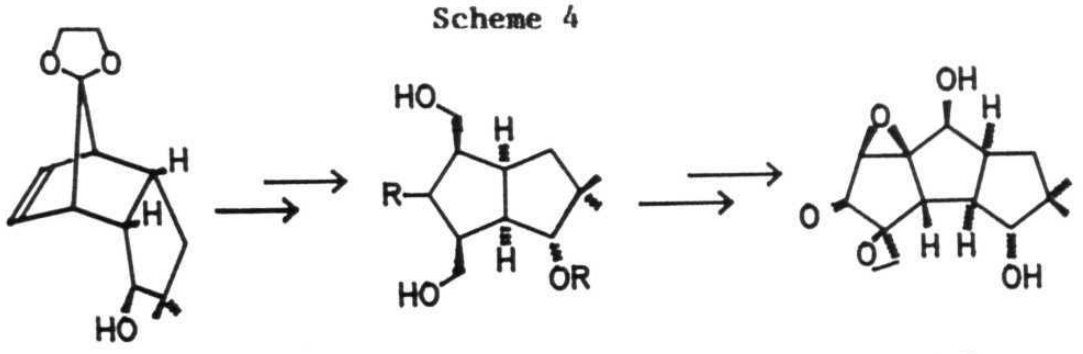
Scheme 3



Terrein

- extraction of diquinane moiety via oxidative scission (e.g., ozonolysis) of the norbornene double bond. This approach is exemplified through the synthesis of a linear triquinane natural product as shown in **Scheme 4**.[9]

Scheme 4

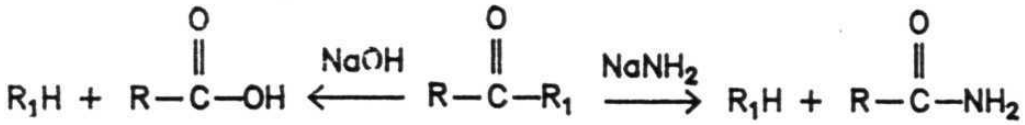


Coriolin

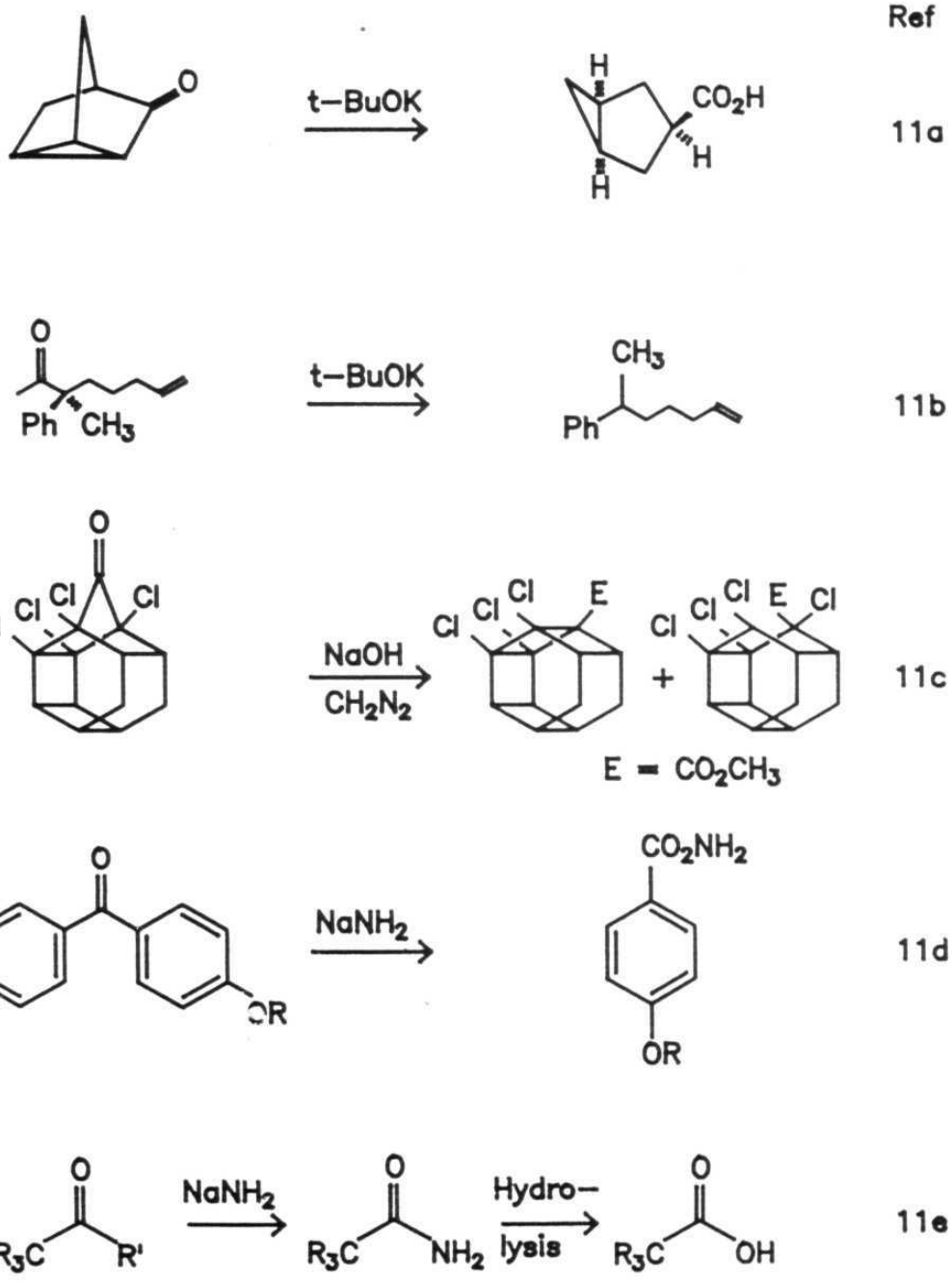
Thus, while cyclopentanoid and diquinane moieties have been extracted from the tricyclo[5.2.1.$0^{2,6}$]decane system, this ring system has not been exploited for accessing the cis-hydrindane moiety so far. As mentioned above, transformation of the tricyclo[5.2.1.$0^{2,6}$]decan-10-one moiety to the cis-hydrindane system requires the removal/scission of the carbonyl bearing bridge and we considered various options for this purpose. Baeyer-Villiger oxidation-hydrolysis and Schmidt fragmentation are two reactions that immediately attracted our attention. However, both these processes were expected to cause excessive functionalization and possibly rearrangements during the bridge scission operation. In our scheme of things, we required the carbonyl bridge scission with minimal functionalization. In this context, we chose the Haller-Bauer cleavage as the key reaction, which despite its rich potential has been only marginally exploited in synthesis.

Haller-Bauer reaction is a classical organic reaction in which non-enolizable ketones undergo C-C bond cleavage in the presence of a base like sodamide or sodium hydroxide to furnish an amide or an acid depending upon the base used, Scheme 5.[10]

Scheme 5



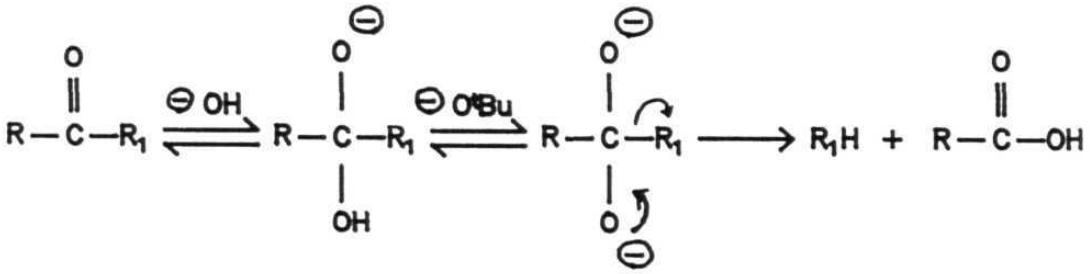
Scheme 6


Ref
t–BuOK
CO2H
11a
Ph
CH3
t–BuOK
11b
Cl
E
NaOH
CH2N2
E = CO2CH3
11c
RO
OR
NaNH2
CO2NH2
11d
R3C
R'
NaNH2
NH2
Hydro–
lysis
OH
11e

The Haller-Bauer reaction has been applied to many non-enolizable ketones and when applied to certain types of compounds, it has the potential for considerable synthetic utility. A few examples are shown in Scheme 6.[11] Haller-Bauer reaction is sometimes observed as a competing reaction during the Favorski rearrangement in bridged polycyclic ketones (see, Scheme 6).[11c] A variety of bases and solvents have been used for performing the reaction. It is one of the few general methods for the synthesis of tertiary carboxamides, which are useful as intermediates for the preparation of tertiary carboxylic acids, Scheme 6.[11e]

Extensive studies have been carried out on the regioselectivity and mechanism of the Haller-Bauer reaction. The commonly accepted mechanism is shown in Scheme 7.[10]

Scheme 7



With the identification of the Haller-Bauer reaction as the key reaction for the carbonyl bridge scission in the tricyclo[5.2.1.$0^{2,6}$]decan-10-ones, a strategy for the general synthesis of cis-hydrindanes emerged. Giving

practical shape to this strategy required:

1. Rapid and convenient access to variably functionlized tricyclo[5.2.1.$0^{2,6}$]decan-10-one derivatives.

2. Demonstration of the efficacy and generality of the Haller-Bauer reaction for the bridge scission in the tricyclo[5.2.1.$0^{2,6}$]decan-10-ones and the extraction of cis-hydrindane moiety.

3. Elaboration, mainly through functional group manipulations, of some of the cis-hydrindanes in to a few natural products displayed in Chart 2.

4. Access to chiral cis-hydrindanone from the corresponding chiral tricyclo[5.2.1.$0^{2,6}$]decane derivatives, obtained via enzymatic resolution, by employing the Haller-Bauer methodology.

In the following section our accomplishments in pursuit f the above mentioned objectives are described.

.3. RESULTS AND DISCUSSION:

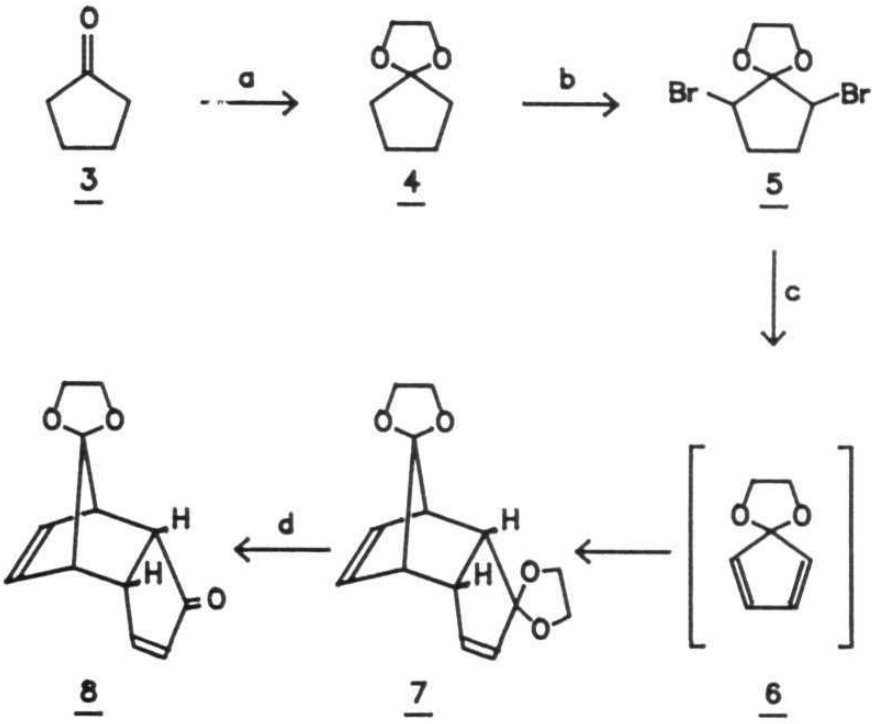
.3.1. Synthesis of substrates:

As indicated in the introduction, our first objective as to access through short, convenient steps, a range of ricyclo[5.2.1.$0^{2,6}$]decan-10-one derivatives. A literature earch revealed that tricyclo[5.2.1.$0^{2,6}$]dienone 8 can be eadily prepared from the commercially available yclopentanone 3 as shown in Scheme 8.[12] The tricyclic lienone 8 with its diverse functionalization and protected :arbonyl group appeared to be a suitable precursor for the ;ynthesis of tricyclo[5.2.1.$0^{2,6}$]decan-10-ones 9-13, substrates chosen by us for the Haller-Bauer reaction, Scheme 9. The tricyclic enone 8 could be prepared in good quantities as shown in the Scheme 8.

Carefully controlled bromination (2 equivalents) of :yclopentanone ethylene ketal 4, obtained from ketalization of cyclopentanone 3, gave the dibromoketal 5 . Dehydrobromination of 5 was smoothly effected with methanolic sodium methoxide to afford the dimer 7 via the intermediate cyclopentadienone ethylene ketal 6. Mild hydrolysis of 7 with dilute hydrochloric acid resulted in

the selective removal of one of the ketal groups to yield the enone 8 . This three step process produced the tricyclic enone 8 in 60-70% overall yield from cyclopentanone 3.

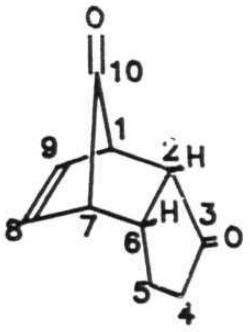
Scheme 8



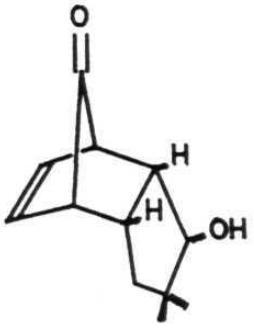
Reagents: a) $(CH_2OH)_2$, PTSA, Benzene, reflux, 9h, 90%; b) $2Br_2$, dioxane, r.t., 3h, 60%; c) NaOMe, MeOH, reflux, 6h, 70%; d) dil.HCl, r.t., 1h, 80%.

For the sake of convenience and expediency, we chose ive tricyclo[5.2.1.$0^{2,6}$]decan-3,10-dione derivatives 9, 10, 11, 12, and 13, Scheme 9 which could be prepared from the none 8 through suitable functional group manoeuvres.

Scheme 9



9



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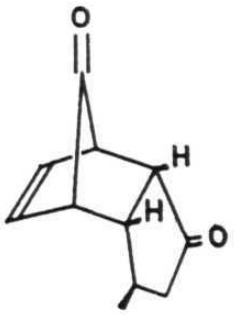

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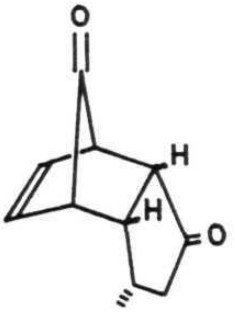
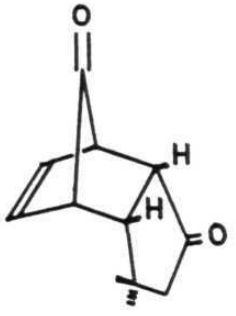


12

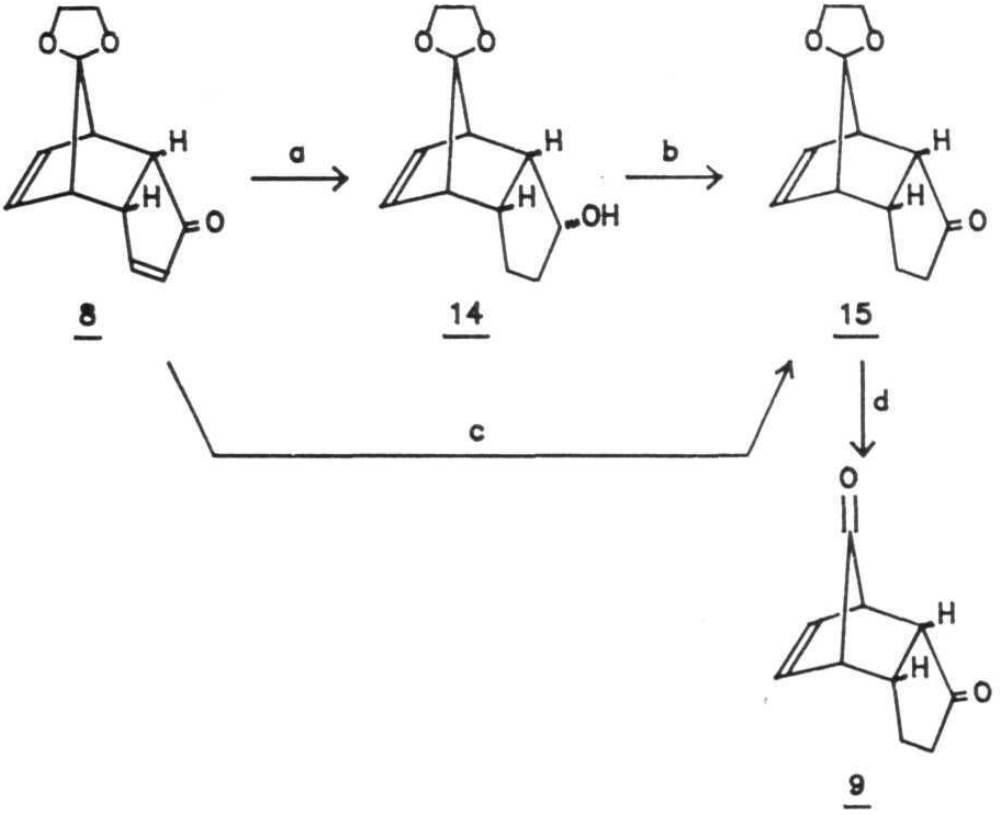


13

Reduction of enone 8 with excess sodium borohydride resulted in 1,4-reduction as well as 1,2-reduction to furnish the alcohol 14.[9] Only one diastereomer was formed as the carbonyl reduction occured from the exo-face to deliver the endo-alcohol 14. Oxidation of 14 with pyridinium

chlorochromate [13] gave the tricyclic keto-ketal 15. Alternatively, ketone 15 could also be prepared directly by 1,4-reduction of 8 with lithium trimethoxy aluminium hydride in the presence of cuprous bromide [14] as shown in **Scheme 10.**

Scheme 10

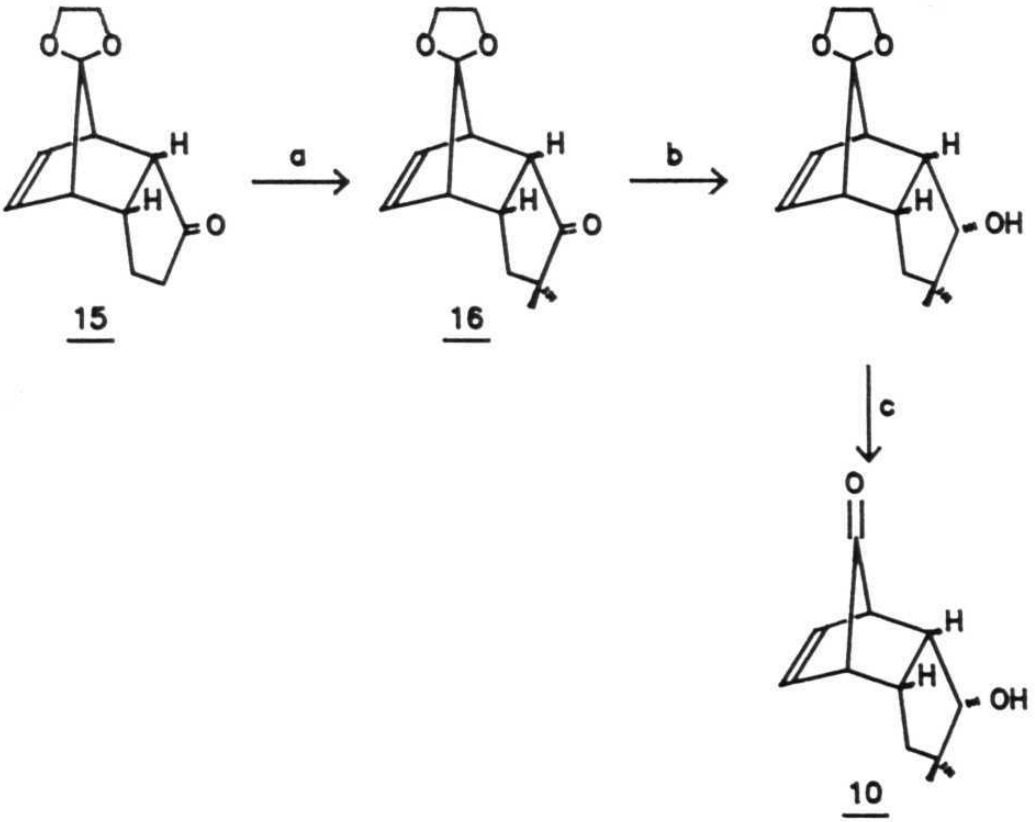


Reagents: a) $NaBH_4$, methanol, r.t., 2h, 99%; b) PCC, DCM, r.t., 7h, 80%; c) $LiAlH(OMe)_3$-THF, CuBr, -78°C, 30 min, 75%; d) 60% aq. H_2SO_4, DCM, 92%.

Hydrolysis of the ketal protecting group in 15 using 60% aq.sulphuric acid in dichloromethane provided the

tricyclic diketone 9 in 92% yield, **Scheme 10**, one of the substrates identified for the Haller-Bauer cleavage. The structure of 9 was revealed through its carbonyl absorptions at 1774 (7-ketonorbornenone) and 1732 (cyclopentanone) cm^{-1} due to the two carbonyls. Its ^{1}H NMR and ^{13}C NMR spectra (Fig I.1 and Fig I.2) exhibited the requisite resonances expected for the structure 9.

Scheme 11



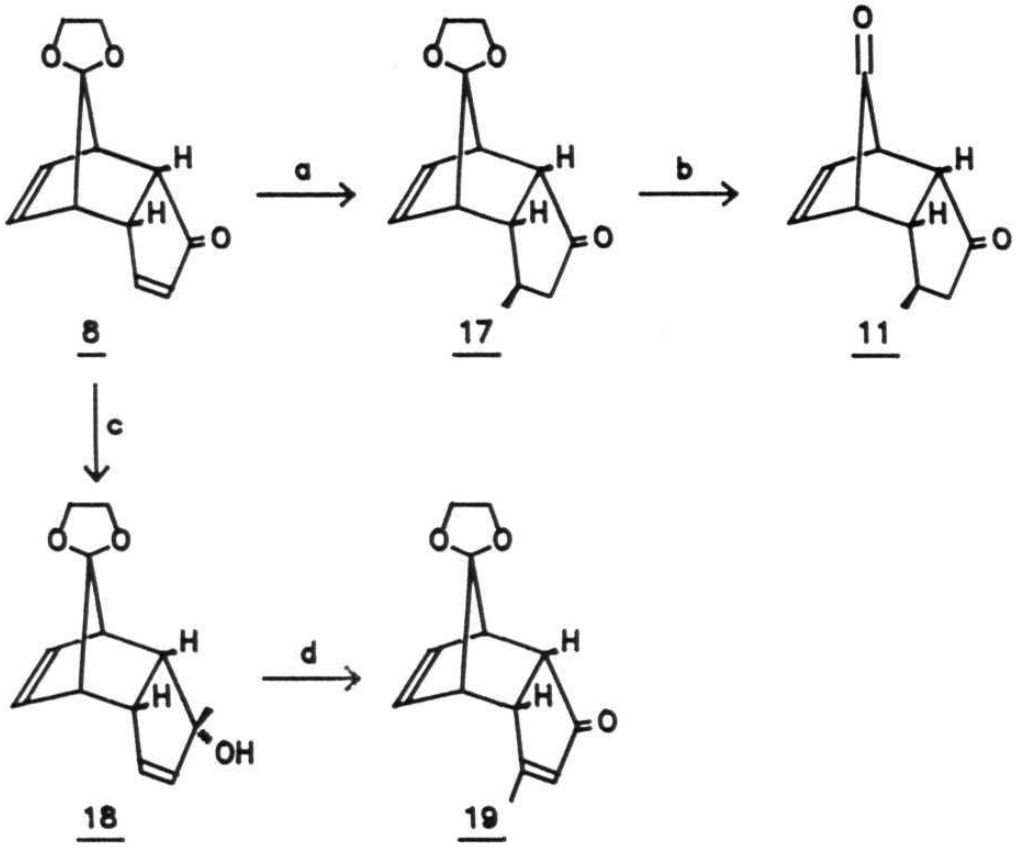
15 16 10

Reagents: a) t-BuOK, MeI, t-BuOH, reflux, 3h, 85%; b) $NaBH_4$, methanol, r.t., 3h, 99%; c) Amberlyst-15, moist acetone, r.t., 10h, 90%.

The tricyclic ketone 15 on exposure to potassium tert-butoxide in the presence of excess methyl iodide furnished the α, α'- dimethylated ketone 16 in 85% yield.[9] Stereoselective reduction of 16 with excess sodium borohydride followed by the removal of the ketal group via transketalization with moist acetone in the presence of amberlyst-15 furnished the endo-hydroxy ketone 10 in 90% yield, **Scheme 11.** As expected, the ^{1}H NMR spectrum of 10 exhibited a signal at δ 4.00 (1H) due to the proton attached to the hydroxy group. There were complementary ^{13}C NMR resonances at δ 83.2 and 202.1 corresponding to the carbon bearing the hydroxyl group and the carbonyl group, respectively.

Conjugate addition of lithium dimethyl cuprate to the enone 8 in the presence of cuprous bromide-DMS complex proceed stereoselctively and furnished a single diastereomer 17 having an exo-methyl group at C_5 in 68% yield.[15] As expected, its ^{1}H NMR spectrum exhibited a methyl doublet at δ 1.13 (J = 6.6 Hz) and the ^{13}C NMR spectrum had an additional carbon resonance (vide experimental). Hydrolysis of 17 using 60% aq.sulphuric acid furnished the diketone 11 in 90% yield, **Scheme 12.** The structure of 11 was in full agreement with ^{1}H and ^{13}C NMR spectral data, particularly the appearence of two carbonyl resonances at δ 216.9 & 199.9 due to the two carbonyl groups.

Scheme 12



8 17 11

18 19

Reagents: a) MeLi-CuBr, $(Me)_2S$, ether, -23°C, 30 min, 68%; b) 60% aq.H_2SO_4, DCM, r.t., 90%; c) MeLi, ether, r.t., 30 min, 90%; d) PCC, DCM, Celite, r.t., 30 min, 71%.

Two related tricyclo ketones 12 and 13 were also synthesized from 8. Addition of methyl lithium to 8 gave the tertiary alcohol 18. Pyridinium chlorochromate oxidation of 18 led to oxidative transposition [16] and formation of β-

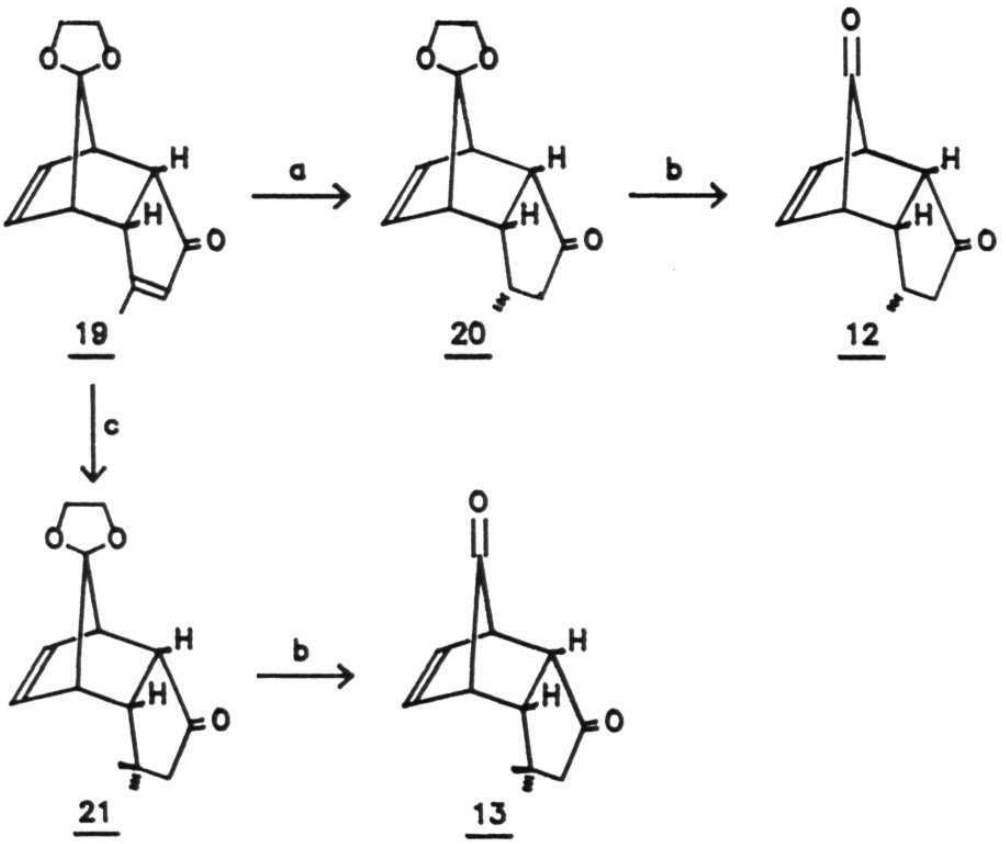
methyl substituted enone 19, **Scheme 12.** The structure of 19 with methyl at the β-position of the enone was arrived at on the basis of its ^{1}H spectrum which exhibited the characteristic deshielded methyl group at δ 2.00. The ^{13}C NMR spectrum confirmed this formulation.

The enone 19 smoothly underwent 1,4-reduction with lithium trimethoxy aluminium hydride to the endo- methyl substituted ketone 20 in the presence of cuprous bromide.[14] The stereochemistry of 20 was supported by the incisive analyses of the ^{1}H and ^{13}C NMR spectral data. The methyl group resonance in 20 was at δ 1.12 (J = 6.8 Hz). Hydrolysis of the ketal-ketone 20 furnished the diketone 12 in 94% yield, **Scheme 13.** The ^{1}H NMR spectrum exhibited a doublet at δ 1.20 (J = 6.8 Hz) corresponding to the methyl group and its ^{13}C NMR spectrum with resonances at δ 218.4 and 199.2 due to the two carbonyl carbons affirmed the structure of 12.

Addition of lithium dimethyl cuprate to the enone 19 in the presence of CuI and BF_3-etherate (Yamamoto condition)[15] furnished the gem-dimethylated compound 21. The presence of two methyl singlets at δ 1.03 and 1.11 in the ^{1}H NMR spectrum confirmed the structure of 21. On acid hydrolysis the dimethylated keto-ketal 21 furnished the diketone 13 in 94% yield, **Scheme 13.** The diketone 13, like other tricyclic diones, exhibited carbonyl absorptions at 1775 and 1730 cm^{-1}

in the IR spectrum and two carbonyl resonances at δ 217.1 and 196.4 in the ^{13}C NMR spectrum.

Scheme 13



Reagents: a) $LiAlH(OMe)_3$, CuBr, -78°C, 30 min, 60%; b) 60% aq.H_2SO_4, r.t., 2h, 94%; c) CuI, MeLi, ether, -15°C, 1h, 60%.

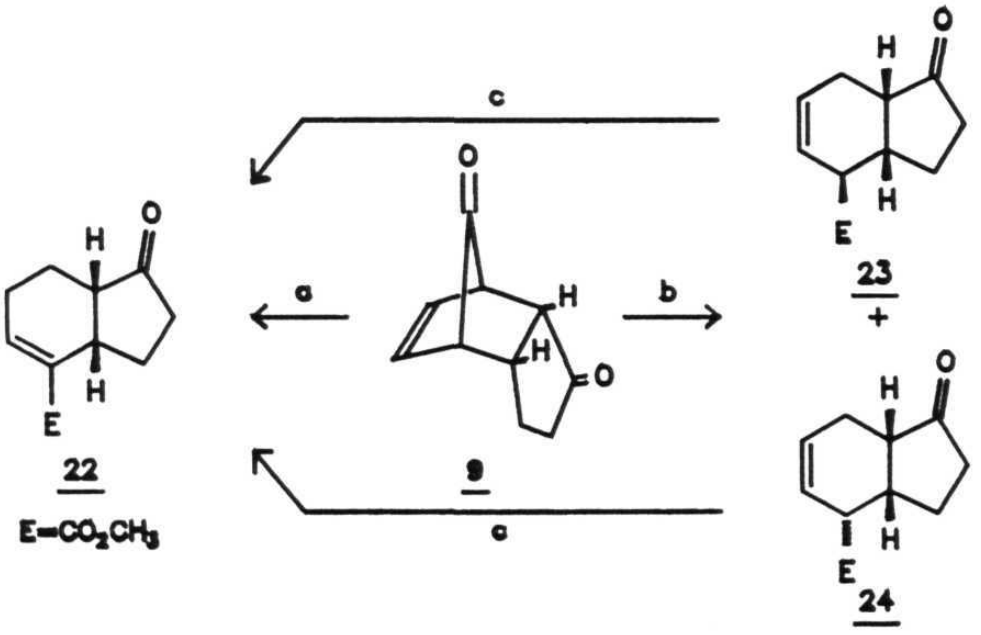
I.3.2. Haller-Bauer cleavage of tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-diones. Synthesis of cis-hydrindanes:

With the acquisition of five endo-tricyclo[5.2.1.$0^{2,6}$]decenone substrates 9 to 13, the stage was set to attempt the Haller-Bauer cleavage to obtain cis-hydrindane acids in acceptable yields. It was also decided for the sake of convenience that acids would be characterized as their methyl esters.

Refluxing the tricyclic dione 9 with 30% aqueous NaOH in benzene for 2-3 h resulted in smooth Haller-Bauer cleavage and esterification gave cis-hydrindanone ester 22 in 70% yield, **Scheme 14**. The structure of 22 followed from its ^{1}H and ^{13}C NMR data (Fig I.3 and Fig I.4). The ^{1}H NMR spectrum exhibited the β-proton of an α,β-unsturated ester at δ 7.03. This feature was confirmed by the ^{13}C NMR resonances at δ 140.5 and 131.5 due to the sp^2 carbon atoms of the conjugated ester double bond. Exclusive formation of 22 showed that the isolated double bond in the initially formed Haller-Bauer product had completely migrated into conjugation under the basic reaction condition. However, when 9 was treated with 1% aqueous NaOH in benzene at room temperature for a prolonged period (24h), a 7:3 epimeric mixture of cis-hydrindanone esters 23 & 24 was obtained after diazomethane esterification. The ^{1}H and ^{13}C NMR characteristics (Fig I.5 and Fig I.6) of this epimeric

mixture were fully consonant with the assigned structure. Pleasingly, double bond isomerization did not take place under these milder conditions but some epimerization of the ester group had obviously occured. The epimeric mixture of 23 and 24 was secured through their base catalysed conversion to the α,β-unsaturated ester 22, Scheme 14. Interestingly, the Haller-Bauer reaction showed high regioselectivity with preferential scission of $C_{(1)}$-$C_{(10)}$bond.

Scheme 14



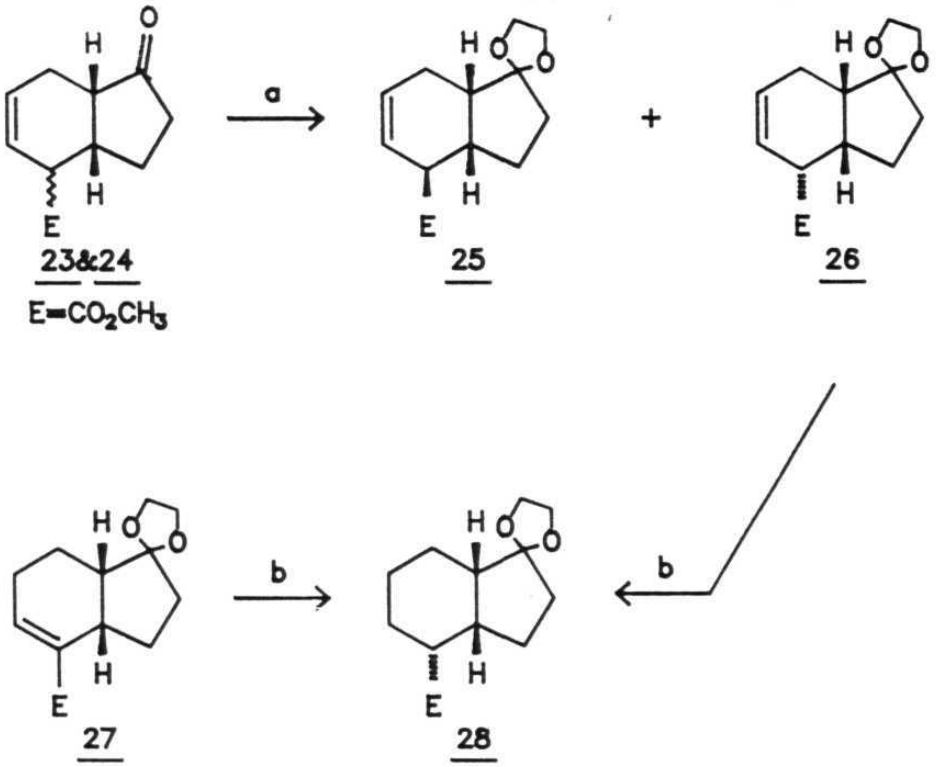
Reagents: a) 30% aq.NaOH, benzene, reflux, 2-3h & CH_2N_2, ether, 65-70%; b) 1% NaOH, benzene, r.t., 24h & CH_2N_2, ether, 65-70%; c) aq.NaOH, benzene, reflux, 3h, 90%.

The epimeric esters 23 and 24 did not separate cleanly on silica gel or alumina but the corresponding ethylene ketals 25 and 26 could be readily resolved and characterized (vide experimental). The stereochemistry of 23 and 24 was secured through the chemical correlation shown in **Scheme 15.** The ketal 27 derived from the α,β-unsaturated ester 22 was catalytically hydrogenated to furnish a single diastereomer 28 with an endo-ester group formed through the addition of hydrogen on the exo-face of this folded molecule. The hydrogenated diastereomer 28 was found to be identical with the product of hydrogenation of the ketal 26. Thus, the minor product formed during the Haller-Bauer cleavage of 9 under mild condition was the endo-isomer 24, the major isomer was therefore the exo-ester 23. This correlation and determination of stereochemistry was essential as we employed 23 for the synthesis of the natural product (±)-pumiliotoxin C 41 (vide infra).

The tricyclic diketones 11,12 & 13 were also treated with 30% aqueous NaOH-benzene mixture in a manner similar to 9. On esterification the corresponding cis-hydrindanone esters 29, 30 and 32,respectively, were isolated in each case in 60-70% yield, **Scheme 16.** In all the three cases, the double bond had migrated into conjugation with the ester moiety. In the case of 11, 12 and 13, the Haller-Bauer cleavage under less basic conditions was not attempted as it was not considered necessary. However, it should be possible

to access cis-hydrindanones without the migration of double bond in these cases also under appropriate conditions.

Scheme 15

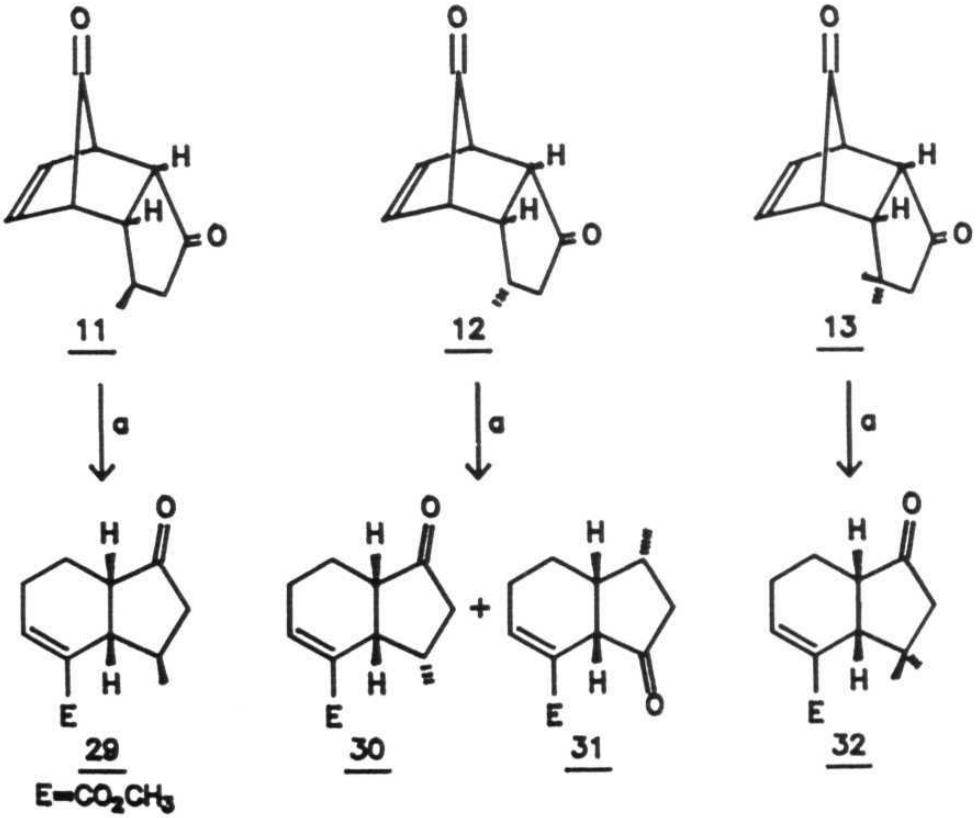


Reagents: a) $(CH_2OH)_2$, PTSA, benzene, reflux, 2h, 90%; b) Pd/C-H_2, ethyl acetate, r.t., 10 min, 95%.

Except in the case of 12, Haller-Bauer cleavage consistently exhibited high regioselectivity with preferential cleavage of the $C_{(1)}$-$C_{(10)}$ bond. In the case of the 12 ---> 30 transformation, a small amount (≈10%) of the other isomer 31 was detected but could not be isolated in pure form. The structures of 29, 30 and 32 followed fror

their ^{1}H and ^{13}C spectral data (Fig I.7-Fig I.12). The ^{1}H spectrum in all the three cases 29, 30 and 32 exhibited the β-proton of an α,β-unsaturated ester at δ 7.05, 7.14 and 7.02, respectively (Fig I.7, Fig I.9 and Fig I.11). The ^{13}C NMR spectra had the complimentary resonances in the expected olefinic region to fully support the formulations (Fig I.8, Fig I.10 and Fig I.12).

Scheme 16

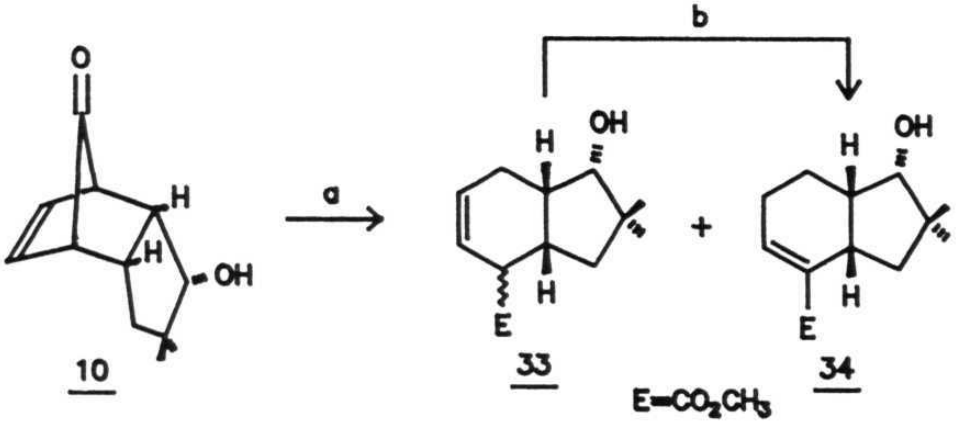


Reagents: a) 30% aq.H_2SO_4, benzene, reflux, 2-3h & CH_2N_2, ether, 65-70%.

Lastly, the remaining substrate 10 was subjected to

Haller-Bauer cleavage in the biphasic medium of 30% aqueous NaOH-benzene for 36 h. On esterification with diazomethane and column chromatography a mixture of bicyclic esters 33 and 34 (1:3) were obtained in 60-70% yield, Scheme 17.

Scheme 17



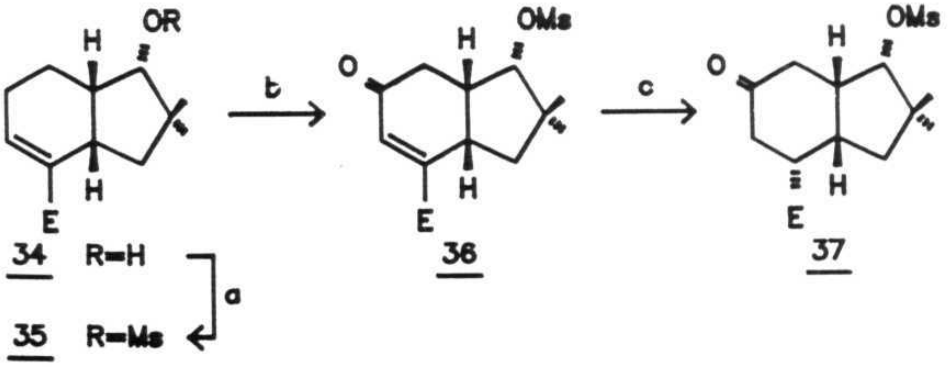
Reagents: a) 30% aq. NaOH, benzene, reflux, 36h & CH_2N_2, ether, 65-70%; b) $RhCl_3$, ethanol, reflux, 6h, 62%.

The two bicyclic esters 33 and 34 were found to be double bond regio-isomers with the α,β-unsaturated isomer 34 predominating over the β,γ-unsaturated isomer 33. The minor isomer 33 could be converted to the conjugated isomer 34 on reaction with $RhCl_3$ in ethanol[17], Scheme 17, thus establishing their relationship. The structure of 34 followed from its ^1H and ^{13}C NMR data (Fig I.13 and Fig I.14). The ^1H NMR spectrum exhibited the β-proton of an α,β-unsaturated ester at δ 7.02. This feature was confirmed by the ^{13}C NMR resonances at δ 139.8 and 133.4 due to the sp^2

carbon atoms of the conjugated ester double bond. The Haller-Bauer cleavage in the case of the hydroxy ketone 10 also exhibited high regioselectivity. However, before proceeding further it was considered prudent to unambiguously establish the structure of the major product 34, particularly in the context of the regiochemistry of the Haller-Bauer cleavage.

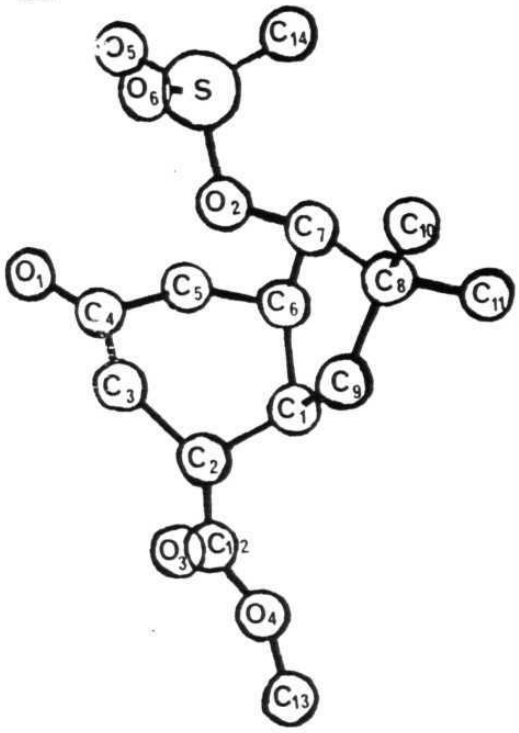
Since 34 was a liquid, it was decided to elaborate it to a more embellished derivative which would be crystalline and amenable to X-ray crystal structure determination. Consequently, the hydroxy-ester 34 was converted to the corresponding mesylate 35 but this too turned out to be a liquid. However, allyilic oxidation of 35 with PDC-t-BuOOH[18] reagent gave the enone 36, which was reduced over Pd/C-H_2 to furnish the crystalline keto-mesylate 37, Scheme 18.

Scheme 18



Reagents: a) MsCl, Pyridine, DCM, 0-5°C, 1h, 60%; b) PDC, t-BuOOH, Celite, benzene, r.t., 1h, 60%; c) Pd/C-H_2, ethyl acetate, r.t., 10 min, 95%.

PLUTO diagram of 37:

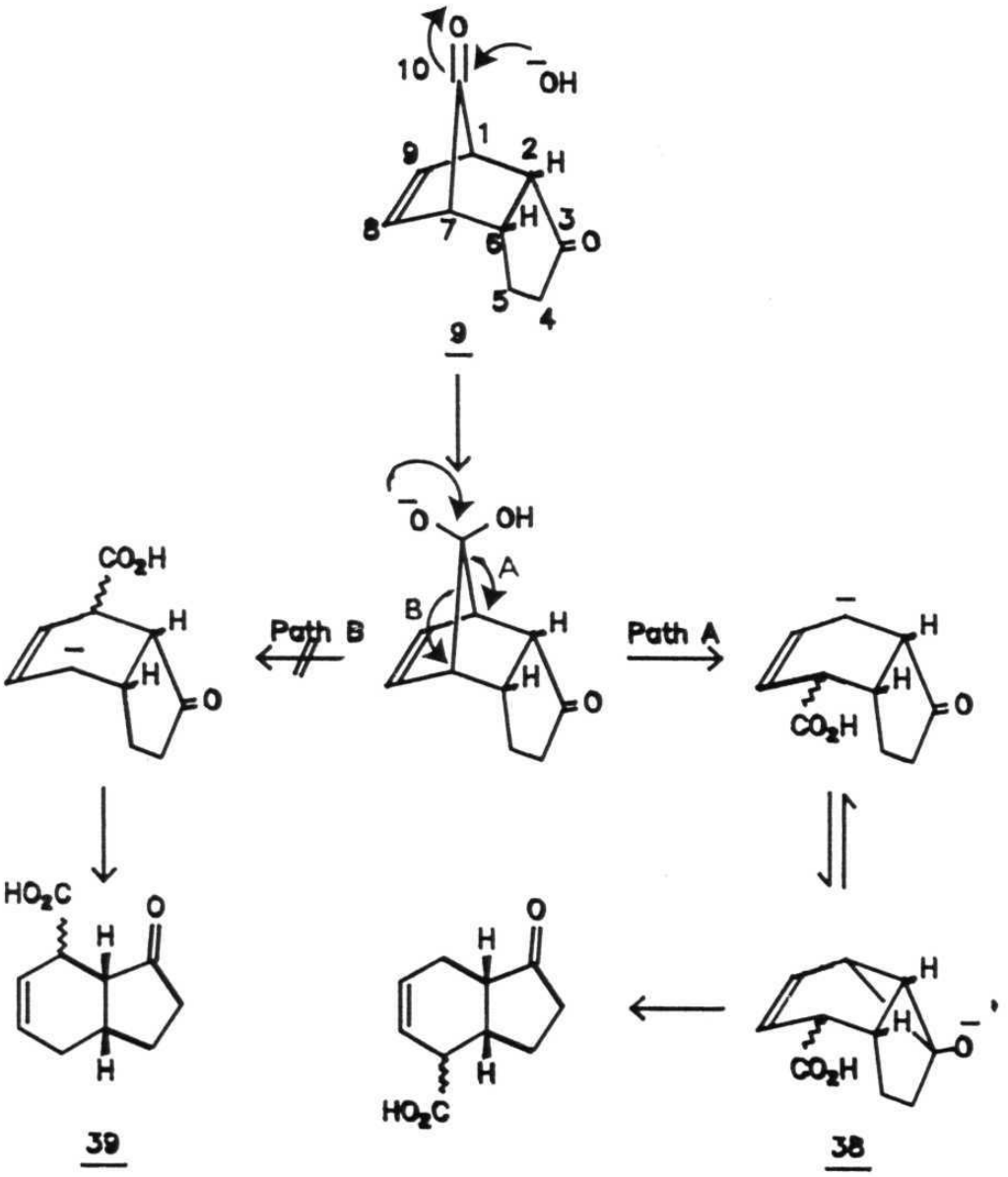


X-ray crystal data of 37: $C_{14}H_{22}O_6S$, crystallized from dichloromethane-hexane, ortho rhombic, space group Pbc21, a = 5.7215(9), b = 17.037(4), c = 31.480(7) Å, β = 90.00(1), V = 3068.58(2) $Å^3$; Z = 8, cu-kα radiation, = 1.5419 Å Intensity data were collected on an Enrat-Nonius CAD-4 diffractometer in the W-2θ mode. 3379 reflections were collected and 2307 reflections with I > 2σ(I) were used in refinement. The Structure has been refined using SDP package.[19] The structure is disordered and could not be refined beyond R = 0.18. We thank Prof. V. Pattabhi, University of Madras, Madras for X-ray crystal structure determination.

The ^{1}H NMR and ^{13}C NMR spectra of 37 (Fig I.15 and Fig I.16) were fully in consonance with its structure. The crystals of 37 were suitable for the X-ray crystal structure determination. The X-ray crystal structure of 37 [#], besides establishing the regiochemistry of the Haller-Bauer cleavage also reinforced our surmize that the reduction of these cis-hydrindanes takes place exclusively from the exo-face. A pluto plot of 37 is shown.

It was satisfying that all the tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one derivatives 9, 10, 11, 12 and 13 synthesized by us underwent smooth, regioselective Haller-Bauer cleavage to furnish the corresponding cis-hydrindanes in preparatively useful yields. What was more gratifying was the consistent observation of high regioselectivity in the Haller-Bauer cleavage. Among the two modes of bridge scission, pathway A is overwhelmingly preferred as product 39 from the pathway B is not encountered, **Scheme 19.** The high regioselectivity of the Haller-Bauer cleavage with preferential scission of $C_{(1)}$-$C_{(10)}$ bond could possibly arise through the remote effect of the bystander $C_{(3)}$-electron withdrawing substituent (carbonyl or hydroxyl). In the case of C_3 carbonyl group, the intermediate carbanion can stabilize through homo-enolate 38 formation.

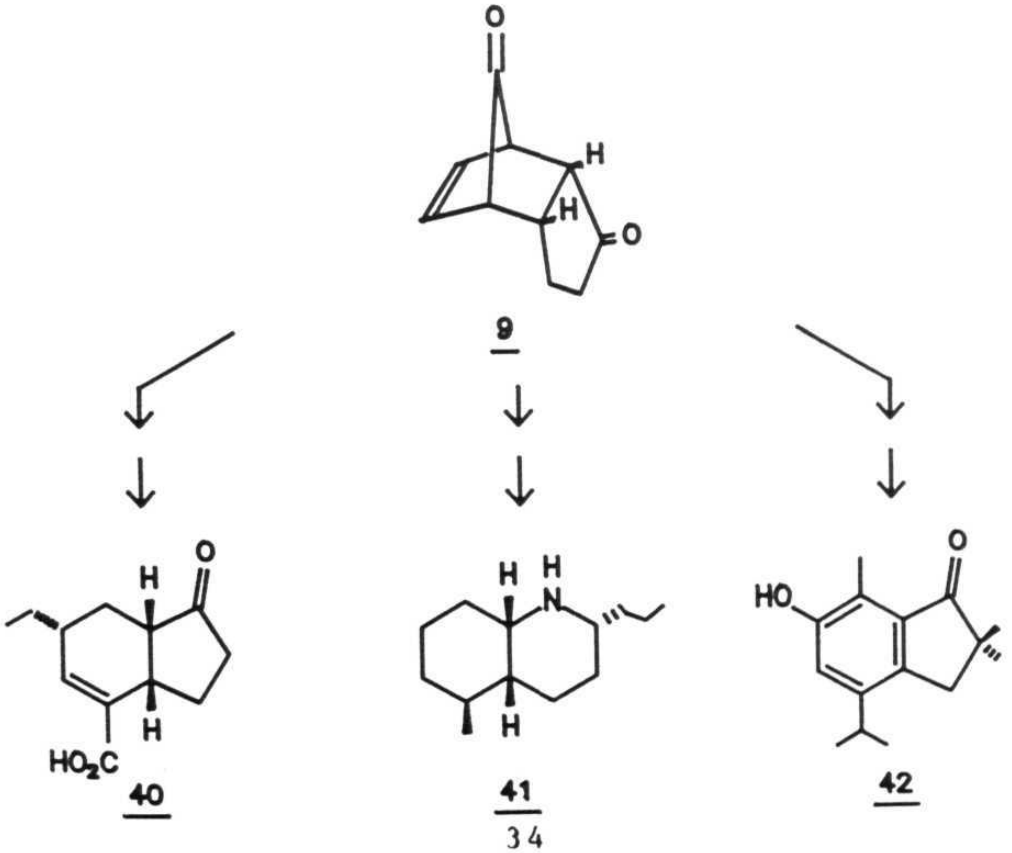
Scheme 19



I.3.3. Application of the cis-hydrindanones to the Synthesis of Diverse Natural Products:

Having demonstrated a short, general and reliable route to cis-hydrindanones, we set out to accomplish our third stated objective, namely to transform the cis-hydrindanone synthon to some natural products of contemperory interest. Earlier, in the **Chart 2**, we have shown several natural products that bear the perhydroindane core as a part of their structure. However for the present study we chose three different types of natural products for our synthetic pursuits, **Scheme 20.**

Scheme 20



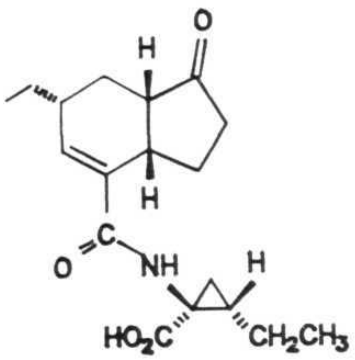
These were the fungal metabolite coronafacic acid 40, alkaloid pumiliotoxin C 41 and the primnoeide-type marine natural product 42. For all these target molecules, we chose the tricyclic[5.2.1.$0^{2,6}$]enedione 9 as the starting point and Haller-Bauer reaction as described above as the key reaction, **Scheme 20.**

Successful accomplishments of the total synthesis of all the three target molecules is detailed below.

a. Synthesis of (±)-Coronafacic acid 40:

Various strains of the bacterial phytopathogens Pseudomonas syringae pv.atropurpurea (Reddy & Godkin) and Pseudomonas syringae pv. glycinea (Coerper) produce the phytotoxic compound coronatine 43 when grown in liquid cultures. Solutions of coronatine 43 cause chlorosis on young leaves 2-3 days after application to wounded sites, a symptom that often characteristically surrounds infection sites on plants diseased by the pathogenic bacteria. Production of coronatine in situ is believed to be the cause of the disease symptoms. Mitchell[21] has reported & characterized coronafacic acid 40 together with norcoronatine 44 and N-coronafacoyl-L-valine 45 from the strain of P-syringae pv.glycinea, **Chart 3.**

Chart 3



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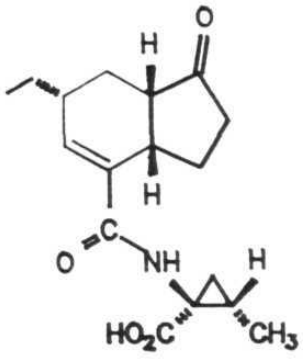

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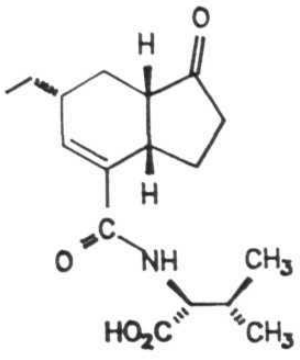

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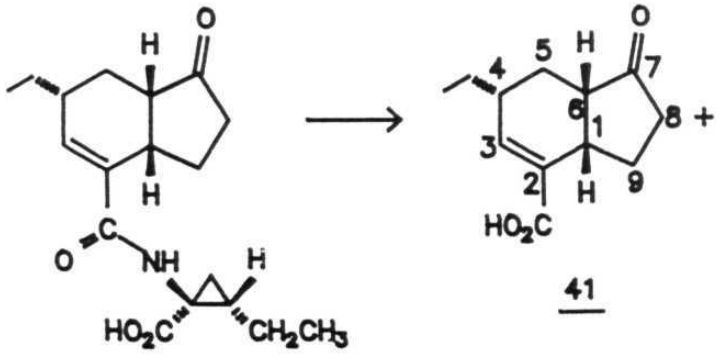
The structure of coronatine 43 was established by a combination of the single crystal X-ray analysis of coronafacic acid 40 and partial synthesis of coronatine 43, from natural coronafacic acid 40 and synthetic coronamic acid 46, **Scheme 21.** Determination of the absolute configuration of coronatine was based on the ORD measurements on coronafacic acid and X-ray diffraction analysis of the N-acetyl derivative of the enantiomer of coronamic acid.[22]

Scheme 21



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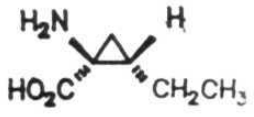

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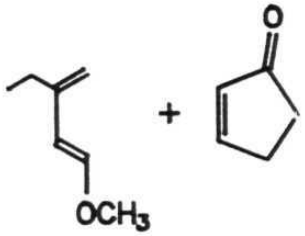
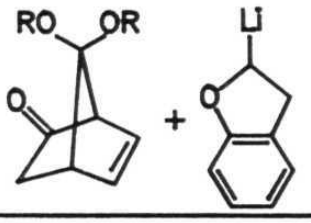
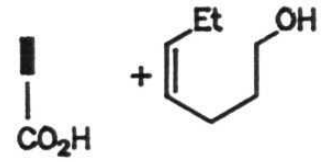
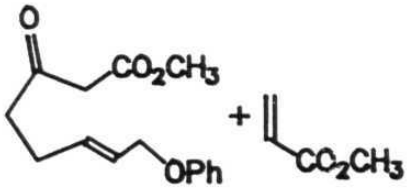
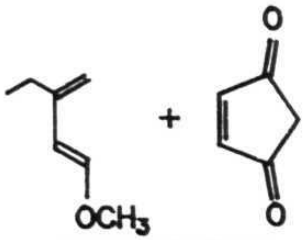
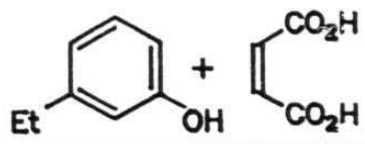
Table 1

Starting materials	Key step in the Approach	NO· of steps	Ref
	Diels–Alder	10	23c
	Oxy–Cope	14	23b
	2+2 cyclo addition	9	23c
	Pd catalyzed cyclization	11	23d
	Diels–Alder	10	23e
	Tandem Wessley Oxidation– Diels–Alder	12	23f

Synthesis of coronafacic acid 40, which also means the total synthesis of coronatine in a formal sense, has been the subject of considerable synthetic activity in recent years and several total synthesis have been accomplished.[23] A brief summary of few of the existing methodologies adopted for the synthesis of coronafacic acid 40 is considered desirable in order to put our own efforts in proper perspective, **Table 1.**[23] The main challenge in the synthesis of coronafacic acid 40 is the creation of the appropriately functionalized cis-hydrindane moiety and stereoselectively install the ethyl group on the six-membered ring. In our scheme of things, cis-hydrindanone 22 derived from the tricyclic[5.2.1.$0^{2,6}$]decandione 9 was chosen as the suitable precursor to attain (±)-coronafacic acid 40.

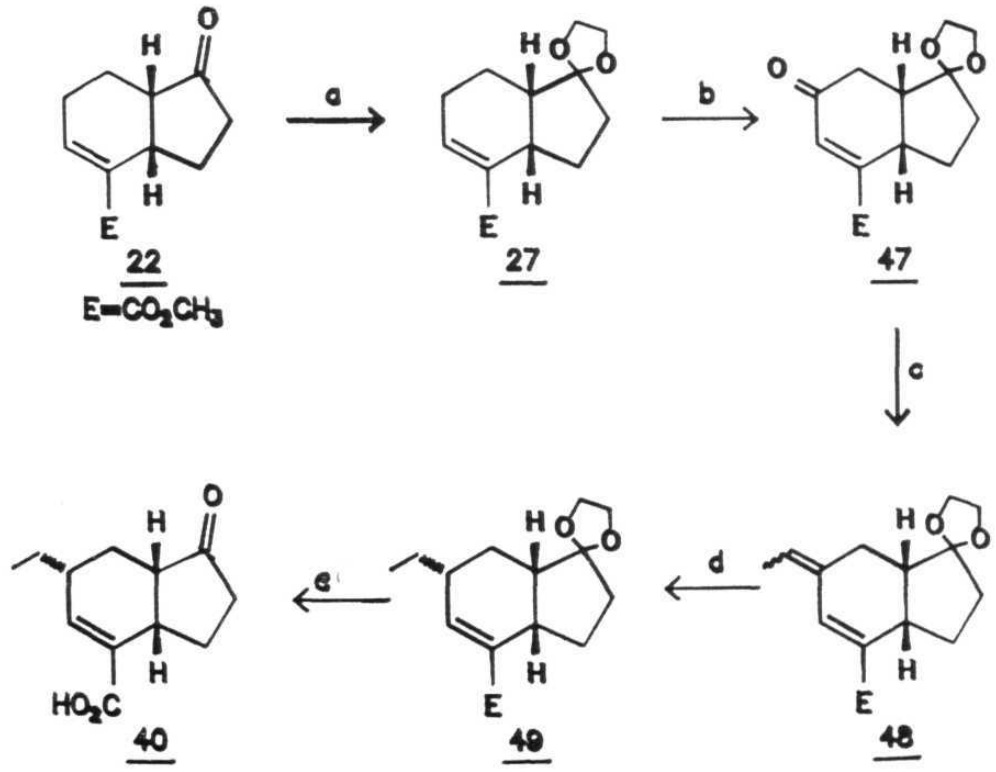
Protection of the carbonyl group in 22 using ethylene glycol in the presence of PTSA gave 27 in 95% yield. The structure of 27 was in full agreement with its ^{1}H and ^{13}C NMR data (Fig I.17 and Fig I.18). The ketal 27 was subjected to allylic oxidation with pyridinium dichromate and t-butyl hydroperoxide[18] in the presence of Celite to furnish the enone ester 47 in 60% yield, Scheme 22. The structure of the enone ester 47 was readily established through its ^{1}H and ^{13}C NMR data (Fig I.19 and Fig I.20). In particular, the ^{1}H NMR spectrum showed the presence of an olefinic proton at δ 6.70 and the ^{13}C NMR spectrum had resonance at δ 149.1 and 131.7 due to the olefinic carbons

conjugated with the ester carbonyl group. Wittig ethylidenation of 47 initially gave us some problem but using the ylide derived from ethyl tris-triphenyphosphonium bromide salt and n-BuLi as the base in benzene at room temperature gave 48 in 60% yield based on the recovery of the starting material. Its ^{1}H and ^{13}C NMR spectra (Fig I.21 and Fig I.22) contained the requisite resonances expected for the structure 48. When ethylidene compound 48 was hydrogenated over 10% Pd-C catalyst in ethyl acetate, it underwent regio-and stereoselective hydrogenation from the convex face to furnish 49 in which the endo-ethyl group stereochemistry was fully secured, **Scheme 22.** The structure of 49 was in full agreement with its ^{1}H and ^{13}C NMR data (Fig I.23 and Fig I.24). The ^{1}H NMR spectrum exhibited a triplet at δ 0.98 (J = 7.3 Hz) corresponding to the ethyl group and a signal at δ 6.84 due to the olefinic proton of the enone. This feature was confirmed by the ^{13}C NMR spectrum (Fig I.24). Exposure of the hydrogenated product 49 to dil.HCl led to the hydrolysis of both the ketal and the ester group and (±) coronafacic acid 40 m.p.120^{o} (lit. 124-125°C)[23a], identical with the natural product, was obtained in a short simple sequence, **Scheme 22.**

The 200 MHz ^{1}H NMR spectrum (Fig I.25) of (±)-coronafacic acid 40 exhibited a triplet at δ 0.99 (J = 7.3 Hz) due to ethyl group and a broad singlet at δ 7.07

representing the β-proton of the α,β-unsaturated ester. In particular, a 12 line ^{13}C NMR spectrum (Fig I.26) which displayed characteristic signals at δ 220.0, 171.4, 146.8, 130.9 was in full agreement with the structure 40 (^{13}C NMR data for the natural product has not been reported in the literature).

Scheme 22



Reagents: a) $(CH_2OH)_2$, PTSA, benzene, reflux, 95%; b) PDC, t-BuOOH, Celite, r.t., 30 min, 61%; c) $EtPPh_3Br$-$^{n}BuLi$, benzene, r.t., 15 min, 60%; d) Pd/C-H_2, ethyl acetate, r.t., 10 min, 86%; e) 25% aq.HCl, reflux, 4h, 70%.

Our synthesis of (±)-coronafacic acid is one of the shortest reported up-to-date and highly stereoselective as no isomer separation is involved in any of the steps. Finally the identity of the synthetic compound and the natural product was fully established by comparing the ^{1}H NMR and IR data with the reference spectra.*

b. Synthesis of (±)-Pumiliotoxin-C:

Frogs of the neotropical family dendrobatidae produce a remarkably diverse set of alkaloids.[24] Over two hundred alkaloids have been detected and grouped into classes, based in many instances only on gas chromatographic-mass spectroscopic (GC-MS) analyses.[25,26]

One major class of dendrobated alkaloids are based on the 2,5-disubstituted, 2,5,6-trisubstituted decahydroquinoline ring system 50 and 51 while the other class of dendrobatid alkaloids are the 5-substituted-8-methylindolizidines 52, **Scheme 23.**

One of the earliest 2,5-disubstituted decahydroquinoline class of alkaloids to be isolated from a Panamanian population of Dendrobates pumilio, was named pumiliotoxin C 41 and shown by X-ray crystallographic

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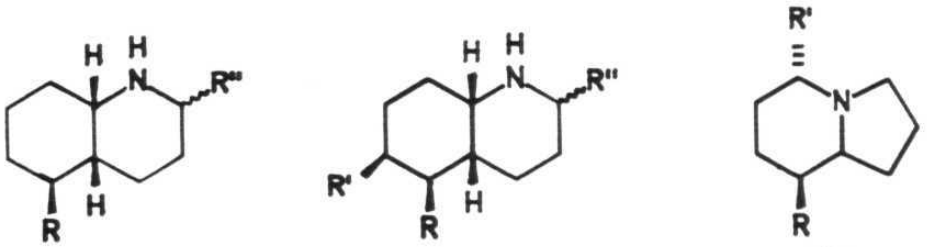
* We thank Prof. M.E. Jung and Prof. A. Ichihara for providing comparison spectra of (±)-coronafacic acid .

analyses to be 2S, 4aS, 5R, 8aR-5-methyl-2-propyl-cis-decahydroquinoline 41.[27]

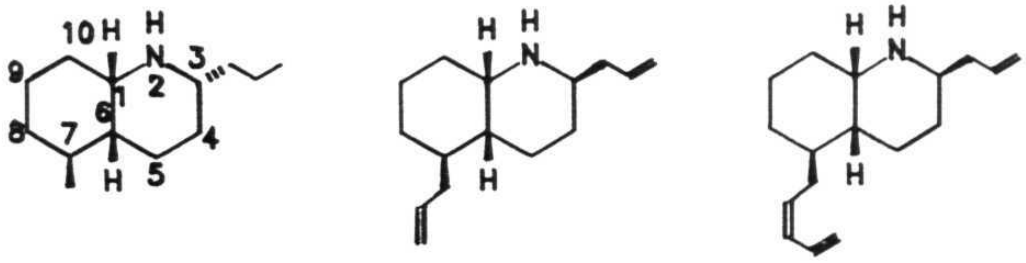
Scheme 23



50 51 52

Recently a few more members of this family e.g., cis-decahydroquinolines, namely 2,5-diallyl cis-decahydroquinoline 53 and 2-allyl-5-(pent-2-en-4-vinyl)-cis-decahydroquinoline 54, have been isolated from a colombian population of dendrobates histrionicas, **Scheme 24.**[27]

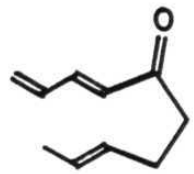
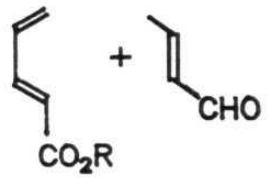
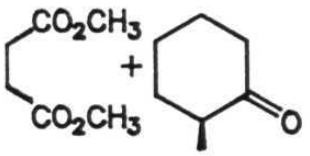
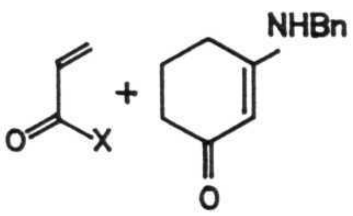
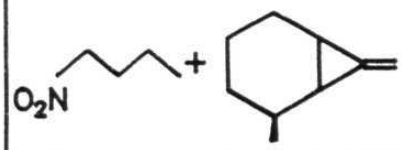
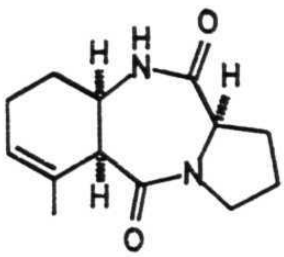
Scheme 24



41 53 54

The decahydroquinoline alkaloids display diverse biological activities. The striking biological properties

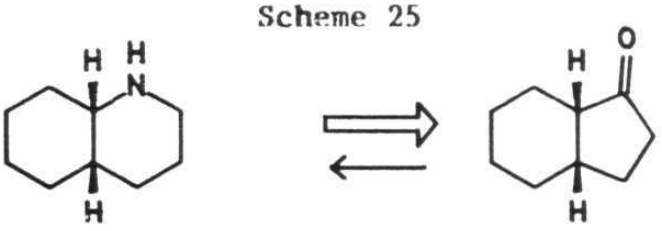
Table 2

Starting materials	Key step in the Approach	NO. of steps	Ref
	Intramolecular Diels–Alder	12	28a
	Diels–Alder	6	28b
	Stobbe condensation	8	28c
	Diels–Alder	8	28d
	Cyclo addition	7	28e
	Birch reduction–Methanolysis	7	28f

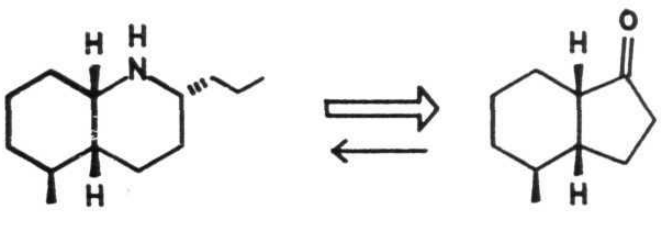
and novel structural features of these alkaloids attracted the attention of organic chemists during the late 1970's. Serious and intensive synthetic efforts commenced with the elucidation of the structure of pumiliotoxin C in 1976 and till now over a dozen syntheses in racemic as well as chiral form have been accomplished, see **Table 2.**[28]

Our interest in pumiliotoxin C 41 emanated from recognition that a cis-decahydroquinoline 55 is an equivalent of a cis-perhydroindanone 56 as shown in **Scheme** 25. The latter could be transformed into the former through a two step sequence involving Beckman rearrangement followed by the reduction of the amide to amine. Extention of this equivalency to pumiliotoxin C 41 identified the cis-perhydroindanone 57 as its equivalent, **Scheme** 25.

Scheme 25



55 56



41 57

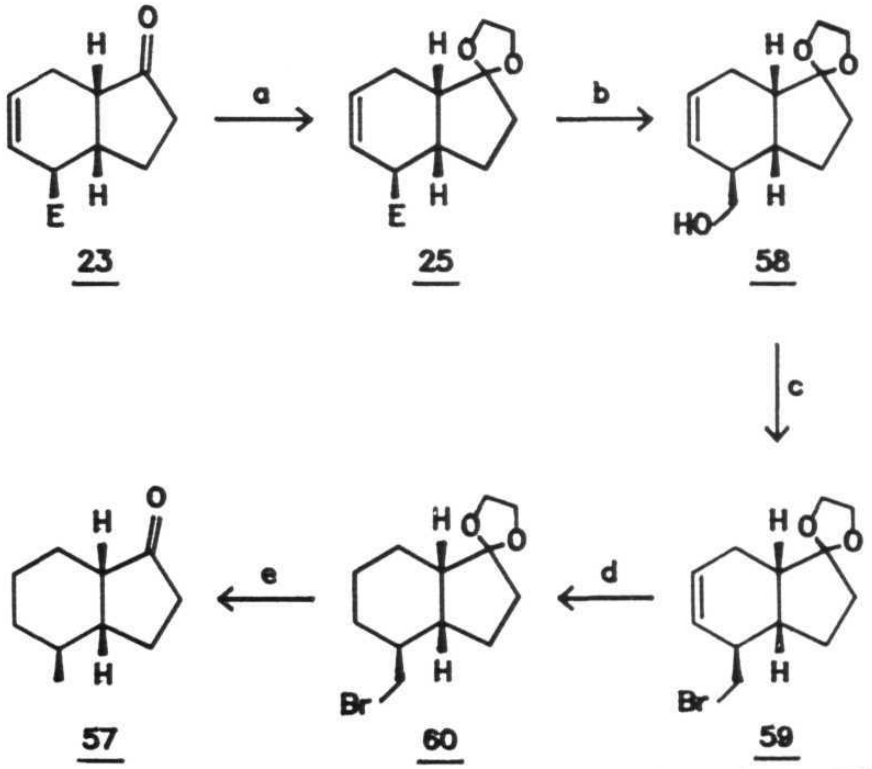
The cis-perhydroindanone 57 in our perception could be readily accessed via the Haller-Bauer cleavage and appropriate functional group modification in the tricyclo[5.2.1.$0^{2,6}$]decan-10-one derivative 9.

To implement the theme shown in the Scheme 25, the tricyclo[5.2.1.$0^{2,6}$]decan-10-one 9 was subjected to controlled Haller-Bauer cleavage in 1% aq.NaOH-benzene at room temperature as described above to furnish a mixture of cis-hydrindanones 23 and 24 via regioselective carbon-carbon bond cleavage, Scheme 14.

The ester functionality in 23 with correct stereochemistry at the three contiguous stereogenic centers for the synthesis of pumiliotoxin C 41 was first transformed to a methyl group. For this purpose, the carbonyl group in 23 was protected as the ethylene ketal 25. The ^{1}H NMR and ^{13}C NMR spectra (Fig I.27 and Fig I.28) of 25 revealed the presence of ketal functionality. LAH reduction in 25 gave the primary alcohol 58 in 75% yield. The IR spectrum of 58 showed hydroxyl absorption at 3300 cm^{-1}. The ^{1}H NMR (Fig I.29) and ^{13}C NMR spectra (Fig I.30), with resonance at δ 65.4 corresponding to the hydroxyl bearing carbon, confirmed its structure. The deoxygenation of 58 proved to be unexpectedly problematic. However, success was achieved through its conversion to the bromide 59 and catalytic hydrogenation over Pd/C catalyst to 60, Scheme 26. The ^{1}H

NMR (Fig I.31) and 12 line ^{13}C NMR spectra (Fig I.32) of 60 were fully consonant with the assigned structure. Reductive removal of bromine in 60 was accomplished with $NaBH_3CN$ in HMPA at $80^{o}C$ and an aqueous acid workup furnished the cis-hydrindanone 57, the key precursor of pumiliotoxin C , in 50% yield, **Scheme 26.**

Scheme 26



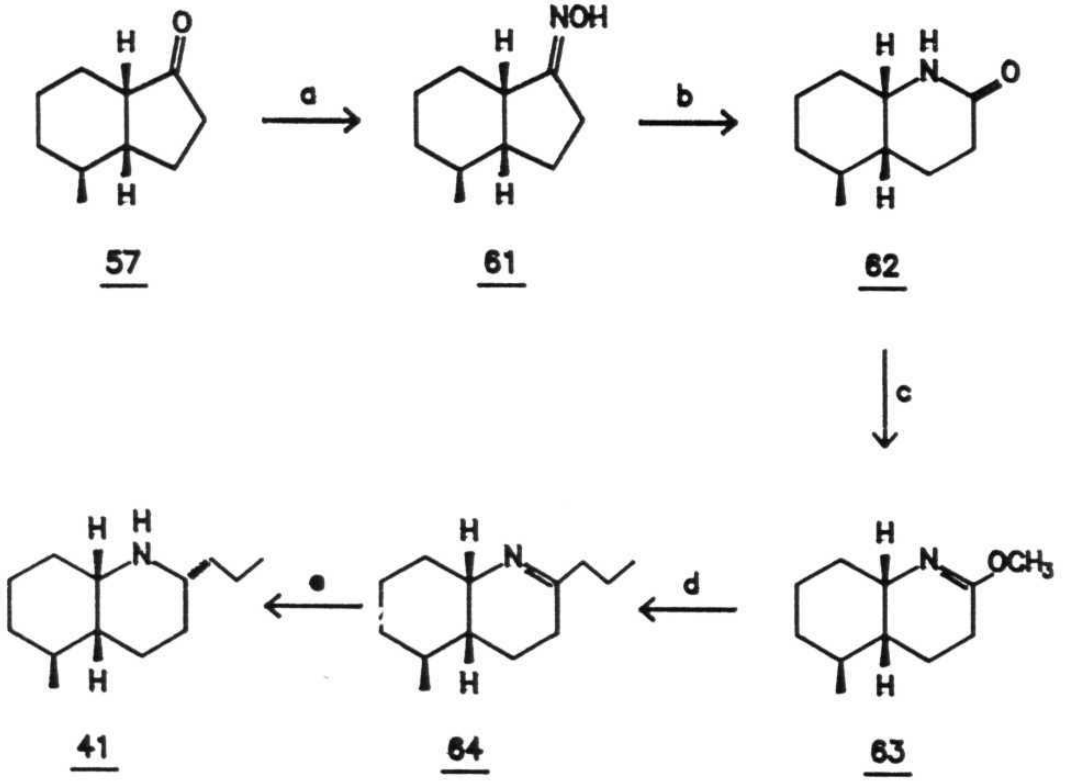
Reagents: a) $(CH_2OH)_2$, PTSA, benzene, reflux, 3h, 90%; b) $LiAlH_4$, THF, reflux, 4h, 75%; c) CBr_4, PPh_3, DCM, r.t., 1h, 70%; d) Pd/C-H_2, ethyl acetate, r.t., 10 min, 90%; e) $NaBH_3CN$, HMPA, 80°C, 4h, 50%.

The ^{1}H NMR spectrum (Fig I.33) and its 10 line ^{13}C spectrum (Fig I.34) with characteristic carbonyl resonance

at δ 219.7 clinched its structure as 57.

The stage was now set for demonstrating the equivalency concept shown in the **Scheme** 25.

Scheme 27



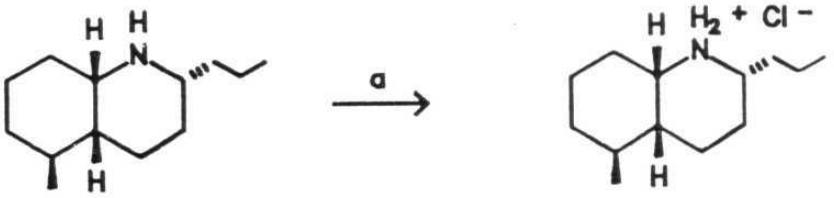
Reagents: a) $NH_2OH.HCl$, NaOAc, methanol, r.t., 45 min, 95% b) p-TsCl, NaOH, dioxane, r.t., 15h, 67%; c) $(CH_3O)_3O^-BF_4$ N-ethyl diisopropyl amine, DCM, 80°C, 1h; d) n-PrMgBr benzene, reflux, 6h, 60%; e) DIBAL-H, DCM, -78°C, 15 min 60%.

The cis-bicyclic ketone 57 was converted to its oxim

61, which on Beckman rearrangement furnished the lactam 62 (Fig I.35 and Fig I.36). The bicyclic lactam 62 was elaborated in a three step sequence to pumiliotoxin C 41 following a protocol similar to that described in the literature[28a] with a few minor modifications. The bicyclic lactam 62 was converted into the lactim ether 63 on treatment with the Meerwein's reagent. Addition of n-propylmagnesium bromide to 63 gave the intermediate imine 64 which was stereoselectively reduced from the exo-face with the DIBAL-H to furnish pumiliotoxin C 41, **Scheme 27.**

The sample of Pumiliotoxin C obtained by us was stereochemically homogeneous and was characterized as its hydrochloride 65, m.p. 235-238°C (Lit. : 238-242°C)[28a], **Scheme 28.**

Scheme 28



41 **65**

a). dry HCl, ether, r.t.

The ^{1}H and ^{13}C spectra of our synthetic pumiliotoxin C are shown in Fig I.37 and Fig I.38. They fully agree with the reported values.[28r]

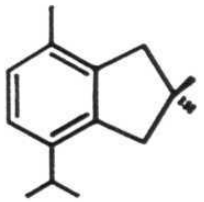
c. Synthetic Studies towards Primnoeid-type sesqiterpenoids:

A new series of sesquiterpenoids containing a 2,2,7 trimethyl-4-(1-methylethyl)indane skeleton have been isolated from an unnamed primnoeide sp., a gorgonian found at intermediate depths (20-30 m) off the north-estern coast of New Zealand. In 1988 Cambie et.al.,[5h] isolated and reported the isolation of five new sesquiterpenoids from a hexane extract of freeze-dried specimens of primnoeides sp. and with the help of extensive spectral data they showed that all these were derivatives of the as yet unreported sesquiterpenoid skeleton 2,2,7-trimethyl-1-4-(1-methylethyl) indane 66 to which they gave the trivial name PRIMNATRIENE, Chart 4.

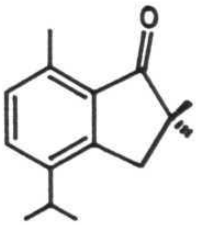
The sesquiterpenoids isolated from primnoeides sp., are aromatic analogues of a number of fungal metabolites which have been reported recently in the literature. Some of the biologically related structures are shown in the Chart 4.

Since we had in our hands a versatile access to hydrindanone framework and the total synthesis of primnoeides sesquiterpene had not been reported in the literature, we became interested in the synthesis of these compounds. We were aware of the fact that the primnoeide-type sesquiterpenes are indanone based and do not pose any stereochemical challenge.

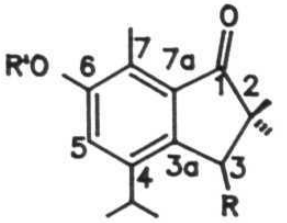
Chart 4



66



67



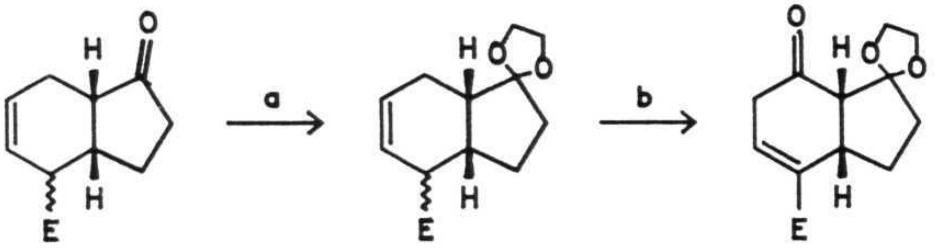
	R	R'
42	H	H
68	H	CH_3
69	OH	CH_3
70	OAc	CH_3
71	O	CH_3

Infact, in order to adopt our cis-hydrindanone synthesis to these compounds, we were required to destroy the ring junction stereochemistry. In our scheme, the nonconjugated keto esters 23 & 24 obtained by the controlled Haller-Bauer cleavage of tricyclic[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 9 were considered to be the appropriate precursors for the construction of C_{15} unit of primnoeides.

Since at a later stage the stereocenters were to be eliminated, we decided to proceed with the mixture of cis-hydrindanones 23 and 24 and converted them to the ketal esters 25 & 26. The mixture of ketal esters 25 and 26 on allylic oxidation with PDC-t-BuOOH reagent[18], quite

surprisingly furnished a single non-conjugated enone 72, Scheme 29. Apparently, the α,β-unsaturated ester is more stable than the corresponding α,β-unsaturated ketone that is initially formed during the allylic oxidation. The structure of 72 was revealed through its carbonyl absorption at 1720 cm^{-1} due to a cyclohexanone moiety. Its ^{1}H and ^{13}C spectra contained the requisite resonances expected for the structure 72 (Fig I.39 and Fig I.40).

Scheme 29



23 β-
24 α-

25 β-
26 α-

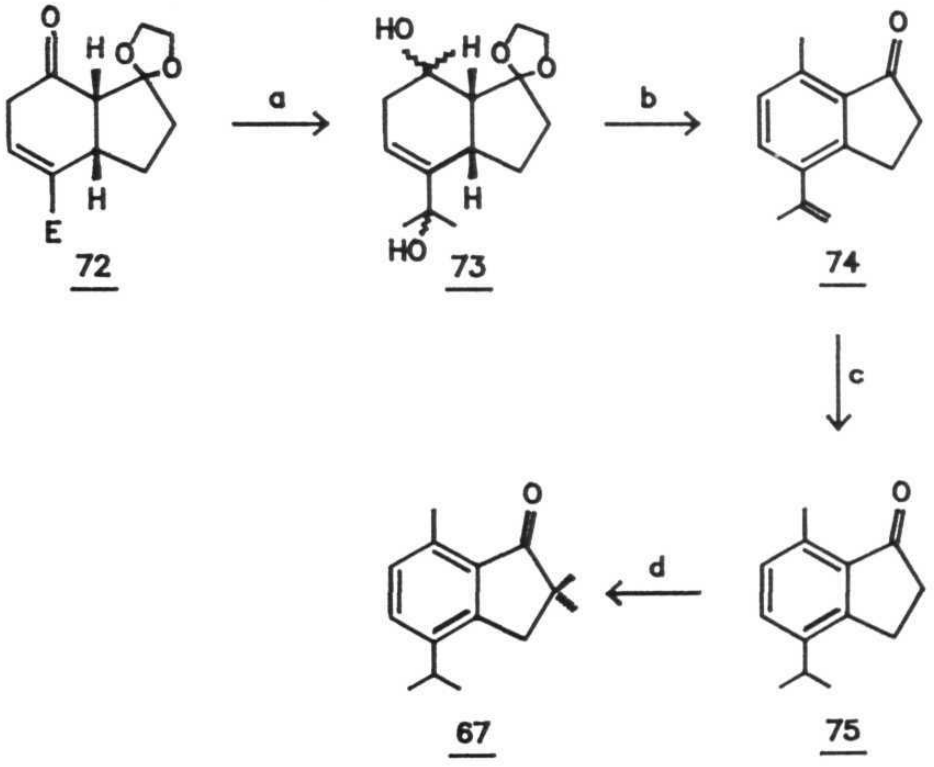
72

Reagents: a) $(CH_2OH)_2$, PTSA, benzene, reflux, 3h, 95%; b) PDC, t-BuOOH, benzene, 2h, 60%.

When the ester ketone 72 was treated with excess methyl lithium, it furnished a diol 73 as a mixture of diastereomers, which was evident from its ^{1}H and ^{13}C NMR spectra. Thus, three methyl groups were loaded on to the framework of 72 in one step. No attempt was made to purify

the diols at this stage and the mixture was subjected to dehydration in PTSA-benzene. Dehydration and concomitant oxidative aromatization and deprotection occured in a one pot reaction and isopropenylated indanone 74 was obtained in 30% yield, **Scheme 30.**

Scheme 30



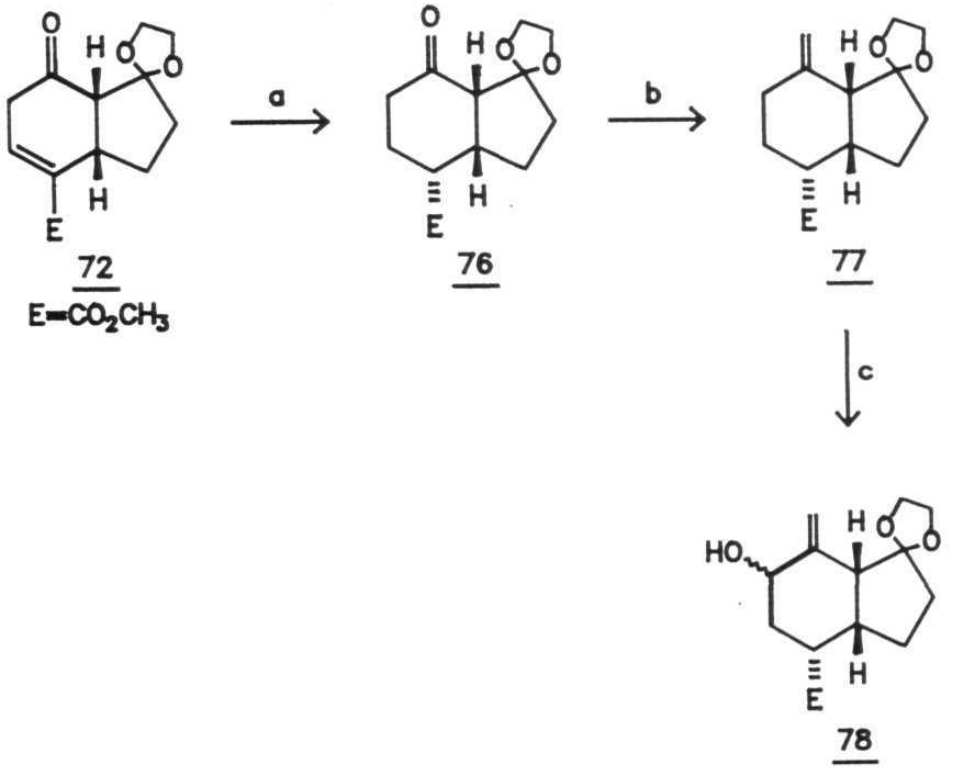
Reagents: a) MeLi, ether, reflux, 2.5h, 60%; b) PTSA, benzene, r.t., 6-7h, 30%; c) Pd/C-H_2, ethyl acetate, r.t., 30 min, 90%; d) NaH, MeI, THF, reflux, 3h, 70%.

The structure 74 was in agreement with the ^{1}H and ^{13}C NMR spectral data (Fig I.43 and Fig I.44), which showed two singlets at 2.42 & 2.15 due to two methyl groups and peaks at δ 5.29 and 5.10 corresponding to the terminal methylene group. The ^{13}C NMR spectrum (Fig I.44) further fortified the structural assignments. Unsaturated aromatic ketone 74 on hydrogenation over Pd/C established the isopropyl group in place to yield 75. The structure of 75 was supported by its ^{1}H and ^{13}C NMR spectral data (Fig I.45 and Fig I.46). To complete the aquisition of the C_{15} sesquiterpene skeleton of the primnatriene, 75 was subjected to methylation with potassium t-butoxide in t-butanol to furnish the gem-dimethylated product 67, **Scheme 30**. The structure of 67 was fully consonant with the IR and ^{1}H NMR (Fig I.47) spectra. The 15 line ^{13}C NMR spectrum (Fig I.48) with characteristic resonances at δ 211.7, 147.1, 146.0, 137.9, 135.4, 132.2, 121.9 reinforced its formulation.

Having successfully accomplished the synthesis of the framework of this newly discovered family of marine natural products, we decided to adopt our basic strategy to synthesize one or more of the natural products, **Chart 4**. This required introduction of oxygen functionality at C_6 carbon α to the C_7 methyl group. For this purpose, two strategies were considered. The first envisaged introduction of an oxygen functionality in 72 employing the reaction of

the derived enolate with MoO_3, hypervalent iodine etc. However, in view of the likely formation of dienolate anion, this approach was not pursued. Alternatively, we considered the possibility of introduction of C_6 oxygen functionality through allylic oxidation, **Scheme 31.**

Scheme 31



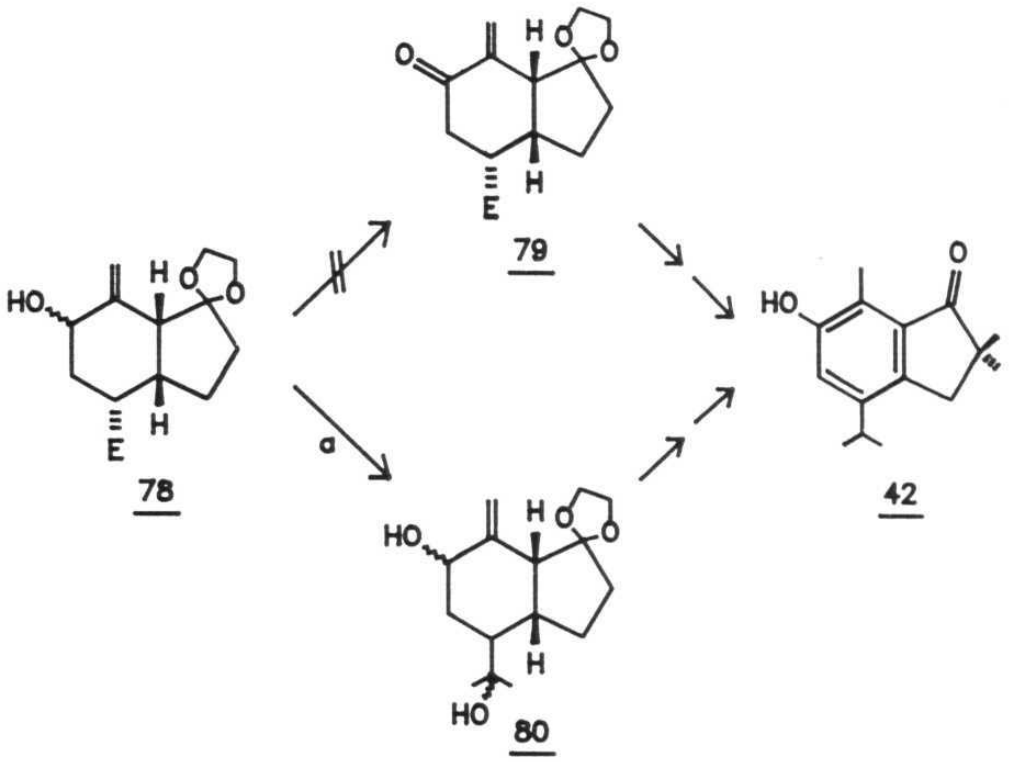
Reagents: a) $Pd/C-H_2$, ethyl acetate, r.t., 15 min, 99%; b) Ph_3PCH_3Br, t-AmONa, benzene, r.t., 30 min, 60%; c) SeO_2, t-BuOOH, DCM, r.t., 4h, 60%.

For this purpose, 72 was reduced through catalytic hydrogenation to 76 and subjected to Wittig olefination using the ylide derived from methyl tris-triphenylphophonium bromide and t-amyl oxide as a base. The desired exo-cyclic methylene compound 77 was readily obtained and showed a peak at δ 4.75 corresponding to the terminal methylene group in its ^{1}H NMR spectrum. Allylic oxidation of 77 with SeO_2-t-BuOOH using Sharpless conditions[29] furnished the allylic alcohol 78, **Scheme 31**.

The structure of the alcohol 78 was readily established through its ^{1}H and ^{13}C NMR data In particular, the ^{1}H NMR spectrum showed the presence of a proton attached to a hydroxy group at δ 4.45 and the ^{13}C NMR spectrum had resonance at δ 73.0 due to the hydroxy attached carbon (vide experimental).

To our great surprise, we found that the allylic alcohol 78 resisted all attempts at oxidation to the ketone 79. Oxidation of 78 was attempted using TPAP, PCC, PDC, Swern, Des-Martin and MnO_2 reagents. We had expected that enone 79 could be readily aromatized with the introduction of the oxygen functionality enroute to 42. As a last resort, we reacted the hydroxy ester 78 with excess of methyl lithium to obtain the diol 80, **Scheme 32**.

Scheme 32



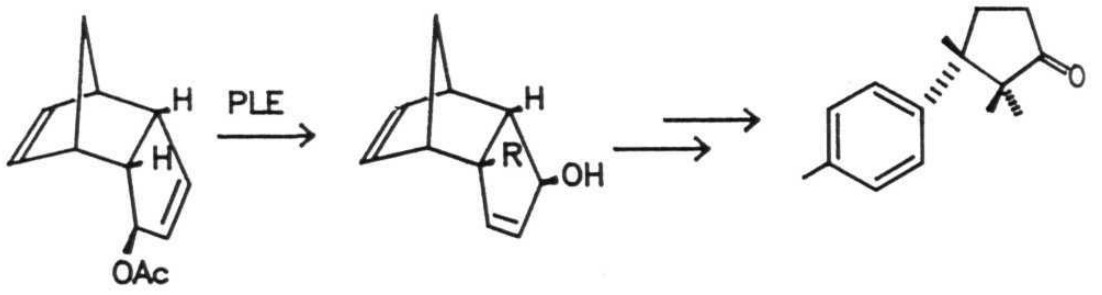
Reagents: a) MeLi, ether, reflux, 45 min, 60%.

However, diol 80 too could not be aromatized. When treated with PTSA-benzene and other dehydrating agents cyclic ether like non-aromatic products only were obtained. These were not characterized. At this stage, further efforts to synthesize the natural products were abondoned. Nonethe less, the first synthesis of primnoeid skeleton had been successfully accomplished.

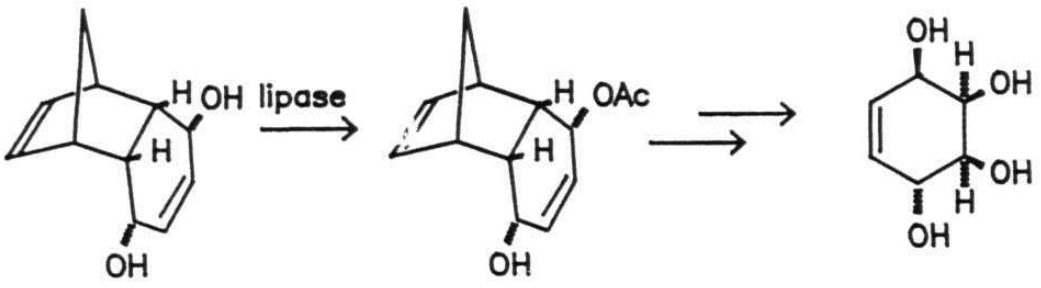
I.3.4. Synthesis of optically active Hydrindanes:

The functionalized cis-hydrindanes are essential synthetic intermediates in many routes to important natural products containing this bicyclic frame as a core unit, **Chart 2.** Synthesis of most of these hydrindane based natural products in enantiomerically pure form can be achieved if one gets access to suitably functionalized precursors in optically pure form.

Scheme 33



(±) (+) (+)– Cuparenone



(±) (+) (–)– Conduritol C

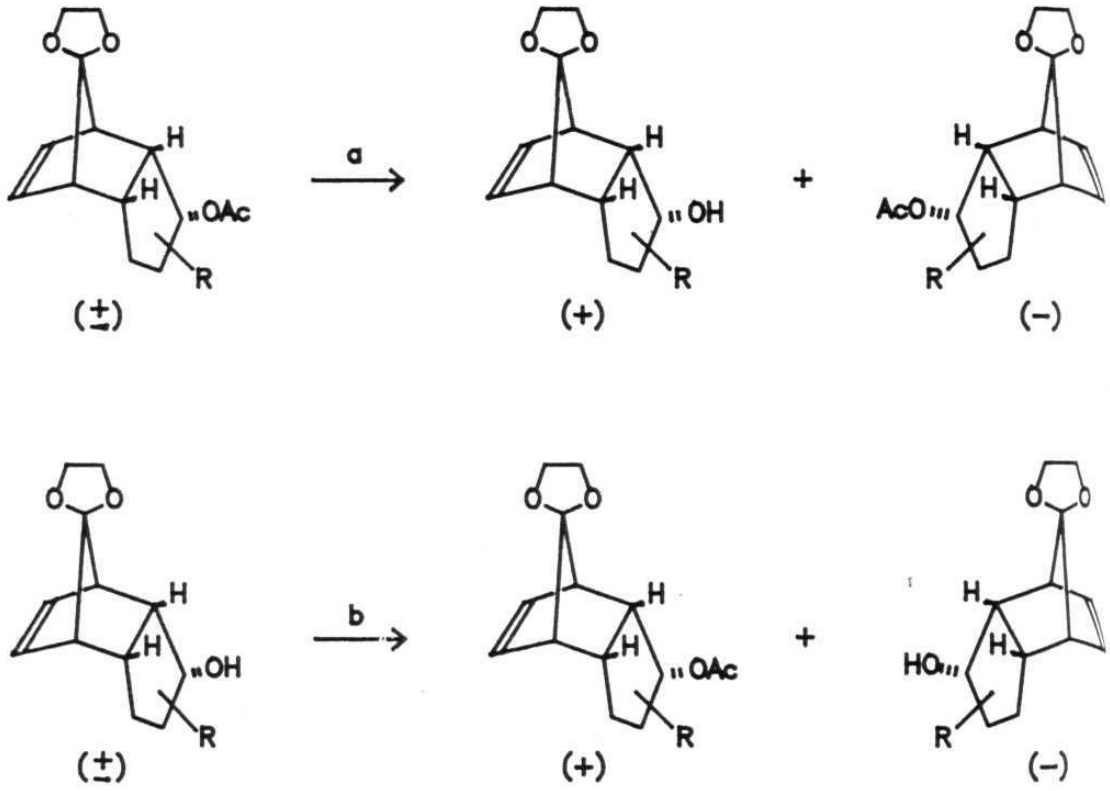
Attracted by considerable attention by chemists in the recent years on kinetic resolutions[30] of unsubstituted tricyclodecane ring system, leading to the enantioselective synthesis of many natural products [31], **Scheme 33**, we considered it worthwhile to extend this enzymatic resolution technique to substituted tricyclo[5.2.1.$0^{2,6}$]decanone systems to obtain them in enantiomerically pure form.

As the tricyclo[5.2.1.0]decane system also possess intrinsic chirality, our Haller-Bauer strategy offers the interesting prospect for the synthesis of chiral cis-hydrindanes, which in turn can be used for the synthesis of natural products in optically active form. Among the various ways in which the chiral tricyclo[5.2.1.$0^{2,6}$]decanes can be obtained, the kinetic resolution using enzymes (PLE) appeared to be the most convenient one. We have investigated the kinetic resolution of several of the tricyclodecane systems having a hydroxyl functional group at C_3 by employing:

a) PLE catalyzed hydrolysis of the derived acetates and

b) transesterification of the alcohols, **Scheme 34.**

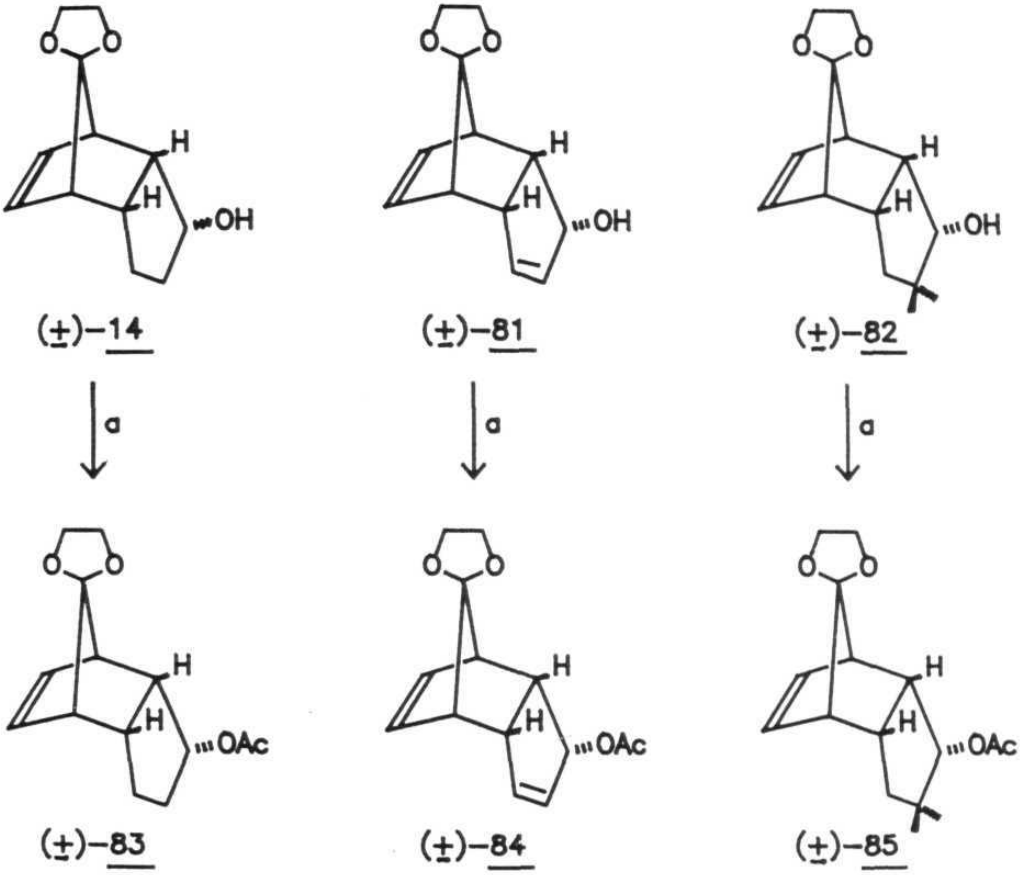
Scheme 34



Reagents: a) PLE, acetone, buffer; b) PLE, vinyl acetate.

We thought that tricyclo[5.2.1.$0^{2,6}$]decan-3-ols 14, 81 and 82, readily available in good quantities, and their acetates 83, 84 and 85 are the suitable substrates for chemoenzymatic resolution. All the three acetates 83-85 were synthesized from the corresponding alcohols by using pyridine and Ac_2O, in quantitative yields, **Scheme 35**.

Scheme 35



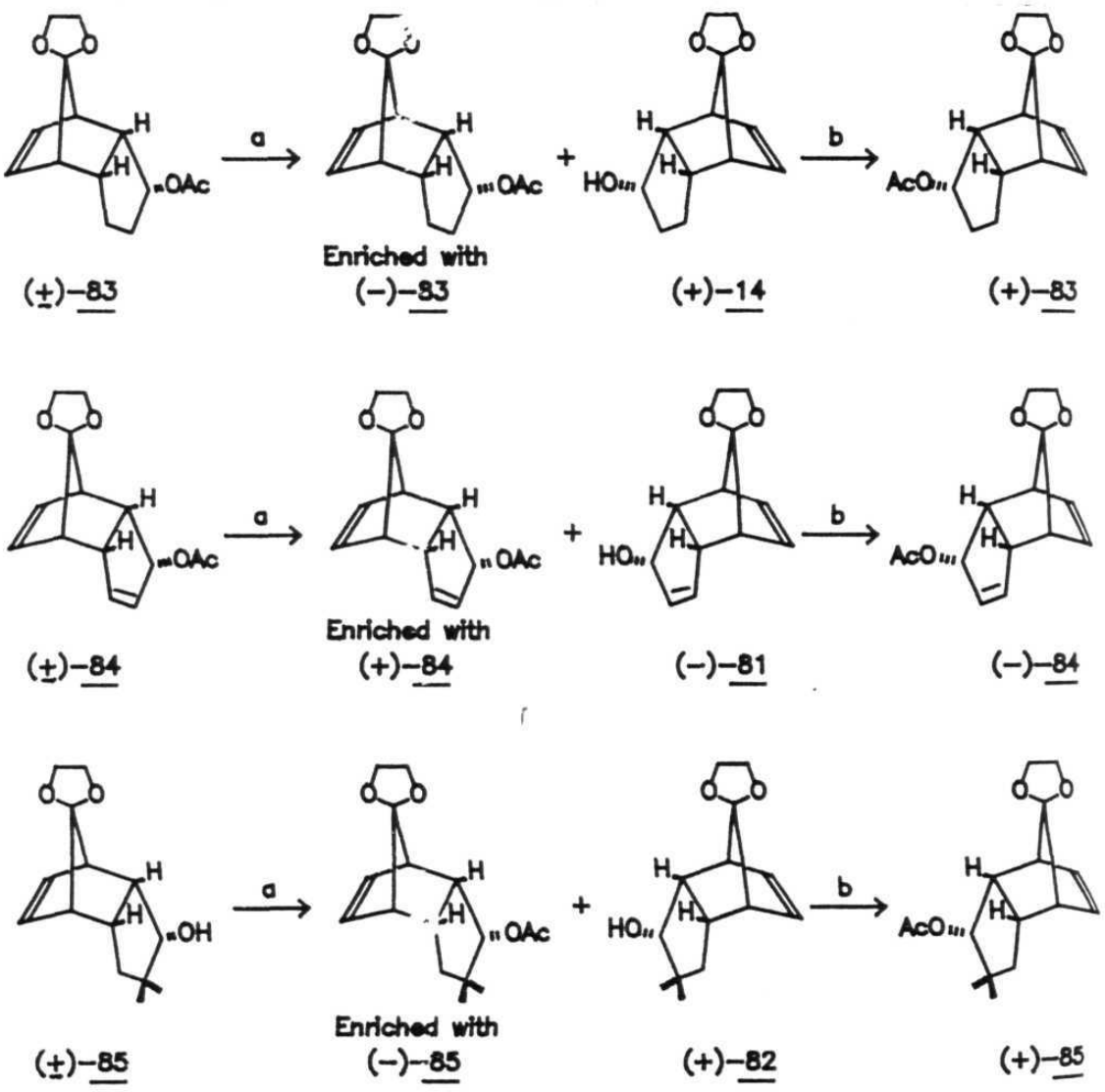
Reagents: a) Pyridine, Ac_2O, r.t., 1h, 99%.

a. PLE catalyzed hydrolysis of the acetates :

All the three racemic tricyclo[5.2.1.$0^{2,6}$]decan-3-acetates 83-85 were treated with PLE (candida cylindrica) at room temperature for 1 - 4 days in 0.1 M phosphate buffer (pH 8.0) containing ether (10% by volume) as a co-solvent. Under these conditions all racemic acetates 83, 84 and 85 slowly hydrolyzed to give optically active alcohols (+)-14, (-)-81 and (+)-82 in moderate yields (60-70%) but with a

high optical purity (>90% ee). Except 84, other two acetates 83 and 85 furnished only one enantiomer in the hydrolysis, **Scheme 36**.

Scheme 36



Reagents: a) PLE, phophate buffer, ether, r.t.,; b) Pyridine, Ac_2O, r.t., 99%.

The enantiomeric purity of the hydrolyzed alchols was confirmed by NMR using chiral shift reagent [Eu(fod)$_3$] studies on the acetates (+)-83, (-)-84 and (+)-85, prepared from the resolved alcohols by using pyridine and Ac_2O, in quantitative yield. Optical rotations of all the enantiomers are shown in **Table 3.**

Table 3: Optical rotations and enantiomeric excess (ee) of the resolved alcohols and their acetates.

substrate[#]	$[\alpha]_D^{25}$	ee[*]	conversion	yield[+]
(+)-14	(+)14.8°	-	≈30%	60%
(-)-81	(-)106°	-	≈45%	60%
(+)-82	(+)16.4°	-	≈30%	60%
(+)-83	(+)29.1°	>95	-	-
(+)-84	(+)23.5°	>95	-	-
(-)-84	(-)18.5°	>95	-	-
(+)-85	(+)28°	>95	-	-

* based on ^{1}H NMR using chiral shift reagent Eu(fod)3.

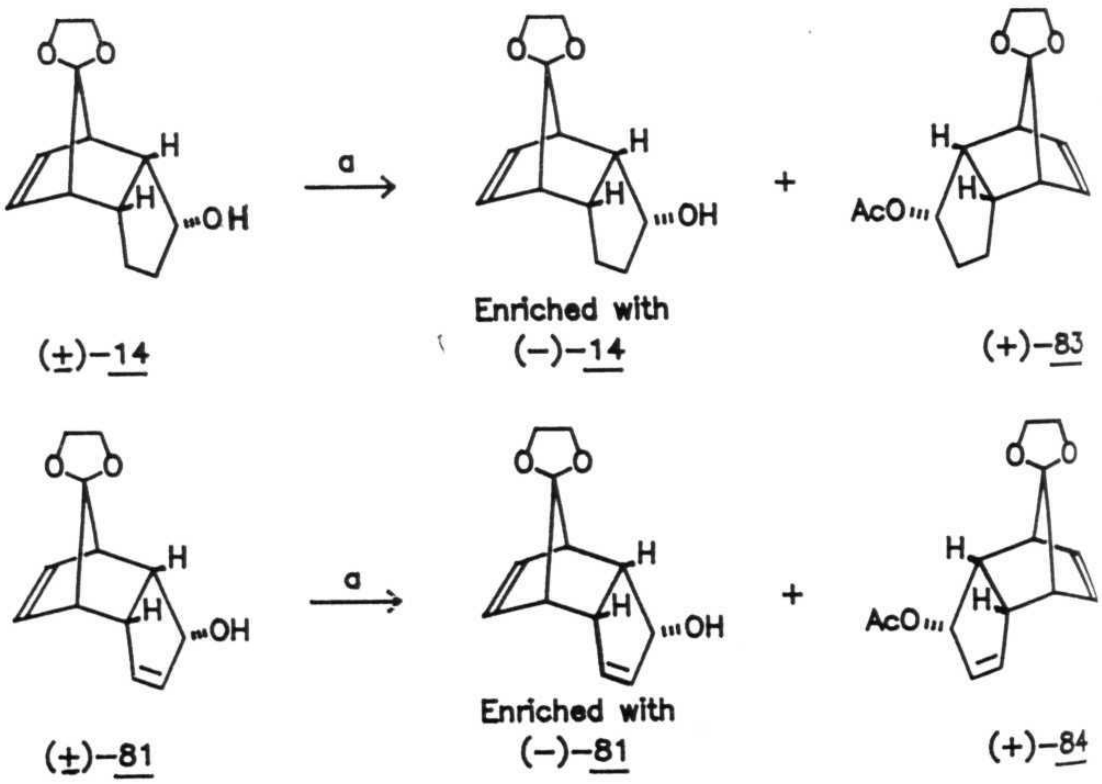
+ Yields based on starting material recovered.

Since the absolute configuration of the substrates are not known, we indicated the structures with (+) or (-) sign based on the sign of their optical rotation.

b. Transesterification of the alcohols :

In the second approach the racemic alcohols 14 and 81 were treated with porcine liver esterase at room temperature using vinyl acetate as a solvent and acyl transfer reagent. Under these conditions alcohols (±)-14 and (±)-81 esterified slowly to the corresponding acetates (+)-83 and (+)-84 in moderate yields but with high optical purity (>90% ee), **Scheme 37.**

Scheme 37



Reagents: a) PLE, vinyl acetate, r.t.

The enantiomeric purity of the chiral acetates was evaluated through chiral shift reagent studies. The optical rotations of the enantiomers were shown in the **Table 4.**

Table 4: Optical rotations and enantiomeric excess (ee) of the resolved alcohols and their acetates.

substrate	$[\alpha]_D^{25}$	ee*	conversion	yield+
(+)-83	(+)27.6°	>92	≈30%	60%
(+)-84	(+)18.5°	>90	≈30%	60%

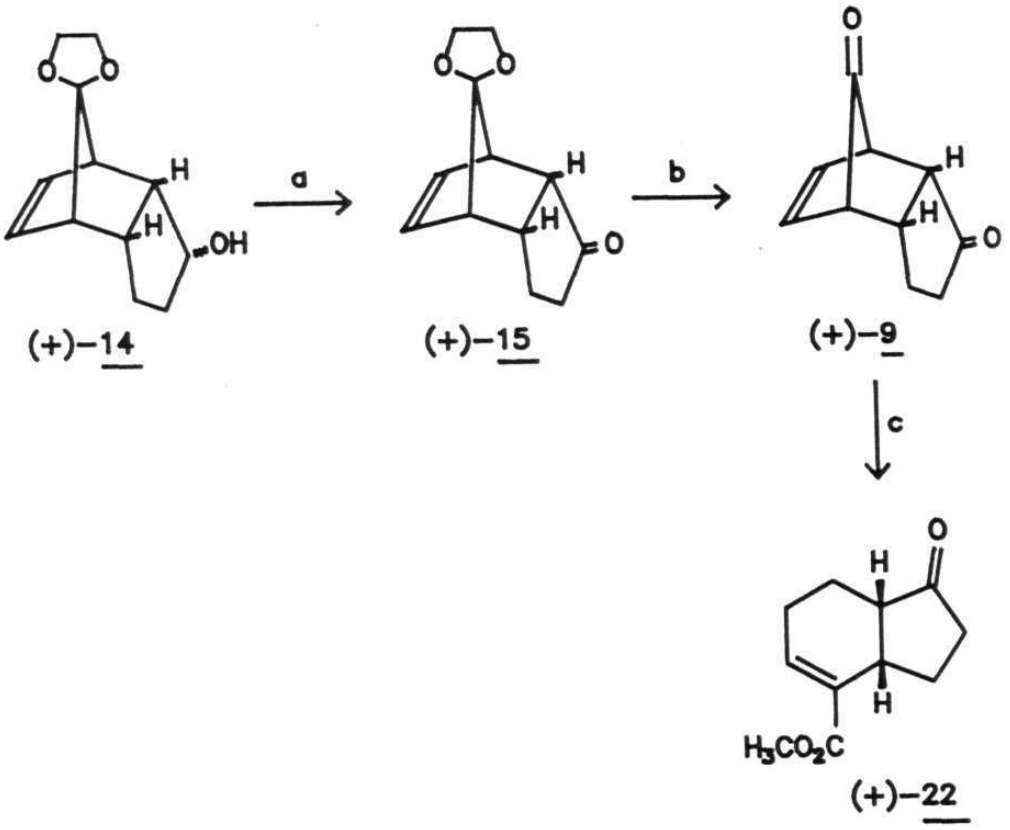
* based on ^{1}H NMR using chiral shift reagent Eu(fod)$_3$.

+ Yields based on starting material recovered.

The attainment of practical route to optically active tricyclo[5.2.1.$0^{2,6}$]decanone systems now allows the preparation of cis-hydrindanes in enantiomerically pure form. Enantiomerically pure alcohol (+)-14 thus obtained was subjected to oxidation to give ketone (+)-15 in 80% yield. Hydrolysis of (+)-15 gave diketone (+)-9 in high optical purity (vide experimental). The diketone (+)-9 was subjected to base mediate Haller-Bauer cleavage to furnish the optically active cis-hydrindanone (+)-22 ($[\alpha]_D$ = (+) 21°), **Scheme 38**, following the same procedure used for the racemic compounds.

The optically active cis-hydrindanone (+)-22 synthesized can be further employed for the synthesis of optically active natural products following the same protocol used for the racemic forms.

Scheme 38



Reagents: a) PCC, Celite, DCM, r.t., 80%; b) 60% aq.H_2SO_4, DCM, r.t., 92%; c) 30% aq.NaOH, benzene, reflux & CH_2N_2, ether, 70%.

I.4. SUMMARY:

We have outlined practical and efficient approach to cis-hydrindanes from tricyclo[5.2.1.$0^{2,6}$]deca-3,10-diones 9-13 via regioselective Haller-Bauer cleavage as the key reaction. These cis-hydrindanes available in quantities are potentially serviceable for the synthesis of hydrindane based natural products. As a demonstration of their utility, we have achieved total synthesis of diverse natural products namely (±)-coronafacic acid, (±)-pumiliotoxin C and primnoeid sesquiterpene skeleton. A simple and expedient route to chiral cis-hydrindanone has been developed.

I.5. EXPERIMENTAL:

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

Boiling Points : Bulb to bulb distillations were carried out using oil bath for all liquid samples and boiling point refers to oil bath temperature.

Infrared spectra : Infrared spectra were recorded on JASCO FT-IR 5300 or Perkin-Elmer Model 1310. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin films between NaCl plates.

Nuclear magnetic Resonance spectra : Proton magnetic resonance spectra were recorded on Bruker AC 200 (200 MHz) or JEOL FX-100 (100 MHz) spectrometer. Carbon-13 magnetic resonance spectra were recorded on Bruker AC 200 (50 MHz) or JEOL FX-100 (25 MHz) spectrometer. ^{1}H and ^{13}C-NMR samples were made in chloroform-D solvent and chemical shifts are reported in δ scale using tetramethylsilane (Me_4Si)

as the internal standard. The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet respectively. ^{13}C-nmr assignment differing by only 2-3 ppm can in some cases be interchanged.

Mass spectra : Mass spectral measurements were carried-out on JEOL, JMS DX-303 spectrometer.

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

Optical rotation : Optical rotations were measured on AUTOPOL II™ polarimeter and JASCO DIP 370 digital polarimeter

Chromatography : Analytical thin-layer chromatographies (tlc) were performed on (10 x 5 cm) glass plates coated (250 mμ) with Acme's Silica gel G or GF_{254} (containing 13% of calcium sulphate as binder). Visualization of the spots on tlc plates was achieved either by exposure to iodine vapour or UV light or by spraying sulfuric acid and heating the plates at 120°C . Column chromatography was performed using Acme's silica gel (100-200 mesh) and

the column was usually eluted with ethyl acetate-hexane, unless mentioned otherwise.

General : All reactions were monitored by employing tlc technique using appropriate solvent systems for development. Moisture-sensitive reactions were carried out by using standard syringe septum techniques. Petrolium ether refers to the fraction boiling between 60-80°C. Dichloromethane was distilled over P_2O_5. Benzene was distilled over sodium and stored over pressed sodium wire. Ethyl acetate was distilled over potassium carbonate. Absolute ethanol and methanol were prepared by distilling them over freshly ignited Calcium oxide followed by distillation over Magnesium metal. Dry ether and dry THF were made by distilling them from sodium-benzophenone ketyl. Hydrogenations were carried out on a Parr-hydrogenation apparatus in 250 ml pressure bottles. All solvent extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated

at reduced pressure on a Buchi-El rotary evaporator. Yields reported are isolated yields of material judged homogenous by tlc and NMR spectroscopy.

10,10-(Ethylenedioxy)-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one 8:

The methods of Chapman [12a] and Paquette[12b] for the preparation of the 3,10-diketal 7 were modified. The crude 2,5-dibromocyclopentanone ethylene ketal 5 (314 g), obtained via bromination[12a] (Br_2/dioxane) of cyclopentanone ethylene ketal 4 (128 g, 1.00 mol), in 600 ml of methanol was added over a 20-min period to a cold (5-10°C solution of sodium methoxide (324 g, 6.0 mol) in 1000 ml of methanol. The resulting black solution was refluxed under nitrogen atmosphere for 15h, then cooled and poured into 3 L cold water. The black, aqueous solution was filtered through Celite, acidified by cautious addition of cold, concentrated aqueous HCl (pH 1-2), and allowed to stand for 15 min before extraction with 3 x 200 ml of DCM. The combined extracts were washed with water (2 x 100 ml), dried and concentrated to ≈150 ml. The resulting viscous, black solution was diluted with 1 l of ether and filtered through a layer of celite, and the filtrate was concentrated in vacuo to 87 g of waxy, tan crystals, which were recrystallized from DCM-hexane to furnish the enone 8 (60 g) in 60% yield.

m.p. : 92-93°C (lit. 93-94°C)[12]

10,10-(Ethylenedioxy)-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one 15:

To a suspension of anhydrous cuprous bromide (9 g, 63 mmol) in 10 ml of THF maintained under nitrogen atmosphere at 0 to -5°C was added lithium trimethoxyaluminium hydride (120 ml, 54 mmol) in THF. The resulting black solution was stirred for 30 min, cooled to -78°C and enone 8 (4 g, 19.6 mmol) in 30 ml of THF was added rapidly. After 10 min, 10 ml of methanol was added, the mixture was poured into 125 ml of saturated aqueous NH_4Cl solution and extracted with ether (3 x 50 ml). The combined extracts were washed, dried and concentrated to furnish the ketone 15 (3.4 g) in 84% yield.

IR : 3010, 2980, 2950, 2880, 1725 cm^{-1}

^{1}H NMR : δ 6.26-6.20 (m, 2H, olefinic), 3.88 (br s, 4H, ketal), 3.40-2.75 (m, 4H), 2.40-1.25 (m, 4H).

1α.2β,6β,7α-Tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 9:

To a cooled solution of ketone 15 (2.5 g, 12 mmol) in dichloromethane (30 ml) was added 60% aq.H_2SO_4 (10 ml) and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 50 ml). The combined extract was washed and dried. The crude material obtained after removal

of the solvent was charged on a silica gel (50 g) column and eluted with 25% ethyl acetate-hexane to furnish the enedione 9 (1.8 g) in 92% yield.

IR : 3011, 1774, 1732 cm^{-1}

^1H NMR (Fig I.1) : δ 6.50-6.42 (m, 2H, olefinic), 3.32-2.93 (m, 4H), 2.29-1.60 (m, 4H).

^{13}C NMR (Fig I.2) : δ 218.5, 200.3, 132.4, 131.1, 51.6, 49.0, 47.5, 39.5, 34.8, 23.1.

Analysis : $C_{10}H_{10}O_2$ Calcd. : C, 74.05; H, 6.22
Found : C, 73.99; H, 6.20.

3α-hydroxy-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec--8-en-10-one 10:

To a solution of dimethyl ketone 16 (1 g, 4.27 mmol) in 10 ml of dry methanol was added sodium borohydride (324 mg, 854 mmol) and the reaction mixture was stirred for 5h at room temperature. The methanolic solution was concentrated under reduced pressure to ≈1 ml, diluted to 10 ml with water and extracted with dichloromethane (3 x 25 ml). The combined extract was washed, dried and concentrated to give a alcohol as a clear oil (1 g, 100%). A solution of this alcohol (800 mg, 3.38 mmol) in moist acetone (10 ml acetone, 1 drop H_2O) and amberlyst -15 (50 mg) was stirred at room temperature. After 10h the reaction mixture was filtered and concentrated. The crude product was filtered through a silica gel (10 g) column by eluting with 20% ethyl acetate-

hexane to furnish the ketone 10 (585 mg) in 90% yield.

IR : 3450, 3000, 1740, 1100 cm^{-1}

^1H NMR : δ 6.67-6.63 (m, 1H, olefinic), 6.33-6.29 (m, 1H, olefinic), 3.78-3.73 (m, 1H), 3.11-2.87 (m, 3H), 1.58-1.48 (m, 1H), 1.05-0.99 (m, 1H), 0.96 (s, 3H, methyl), 0.95 (s, 3H, methyl).

^{13}C NMR : δ 202.1, 134.5, 127.4, 81.5, 50.1, 49.8, 45.9, 44.9, 41.2, 38.7, 26.5, 22.0.

Analysis : $C_{12}H_{16}O_2$ Calcd. : C, 74.97; H, 8.39
Found : C, 74.85; H, 8.31.

10,10-(Ethylenedioxy)-5β-methyl-1α,2β,6β,7α-tricyclo-[5.2.1.$0^{2,6}$]dec-8-en-3-one 17:

To a solution of freshly crystallized cuprous bromide-dimethyl sulfide complex (200 mg, 0.98 mmol) in 4 ml of dimethyl sulfide and dry ether (2 ml) at -23°C under nitrogen was added 1 ml of methyl lithium (addition of the methyl lithium was stopped when the initially formed yellow precipitate turned in to a clear solution). After 10 min a solution of enone 8 (100 mg, 0.49 mmol) in dry ether (3 ml) was added. The reaction mixture was stirred at the same temperature (-23°C) for 20 min. Quenched the reaction mixture with 4-5 ml of brine and extracted with ether (3 x 30 ml). Combined extract was washed with basic ammonium chloride solution, brine and dried. The solvent was evaporated and the residue was filtered through a silica gel

(2 g) column by eluting with 30% ethyl acetate-hexane to furnish methyl ketone 17 (73 mg) in 68% yield.

IR : 3000, 1720, 1290 cm^{-1}

^1H NMR : δ 6.24-6.22 (m, 2H, olefinic), 3.90-3.80 (m, 4H, ketal), 3.17-3.10 (m, 1H), 2.95-2.84 (m, 2H), 2.80-2.70 (m, 1H), 2.26-2.10 (m, 1H), 1.98-1.83 (m, 2H), 1.12 (d, J = 6.6 Hz, 3H)

^{13}C NMR : δ 219.5, 134.2, 133.5, 127.4, 65.0, 64.5, 52.0, 50.4, 49.6, 49.1, 47.2, 30.7, 22.7

Analysis : $C_{13}H_{16}O_3$ Calcd. : C, 70.89; H, 7.32
Found : C, 70.79; H, 7.29.

5β-Methyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 11:

To a cooled solution of methyl ketone 17 (150 mg, 0.68 mmol) in dichloromethane (5 ml) was added 60% aqueous sulphuric acid (2 ml) and the mixture was stirred at room temperature for 2h. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 25 ml). The residue obtained after the evaporation of the solvent was filtered through a silica gel (3 g) column by eluting with 25% ethyl acetate-hexane to furnish the diketone 11 (108 mg) 90% yield.

IR : 3000, 1775, 1730 cm^{-1}

^1H NMR : δ 6.50-6.48 (m, 2H, olefinic), 3.30-3.25 (m, 2H), 3.10-3.05 (m, 1H), 2.70-2.60 (m, 1H), 2.10-

1.93 (m, 3H), 1.18 (d, J = 6.6 Hz, 3H, methyl).

^{13}C NMR δ 216.9, 199.9, 132.5, 131.4, 51.1, 49.0, 48.5, 48.2, 43.8, 32.0, 22.2.

Analysis : $C_{11}H_{12}O_2$ Calcd. : C, 74.97; H, 6.86
Found : C, 74.89; H, 6.81.

10,10-(Ethylenedioxy)-3β-methyl-1α,2β,6β,7α-tricyclo-[5.2.1.$0^{2,6}$]deca-4,8-dien-3α-ol 18:

To a solution of enone 8 (500 mg, 2.45 mmol) in dry ether (5 ml) was added methyl lithium (80 mg, 3.67 mmol) in ether at ice temperature and the reaction mixture was stirred for 30 minutes. The reaction mixture was quenched with water and extracted with ether. The combined extract was washed and dried. Solvent was evaporated and the residue was filtered through a silica gel (10 g) column by eluting with 30% ethyl acetate-hexane to furnish the alcohol 18 (450 mg) in 90% yield.

IR : 3400, 3000, 1300, 1100 cm^{-1}

^{1}H NMR : δ 6.20-6.19 (m, 1H, olefinic), 5.85-5.81 (m, 1H, olefinic), 5.47-5.43 (m, 1H, olefinic), 5.33-5.30 (m, 1H, olefinic), 3.87-3.71 (m, 4H, ketal), 3.42 (bs, 1H), 2.69-2.66 (m, 3H), 1.54-1.52 (m, 1H), 1.24 (s, 3H, methyl)

^{13}C NMR : δ 140.7, 132.3, 131.6, 131.3, 127.6, 81.9, 64.7, 64.1, 50.9, 50.8, 50.4, 49.2, 30.6

Analysis : $C_{13}H_{16}O_3$ Calcd. : C, 70.89; H, 7.32
Found : C, 70.81; H, 7.29.

10,10-(Ethylenedioxy)-5-methyl-1α,2β,6β,7α-tricyclo-[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one 19:

To a solution of alcohol 18 (400 mg, 1.81 mmol) in dichloromethane (10 ml) was added Celite (100 mg) and PCC (780 mg, 3.62 mmol) at ice temperature. The reaction mixture was stirred for 1h and filtered through a small Celite pad. Solvent was evaporated and the residue was filtered through a silica gel (10 g) column by eluting with 25% ethyl acetate-hexane to furnish enone 19 (280 mg) in 71% yield.

IR : 3000, 1690, 1300, 1100 cm^{-1}
^1H NMR : δ 6.10-6.02 (m, 1H, olefinic), 5.93-5.83 (m, 2H, olefinic), 3.96-3.85 (m, 4H, ketal), 3.40-3.35 (m, 1H), 3.01-2.96 (m, 2H), 2.87-2.85 (m, 1H), 2.00 (s, 3H, methyl)
^{13}C NMR : δ 208.6, 176.8, 134.8, 131.6, 129.6, 127.7, 64.9, 64.5, 48.8 (2c), 47.9 (2c), 18.0
Analysis : $C_{13}H_{14}O_3$ Calcd. : C, 71.54; H, 6.47
Found : C, 71.46; H, 6.42.

10,10-(Ethylenedioxy)-5α-methyl-1α,2β,6β,7α-tricyclo-[5.2.1.$0^{2,6}$]dec-8-en-3-one 20:

Lithium trimethoxyaluminium hydride (2.7 mmol, 6 ml) in

THF was added to a suspension of anhydrous Cuprous bromide (450 mg, 3.15 mmol) in 10 ml of THF maintained under nitrogen atmosphere at 0 to $-5^{o}C$. The resulting black solution was stirred for 30 min, cooled to $-78^{o}C$ and enone 19 (200 mg, 0.917 mmol) in 10 ml of THF was added rapidly. After 10 min MeOH (10 ml) was added, the mixture was poured into 125 ml of saturated aqueous ammonium chloride solution and then extracted with ether (3 x 50 ml). The combined extract was washed, dried and concentrated. The crude product was filtered through a silica gel (4 g) column by eluting with 25% ethyl acetate-hexane to furnish 20 (120 mg) in 60% yield.

IR : 3000, 1720, 1300 cm^{-1}

^{1}H NMR : δ 6.39-6.33 (m, 1H, olefinic), 6.13-6.08 (m, 1H, olefinic), 3.95-3.78 (m, 4H, ketal), 3.24-3.07 (m, 2H), 3.01-2.94 (m, 1H), 2.84-2.78 (m, 1H), 2.77-2.58 (m, 1H), 2.30-2.05 (m, 1H), 1.80-1.41 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H, methyl).

^{13}C NMR : δ 221.1, 133.9, 133.4, 127.2, 65.0, 64.3, 53.5, 50.1, 49.2 (2c), 43.5, 31.1, 16.8

Analysis : $C_{13}H_{16}O_3$ Calcd. : C, 70.89; H, 7.32
Found : C, 70.78; H, 7.28.

5α-methyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 12:

To a cooled solution of ketone 20(120 mg, 0.545 mmol)

in dichloromethane (5 ml) was added 60% aqueous sulfuric acid (2 ml) and the mixture was stirred at room temperature for 2h. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 25 ml). The combined extract was washed and dried. Residue obtained after the evaporation of the solvent was filtered through a silica gel (2.5 g) column by eluting with 25% ethyl acetate-hexane to furnish the dione 12 (90 mg) in 94% yield.

IR : 3000, 1720, 1690, 1610, 1300 cm^{-1}

^1H NMR : δ 6.70-6.51 (m, 1H, olefinic), 6.44-6.24 (m,1H, olefinic), 3.40-3.22 (m, 1H), 3.21-2.94 (m, 3H), 2.62-2.20 (m, 2H), 1.80-1.42 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H, methyl).

^{13}C NMR : δ 218.4, 199.2, 131.5 (2c), 49.9, 49.8, 49.5, 44.3, 40.9, 32.8, 17.1.

Analysis : $C_{11}H_{12}O_2$ Calcd. : C, 74.97; H, 6.86
Found : C, 74.82; H, 6.80.

10,10-(Ethylenedioxy)-5,5-dimethyl-1α,2β,6β,7α-tricyclo-[5.2.1.$0^{2,6}$]dec-8-en-3-one 21:

To a stirred solution of curpous iodide 1.8 g (94 mmol) in dry ether (10 ml) at -15°C, methyl lithium (4 ml, 18.5 mmol) in ether was added slowly till the yellow colour persisted. To this mixture BF_3-etherate (0.6 ml excess) was added followed by the enone 19 (200 mg, 0.917mmol) in dry ether (10 ml) and the mixture was stirred for 1h. The

reaction was quenched with saturated ammonium chloride and ammonium hydroxide solution (pH ≈ 8) and extracted with ether (3 x 50 ml). The ethereal layer was washed and dried. Residue obtained after the evaporation of the Solvent was filtered through a silica gel (4 g) column by eluting with 25% ethyl acetate-hexane to furnish dimethyl ketal 21 (128 mg) in 60% yield.

IR : 3000, 1720, 1300 cm^{-1}

^1H NMR : δ 6.39-6.34 (m, 1H, olefinic), 6.16-6.10 (m, 1H, olefinic), 3.95-3.75 (m, 4H, ketal), 3.17-3.10 (m, 1H), 3.00-2.95 (m, 1H), 2.82-2.73 (m, 1H), 1.87 (s, 3H), 1.11 (s, 3H, methyl), 1.03 (s, 3H, methyl)

^{13}C NMR : δ 220.4, 133.4, 133.1, 127.1, 65.1, 64.5, 56.1, 52.7, 50.5, 50.3, 50.1, 36.5, 33.5, 25.3

Analysis : $C_{14}H_{18}O_3$ Calcd. : C, 71.77; H, 7.74
Found : C, 71.69; H, 7.65.

5,5,-Dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione 13:

To a solution of the dimethyl ketal 21(120 mg, 0.545 mmol) in dichloromethane (5 ml) was added 60% aqueous sulfuric acid (2 ml) and the mixture was stirred at room temperature for 2h. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 25 ml). The combined extract was washed and dried. Residue obtained

after the evaporation of the solvent was filtered through a silica gel (2.5 g) column by eluting with 25% ethyl acetate-hexane to furnish the dione 13 (90 mg) in 94% yield.

IR : 3000, 1720, 1690, 1610 cm^{-1}

^1H NMR : δ 6.64-6.58 (m, 1H, olefinic), 6.44-6.38 (m, 1H, olefinic), 3.38-3.33 (m, 1H), 3.22-3.13 (m, 2H), 2.61-2.55 (m, 1H), 2.00 (½ ABq, J = 1.8 HZ, 1H), 1.73 (½ ABq, J = 1.8 HZ, 1H), 1.19 (s, 3H, methyl), 1.06 (s, 3H, methyl)

^{13}C NMR : δ 217.1, 196.4, 131.4, 130.7, 56.3, 50.4, 50.1, 49.0, 47.5, 38.4, 32.8, 25.6.

Analysis : $C_{12}H_{14}O_2$ Calcd. : C, 75.76; H, 7.42
Found : C, 75.66; H, 7.36.

Methyl-1β,6β-7-oxobicyclo[4.3.0]non-2-en-2-carboxylate 22:

To a solution of diketone 9 (1 g, 6.17 mmol) in benzene (400 ml) was added 30% aqueous sodium hydroxide (200 ml) and the mixture was refluxed for 3h. The reaction mixture was cooled and the benzene layer was separated. The aqueous layer was acidified (pH ≈ 2) and extracted with ethyl acetate. The combined extracts after washing, drying and removal of the solvent furnished the crude acid (830 mg) in 75% yield.

Esterification:

To a solution of the acid (830 mg, 4.61 mmol) in ether

(5 ml) was added excess of distilled ethereal diazomethane at 0°C until the yellow color persisted. After 30 min, excess diazomethane was destroyed with 2-3 drops of glacial acetic acid. Thr residue obtained after evaporation of the solvent was charged on a silica gel (20 g) column and eluted with 30% ethyl acetate-hexane to furnish the bicyclic ester 22 (581 mg) in 65% yield.

IR : 3000, 1730, 1270 cm^{-1}

^{1}H NMR (Fig I.3) : δ 7.05-7.01 (m, 1H, olefinic), 3.37 (s, 3H, ester methyl), 3.20-3.10 (m, 1H), 2.50-1.62 (m, 9H).

^{13}C NMR (Fig I.4) : δ 220.5, 167.8, 140.5, 131.5, 51.4, 46.4, 36.9, 35.6, 27.2, 23.7, 19.3.

Analysis : $C_{11}H_{14}O_3$ Calcd. : C, 68.02; H, 7.27
Found : C, 68.10; H, 7.25.

Methyl-1β,2α or 2β,6β-7-oxobicyclo[4.3.0]non-3-en-2-carboxylate 23 & 24:

To a solution of 9 (1.25 g, 7.71 mmol) in benzene (50 ml) was added 20 ml of 1% aq.sodium hydroxide and the mixture was stirred at room temperature for 24h. The benzene layer was separated, acidified (pH ≈ 2) the aqueous layer and extracted with ethyl acetate (3 x 50 ml). The combined organic extract after washing, drying and removal of the solvent furnished a mixture of acids. To a solution of this mixture of acids in dry ether was added excess of distilled ethereal diazomethane at 0°C till the yellow

colour persisted. After 30 min, excess of diazomethane was destroyed and the residue after removal of the solvent was filtered through silica gel (20 g) column by eluting with 35% ethyl acetate-hexane to furnish a mixture of esters 23 and 24 (980 mg, 65%) in 67:33 ratio.

IR : 3000, 2900, 1730, 1440, 1200 cm^{-1}

^1H NMR (Fig I.5) : δ 5.89-5.70 (m, 2H, olefinic), 5.68-5.54 (m, 2H, olefinic), 3.69 (s, 3H, ester methyl), 3.68 (s, 3H, ester methyl), 3.18-3.05 (m, 1H), 2.78-2.69 (m, 1H), 2.42-1.82 (m, 6H), 1.61-1.42 (m, 1H).

^{13}C NMR (Fig I.6) : δ 218.0, 217.0, 173.9, 173.4, 128.3, 127.1, 125.1, 123.0, 52.1, 52.0, 50.0, 49.4, 45.8, 42.1, 40.5, 37.0, 35.0, 27.0, 25.6, 24.8, 20.9.

Methyl-1β,2α or 2β,6β-7,7-(ethylenedioxy)bicyclo[4.3.0]non-3-en-2-carboxylate 25 & 26:

To a solution of mixture of esters 23 & 24 (950 mg, 4.85 mmol) in benzene (100 ml) was added ethylene glycol (0.2ml, 3.6 mmol) and catalytic amount of p-toluenesulfonic acid (PTS) and the mixture was refluxed using a Dean-Stark water separator for 3h. The cooled reaction mixture was washed, dried and removed solvent to furnish a mixture of ketals 25 & 26 which were separated on a silica gel (20 g) column by eluting with 10% ethyl acetate-hexane (70:30).

Methyl-1β,2β,6β-7,7-(ethylenedioxy)bicyclo[4.3.0]non-3-en-2-

carboxylate 25:

IR : 3000, 1720, 1460, 1200 cm^{-1}

^1H NMR (Fig I.27) : δ 5.89-5.79 (m, 1H, olefinic), 5.67-5.59 (m, 1H, olefinic), 3.91-3.85 (m, 4H, ketal), 3.68 (s, 3H, ester methyl), 2.98-2.91 (m, 1H), 2.15-1.35 (m, 8H).

^{13}C NMR (Fig I.28) : δ 174.1, 128.9, 124.4, 116.6, 64.9, 64.8, 51.6, 49.8, 47.8, 40.4, 36.0, 27.8, 24.2.

Analysis : $C_{13}H_{18}O_4$ Calcd. : C, 65.53; H, 7.61
Found : C, 65.47; H, 7.60.

Methyl-1β,2α,6β-7,7-(ethylenedioxy)bicyclo[4.3.0]non-3-en-2-carboxylate 26:

IR : 3000, 1720, 1460, 1200 cm^{-1}

^1H NMR : δ 5.92-5.83 (m, 1H, olefinic), 5.72-5.64 (m, 1H, olefinic), 3.91-3.89 (m, 4H, ketal), 3.69 (s, 3H, ester methyl), 2.94-2.71 (m, 1H), 2.59-2.42 (m, 1H), 2.20-1.01 (m, 7H).

^{13}C NMR : δ 174.8, 128.3, 122.6, 118.8, 64.8, 64.0, 51.9, 43.3, 40.1, 36.5, 33.4, 26.4, 21.5.

Analysis : $C_{13}H_{18}O_4$ Calcd. : C, 65.53; H, 7.61
Found : C, 65.42; H, 7.58.

Methyl-1β,6β-7,7-(ethylenedioxy)bicyclo[4.3.0]non-2-en-2-carboxylate 27:

To a solution of ketone 22 (500 mg, 2.57 mmol) in

benzene (10 ml) was added ethylene glycol (0.15 ml, 2.57 mmol) and catalytic amount of PTS and the mixture was refluxed for 8h. The reaction mixture was cooled, washed and dried. The residue obtained after the removal of the solvent was filtered through a silica gel (10 g) column by eluting with 20% ethyl acetate-hexane to furnish the ketal 27 (583 mg) in 95% yield.

IR : 3000, 1730, 1280 cm^{-1}

^1H NMR (Fig I.17) : δ 6.98-6.93 (m, 1H, olefinic), 3.91-3.85 (m, 4H, ketal), 3.71 (S, 3H,ester methyl), 3.05-3.01 (m, 1H), 2.40-1.20 (m, 9H).

^{13}C NMR (Fig I.18) : δ 167.6, 139.1, 133.2, 118.7, 64.7, 63.7, 51.3, 43.6, 35.8, 33.1, 28.0, 25.0, 19.5.

Analysis : $C_{13}H_{18}O_4$ Calcd. : C, 65.53; H, 7.61
Found : C, 65.60; H, 7.64.

Methyl-1β,2α,6β-7,7-(ethylenedioxy)bicyclo[4.3.0]nona-2-carboxylate 28:

A solution of β,γ-unsaturated ester ketal 26 or α,β-unsaturated ester ketal 27 (20 mg, 0.08 mmol) in dry ethyl acetate (3 ml) was stirred at room temperature under hydrogen atmosphere over 10% Pd/C (2 mg). After 10 min, the catalyst was filtered and the solvent was evaporated to furnish saturated ester ketal 28 (20 mg, 100%).

IR : 3000, 1720, 1200 cm^{-1}

^1H NMR : δ 3.95-3.80 (m, 4H, ketal), 3.65 (s, 3H, ester

methyl), 2.72-2.55(m, 2H), 2.12-0.97 (m, 11H).

^{13}C NMR : δ 175.2, 118.7, 64.7, 63.7, 51.3, 46.1, 42.8, 37.9, 32.7, 23.9, 22.5, 22.3,19.9.

Analysis : $C_{13}H_{20}O_4$ Calcd. : C, 64.98; H, 8.39

Found : C, 64.85; H, 8.29.

Methyl-1β,6β,9β-7-oxo-9-methylbicyclo[4.3.0]non-2-en-2-carboxylate 29:

To a solution of diketone 11 (90 mg, .51 mmol) in benzene (400 ml) was added 30% aqueous sodium hydroxide (200 ml) and the mixture was refluxed for 3h. The reaction mixture was cooled and the benzene layer was separated. The aqueous layer was acidified (pH ≈ 2) and extracted with ethyl acetate. The combined extracts after washing, drying and removal of the solvent furnished the crude acid (80 mg) in 66% yield.

Esterification:

To a solution of the acid (70 mg, .42 mmol) in ether (5 ml) was added excess of distilled ethereal diazomethane at 0°C until the yellow color persisted. After 30 min, excess diazomethane was destroyed with 2-3 drops of glacial acetic acid. The residue obtained after evaporation of the solvent was charged on a silica gel (20 g) column and eluted with 30% ethyl acetate-hexane to furnish the bicyclic ester 22 (70 mg) in 65% yield.

IR : 3000, 1730, 1700, 1420, 1220 cm^{-1}

^1H NMR (Fig I.7) : δ 7.04 (m, 1H, olefinic), 3.76 (s, 3H, ester methyl), 3.07-3.01 (m, 1H), 2.68-2.57 (m, 1H), 2.36-1.90 (m, 6H), 1.68-1.50 (m, 1H), 1.17 (d, J = 7 Hz, 3H, methyl).

^{13}C NMR (Fig I.8) : δ 220.5,167.7, 140.6, 132.1, 51.6, 45.3, 44.9, 42.2, 35.0, 23.0, 20.7, 20.0.

Analysis : $C_{12}H_{16}O_3$ Calcd. : C, 69.21; H, 7.74
Found : C, 69.13; H, 7.70.

Methyl-1β,6β,9α-7-oxo-9-methylbicyclo[4.3.0]non-2-en-2-carboxylate 30:

To a solution of diketone 12 (90 mg, .51 mmol) in benzene (400 ml) was added 30% aqueous sodium hydroxide (200 ml) and the mixture was refluxed for 3h. The reaction mixture was cooled and the benzene layer was separated. The aqueous layer was acidified (pH ≈ 2) and extracted with ethyl acetate. The combined extracts after washing, drying and removal of the solvent furnished the crude acid (90 mg) in 75% yield.

Esterification:

To a solution of the acid (90 mg, .50 mmol) in ether (5 ml) was added excess of distilled ethereal diazomethane at 0°C until the yellow color persisted. After 30 min, excess diazomethane was destroyed with 2-3 drops of glacial acetic

acid. The residue obtained after evaporation of the solvent was charged on a silica gel (20 g) column and eluted with 30% ethyl acetate-hexane to furnish a mixture of bicyclic esters 30 and 31 (70 mg) in 65% yield.

IR : 3000, 1720, 1700, 1600, 1420, 1240 cm^{-1}

^1H NMR (Fig I.9) : δ 7.16-711 (m, 1H, olefinic), 3.77 (s, 3H, ester methyl), 3.40-3.22 (m, 1H), 2.95-2.80 (m, 1H), 2.60-1.20 (series of m, 7H), 0.98 (d, J = 6.4 Hz, 3H, methyl).

^{13}C NMR (Fig I.10) : δ 221.1, 168.0, 141.5, 130.1, 51.6, 46.5, 45.4, 38.7, 32.4, 24.3, 21.8, 18.3.

Analysis : $C_{12}H_{16}O_3$ Calcd. : C, 69.21; H, 7.74
Found : C, 69.15; H, 7.69.

Methyl-1β,6β-7-oxo-9,9-dimethylbicyclo[4.3.0]non-2-en-2-carboxylate 32:

To a solution of diketone 13 (90 mg, .473 mmol) in benzene (400 ml) was added 30% aqueous sodium hydroxide (200 ml) and the mixture was refluxed for 3h. The reaction mixture was cooled and the benzene layer was separated. The aqueous layer was acidified (pH ≈ 2) and extracted with ethyl acetate. The combined extracts after washing, drying and removal of the solvent furnished the crude acid (80 mg) in 75% yield.

Esterification:

To a solution of the acid (830 mg, 4.61 mmol) in ether

(5 ml) was added excess of distilled ethereal diazomethane at 0°C until the yellow color persisted. After 30 min, excess diazomethane was destroyed with 2-3 drops of glacial acetic acid. The residue obtained after evaporation of the solvent was charged on a silica gel (20 g) column and eluted with 30% ethyl acetate-hexane to furnish the bicyclic ester 32 (70 mg) in 67% yield.

IR : 3000, 1720, 1280 cm^{-1}

^1H NMR (Fig I.11) : δ 7.02-6.98 (m, 1H, olefinic), 3.76 (s, 3H, ester methyl), 3.30-3.26 (m, 1H), 2.80-2.60 (m, 1H), 2.20-1.85 (m, 4H), 1.69-1.51 (m, 2H), 1.20 (s, 3H, methyl), 1.01 (s, 3H, methyl)

^{13}C NMR (Fig I.12) : δ 220.4, 169.3, 140.6, 132.1, 53.4, 51.7, 46.8, 44.7, 39.9, 30.2, 25.8, 22.9, 22.3.

Analysis : $C_{13}H_{18}O_3$ Calcd. : C, 70.24; H, 8.16
Found : C, 70.17; H, 8.10.

Methyl-1β.6β,7α-7-hydroxy-8,8-dimethylbicyclo[4.3.0]non-2 or -3-en-2-carboxylate 33 & 34:

To a solution of diketone 10 (200 mg, 1.04 mmol) in benzene (400 ml) was added 30% aqueous sodium hydroxide (200 ml) and the mixture was refluxed for 3h. The reaction mixture was cooled and the benzene layer was separated. The aqueous layer was acidified (pH ≈ 2) and extracted with ethyl acetate. The combined extracts after washing, drying and removal of the solvent furnished a mixture of crude

acids in 75% yield.

Esterification:

To a solution of acid mixture (120 mg, .94 mmol) in ether (5 ml) was added excess of distilled ethereal diazomethane at 0°C until the yellow color persisted. After 30 min, excess diazomethane was destroyed with 2-3 drops of glacial acetic acid. The residue obtained after evaporation of the solvent was charged on a silica gel (20 g) column and eluted with 30% ethyl acetate-hexane to furnish a mixture of bicyclic esters 33 and 34 (100 mg) in 70% yield.

Methyl-1β,6β,7α-7-hydroxy-8,8-dimethylbicyclo[4.3.0]non-3-en-2-carboxylate 33:

IR : 3500, 2900, 1720, 1420, 1180 cm^{-1}

^{1}H NMR : δ 6.10-6.01 (m, 1H, olefinic), 5.92-5.82 (m, 1H, olefinic), 3.82 (s, 3H, ester methyl), 3.81 (s, 3H, methyl), 3.70 (m, 1H), 3.01-2.91 (m, 1H), 2.64-2.48 (m, 1H), 2.10-1.30 (series of m, 6H), 1.16 (s, 3H, methyl), 1.10 (s, 3H, methyl).

^{13}C NMR : δ 176.9 (131.2), 130.0, 125.6 (124.5), 82.3 (81.1), (51.8), 51.5, 46.2 (44.3), 43.9, 43.6, 42.7, 36.6 (27.8), 27.7, 27.4, (23.6), 23.3. (Values given in brackets are of minor isomer)

Methyl-1β,6β,7α-7-hydroxy-8,8-dimethylbicyclo[4.3.0]non-2-en

-2-carboxylate 34:

IR : 3500, 2900, 1700, 1420 cm^{-1}

^1H NMR (Fig I.13) : δ 7.02-6.92 (m, 1H, olefinic), 4.01-3.92 (m, 1H), 3.82 (s, 3H, ester methyl), 3.10-2.82 (m, 1H), 2.70-1.92 (m, 4H), 1.90-1.30 (m, 4H), 1.14 (s, 3H, methyl), 1.12 (s, 3H, methyl)

^{13}C NMR (Fig I.14) : δ 162.0, 139.8, 133.4, 83.2, 51.4, 46.0, 42.0, 40.9, 33.8, 30.1, 25.2, 25.1, 18.4.

Analysis : $C_{13}H_{20}O_3$ Calcd. : C, 69.61; H, 8.99

Found : C, 69.52; H, 8.90.

Conversion of β,γ-unsaturated ester 33 to α,β-unsaturated ester 34:

To a solution of 33 (50 mg, 0.223 mmol) in ethanol (5 ml) was added catalytic amount of rhodium trichloride (8 mg) and refluxed the mixture for 6h. Removal of ethanol under reduced pressure and on filtration of the curde product through a small Celite pad furnished 34 (32 mg, 62%).

Methyl-1β,6β,7α-7-methanesulfonyloxy-8,8-dimethylbicyclo-[4.3.0]non-2-en-2-carboxylate 35:

To a solution of 34 (500 mg, 2.23 mmol) in 3 ml of dry pyridine was added distilled methanesulfonyl chloride (250 mg, 2.23 mmol) at ice temperature under nitrogen atmosphere. After 1h, the reaction mixture was poured in to cold water and extracted with ether (3 x 20 ml). The combined extract was washed and dried. The residue obtained after

evaporation of the solvent was filtered through a silica gel (10 g) column by eluting with 25% ethyl acetate-hexane to furnish 35 (405 mg) in 60% yield.

IR : 3000, 2900, 1700, 1350, 1200 cm^{-1}

^{1}H NMR : δ 7.04-6.95 (m, 1H, olefinic), 4.80-4.76 (d, J = 6.8 Hz, 1H, H attached to OMs), 3.73 (s, 3H, ester methyl), 3.04 (s, 3H, mesylate methyl), 2.98-1.38 (series of m, 8H), 1.17 (s, 3H, methyl), 1.09 (s, 3H, methyl).

^{13}C NMR : δ 167.4, 139.7, 132.2, 91.4, 51.6, 45.6, 41.5, 40.9, 38.0, 34.1, 29.7, 25.8, 25.0, 18.9.

Methyl-1β,6β,7α-4-oxo-7-methanesulfonyloxy-8,8-dimethylbicyclo[4.3.0]nona-2-carboxylate 36:

To a solution of 35 (300 mg, 0.993 mmol) in benzene (5 ml) was added celite (100 mg), PDC (700 mg, 1.98 mmol), and 0.1 ml of 80% t-butyl hydroperoxide and the mixture was stirred under nitrogen at room temperature for 1h. The reaction mixture was filtered through a small celite pad. The crude product obtained after the removal of the solvent was charged on silica gel (6 g) column and eluted with 30% ethyl acetate-hexane to furnish enone 36 (188 mg) in 60% yield.

IR : 3000, 1720, 1680, 1350, 1200 cm^{-1}

^{1}H NMR : δ 6.71 (s, 1H, olefinic), 4.78-4.76 (d, J = 4.6

Hz, 1H, H attached to OMs), 3.83 (s, 3H, ester methyl), 3.45-3.00 (series of m, 2H), 2.95 (s, 3H, mesylate methyl), 2.75-2.20 (series of m, 3H), 1.60-1.40 (m, 1H), 1.14 (s, 6H, dimethyl).

^{13}C NMR : δ 198.5, 166.9, 150.7, 131.1, 92.5, 52.6, 45.4, 41.5, 39.4, 38.0, 36.1, 34.4, 27.6, 24.3.

Methyl-1β,2α,6β,7α-4-oxo-7-methanesulfonyloxy-8,8-dimethylbicyclo[4.3.0]nona-2-carboxylate 37:

A solution of 36 (10 mg, 0.031 mmol) in dry ethyl acetate (2 ml) was stirred at room temperature under hydrogen atmosphere over 10% Pd/C (2 mg). After 10 min the catalyst was filtered and the solvent was evaporated to furnish the saturated ketone 37.

m.p. : 125°C

IR : 3000, 2900, 1720, 1350, 1200 cm^{-1}

^{1}H NMR (Fig I.15) : δ 4.70-4.67 (d, J = 4.4 Hz, 1H, H attached to OMs), 3.72 (s, 3H, ester methyl), 3.12-3.04 (m, 1H), 2.96 (s, 3H, mesylate methyl), 2.70-2.31 (series of m, 4H), 1.70-1.45 (series of m, 4H), 1.14 (s, 3H, methyl), 1.06 (s, 3H, methyl).

^{13}C NMR (Fig I.16) : δ 209.9, 172.8, 91.4, 52.1, 42.7, 39.3 (2c), 38.3 (2c), 37.6, 36.5, 34.6, 25.8, 23.8.

LRMS : $C_{14}H_{22}O_6S$ Calcd. : 318 (M^+)

Found : 318 (M^+)

Methyl-1β,6β-4-oxo-7,7-(ethylenedioxy)bicyclo[4.3.0]non-2-en-2-crboxylate 47:

To a solution of 27 (500 mg, 2.1 mmol) in benzene (10 ml) at ice-temperature was added celite (100 mg), PDC (1.5 g, 4.2 mmol) and 0.1 ml of 80% t-butyl hydroperoxide and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was filtered through a small celite pad. The crude product obtained after evaporation of the solvent was charged on a silica gel (10 g) column and eluted with 30% ethyl acetate-hexane to furnish enone 47 (323 mg) in 61% yield.

IR : 3000, 1730, 1690, 1220 cm^{-1}

^1H NMR (Fig I.19) : δ 6.70-6.69 (d, J = 1.6 Hz, 1H, olefinic), 3.90-3.84 (m, 4H, ketal), 3.82 (s, 3H, ester methyl), 3.30-3.26 (m, 1H), 2.62-2.58 (m, 1H), 2.44-1.54 (m, 6H).

^{13}C NMR (Fig I.20) : δ 198.2, 166.7, 149.1, 131.7, 117.3, 65.0, 64.7, 52.2, 43.9, 35.4, 35.1, 33.8, 27.8.

Analysis : $C_{13}H_{16}O_5$ Calcd. : C, 61.89; H, 6.39
Found : C, 61.79; H, 6.35.

Methyl-1β,6β-4-ethylidene-7,7-(ethylenedioxy)bicyclo[4.3.0]-non-2-en-2-carboxylate 48:

To a suspension of ethyltriphenylphosphonium bromide

(662 mg, 1.785 mmol) in dry benzene (4 ml) was added n-butyl lithium in hexane (115 mg, 1.785 mmol) at room temperature under nitrogen atmosphere. To the so formed red orange colour ylide was added immediately enone 47 (300 mg, 1.19 mmol) in 5 ml of dry benzene and the mixture was stirred at room temperature for 15 min. The reaction mixture was quenched with water, extracted with ethyl acetate (3 x 50 ml). The combined extract was washed and dried. The residue obtained after the evaporation of the solvent was filtered through a silica gel (10 g) column by eluting with 20% ethyl acetate-hexane to furnish the Wittig product 48 (180 mg) in 57% yield.

IR : 3000, 1720, 1250 cm^{-1}

^{1}H NMR (Fig I.21) : δ 7.11 (s, 1H, olefinic), 5.86 (m, 1H, ethylidenic), 3.95-3.78 (m, 4H, ketal), 3.74 (s, 3H, ester methyl), 3.11-2.93 (m, 1H), 2.61 (m, 1H), 2.28-1.84 (m, 6H), 1.80 (d, J = 6 Hz, 3H, methyl).

^{13}C NMR (Fig I.22) : δ 168.0, 139.4, 134.7, 132.9, 131.9, 131.2, 129.5, 128.6, 118.7, 64.9, 63.9, 51.4, 44.8, 43.9, 37.1, 36.7, 33.7, 29.2, 27.8, 21.9, 13.9, 13.3.

Analysis : $C_{15}H_{20}O_4$ Calcd. : C, 68.16; H, 7.63
Found : C, 68.09; H, 7.53.

Methyl-1β,4α,6β-4-ethyl-7,7-(ethylenedioxy)bicyclo[4.3.0]non

-2-en-2-carboxylate 49:

A solution of the diene 48 (100 mg, 0.378 mmol) in 4 ml of dry ethyl acetate was stirred at room temperature over 10% Pd-C (10 mg) under hydrogen atmosphere. After 10 min, the catalyst was filtered-off and the solvent was evaporated to furnish the α,β- unsaturated ester 49 (86 mg) in 86% yield.

IR : 3000, 1720, 1420, 1250 cm^{-1}

^1H NMR (Fig I.23) : δ 6.84 (m, 1H, olefinic), 3.91 (m, 4H, ketal), 3.73 (s, 3H, ester methyl), 2.96 (m, 1H), 2.30-1.80 (m, 6H), 1.60-1.25 (m, 4H), 0.98 (t, J = 7.3 Hz, 3H, methyl).

^{13}C NMR (Fig I.24) : δ 167.8, 143.4, 133.1, 118.8, 64.9, 63.8, 51.5, 44.9, 37.9, 36.5, 33.1, 28.3, 28.1, 26.5, 11.3.

Analysis : $C_{15}H_{22}O_4$ Calcd. : C, 67.64; H, 8.33
Found : C, 67.55; H, 8.28.

1β,4α,6β-4-ethyl-7-oxobicyclo[4.3.0]non-2-en-2-carboxylate (CORONAFACIC ACID) 40:

A solution of the ketal ester 49 (15 mg, 0.056 mmol) in 5 ml of 25% aqueous hydrochloric acid was refluxed for 4h. The reaction mixture was cooled, diluted with water (5 ml) and extracted with ethyl acetate (3 x 10 ml), the combined extract was washed and dried. Solvent was evaporated and the residue was filtered through a silica gel (30 mg) column by eluting with 50% ethyl acetate-hexane to furnish the acid

40 (9.5 mg) in 70% yield.

m.p. : 120°C (lit. 124-125°C)[23a]

IR : 3300, 3000, 1730, 1690, 1450, 1260 cm^{-1}

^1H NMR (Fig I.25) : δ 7.07 (br s, 1H, olefinic), 3.08 (m, 1H), 2.70-2.10 (m, 5H), 2.01-1.05 (m, 5H), 0.99 (t, J = 7.3 Hz, 3H, methyl).

^{13}C NMR (Fig I.26) : δ 220.0, 171.4, 146.8, 130.9, 46.7, 38.2, 38.0, 36.1, 28.2, 27.8, 25.8, 11.2.

Analysis : $C_{12}H_{16}O_3$ Calcd. : C, 69.21; H, 7.74
Found : C, 69.31; H, 7.81.

1β,2β,6β-2-hydroxymethyl-7,7-(ethylenedioxy)bicyclo[4.3.0]-non-3-ene 58:

A solution of 25 (680 mg, 2.55 mmol) in dry THF (30 ml) and LAH (162 mg, 4.27 mmol) was refluxed overnight. The reaction mixture was quenched with saturated sodium sulphate and extracted with ethyl acetate (3 x 50 ml). The combined extract was washed, dried and evaporation of the solvent furnished alcohol 58 (450 mg, 75%).

IR : 3300, 3000, 1300, 1050 cm^{-1}

^1H NMR (Fig I.29) : δ 5.85-5.78 (m, 1H, olefinic), 5.62-5.56 (m, 1H, olefinic), 3.95-3.81 (m, 4H, ketal), 3.72-3.64 (m, 1H), 3.54-3.46 (m, 1H), 2.20-1.20 (m, 9H).

^{13}C NMR (Fig I.30) : δ 128.8, 127.9, 117.0, 65.4, 64.9, 64.7, 48.2, 46.7, 40.3, 36.3, 27.4, 24.4.

Analysis : $C_{12}H_{18}O_3$ Calcd. : C, 68.54; H, 8.63
Found : C, 68.48; H, 8.60.

1β,2β,6β-2-bromomethyl-7,7-(ethylenedioxy)bicyclo[4.3.0]non-3-ene 59:

To a solution of 58 (450 mg, 2.14 mmol) in dry dichloromethane (10 ml) was added triphenylphosphine (1.1 g, 4.28 mmol) and carbon tetrabromide (1.4 g, 4.28 mmol) at $0^{o}C$ and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was diluted with dichloromethane, washed and dried. The residue obtained after the evaporation of the solvent was filtered through a silica gel (10 g) column to furnish the unsaturated bromoketal 59 (400 mg) in 70% yield.

IR : 3000, 1450, 1300 cm^{-1}
^{1}H NMR : δ 5.85-5.78 (m, 1H, olefinic) 5.62-5.52 (m, 1H, olefinic), 3.90-3.50 (m, 4H, ketal), 3.36-3.29 (m, 2H), 2.40-1.20 (m, 9H).
^{13}C NMR : δ 128.8, 128.5, 116.8, 64.9, 64.8, 48.0, 45.6, 42.2, 37.3, 36.1, 26.8, 24.4.
Analysis : $C_{12}H_{17}O_2Br$ Calcd. : C, 52.76; H, 6.27
Found : C, 52.69; H, 6.25.

1β,2β,6β-2-bromomethyl-7,7-(ethylenedioxy)bicyclo[4.3.0]nonane 60:

A solution of the unsaturated bromomethyl ketal 59(400 mg, 1.46 mmol) in dry ethyl acetate (5 ml) was stirred at

room temperature under hydrogen atmosphere over 10% Pd/C (5 mg). After 10 min, the catalyst was filtered and the solvent was evaporated to furnish saturated bromoketal 60 (360 mg) in 90% yield.

IR : 2900, 1450, 1300 cm^{-1}

^1H NMR (Fig I.31) : δ 3.98-3.82 (m, 4H), 3.55-3.48 (m, 1H), 3.31-3.23 (m, 1H), 2.02-1.02 (m,13H).

^{13}C NMR (Fig I.32) : δ 117.0, 65.0, 64.8, 52.5, 45.7, 45.5, 38.6, 35.9, 30.9, 26.3, 25.4, 24.2.

Analysis : $C_{12}H_{19}O_2Br$ Calcd. : C, 52.38; H, 6.96
Found : C, 52.30; H, 6.92.

1β,2β,6β-2-Methylbicyclo[4.3.0]nonan-7-one 57:

To a solution of 60 (360 mg, 1.3 mmol) in dry HMPA (5 ml) was added $NaCNBH_3$ (163 mg, 2.6 mmol) and the mixture was stirred at 80°C for 4h. The reaction mixture was diluted with water and extracted with ether (3 x 50 ml). The ethereal extract was washed and dried. The residue obtained after the evaporation of the solvent was filtered through a silica gel (2 g) column by eluting with 2% ethyl acetate-hexane to furnish 57 (100 mg) in 50% yield.

IR : 2930, 1740, 1450 cm^{-1}

^1H NMR (Fig I.33) : δ 2.30-1.02 (m, 13H), 0.96 (s, 3H).

^{13}C NMR (Fig I.34) : δ 219.7, 50.2, 43.8, 34.7, 33.5, 32.2, 23.4, 22.7 (2c), 20.6.

Analysis : $C_{10}H_{16}O$ Calcd. : C, 78.89; H, 10.59
Found : C, 78.72; H, 10.50.

1β,2β,6β-2-Methylbicyclo[4.3.0]nona-7-oxime 61:

A mixture of 57 (100 mg, 0.65 mmol), hydroxylamine hydrochloride (76 mg, 1.1 mmol), sodium acetate (98 mg, 6 mmol) and methanol (3 ml) was stirred at room temperature for 45 min. The residue after evaporation of the solvent was diluted with water and extracted with ether (3 x 15 ml). The solvent was evaporated and the residue was filtered through a silica gel (2 g) column to furnish oxime 60 (105 mg) in 95% yield.

IR : 3270, 2950, 1452 cm^{-1}
^1H NMR : δ 2.78-2.21 (m, 3H), 2.18-1.15 (m, 11H), 0.95 (s, 3H, methyl).
^{13}C NMR : δ 166.7, 46.2, 43.2, 33.7, 31.1, 25.6, 25.0, 24.6, 21.5, 20.6.

1β,6β,7β-2-Aza-7-methylbicyclo[4.4.0]decan-3-one 62:

p-Toluenesulfonylchloride (280 mg, 1.48 mmol) was added portion-wise over 10 min to a stirred solution of the oxime 61 (105 mg, 0.628 mm) followed by sodium hydroxide (135 mg, 3.4 mmol) in 10 ml dioxan/water (3:4) at 5°C. The mixture was stirred at room temperature for 15h and dioxane was removed under vacuum. The residue was dissolved in dichloromethane and washed. Removal of solvent and

crystallization gave lactam 62 (70 mg) in 67% yield.

m.p. : 149-150°C (Lit. : 150-152°C)[28a]

IR : 3178, 3074, 1674, 1479 cm^{-1}

^1H NMR (Fig I.35) : δ 5.68 (br s, 1H, NH), 3.65-3.60 (m, 1H), 2.33-2.26 (m, 2H), 2.12-1.95 (m, 1H), 1.79-1.34 (m, 9H), 0.93 (d, J = 6.3 Hz, 3H, methyl).

^{13}C NMR (Fig I.36) : δ 172.8, 52.3, 39.8, 33.7, 31.9, 27.6, 27.3, 23.2, 19.9, 19.3.

1β,3α,6β,7β-2-Aza-3-npropyl-7-methylbicyclo[4.4.0]decane dl-Pumiliotoxin C 41:

The lactam 62 (30 mg, 0.17 mmol) was added to a stirred mixture of trimethyloxoniumtetrafluoroborate (45 mg, 0.3 mmol), N-ethyldiisopropylamine (1 drop) and dichloromethane at 10°C under N_2. After 1h the mixture was diluted with dichloromethane and shaken with saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulphate and evaporation of solvent gave the crude lactim ether 63. A solution of lactim ether 63 in benzene (5 ml) was added to n-propylmagnesiumbromide (2 ml, 0.5 mmol) [prepared from propylbromide (0.2 ml) and magnesium (50 mg in ether)] and refluxed for 6h. The cooled reaction mixture after dilution with ether was washed with aqueous sodium bicarbonate, dried and evaporated to give crude imine 64. The crude imine in dry dichloromethane was cooled to -78°C and DIBAL-H (1 eq.) was added under N_2. After 15 min, the

reaction was quenched with methanol and diluted with dichloromethane, washed and dried. Removal of the solvent and filtration through a silica gel (500 mg) column furnished free pumiliotoxin c , which for characterization was converted to its hydrochloride with dry HCl in ether. Crystallization from 2-propanol/ether gave a white solid 65 (7 mg) in 45% yield.

m.p. : 235-238°C (Lit. : 238-242°C)[28a]

IR (KBr) : 3400, 2530, 1595, 1450 cm^{-1}

^1H NMR (Fig I.37) : δ 9.6 (br s, 1H), 8.3 (br s, 1H), 3.32-3.30 (br d, 1H), 3.12-2.90 (m, 1H), 2.61-1.10 (m, 13H), 0.93 (d, J = 6.8 Hz, 3H, methyl), 0.91 (d, J = 6.8 Hz, 3H, methyl)

^{13}C NMR (Fig I.38) : δ 60.1, 58.0, 40.9, 34.9, 34.4, 29.1, 27.3, 25.2, 23.2, 20.7, 19.7, 19.1, 13.7.

Methyl-1β,6β-5-oxo-7,7-(ethylenedioxy)bicyclo[4.3.0]non-2-en-2-carboxylate 72:

To a solution of 25 & 26 (570 mg, 2.39 mmol) in dry benzene (10 ml) was added celite (100 mg), PDC (1.8 g, 4.78 mmol) and 80% t-butylhydroperoxide (215 mg, 0.24 ml, 2.39 mmol) under nitrogen atmosphere at ice temperature. Stirred the reaction mixture at room temperature for 2h. The reaction mixture was filtered through a small celite pad. Residue obtained after removal of the solvent was filtered through a silica gel (10 g) column by eluting with 35% ethyl

acetate-hexane to furnish ester ketone 72 (360 mg) in 60% yield.

IR : 3000, 2900, 1720, 1690, 1200 cm^{-1}

^1H NMR (Fig I.39) : δ 6.63-6.61 (m, 1H, olefinic), 4.01-3.85 (m, 4H, ketal), 3.82 (s, 3H, ester methyl), 2.85-1.40 (series of m, 8H).

^{13}C NMR (Fig I.40) : δ 200.2, 166.6, 150.7, 134.0, 115.2, 65.4, 65.0, 52.4, 50.2, 40.7, 38.1, 36.2, 26.1.

Analysis : $C_{13}H_{16}O_5$ Calcd. : C, 61.89; H, 6.39
Found : C, 61.72; H, 6.32.

1β,6β-2-(1-Hydroxy-1-methyl ethyl)-5-hydroxy-5-methyl-7,7-(ethylenedioxy)bicyclo[4.3.0]non-2-ene 73:

To a solution of 72 (360 mg, 1.42 mmol) in dry ether (10 ml) was added methyllithium in ether (66 mg = 2.14 ml, 3.02 mmol) under nitrogen. The reaction mixture was refluxed for 2.5h. Quenched the reaction mixture with water and extracted with ethyl acetate. The combined extract was washed and dried. The solvent was evaporated and the residue was filtered through a silica gel (6 g) column by eluting with 50% ethyl acetate-hexane to furnish diol 73 (225 mg, 60%) as a mixture of isomers.

IR : 3300, 2900, 1200 cm^{-1}

^1H NMR (Fig I.41) : δ 5.67-5.58 (m, 1H, olefinic), 4.02-3.83 (m, 4H, ketal), 2.41-1.42 (series of m, 8H), 1.37 (s, 3H, methyl), 1.34 (s, 3H, methyl), 1.33 (s, 3H,

methyl).

^{13}C NMR (Fig I.42) : δ 148.2 (m), 146.1, 128.5, 126.9 (m), 115.5, 72.8, 72.6, 70.2 (m), 65.1, 64.7, 50.5, 48.2, 42.1, 37.6, 37.2, 36.6 (m), 30.8 (m), 29.7, 29.6, 28.3, 28.0 (m).

m = minor

2-(1-methyl ethenyl)-5-methyl-7-oxobicyclo[4.3.0]nona-1,3,-5-triene 74:

To a soution of 73 (210 mg, 0.792 mmol) in dry benzene (4 ml) was added catalytic amount of PTS (77 mg, 0.396 mmol) and stirred the mixture under nitrogen at room temperature. After 6-7h, the reaction mixture was diluted with benzene (10 ml), washed and dried. The solvent was evaporated and the residue was filtered through a silica gel (2 g) column by eluting with 20% ethyl acetate-hexane to furnish the aromatic ketone 74 (30 mg) in 20% yield.

IR : 2900, 1720, 1240 cm^{-1}

^{1}H NMR (Fig I.43) : δ 7.50 (s, 1H, aromatic), 7.33 (s, 1H, aromatic), 5.29 (s, 1H, exo-methylene), 5.10 (s, 1H, exo-methylene), 3.16-3.10 (m, 2H), 2.72-2.66 (m, 2H), 2.42 (s, 3H, aromatic methyl), 2.15 (s, 3H, methyl).

^{13}C NMR (Fig I.44) : δ 207.3, 149.4, 142.8, 141.4, 137.7, 137.4, 134.3, 122.5, 115.8, 36.6, 25.5, 23.5, 21.0.

Analysis : $C_{13}H_{14}O$ Calcd. : C, 83.83; H, 7.58

Found : C, 83.79; H, 7.50.

2-(1-Methyl ethyl)-5-methyl-7-oxobicyclo[4.3.0]nona-1,3,5-triene 75:

A solution of 74 (25 mg, 0.134 mmol) in dry ethyl acetate (3 ml) was stirred at room temperature under hydrogen atmosphere over 10% Pd/C (3 mg). After 30 min, the catalyst was filtered and evaporated the solvent to furnish aromatic ketone 75 (22 mg) in 90% yield.

IR : 2900, 1720, 1500, 1300 cm^{-1}

^1H NMR (Fig I.45) : δ 7.42 (s, 1H, aromatic), 7.32 (s, 1H, aromatic), 3.12-3.03 (m, 3H), 2.72-2.66 (m, 2H), 2.40 (s, 3H, aromatic methyl), 1.23 (d, J = 6.8 Hz, 6H, isopropyl methyl).

^{13}C NMR (Fig I.46) : δ 207.5, 150.1, 146.1, 137.7, 137.2, 132.0, 121.2, 36.4, 29.6, 23.9, 22.9 (2c), 21.2.

Analysis : $C_{13}H_{16}O$ Calcd. : C, 82.93; H, 8.57

Found : C, 82.90; H, 8.51.

2-(1-Methyl ethyl)-5,8,8-trimethyl-7-oxobicyclo[4.3.0]nona-1,3,5-triene 67:

To a solution of 75 (20 mg, 0.106 mm) in dry THF (3 ml) was added NaH (7.6 mg, 318 mmol) and excess methyl iodide under N_2 atmosphere at room temperature. The reaction mixture was refluxed for 3h. The reaction mixture was cooled and quenched with water and extracted with ether (3 x 10

ml). The combined extract was washed and dried. The residue obtained after the evaporation of the solvent was filtered thorough a silica gel (500 mg) column by eluting with 5% ethyl acetate-hexane to furnish de-oxy primnoied 67 (10 mg) in 55% yield.

IR : 3000, 2900, 1720, 1500 cm^{-1}

^1H NMR (Fig I.47) : δ 7.44 (s, 1H, aromatic), 7.34 (s, 1H, aromatic), 3.14-3.00 (m, 1H, hydrogen in isopropyl), 2.93 (s, 2H, α to dimethyl), 2.42 (s, 3H, aromatic methyl), 1.27 (d, J = 7 Hz, isopropyl methyls, 6H), 1.24 (s, 6H, dimethyl).

^{13}C NMR (Fig I.48) : δ 211.7, 147.1, 146.0, 137.9, 135.4, 132.2, 121.9, 45.6, 41.2, 29.6, 25.4 (2c), 22.9 (2c), 21.3.

Analysis : $C_{15}H_{20}O$ Calcd. : C, 83.28; H, 9.32
Found : C, 83.21; H, 9.22.

Methyl-1β,2α,6β-5-oxo-7,7-(ethylenedioxy)bicyclo[4.3.0]nona-2-carboxylate 76:

A solution of 72 (300 mg, 1.19 mmol) in dry ethyl acetate (5 ml) was stirred at room temperature under hydrogen atmosphere over 10% Pd/C (3 mg). After 15 min, the catalyst was filtered and evaporated the solvent to furnish the saturated keto-ester 76 (300 mg) in 99% yield.

IR : 3000, 2900, 1730, 1200 cm^{-1}

^1H NMR : δ 4.02-3.85 (m, 4H, ketal), 3.71 (s, 3H, ester

methyl), 2.60-1.22 (series of m, 11H)

^{13}C NMR : δ 209.0, 173.4, 115.6, 65.3, 65.0, 52.0, 51.5, 46.8, 43.3, 42.9, 40.6, 37.0, 26.2.

Analysis : $C_{13}H_{18}O_5$ Calcd. : C, 61.40; H, 7.14
Found : C, 61.30; H, 7.08.

Methyl-1β,2α,6β-5-methylene-7,7-(ethylenedioxy)bicyclo [4.3.0]nona-2-carboxylate 77:

To a suspension of methyltriphenylphosphonium bromide (1.75 g, 4.92 mmol) in dry benzene (5 ml) was added freshly sublimed sodium t-amyl oxide (324 mg, 2.95 mmol) in benzene (3 ml) and the reaction mixture was stirred for 15 min at room temperature. To the canary yellow ylide that formed immediately was added a solution of 76 (250 mg, 0.98 mmol) in dry benzene (4 ml) and stirring was continued for 15 min. The reaction was quenched with water (5 ml), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 15 ml). The combined organic layer was washed and dried. The solvent was removed and the residue was filtered through a silica gel (6 g) column by eluting with 25% ethyl acetate-hexane to furnish 77 (148 mg, 60%).

IR : 3000, 2900, 1730, 1200 cm^{-1}

^{1}H NMR : δ 4.75 (s, 2H, exo-methylene), 3.98-3.81 (m, 4H, ketal), 3.68 (s, 3H, ester methyl), 2.58-1.21 (series of m, 11H).

^{13}C NMR : δ 174.8, 146.0, 116.2, 110.5, 65.1, 64.8, 52.7,

51.5, 49.3, 43.9, 37.5, 36.4, 33.1, 26.5.

Analysis : $C_{14}H_{20}O_4$ Calcd. : C, 66.64; H, 7.99

Found : C, 66.52; H, 7.90.

Methyl-1β,2α,6β-4-hydroxy-5-methylene-7,7-(ethylenedioxy)bicyclo[4.3.0]nona-2-carboxylate 78:

To a solution of 77 (125 mg, 0.466 mmol) in dry dichloromethane (3 ml) was added selenium dioxide (52 mg, 0.466 mmol) and 80% t-butylhydroperoxide (42 mg, 0.045 ml, 0.466 mmol) under nitrogen at ice temperature. The reaction mixture was stirred at room temperature. After 4h the reaction mixture was filtered through a silica gel (2 g) column by eluting with 30% ethyl acetate-hexane to furnish 78 (93 mg, 70%) as mixture of isomers.

IR : 3300, 3000, 2900, 1730, 1200 cm^{-1}

^1H NMR : δ 4.99-4.91 (m, 2H, exo- methylene), 4.45 (s, 1H, H attached to OH), 4.01-3.86 (m, 4H, ketal), 3.73 (s, 3H, ester methyl), 2.51-1.78 (series of m, 10H).

^{13}C NMR : δ 175.1, 173.6, 147.2, 146.0, 128.3, 115.9, 114.0, 113.1, 73.0, 72.9, 65.1, 64.9, 60.4, 55.6, 53.3, 52.9, 51.7, 37.6, 37.5, 37.3, 36.3, 28.7, 28.5, 26.6, 26.0, 23.0, 22.5, 14.2.

1β,2α,6β-2-(1-Hydroxy-1-methyl ethyl)-4-hydroxy-5-methylene-7,7-(ethylenedioxy)bicyclo[4.3.0]nonane 80:

To a solution of 78 (25 mg, 0.093 mmol) in dry ether (5 ml) was added methyl lithium (2.2 m = 0.07 ml, 0.1mmol) in dry ether under nitrogen at room temperature. After 45 min, the reaction was quenched with water and extracted with ether. The combined organic layer was washed and dried. The solvent was evaporated and the residue was filtered through a silica gel (1 g) column by eluting with 40% ethyl acetate-hexane to furnish 80 (15 mg) in 60% yield.

IR : 3300, 3000, 2900, 1200 cm^{-1}

^1H NMR : δ 4.95-4.85 (m, 1H, exo- methylene), 4.83-4.78 (m, 1H, exo- methylene), 4.52-4.48 (m, 1H, H attached to OH), 3.95-3.85 (m, 4H, ketal), 2.50-1.40 (m, 11H), 1.39 (s, 3H, methyl), 1.25 (s, 3H, methyl).

10,10-(Ethylenedioxy)-3α-acetoxy-1α,2β,6β,7α-tricyclo-[5.2.1.$O^{2,6}$]dec-8-ene 83:

To a cooled solution of alcohol 14 (200 mg, 0.96 mmol) in dry acetic anhydride (1 ml) was added dry pyridine (0.2 ml) under nitrogen atmosphere. The reation mixture was stirred at room temperature for 2h. Poured the reaction mixture in ice water and extracted with ether (3 x 15 ml). The combined organic layer was washed, dried and evaporated the solvent to furnish acetate 83 (200 mg, 96%) as a white solid.

m.p. : 102^oC

IR : 3000, 2900, 1730, 1200 cm^{-1}

^1H NMR : δ 6.23-6.20 (m, 2H, olefinic), 5.15-5.03 (m, 1H, H attained to OAc), 3.93-3.76 (m, 4H, ketal), 3.21-3.13 (m, 1H), 2.72-2.55 (m, 3H), 2.04 (s, 3H, methyl of acetate), 1.85-1.40 (m, 4H).

Analysis : $C_{14}H_{18}O_4$ Calcd. : C, 67.18; H, 7.25

Found : C, 66.99; H, 7.17.

10,10-(Ethylenedioxy)-3α-acetoxy-1α,2β,6β,7α-tricyclo-[5.2.1.$0^{2,6}$]deca-4,8-diene 84:

To a cooled solution of alcohol 81 (200 mg, 0.97 mmol) in dry acetic anhydride (1 ml) was added dry pyridine (0.2 ml) under nitrogen atmosphere. The reation mixture was stirred at room temperature for 1h and poured in to ice water and work-up was done as above. Removal of the solvent furnished acetate 84 (167 mg, 81%) as a white solid.

m.p. : 120°C

IR : 3000, 2900, 1730 1200 cm^{-1}

^1H NMR : δ 6.13-6.08 (m, 1H, olefinic), 5.89-5.83 (m, 1H, olefinic), 5.72-5.54 (m, 3H, oelfinic & H attatched to OAc), 3.93-3.80 (m, 4H, ketal), 3.57-3.24 (m, 2H), 2.82-2.62 (m,2H), 2.05 (s, 3H, methyl of acetate)

^{13}C NMR : δ 170.7, 135.7, 132.5, 132.2, 130.4, 127.2, 79.2, 64.9, 64.3, 50.7, 50.1, 49.0, 42.5, 21.1.

Analysis : $C_{14}H_{16}O_4$ Calcd. : C, 67.73; H, 6.50

Found : C, 67.62; H, 6.43.

10,10-(Ethylenedioxy)-3α-acetoxy-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene 85:

To a cooled solution of dimethyl alcohol 82 (200 mg, 0.84 mmol) in dry acetic anhydride (1 ml) was added dry pyridine (0.2 ml) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 7h and poured in to ice water and the work-up was done as above. Removal of the solvent furnished dimethyl acetate 85 (169 mg, 69%) as white solid.

m.p. : 116°C

IR : 3000, 2900, 1730, 1200 cm^{-1}

^1H NMR : δ 6.20-6.03 (m, 2H, olefinic), 5.76-5.73 (d, 1H, J = 6 Hz, H attached to -OAc), 3.98-3.81 (m, 4H, ketal), 3.27-2.86 (m, 2H), 2.61-2.57 (m, 2H), 2.04 (s, 3H, methyl of acetate), 1.41-1.12 (m, 2H), 1.01 (s, 3H, methyl), 0.86 (s, 3H, methyl).

Analysis : $C_{16}H_{22}O_4$ Calcd. : C, 69.04; H, 7.97

Found : C, 68.89; H, 7.92.

Hydrolysis of acetates by using porcine liver esterease: General procedure:

To a solution of acetate (0.4 mmol) in distilled ether (1 ml) and phosphate buffer (10 ml, pH 8) was added enzyme porcine liver esterase [Candida cylindrica, (0.15 ml = 1.65

mg)] and stirred the reaction mixture at room temperature for required time. Separated the ether layer and extracted the aqueous layer with ethyl acetate (3 x 20 ml). The combined organic layer was washed and dried. The residue obtained after the evaporation of the solvent was filtered through silica gel column to furnish pure alcohol.

Transesterification by using porcine liver esterease:

General procedure:

To a solution of alcohol (0.4 mmol) in distilled vinyl acetate (2 ml) was added enzyme porcine liver esterase [Candida cylindrica (.15 ml = 165 mg)] and stirred the reaction mixture at room temperature. Diluted the reaction mixture with water and extracted with ether (3 x 15 ml). The combined organic layer was washed and dried. The residue obtained after the evaporation of the solvent was filtered through silica gel column to furnish pure acetate.

Enzymatic resoluton of 83:

To a solution of 83 (100 ml, 0.4 mmol) in distilled ether (1 ml) and phosphate buffer (10 ml, pH 8) was added enzyme PLE (0.15 ml) and stirred at room temperature for 4 days. After usual work-up, evaporated the solvent and the residue was purified using silica gel (2 g) column by eluting with 30% ethyl acetate-hexane to obtain pure alcohol (+)-14.

(+)-14: The spectral properties (^{1}H NMR and ^{13}C NMR) of the

product were identical with the racemic substrate.

$[\alpha]_D$: +14.8 (cc 0.08, $CHCl_3$)

The alcohol (+)-14 was converted to the acetate (+)-83 following the procedure used for racemic substrate 83.

(+)-83:

m.p. : 103°C

$[\alpha]_D$: +29.1 (cc 0.16, $CHCl_3$)

ee : 95% (by NMR using chiral shift reagent $Eu(fod)_3$)

Enzymatic resoluton of 84:

To a solution of 84 (100 ml, 0.4 mmol) distilled ether (1 ml) and phosphate buffer (10 ml, pH 8) was added enzyme PLE (0.15 ml) and stirred at room temperature for 24h. After usual work-up, the solvent was evaporated and the residue was purified using silica gel (2 g) column by eluting with 30% ethyl acetate-hexane to obtain pure alcohol (-)-81 and acetate (+)-84.

(-)-81: The spectral properties (^1H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

$[\alpha]_D$: -106^oC (cc 0.11, $CHCl_3$)

The alcohol (-)-81 was converted to the acetate (-)-84 following the procedure used for racemic substrate 84.

(-)-84: The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

m.p. : 121°C
$[\alpha]_D$: -18.5^o (cc 0.11, $CHCl_3$)
ee : >92% (by NMR using chiral shift reagent Eu(fod)$_3$)

(+)-84: The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

m.p. : 120°C
$[\alpha]_D$: $+23.5^o$ (cc 0.11, $CHCl_3$)
ee : >95% (by NMR using chiral shift reagent Eu(fod)$_3$)

Enzymatic resoluton of 85:

To a solution of 85 (100 mg, 0.36 mmol) in distilled ether (1 ml) and phosphate buffer (10 ml, pH 8) was added enzyme PLE (0.13 m) and stirred at room temperature for 4 days. After usual work-up, the solvent was evaporated and the residue was purified using silica gel (2 g) column by eluting with 20% ethyl acetate-hexane to obtain pure alcohol (+)-82.

(-)-82: The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

$[\alpha]_D$: $+16.4^o$ (cc 0.05, $CHCl_3$)

The alcohol (+)-82 was converted to the acetate (+)-85 following the procedure used for racemic substrate 85.

(+)-85: The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

m.p.	: 116°C	
$[\alpha]_D$	: $+28^o$	(cc 0.05, $CHCl_3$)
ee	: >95%	(by NMR using chiral shift reagent $Eu(fod)_3$)

Transesterification of alcohol at 14:

To a solution of alcohol 14 (100 mg, 0.4 mmol) in vinyl acetate (2 m) was added PLE (0.15 ml) and stirred at room temperature for 4 days. After usual workup the solvent was evaporated and the residue was purified to furnish the pure acetate (+)-83.

(+)-83: The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

m.p.	: 102°C	
$[\alpha]_D$	: $+27.6^o$	(cc 0.16, $CHCl_3$)
ee	: >92%	(by NMR using chiral shift reagent $Eu(fod)_3$)

Transesterification of alcohol of 81:

To a solution of alcohol 81 (100 mg, 0.36 mmol) in vinyl acetate (2 ml) was added PLE (0.15 ml) and stirred at

room temperature for 4 days. After usual workup the solvent was evaporated and the residue was purified to furnish the pure acetate (+)-84.

(+)-84: The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

m.p.	: 120°C	
$[\alpha]_D$	: +18.5°	(cc 0.12, $CHCl_3$)
ee	: >90%	(by NMR using chiral shift reagent $Eu(fod)_3$)

Oxidation of (+)-14:

Alcohol (+)-14 was oxidized by using PCC following the procedure used for racemic alcohol 14 to obtain optically active ketone (+)-15 in 90% yield.

The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

$[\alpha]_D$: +18°C (cc 0.13, $CHCl_3$)

Hydrolysis of (+)-15:

The ketone (+)-15 was subjected to hydrolysis following the procedure used for racemic ketone 15 to obtain diketone (+)-9 in 90% yield.

The spectral properties (^{1}H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

$[\alpha]_D$: $+42^o$ (cc 0.03, $CHCl_3$)

Haller-Bauer reaction of (+)-9:

The diketone (+)-9 was subjected to Haller-Bauer cleavage following the general Haller-Bauer reaction procedure to obtain optically bicyclic ester (+)-22 in 65% yield.

The spectral properties (^1H NMR and ^{13}C NMR) of the product were identical with the racemic substrate.

$[\alpha]_D$: $+21^o$ (cc 0.02, $CHCl_3$)

I.6. SPECTRA:

Fig I.

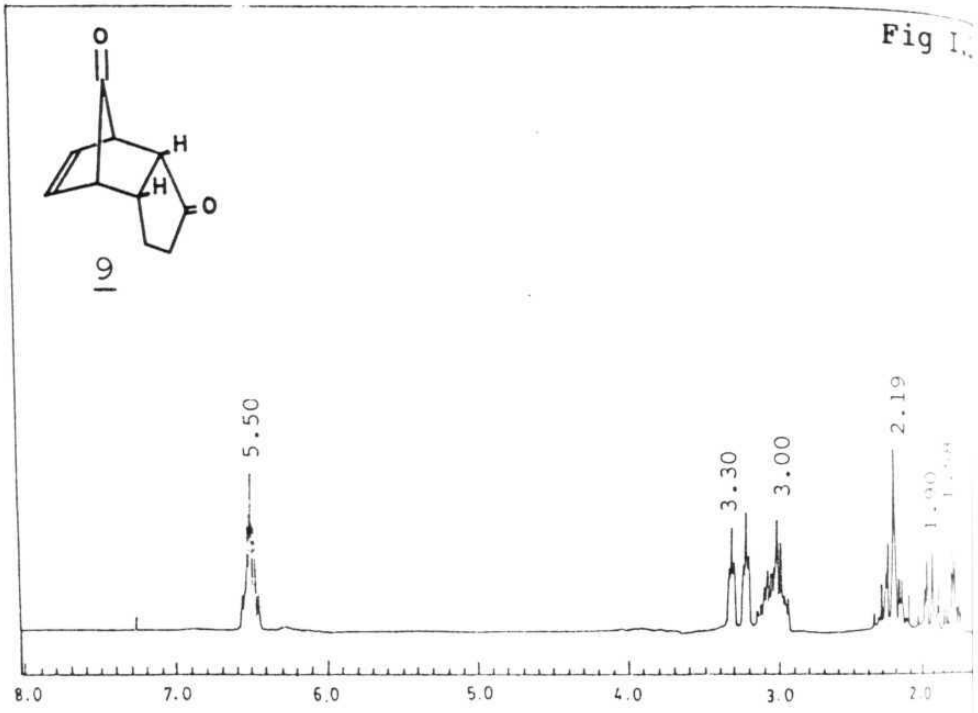
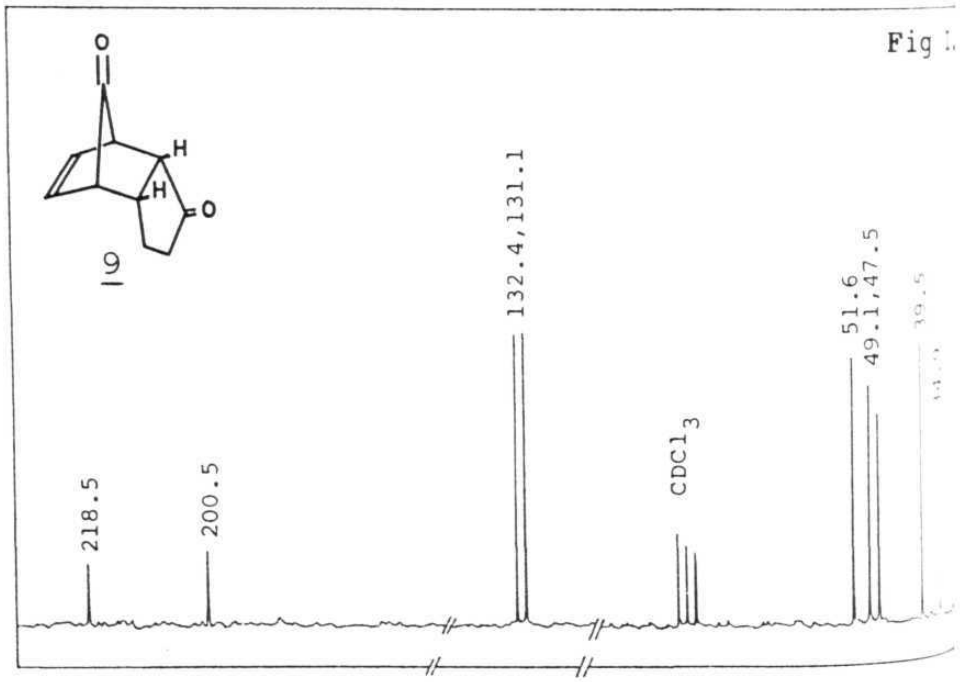


Fig I.



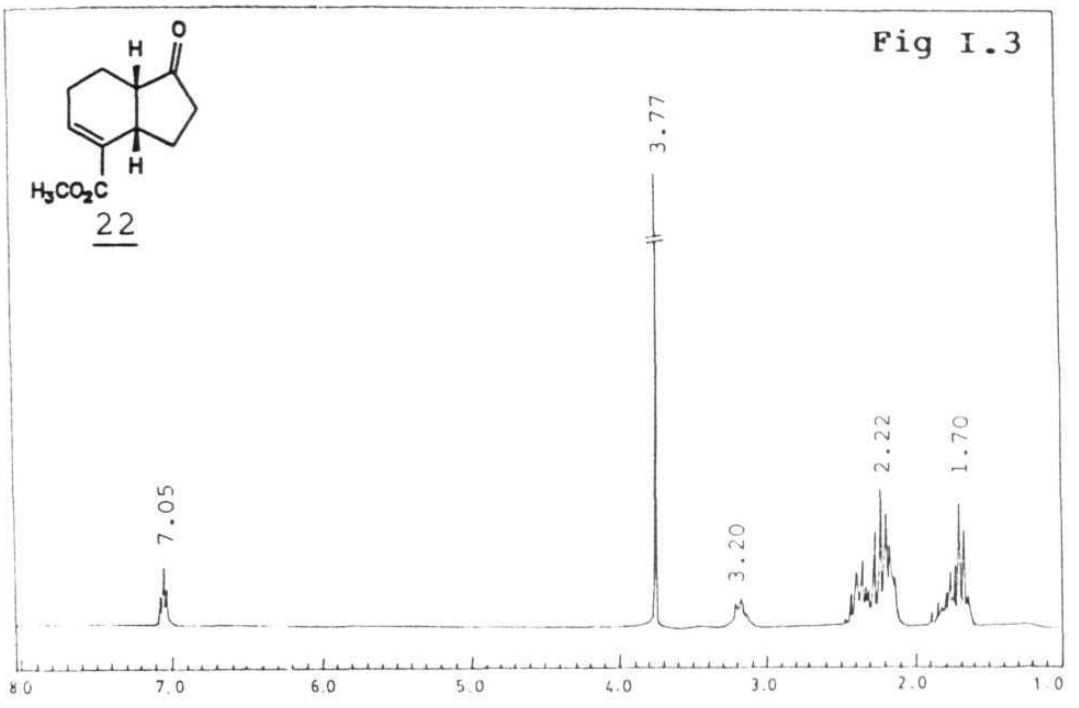


Fig I.3
H
O
H
H_3CO_2C
22
3.77
7.05
3.20
2.22
1.70
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

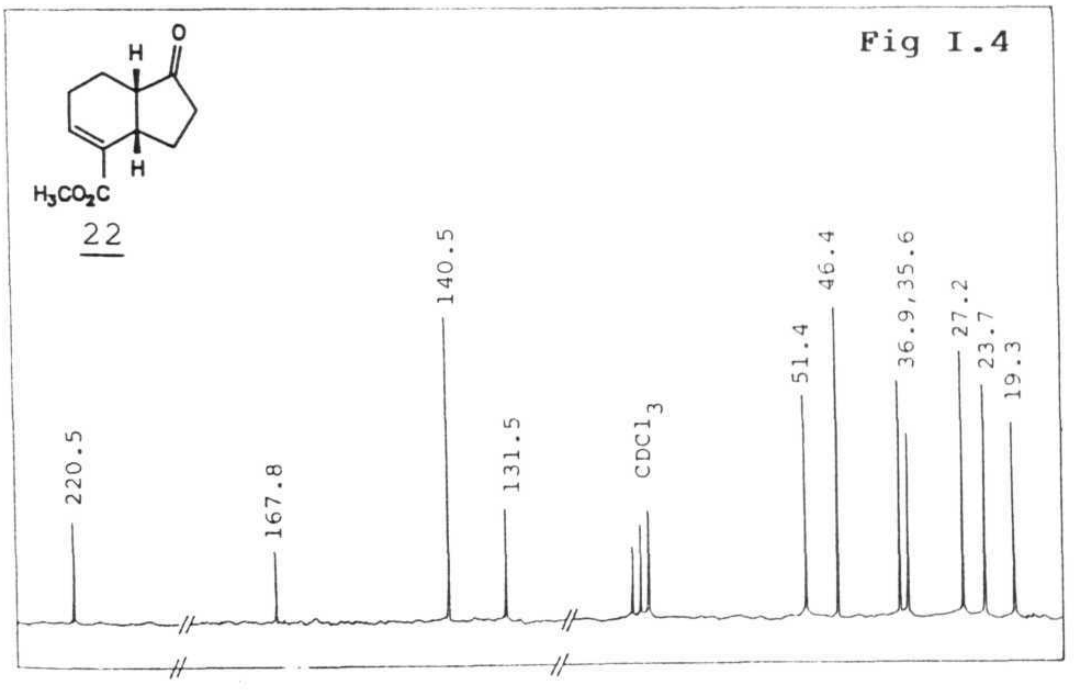


Fig I.4
H
O
H
H_3CO_2C
22
220.5
167.8
140.5
131.5
$CDCl_3$
51.4
46.4
36.9,35.6
27.2
23.7
19.3

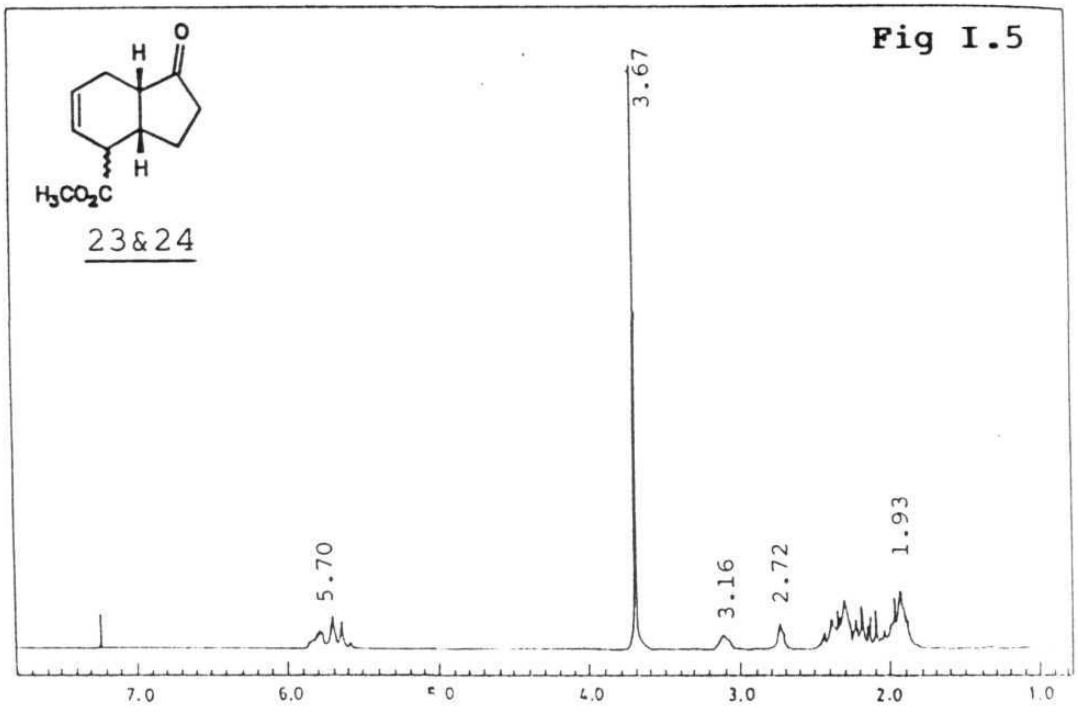


Fig I.5
H
O
H
H3CO2C
23&24
3.67
5.70
3.16
2.72
1.93
7.0
6.0
5.0
4.0
3.0
2.0
1.0

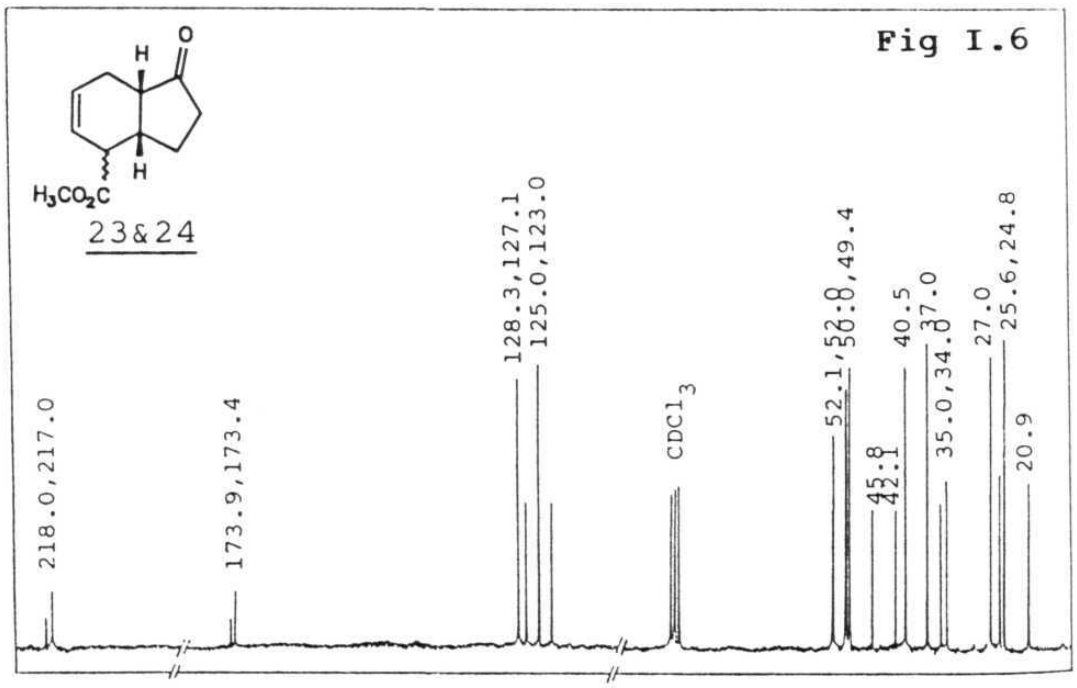


Fig I.6
H
O
H
H3CO2C
23&24
218.0,217.0
173.9,173.4
128.3,127.1
125.0,123.0
CDCl3
52.1,50.8,49.4
45.8
42.1
40.5
37.0
35.0,34.8
27.0
25.6,24.8
20.9

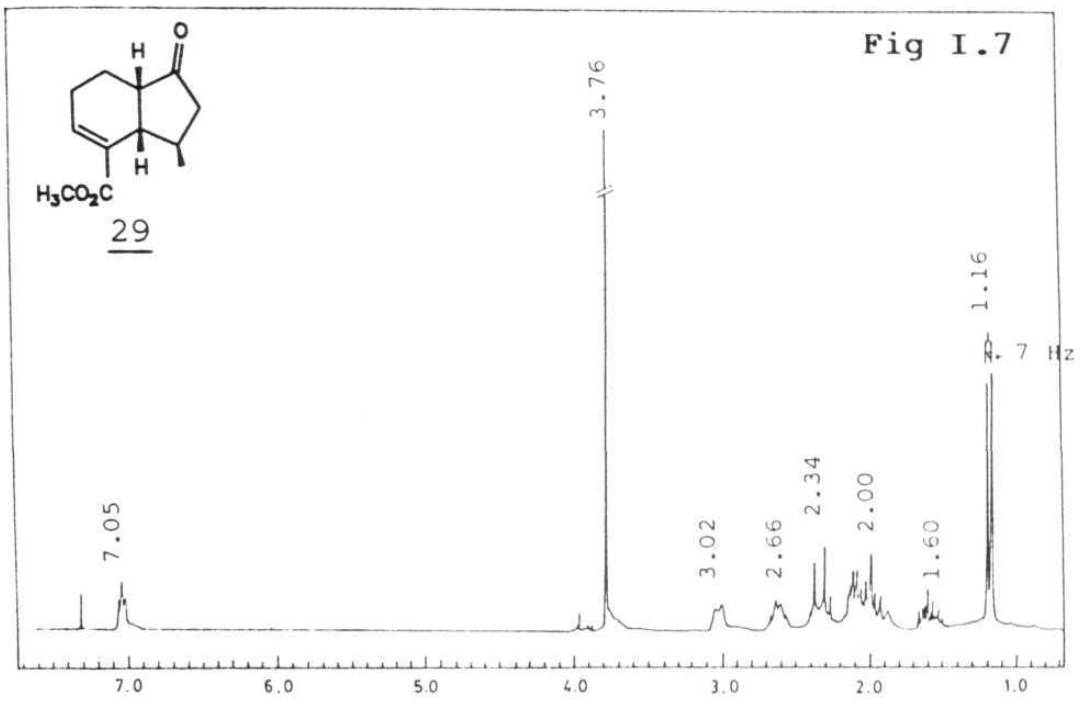


Fig I.7
H
O
H
H3CO2C
29
3.76
1.16
7 Hz
7.05
3.02
2.66
2.34
2.00
1.60
7.0
6.0
5.0
4.0
3.0
2.0
1.0

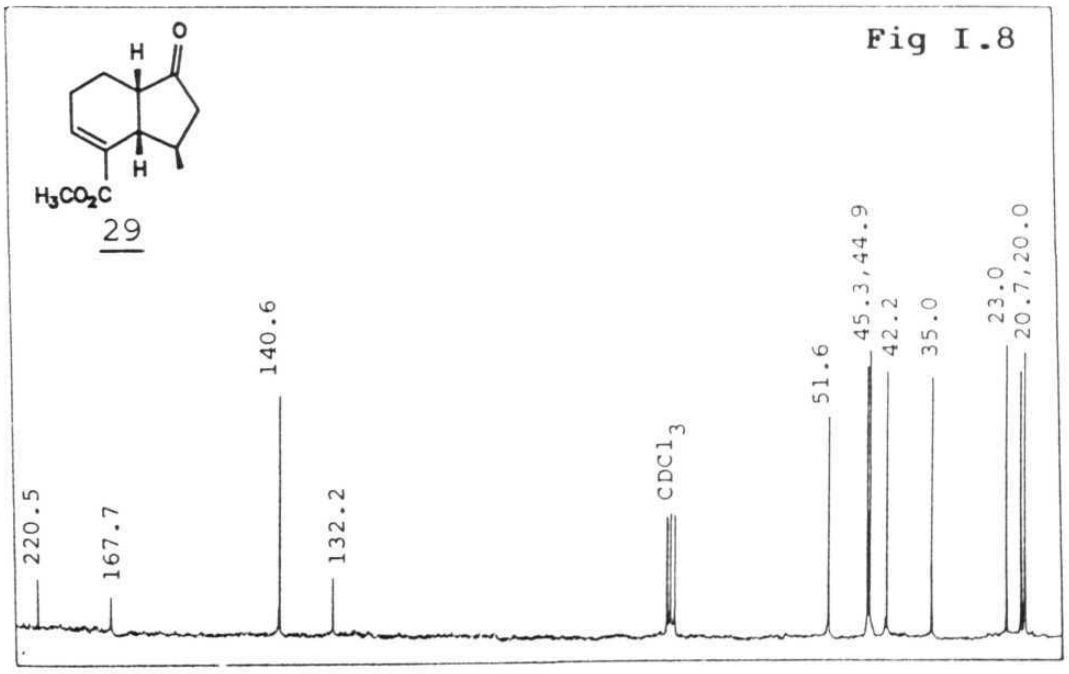


Fig I.8
H
O
H
H3CO2C
29
220.5
167.7
140.6
132.2
CDCl3
51.6
45.3,44.9
42.2
35.0
23.0
20.7,20.0

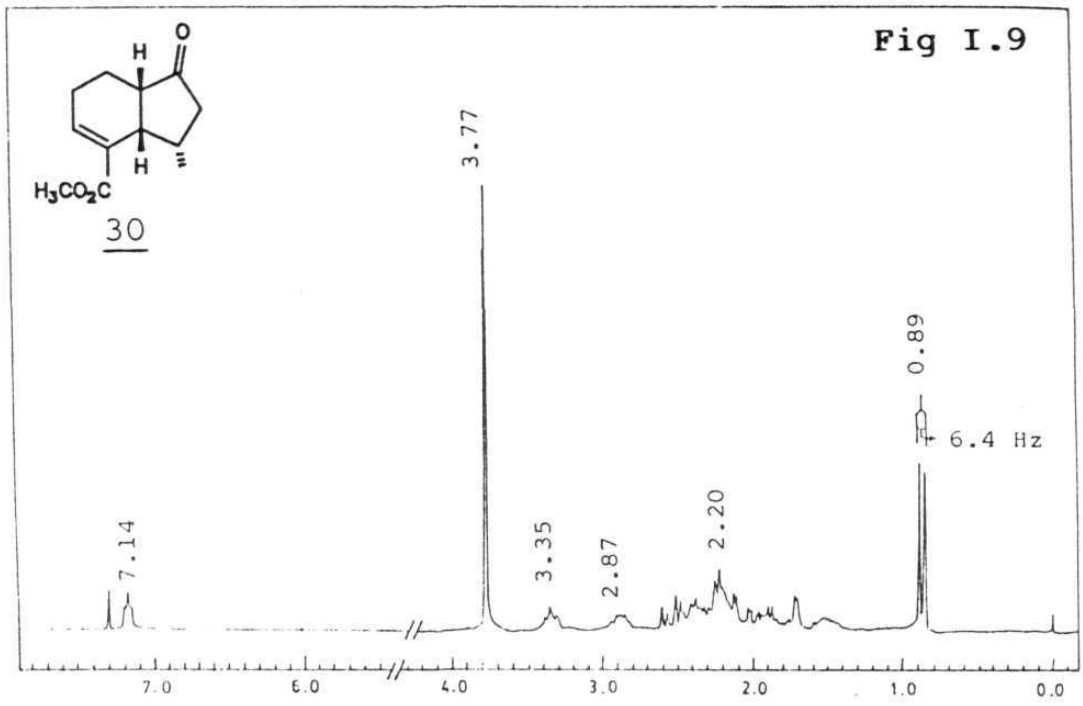


Fig I.9
H
O
H
H
H3CO2C
30
3.77
0.89
6.4 Hz
7.14
3.35
2.87
2.20
7.0
6.0
4.0
3.0
2.0
1.0
0.0

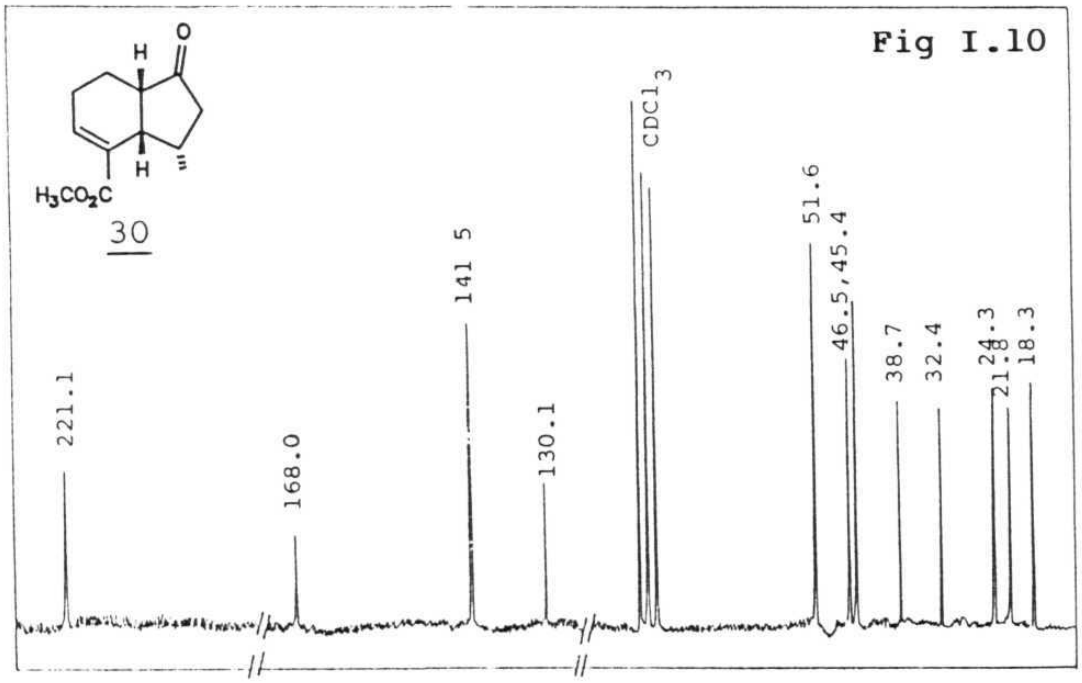


Fig I.10
H
O
H
H
H3CO2C
30
221.1
168.0
141 5
130.1
CDCl3
51.6
46.5,45.4
38.7
32.4
24.3
21.8
18.3

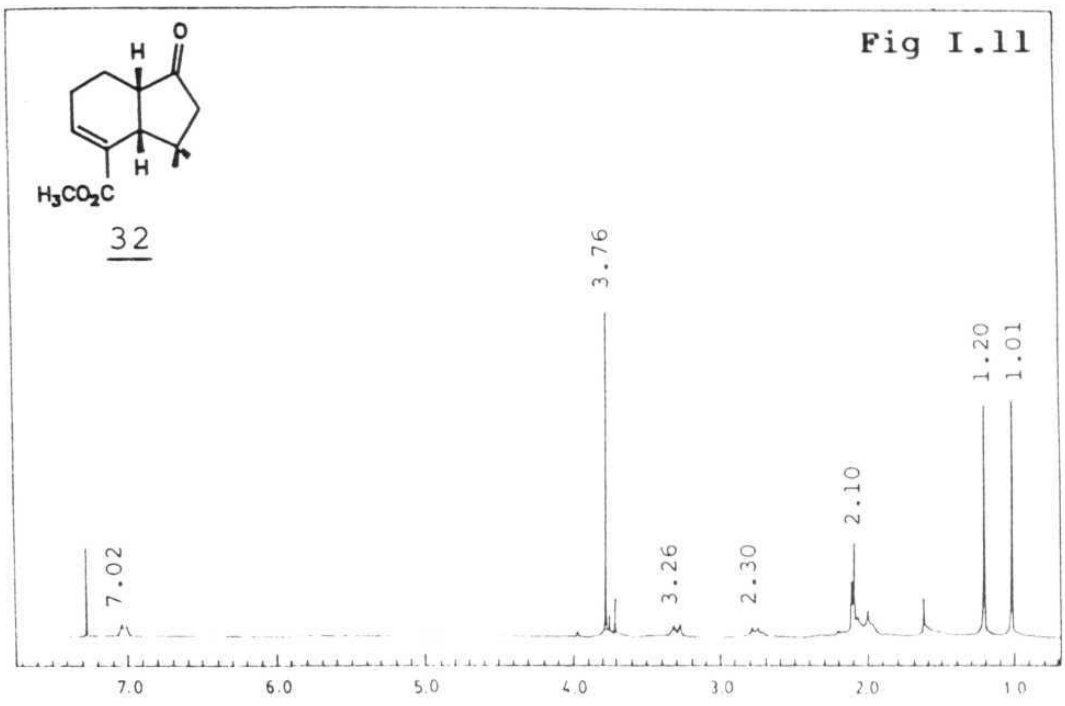


Fig I.11
H
O
H
H3CO2C
32
3.76
1.20
1.01
2.10
7.02
3.26
2.30
7.0
6.0
5.0
4.0
3.0
2.0
1.0

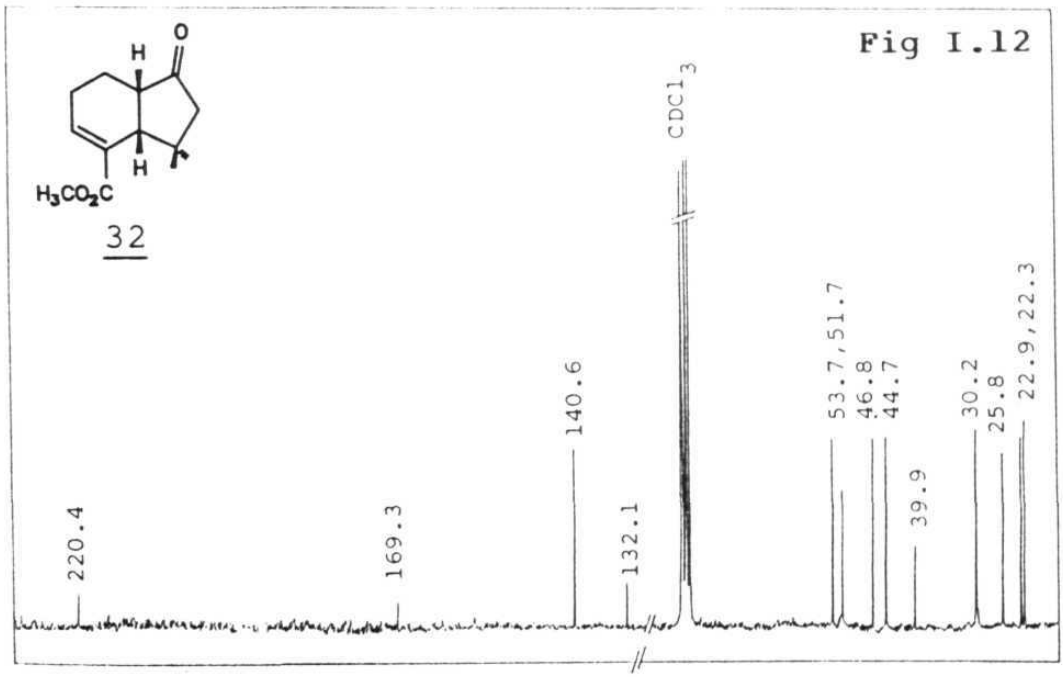


Fig I.12
H
O
H
H3CO2C
32
CDCl3
220.4
169.3
140.6
132.1
53.7,51.7
46.8
44.7
39.9
30.2
25.8
22.9,22.3

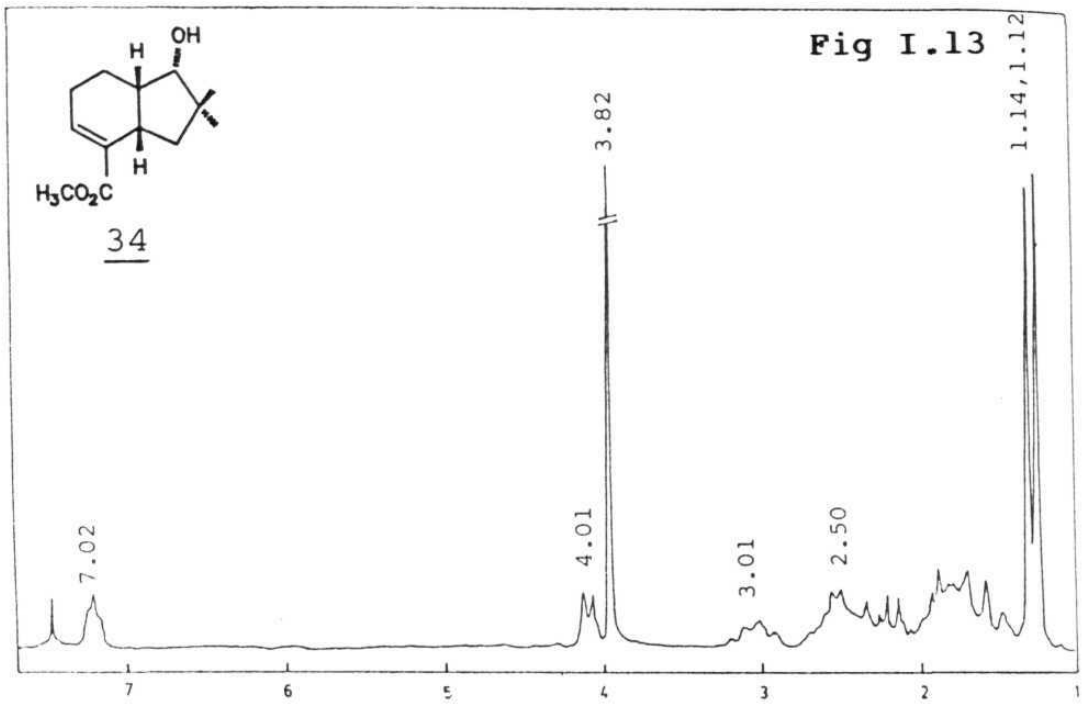


Fig I.13

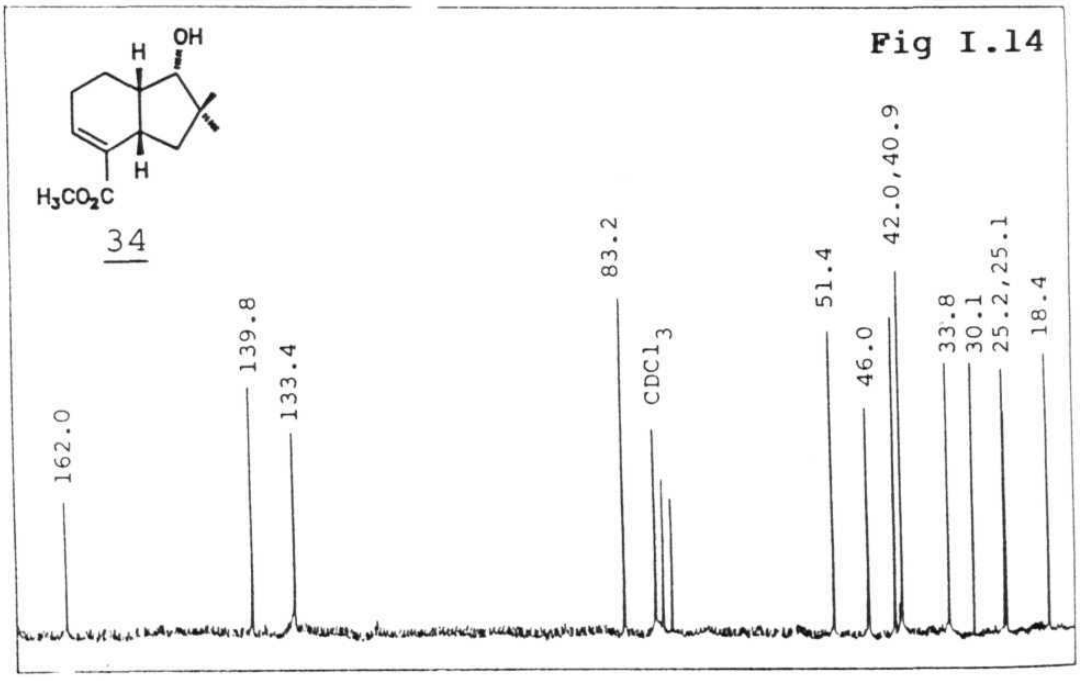
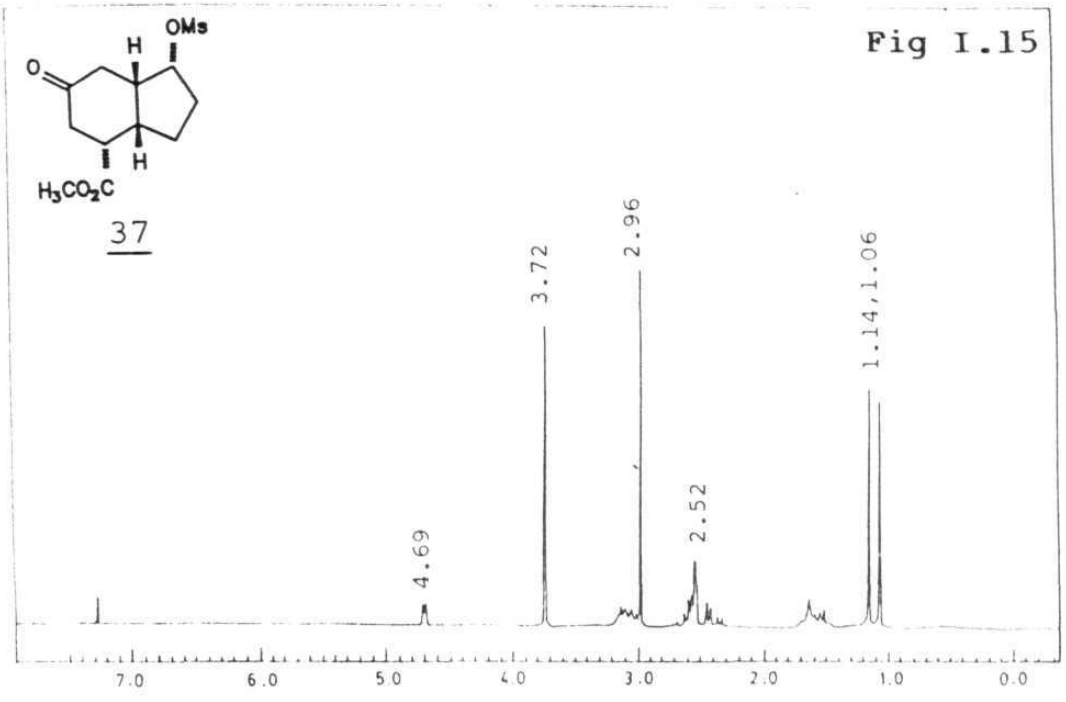
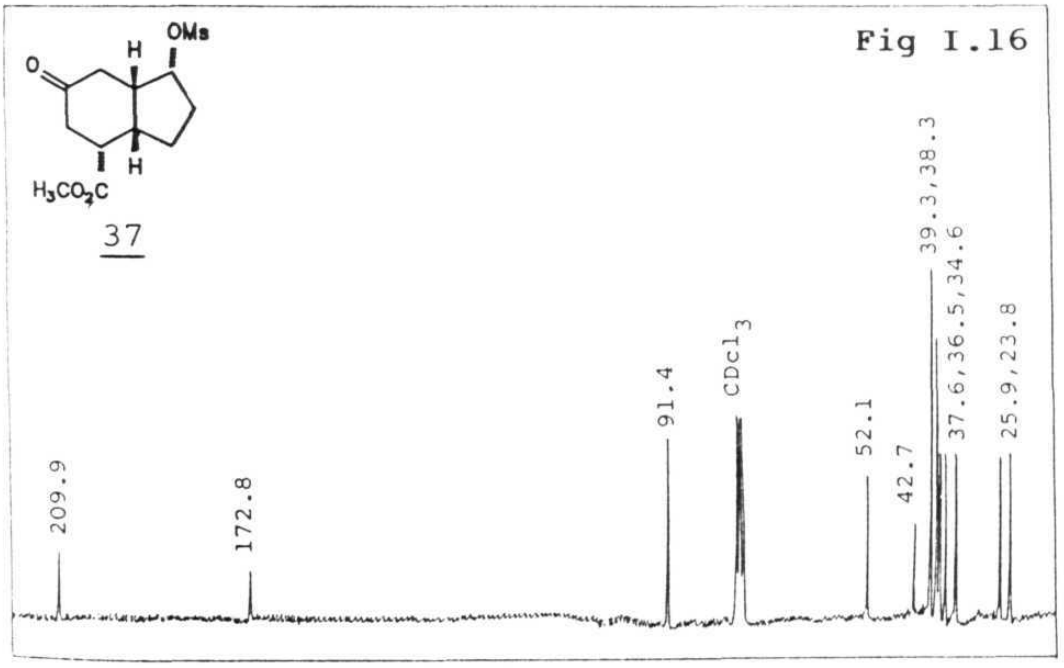


Fig I.14


OMs
H
O
H
H_3CO_2C
37
Fig I.15
4.69
3.72
2.96
2.52
1.14,1.06
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


OMs
H
O
H
H_3CO_2C
37
Fig I.16
209.9
172.8
91.4
$CDCl_3$
52.1
42.7
39.3,38.3
37.6,36.5,34.6
25.9,23.8

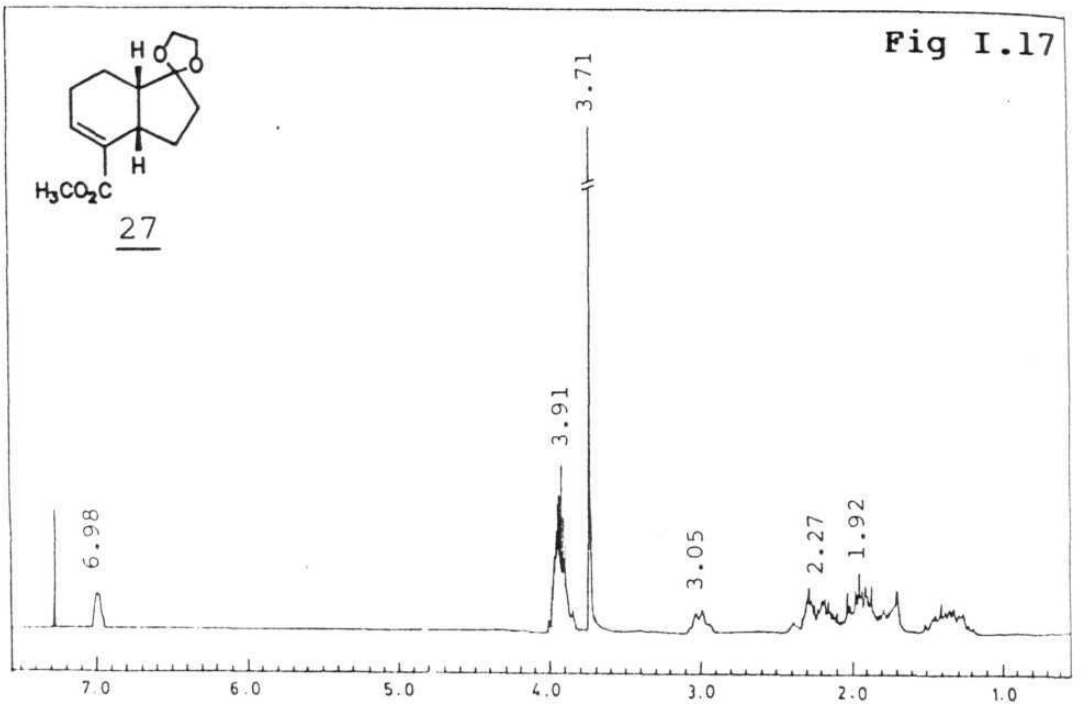


Fig I.17
H
O
O
H
H_3CO_2C
27
3.71
3.91
6.98
3.05
2.27
1.92
7.0
6.0
5.0
4.0
3.0
2.0
1.0

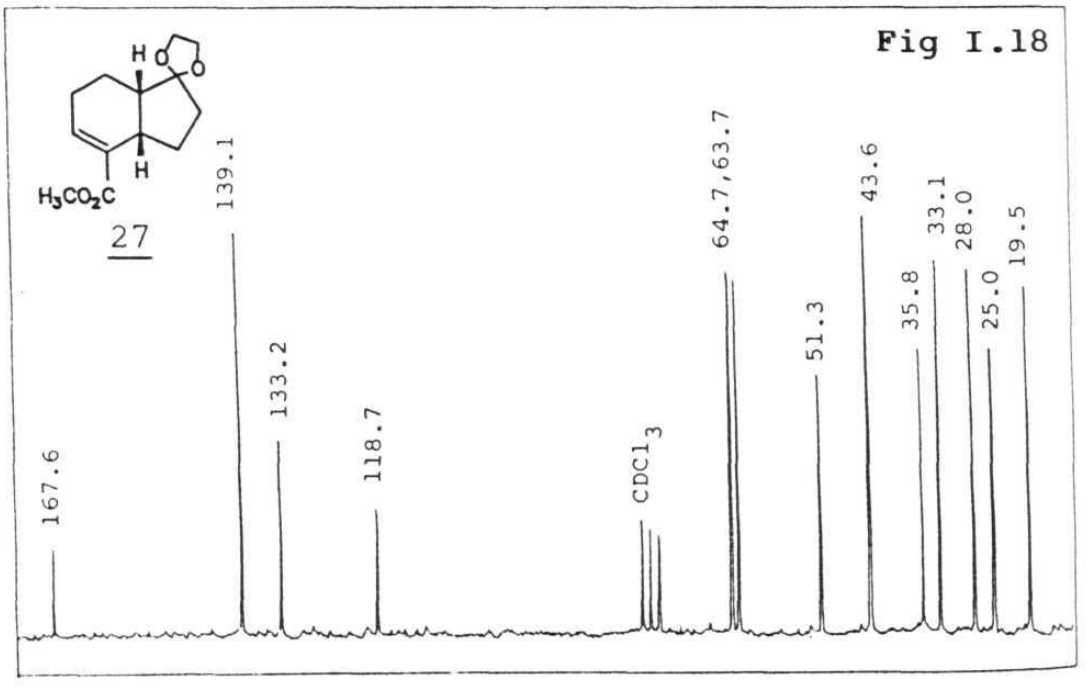


Fig I.18
H
O
O
H
H_3CO_2C
27
139.1
64.7,63.7
43.6
33.1
28.0
19.5
133.2
51.3
35.8
25.0
167.6
118.7
$CDCl_3$

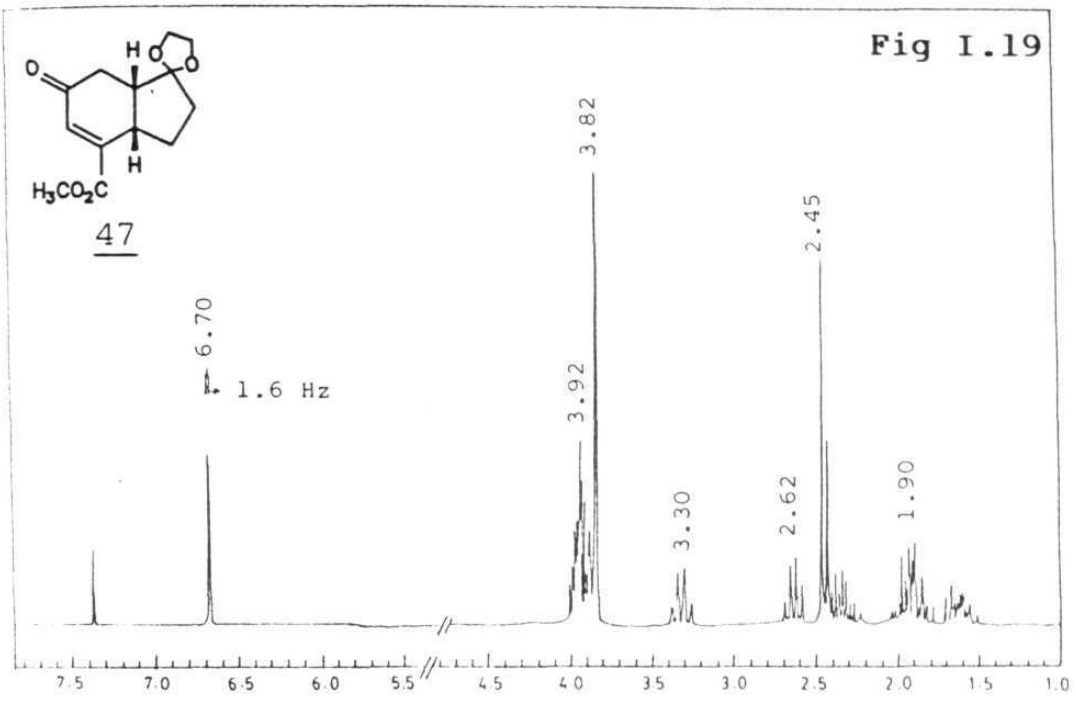


Fig I.19
47
6.70
1.6 Hz
3.92
3.82
3.30
2.62
2.45
1.90
7.5
7.0
6.5
6.0
5.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

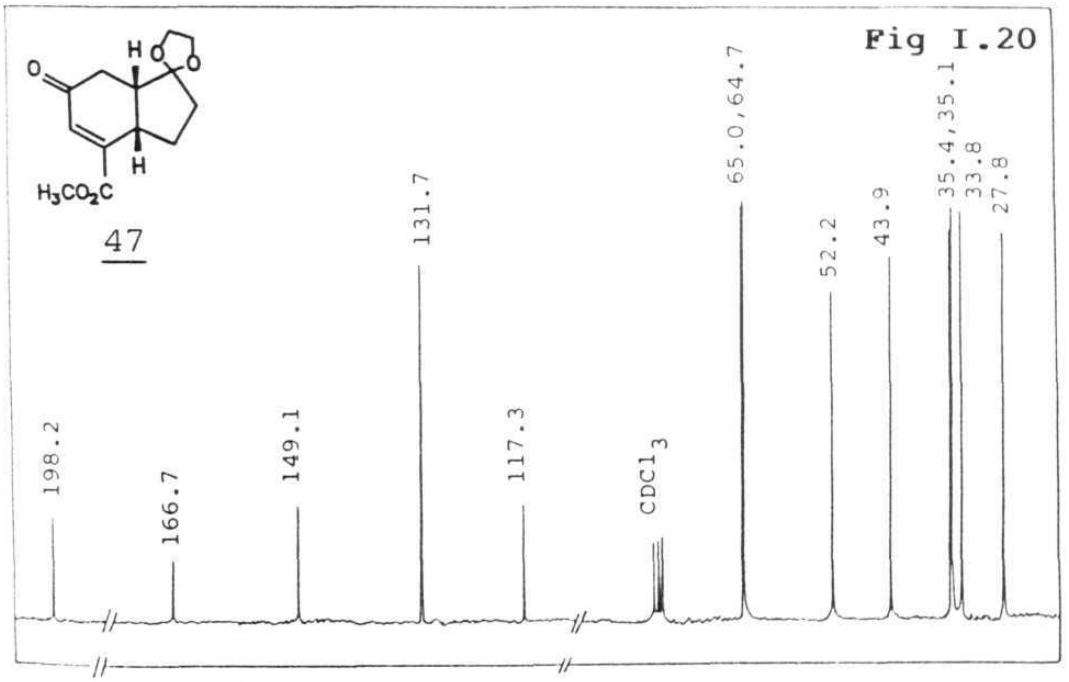


Fig I.20
47
198.2
166.7
149.1
131.7
117.3
CDCl3
65.0,64.7
52.2
43.9
35.4,35.1
33.8
27.8

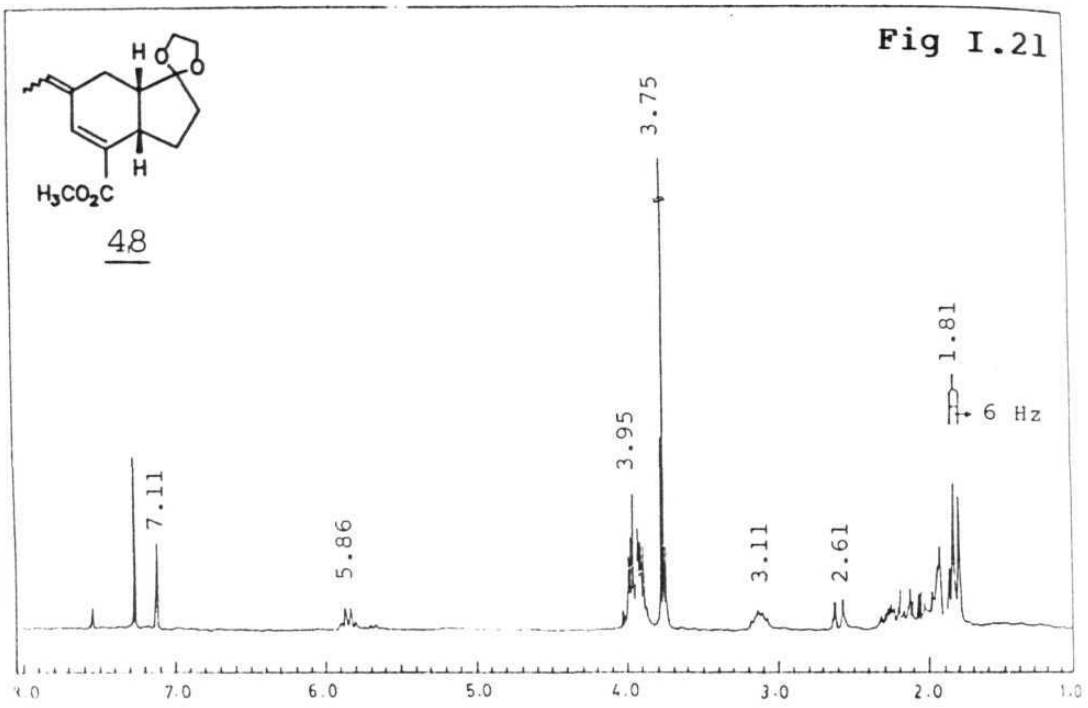


Fig I.21

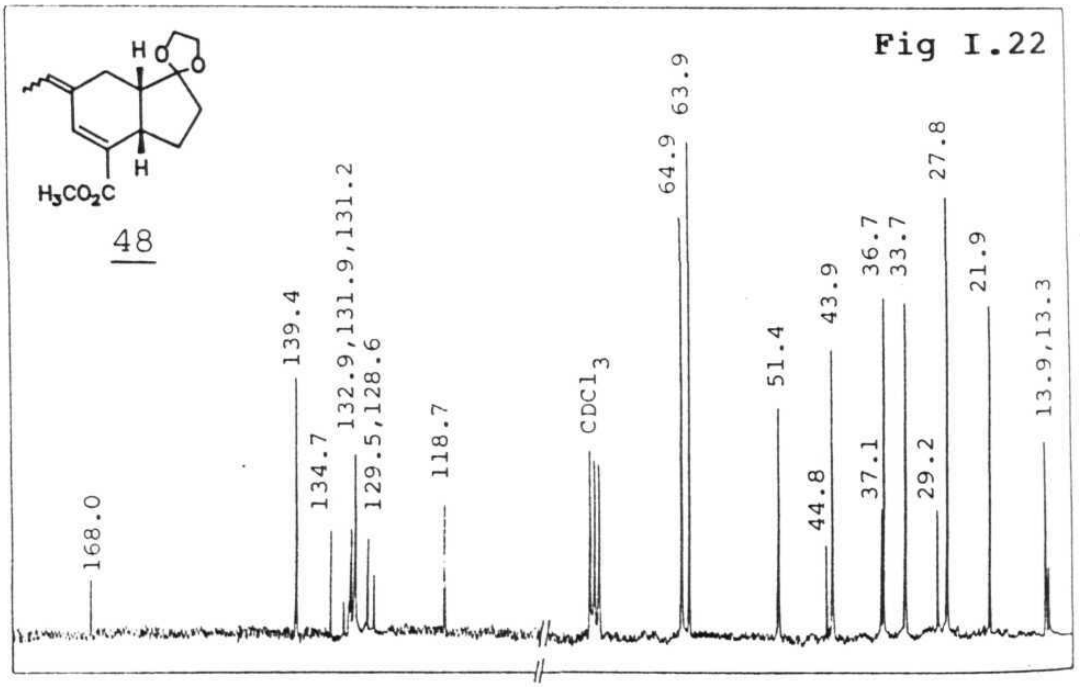


Fig I.22

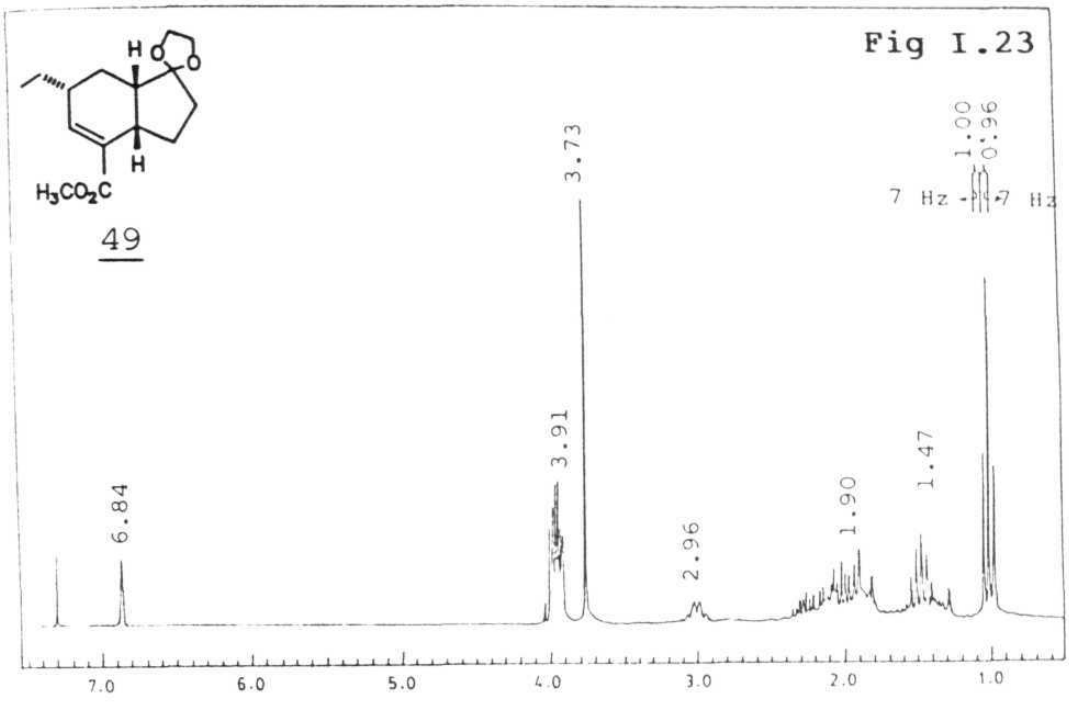


Fig I.23
H
O
O
H
H_3CO_2C
49
3.73
1.00
0.96
7 Hz
7 Hz
6.84
3.91
2.96
1.90
1.47
7.0
6.0
5.0
4.0
3.0
2.0
1.0

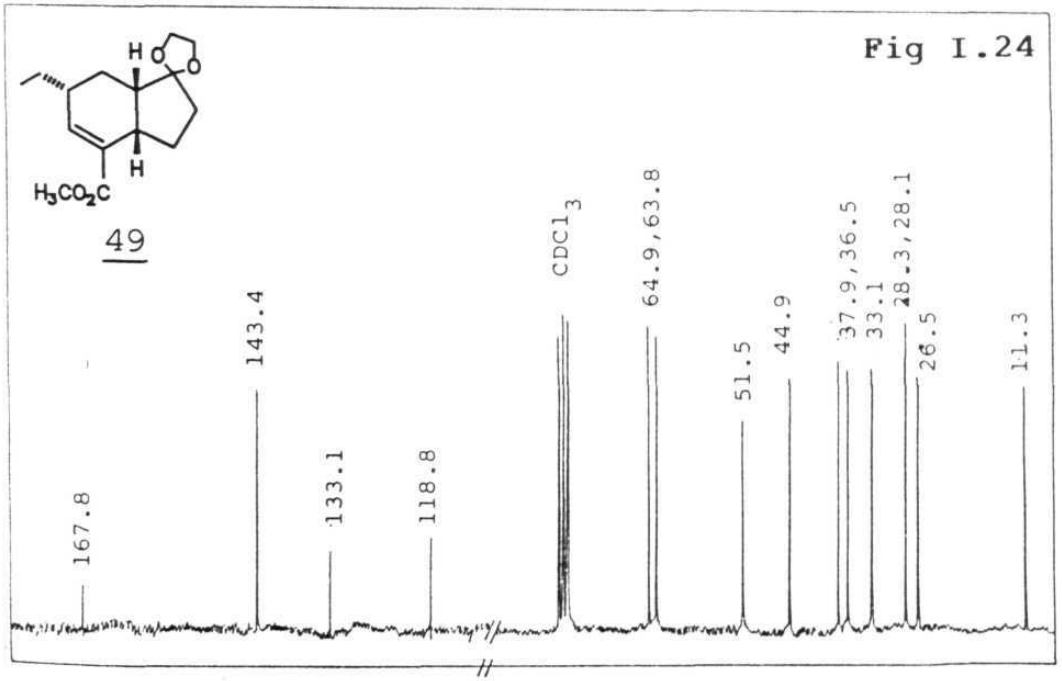


Fig I.24
H
O
O
H
H_3CO_2C
49
167.8
143.4
133.1
118.8
$CDCl_3$
64.9,63.8
51.5
44.9
37.9,36.5
33.1
28.3,28.1
26.5
11.3

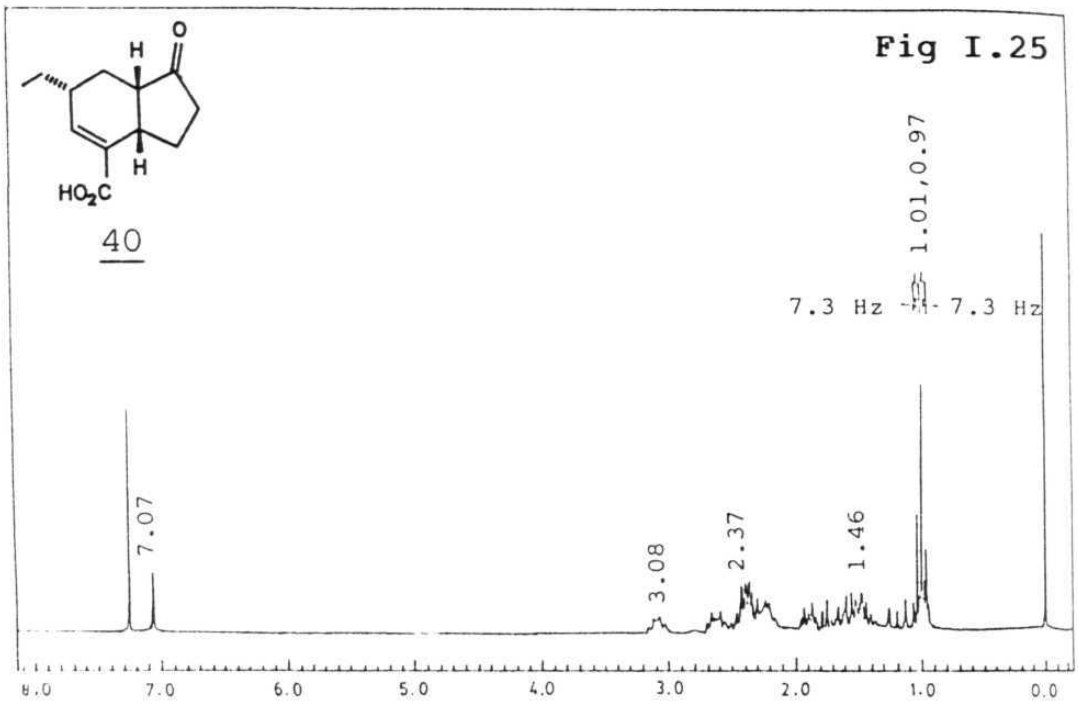


Fig I.25
H
O
H
HO2C
40
1.01,0.97
7.3 Hz
7.3 Hz
7.07
3.08
2.37
1.46
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

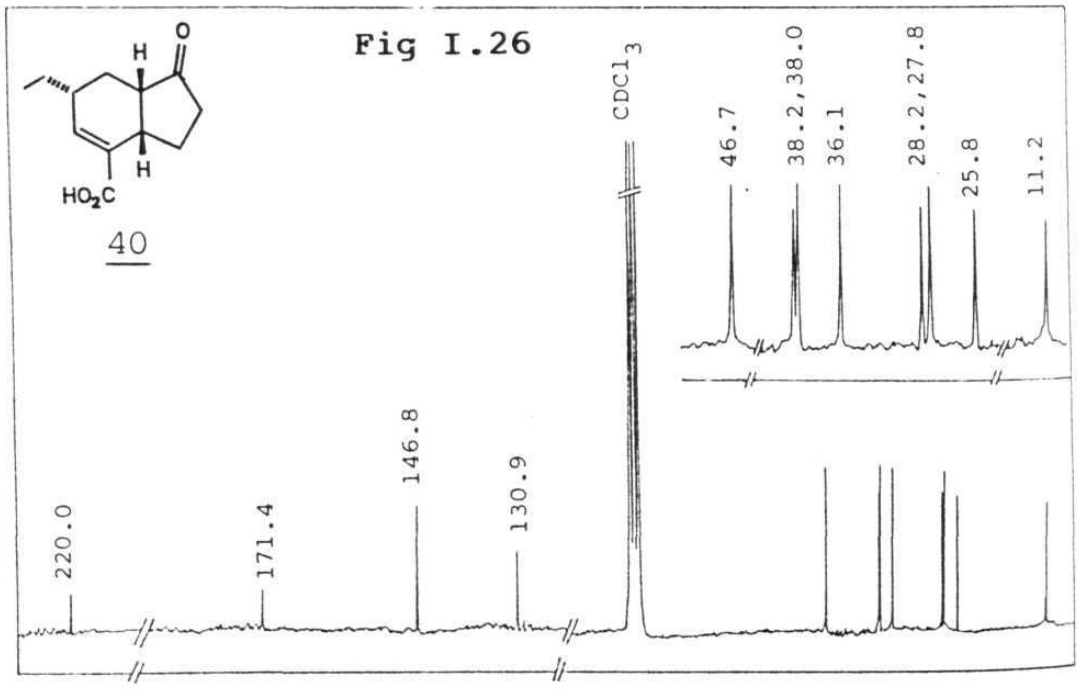


Fig I.26
H
O
H
HO2C
40
CDCl3
46.7
38.2,38.0
36.1
28.2,27.8
25.8
11.2
220.0
171.4
146.8
130.9

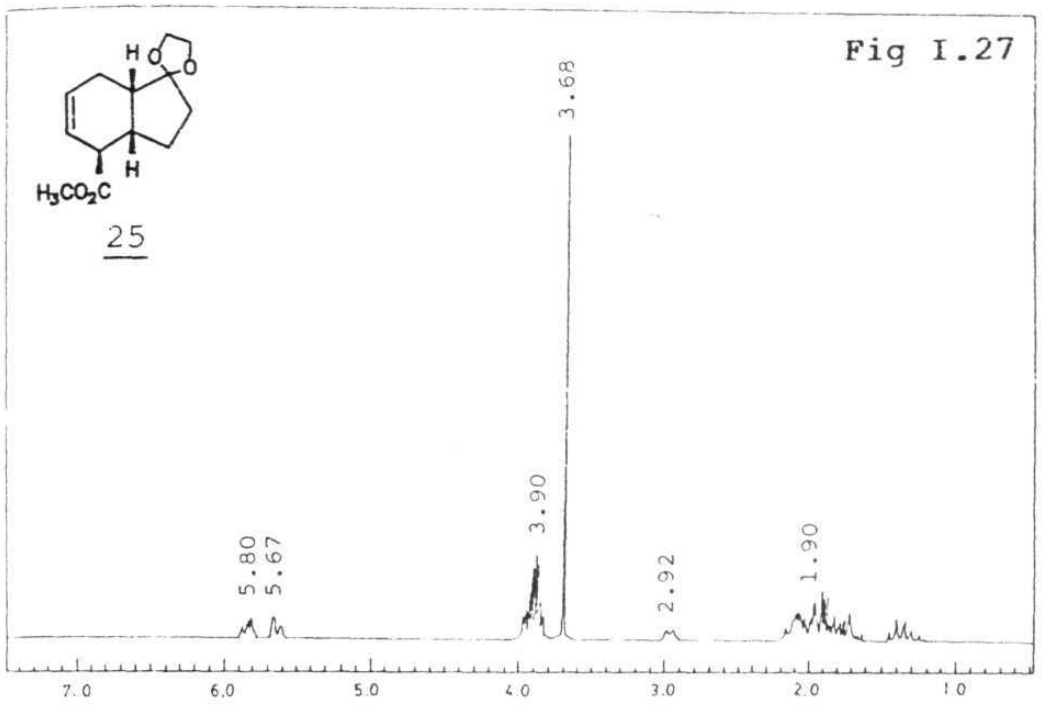


Fig I.27
H
O
O
H
H_3CO_2C
25
3.68
3.90
5.80
5.67
2.92
1.90
7.0
6.0
5.0
4.0
3.0
2.0
1.0

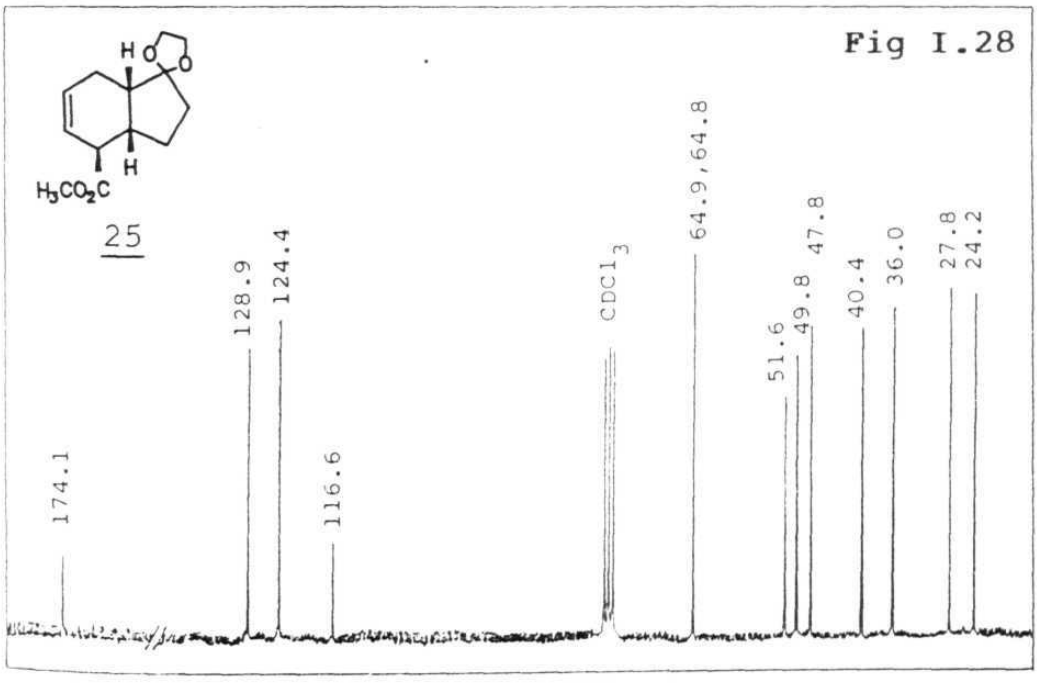


Fig I.28
H
O
O
H
H_3CO_2C
25
174.1
128.9
124.4
116.6
$CDCl_3$
64.9,64.8
51.6
49.8
47.8
40.4
36.0
27.8
24.2

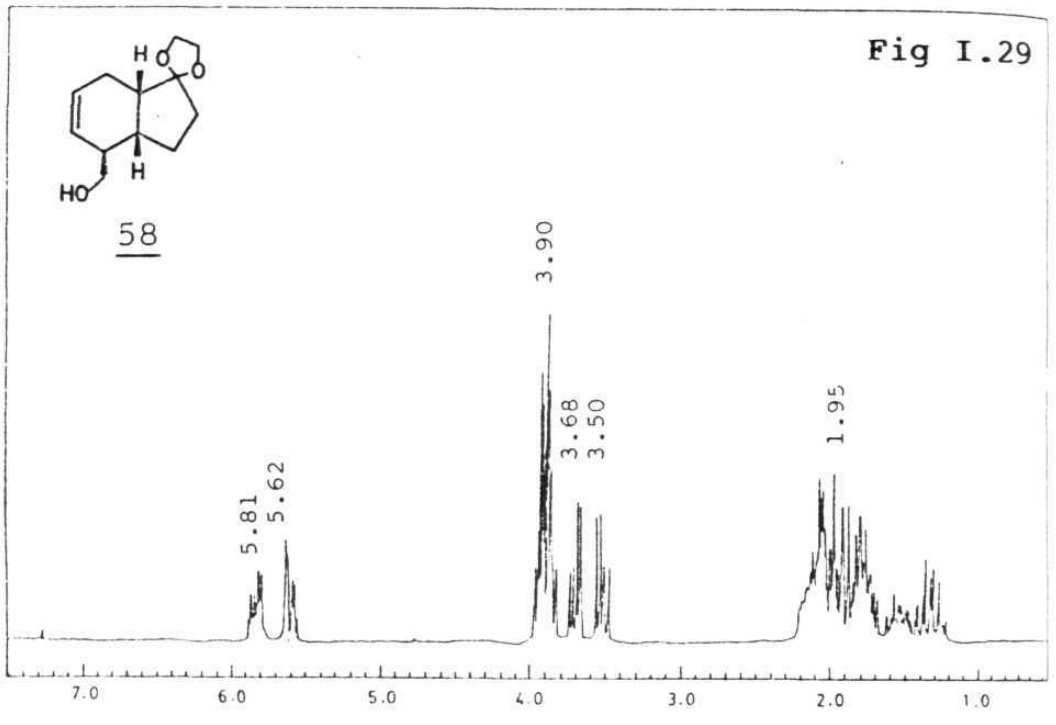


Fig I.29
58
5.81
5.62
3.90
3.68
3.50
1.95
7.0
6.0
5.0
4.0
3.0
2.0
1.0

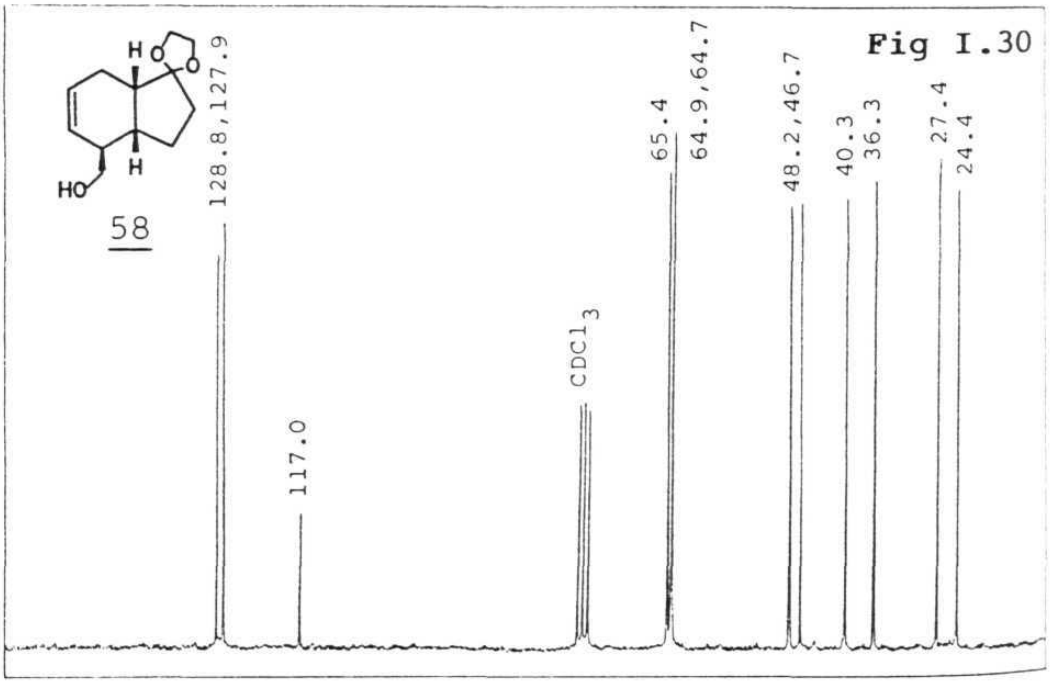
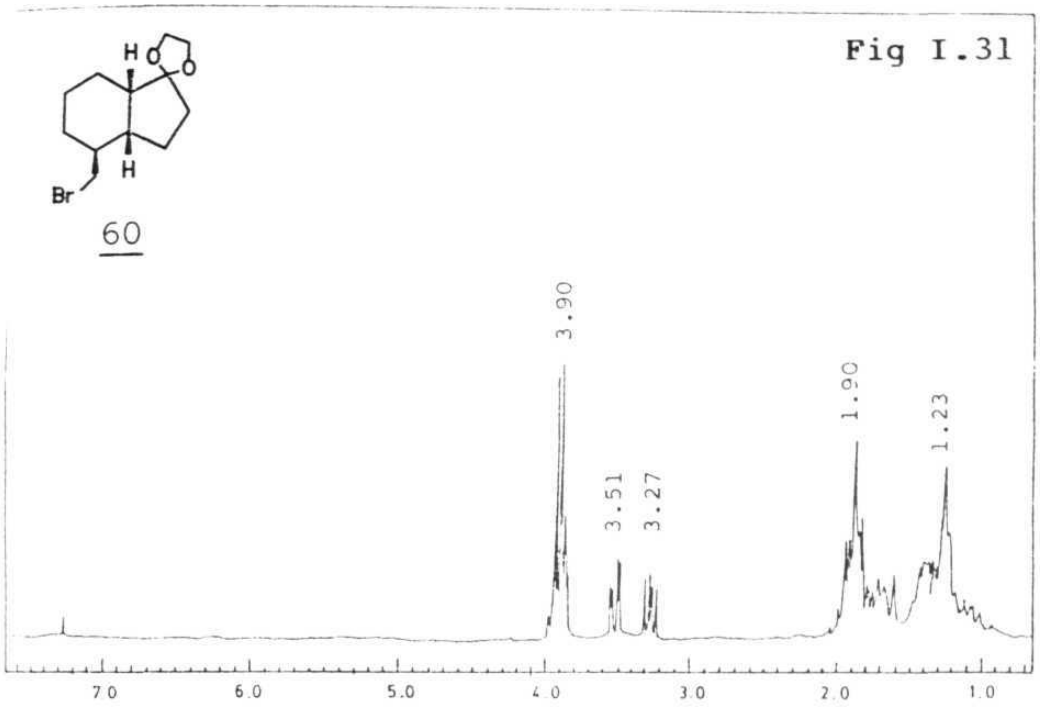
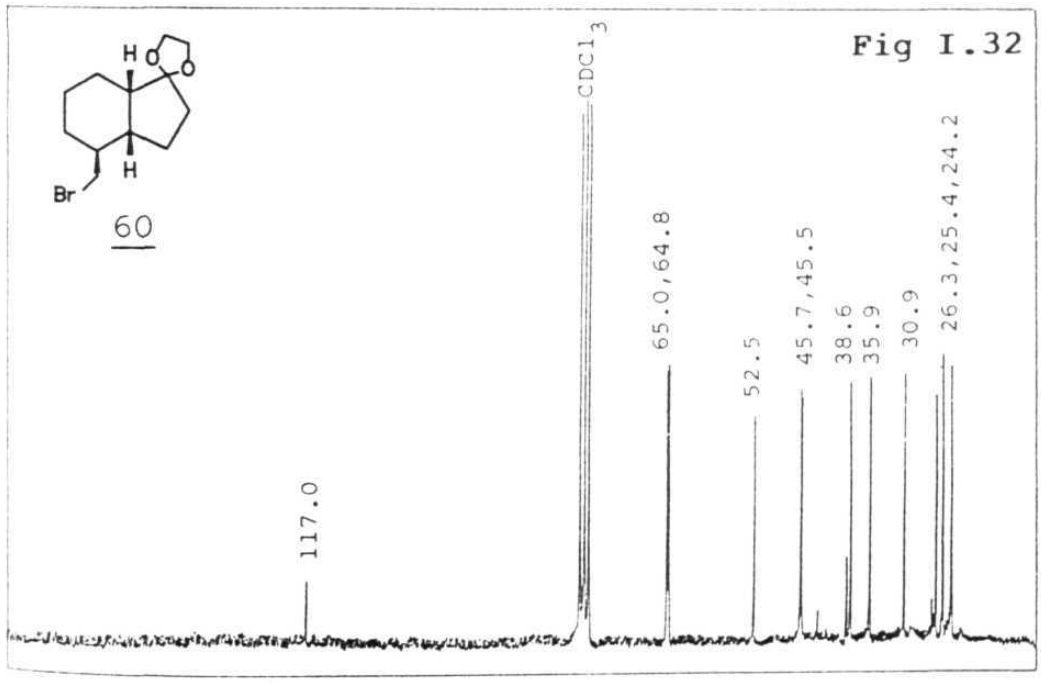
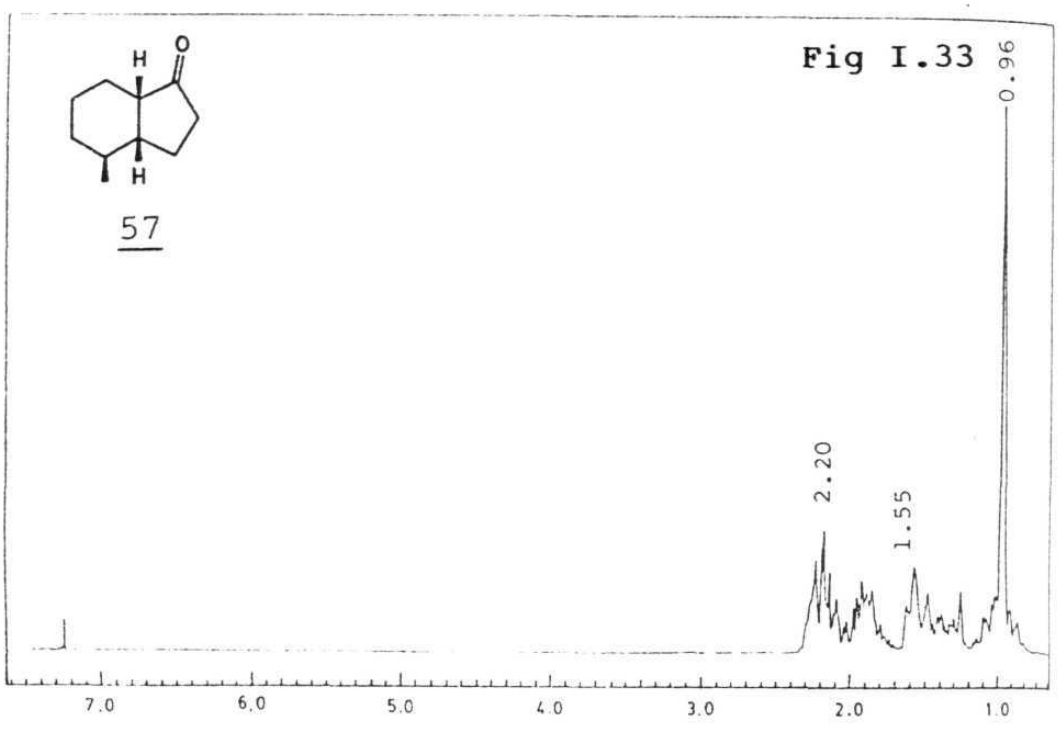
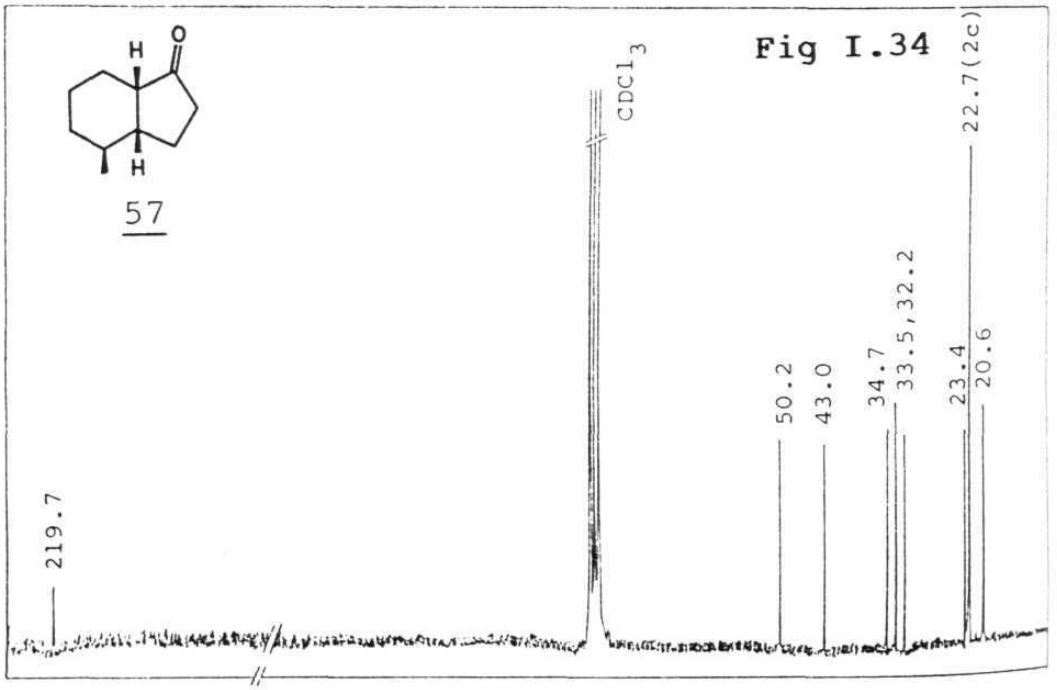


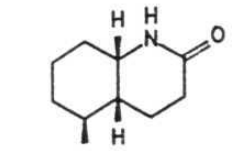
Fig I.30
58
128.8,127.9
117.0
CDCl3
65.4
64.9,64.7
48.2,46.7
40.3
36.3
27.4
24.4


H
O
O
H
Br
60
Fig I.31
3.90
3.51
3.27
1.90
1.23
7.0
6.0
5.0
4.0
3.0
2.0
1.0


H
O
O
H
Br
60
Fig I.32
CDCl3
117.0
65.0,64.8
52.5
45.7,45.5
38.6
35.9
30.9
26.3,25.4,24.2

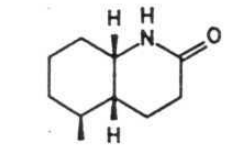

H
O
H
57
Fig I.33
0.96
2.20
1.55
7.0
6.0
5.0
4.0
3.0
2.0
1.0


H
O
H
57
Fig I.34
CDCl3
22.7(2c)
219.7
50.2
43.0
34.7
33.5,32.2
23.4
20.6



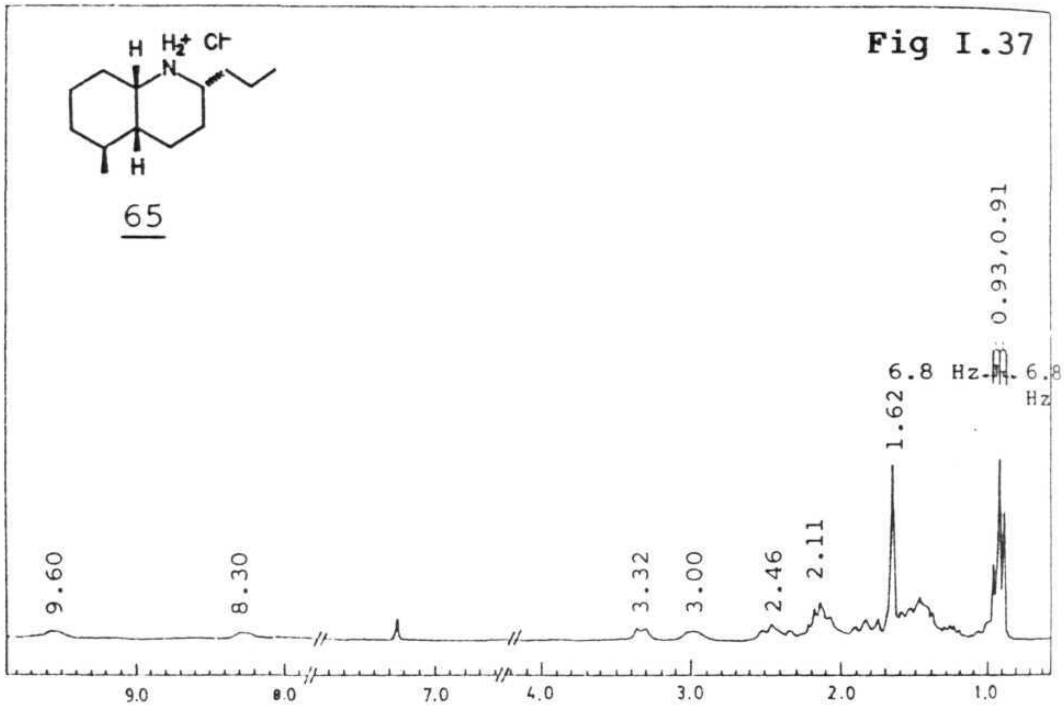
62

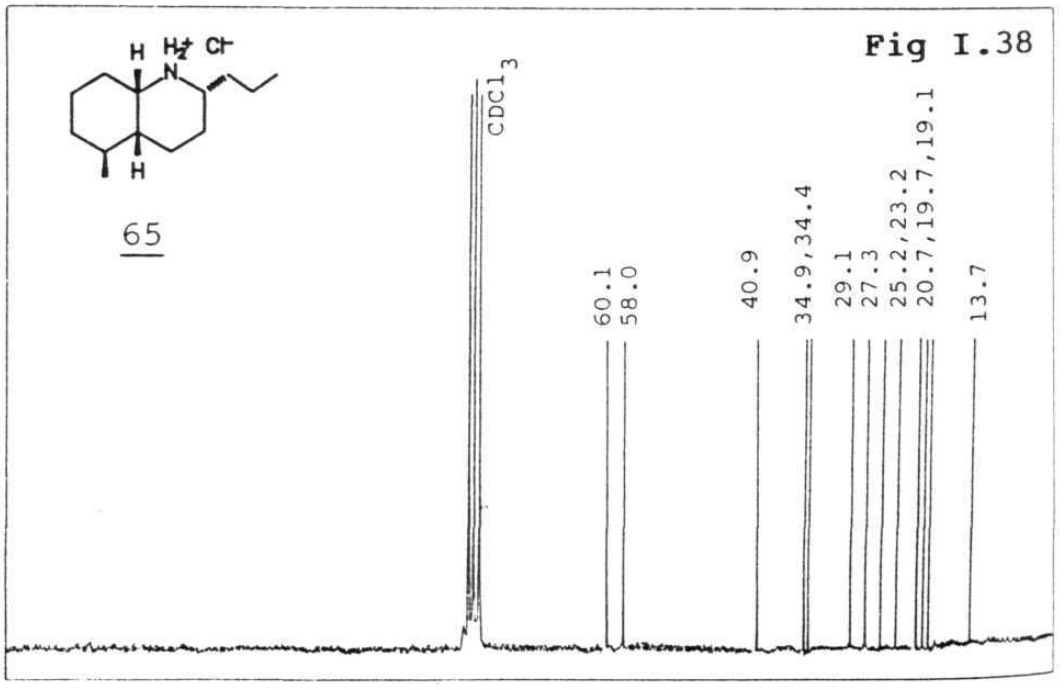
Fig I.35



62

Fig I.36


H
H2+ Cl-
N
H
65
Fig I.37
9.60
8.30
3.32
3.00
2.46
2.11
1.62
6.8 Hz
0.93,0.91
6.8 Hz
9.0
8.0
7.0
4.0
3.0
2.0
1.0


H
H2+ Cl-
N
H
65
Fig I.38
CDCl3
60.1
58.0
40.9
34.9,34.4
29.1
27.3
25.2,23.2
20.7,19.7,19.1
13.7

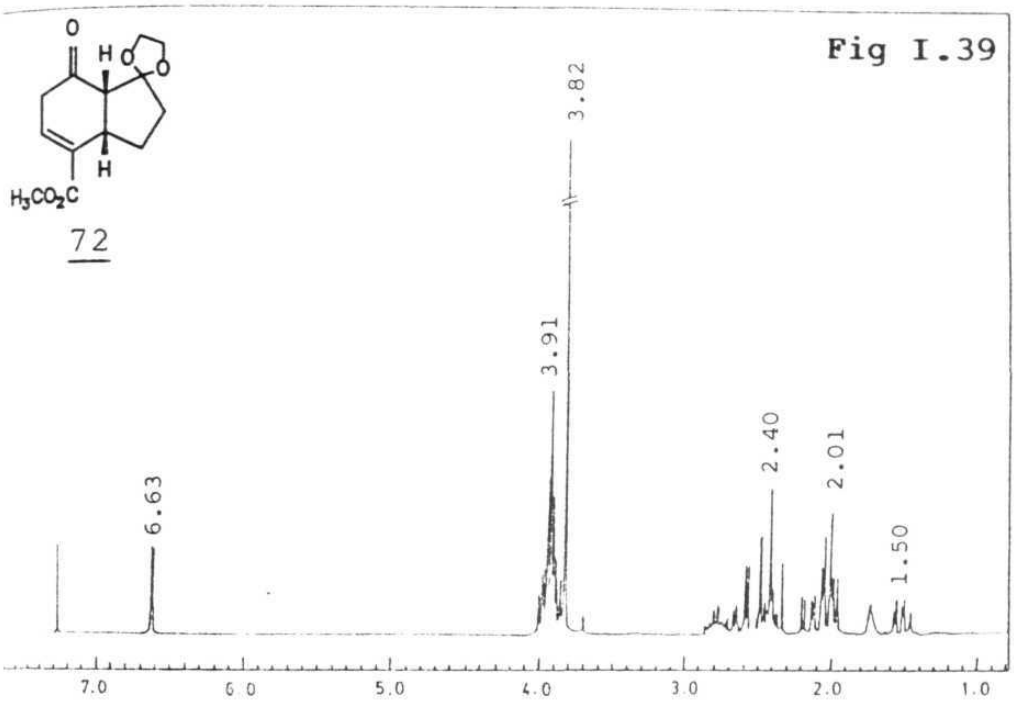


Fig I.39
72
6.63
3.91
3.82
2.40
2.01
1.50
7.0
6.0
5.0
4.0
3.0
2.0
1.0

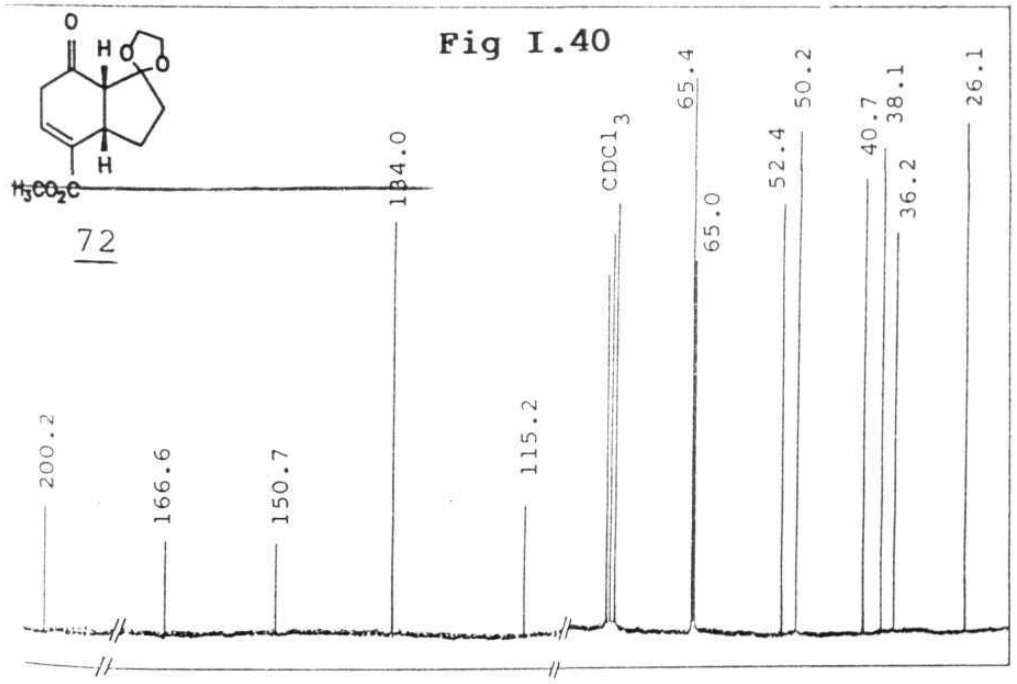


Fig I.40
72
200.2
166.6
150.7
134.0
115.2
CDCl3
65.4
65.0
52.4
50.2
40.7
38.1
36.2
26.1

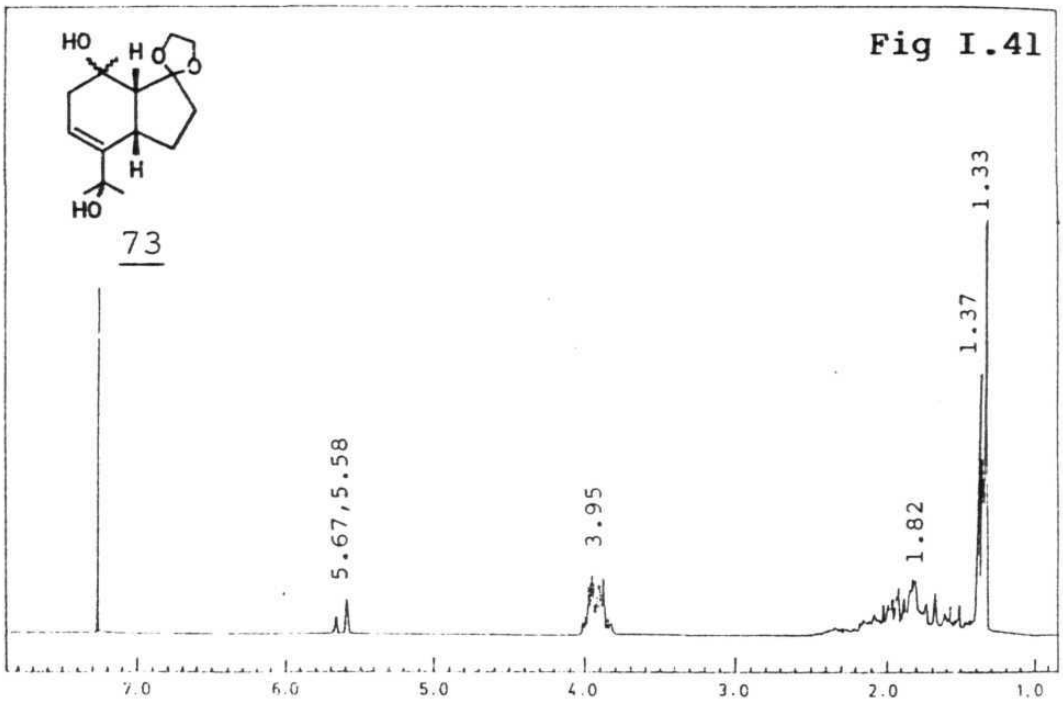


Fig I.41

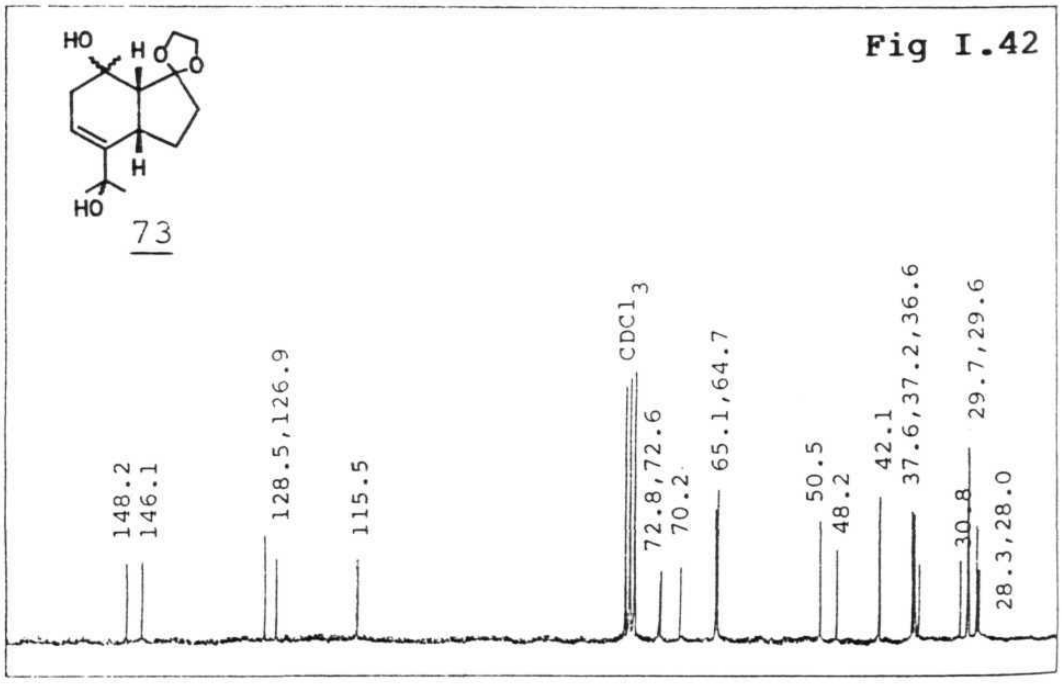


Fig I.42

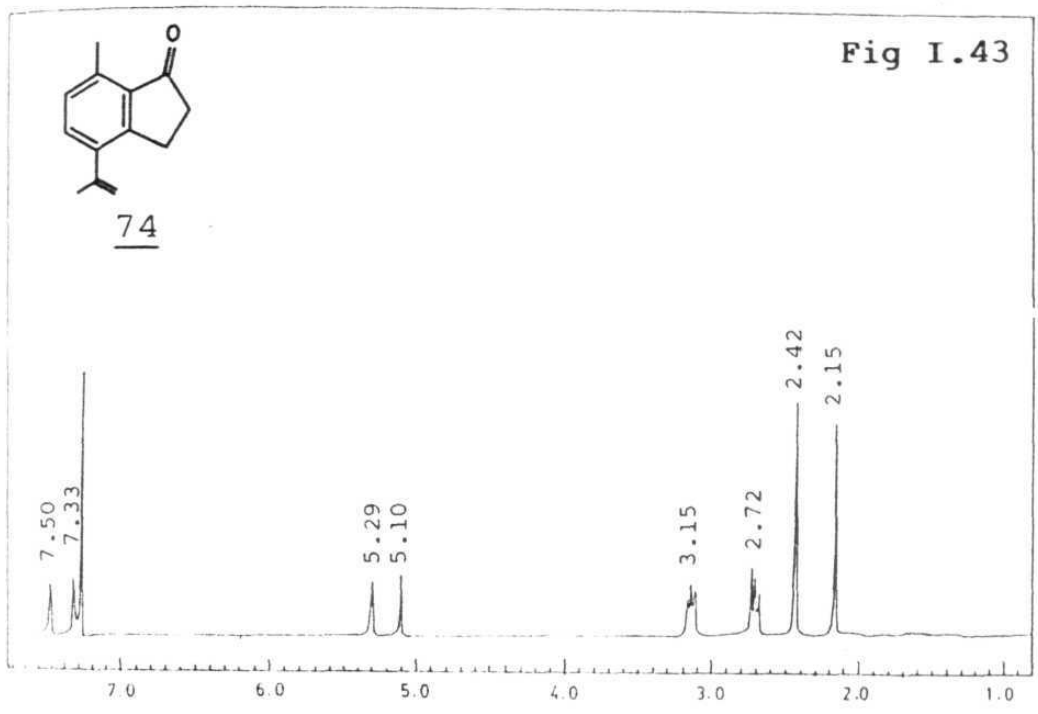


Fig I.43

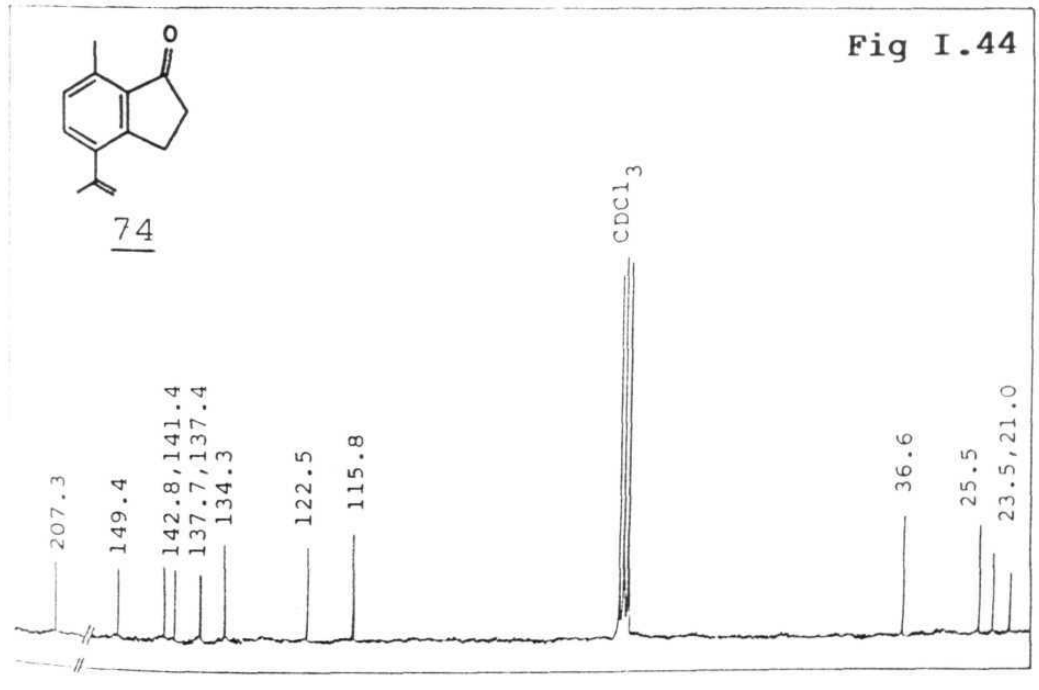
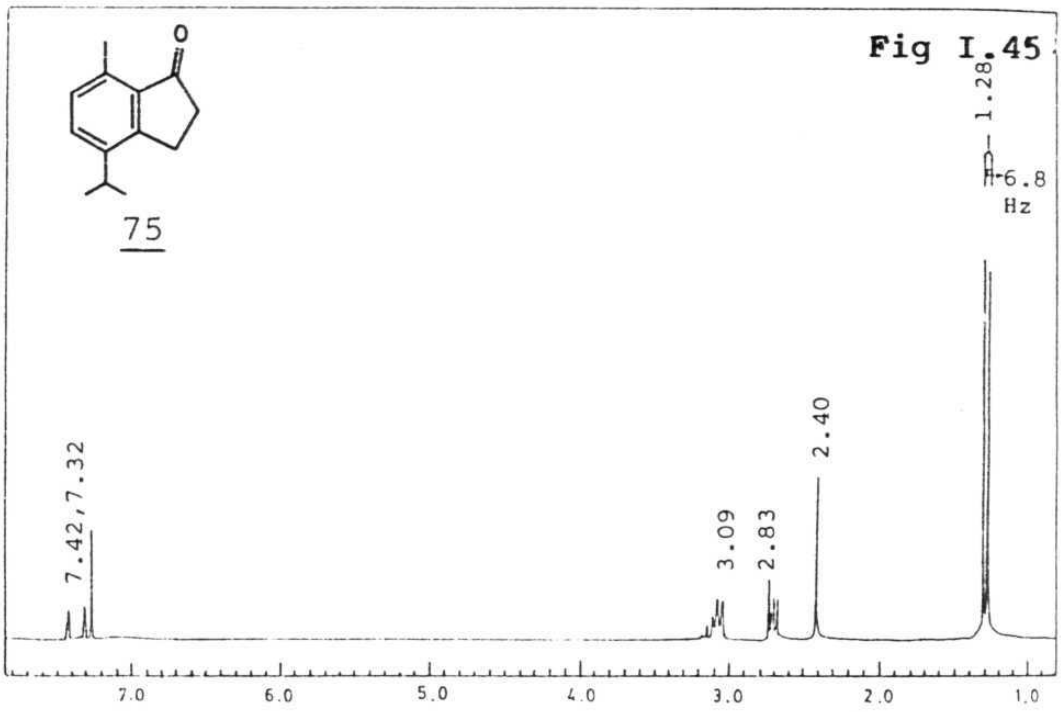
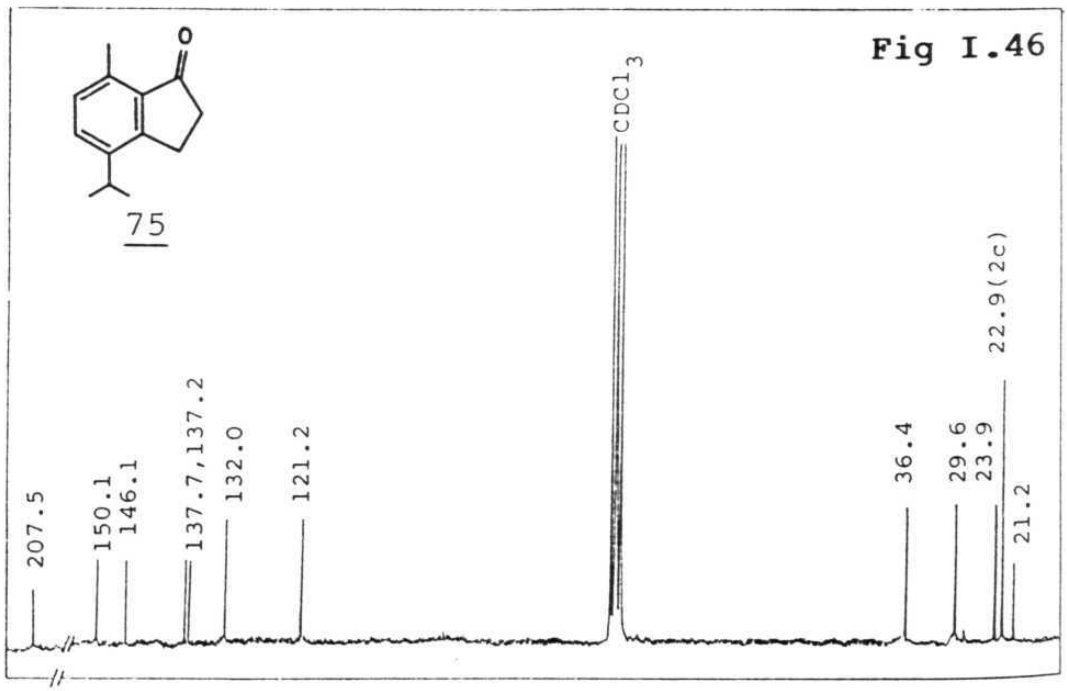


Fig I.44


O
75
Fig I.45
1.28
6.8
Hz
7.42,7.32
3.09
2.83
2.40
7.0
6.0
5.0
4.0
3.0
2.0
1.0


O
75
Fig I.46
CDCl3
207.5
150.1
146.1
137.7,137.2
132.0
121.2
36.4
29.6
23.9
22.9(2c)
21.2

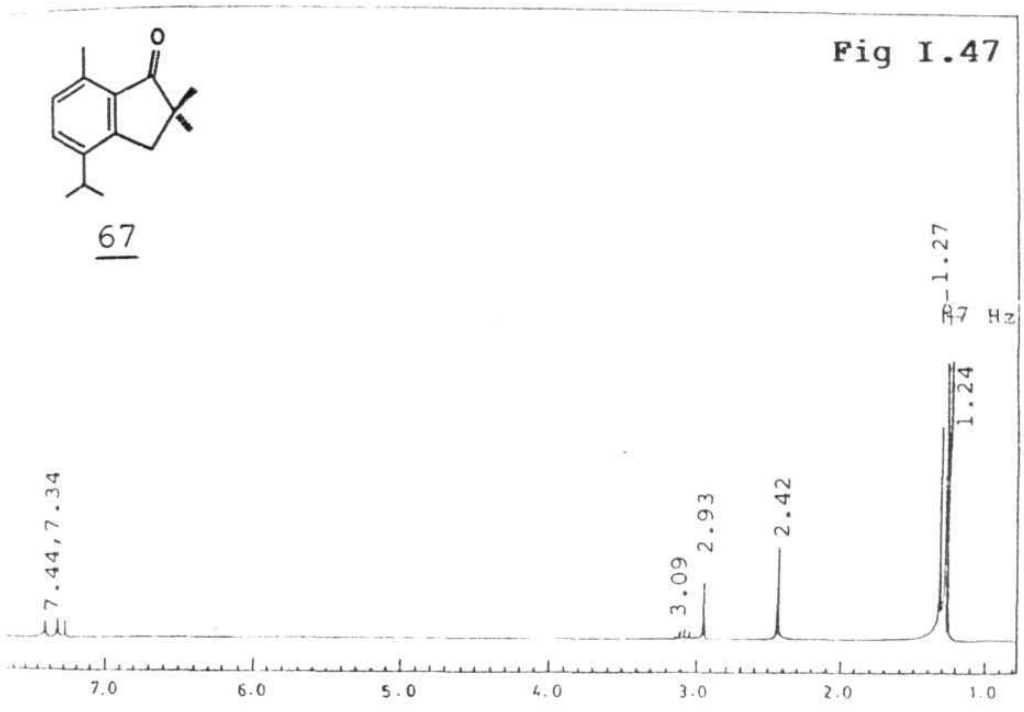


Fig I.47
67
7.44,7.34
3.09
2.93
2.42
1.27
1.24
7.0
6.0
5.0
4.0
3.0
2.0
1.0

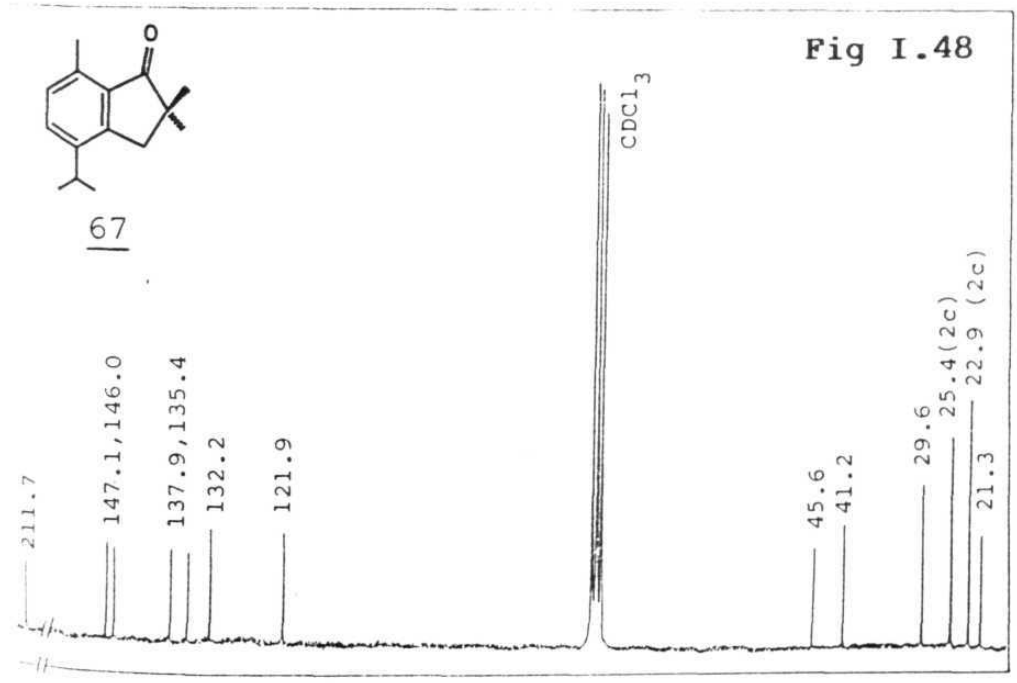


Fig I.48
67
211.7
147.1,146.0
137.9,135.4
132.2
121.9
CDCl3
45.6
41.2
29.6
25.4(2c)
22.9 (2c)
21.3

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Part II

Diastereoselectivities in Nucleophilic additions to Tricylo[5.2.1.$0^{2,6}$]decan-10-ones and potential application to natural product synthesis

II.1. ABSTRACT

We have carried out a systematic study of diastereoselectivities during nucleophilic additions to tricyclo[5.2.1.$0^{2,6}$]decan-10-ones 8-12 employing metal hydrides (e.g., $NaBH_4$, LAH, DIBAL-H) and alkyllithium (e.g., MeLi). The results described convincingly demonstrate the profound influence of the remote substituents in the endo-five-membered ring in controlling π-facial diastereoselection during nucleophilic additions. Extension of our studies to tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-ones 52-55 was undertaken to make our observation more general. The major vinyl alcohol 72, a suitable system for oxy-Cope phenomenon, obtained during diastereoselective nucleophilic addition of vinyl grignard to tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one 52 has been used in the construction of 5,6,5 fused system.

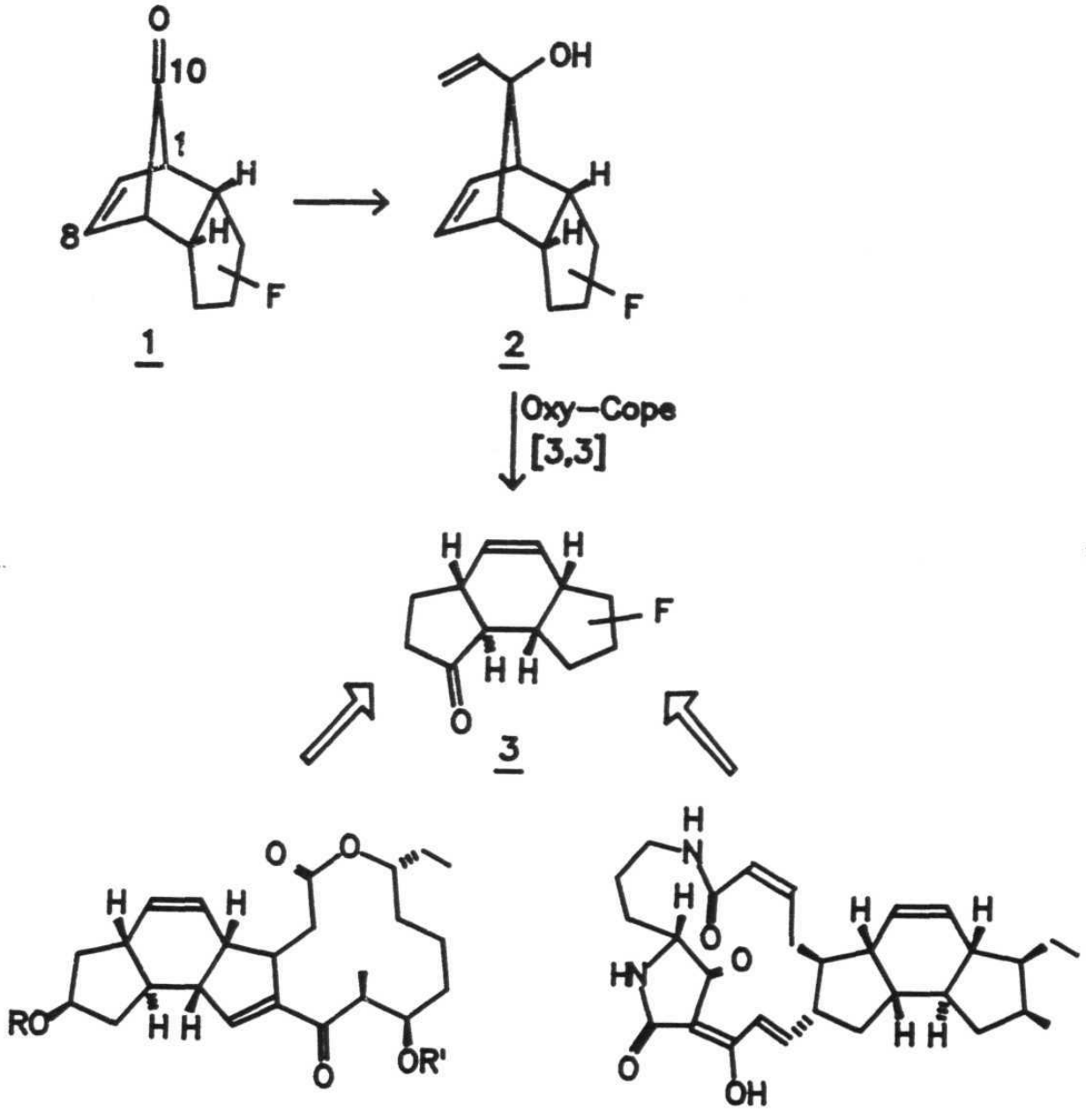
II.2. INTRODUCTION:

In the first part of this thesis, we have demonstrated that the readily available tricyclo[5.2.1.$0^{2,6}$]decan-10-ones can serve as convenient precursors of the cis-hydrindane system via Haller-Bauer reaction. The utility of this protocol was amply demonstrated through the synthesis of a few diverse natural products. As part of our continuing interest in the synthesis of fused polycyclic systems, we thought of further utilizing the tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one 1 system for constructing some newer fused systems, e.g., the 5,6,5 tricyclic system, an important building block for many natural products, Scheme 1. For effecting the transformation of 1 to an cis-hydroindacene system 3, an oxy-Cope rearrangement in the vinyl alcohol 2 was identified as the pivotal step. The feasibility of this plan hinged on our ability to acquire a derivative in which the vinyl group is positioned syn to the norbornene double bond of the tricyclo[5.2.1.$0^{2,6}$]decane system 1, Scheme 1. Since a derivative like 2 could be directly acquired through addition of the appropriate Grignard or organometallic reagent to 1, getting the desired stereoisomer 2 required diastereoselective nucleophilic addition to 1.

A literature search revealed that practically nothing was known regarding diastereoselection in nucleophilic addition to the C_{10}-carbonyl group in

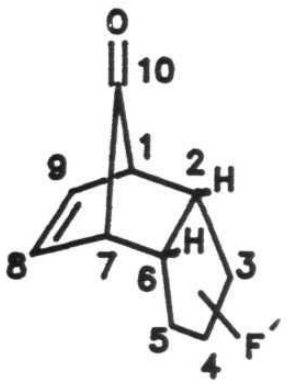
tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one 4 and tricyclo-[5.2.1.$0^{2,6}$]decan-10-one 5 ring systems, Scheme 2.

Scheme 1

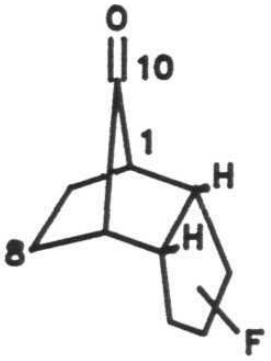


As the stereochemical outcome (π-face selectivity) during the addition to 4 and 5 was crucial to the outcome of the projected theme of **Scheme** 1, we have carried out a systematic study of diastereoselectivities during nucleophilic addition to tricyclo[5.2.1.$0^{2,6}$]decan-10-one derivatives 4 and 5.

Scheme 2



4



5

Synthetic organic chemists around the world are actively involved in devising methods to control stereoselectivity, so that stereogenic centers in natural products or other synthetic targets may be introduced with great economy. In this pursuit an adequate number of synthetic methods for introducing molecular functionality with control of diastereoselectivity or enantioselectivity has been created.[1] Most conventional way of generating stereogenic centre is by addition of reagent to trigonal carbon to give tetrahedral center involving stereogenic

aspects, known as FACIAL SELECTION, which has divergency through out the organic chemistry.[2]

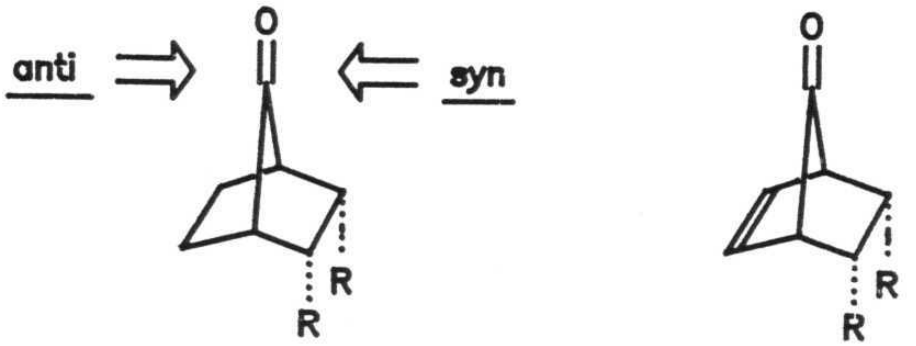
The prediction and control of diastereoselectivity in nucleophilic additions to carbonyl group has been a subject of considerable scrutiny and intense debate in recent years.[3] A multitude of factors can influence this face selection, they include steric effects, conformation of the flanking groups, complexation of reagents, product stability and stereoelectronic effects.

Initiated by Cram in 1952 recent years witnessed several interpretations of face selection involving the above factors, as a result of which several models for stereoselection have been proposed by different groups.[4-19]

In a recent study in our lab, we have described the profound effect of remote substituents in controlling diastereoselectivity in nucleophilic additions to sterically neutral-2,3-endo,endo-substituted-7-ketonorbornanes 6. These studies have been further extended to the endo-substituted-7-ketonorbornenes 7, Scheme 3.[20]

It has been observed that electron withdrawing endo-substituents (R=CN, esters etc.,) direct the nucleophile from the syn-face while electron donating substituents (R=Et) direct the nucleophiles from the anti-face.

Scheme 3



6 7

We have interpreted these observations in terms of Cieplak hyperconjugative theory[13,14] which states that nucleophile attack from the face opposite to the most electronrich anti-periplanar bonds. The two transition states for the nucleophilic addition, where R is an electron withdrawing or electron donating are shown in Scheme 4. We have also recognized, on the basis of extensive calculations, that there is also a contribution from electrostatic effects, particularly in the case of the 7-ketonorbornene system 7.

Besides the synthetic interest in the derivatives of endo-tricyclo[5.2.1.$0^{2,6}$]decan-10-ones, we also consider this ring system as a fine probe system for the study of π-face selectivity to complement our earlier studies on the endo-7-ketonorbornanes 6 and 7.

Scheme 4

R = Electron withdrawing R = Electron donating

There were several attractive features present in the tricyclo[5.2.1.$0^{2,6}$]decan-10-one ring system 4 and 5 that make them attractive substrates for the study of π-face selectivity during nucleophilic addition to the C_{10}-carbonyl group. These are:

a. the two faces of the trigonal carbon at C_{10} are more or less sterically equivalent (MMX calculations) as the five membered ring is endo-fused on the norbornane frame work.
b. the rigid tricyclic skeleton forestalls any ambiguity arising from the conformational uncertainty and
c. the substitution on the endo-fused five membered ring provides a handle for electronic fine-tuning of the two faces of distal C_{10}-carbonyl group.

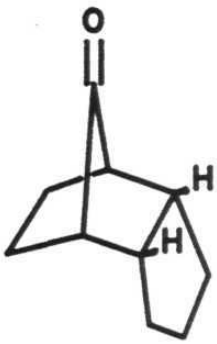
In the results and discussion section we described our results of π-facial diastereoselection in nucleophilic addition reaction on endo-tricyclo[5.2.1.$0^{2,6}$]decan-10-ones and endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-ones.

II.3. RESULTS AND DISCUSSION:

II.3.1. Nucleophilic additions to endo-tricyclo[5.2.1.$0^{2,6}$]-decan-10-ones:

The diastereoselectivities exhibited by sterically unbiased endo-tricyclo[5.2.1.$0^{2,6}$]decan-10-one in nucleophilic additions can be modulated through substituents in the distal five membered ring. We selected five substrates 8-12, Scheme 5, by varying the functionalities in the five membered ring to study the selectivity.

Scheme 5



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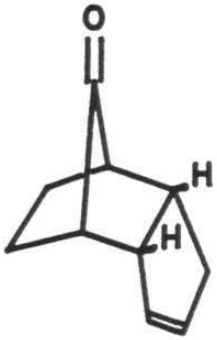

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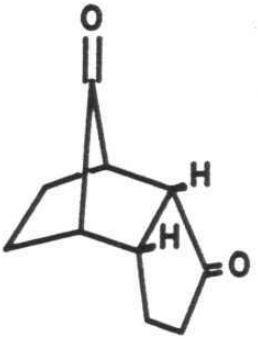

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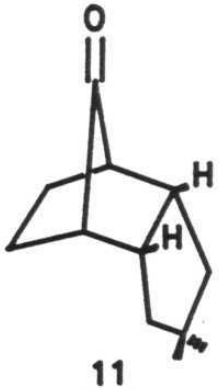

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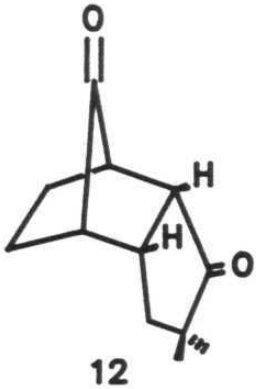


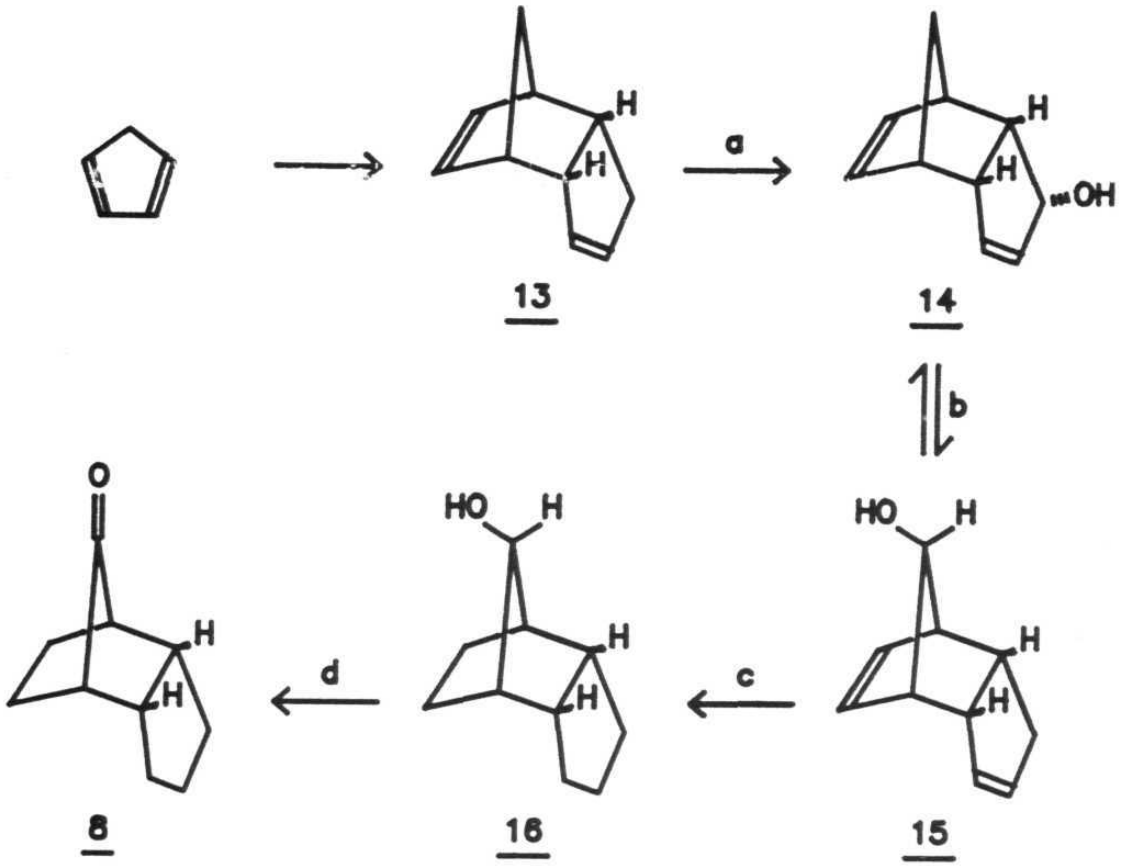
12

All the five endo-tricyclo[5.2.1.$0^{2,6}$]decanones 8 ---> 12 were synthesized through unambiguous methods. Simple unsubstituted tricyclicdecanone 8 was synthesized following the literature procedure with little modification.[21]

Commercially available dicyclopentadiene 13 on selenium dioxide oxidation to 14, followed by [3,3] sigmatropic rearrangement furnished the alcohol 15. The alcohol 15 was subjected to catalytic hydrogenation to give unsaturated alcohol 16 in quantitative yield. The alcohol 16 on oxidation by PCC furnished tricyclodecan-10-one 8 in 80% yield, **Scheme 6**. The characteristic carbonyl absorption of norbornanone at 1770 cm^{-1} in the IR spectrum and a 6 line ^{13}C NMR spectrum (Fig II.2) with carbonyl carbon resonance at δ 215.60 secured structure 8.

Remaining four tricyclodecanones 9-12 were synthesized from the precursor 21, which was prepared in good quantities following the literature procedure from cyclopentanone ethyleneketal 17.[22] Cyclopentanone ketal 17 on dibromination and dehydrobromination gave the intermediate cyclopentadiene ketal 18 which underwent Diels-Alder dimerization to give adduct 19.

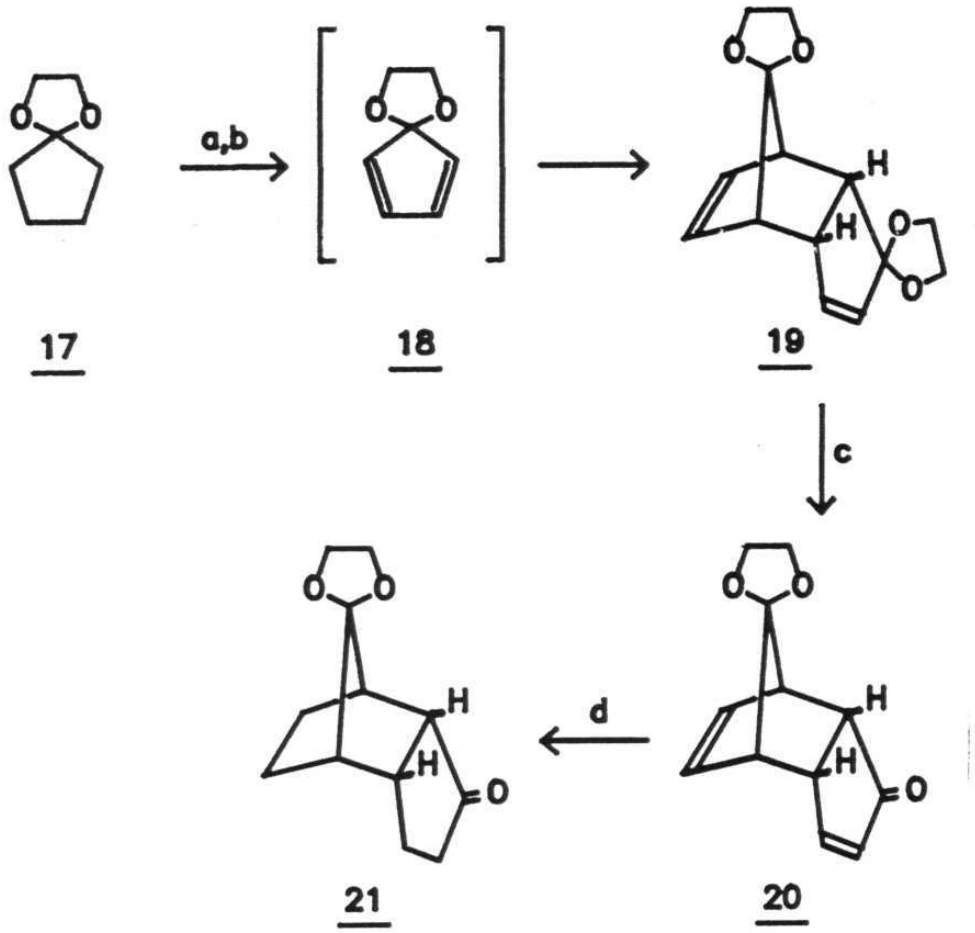
Scheme 6



Reagents: a) SeO_2, dioxane, potassium dihydrogen phosphate, reflux, 3h, 63%; b) 135-150°C, neat, 6h, 60%; c) H_2-PtO_2, ethyl acetate, r.t., 1h, 99%; d) PCC, Celite, DCM, r.t., 77%

Regioselective hydrolysis to 20 followed by catalytic hydrogenation furnished the saturated ketone-ketal 21 in good quantities in 60% yield, **Scheme 7.**

Scheme 7



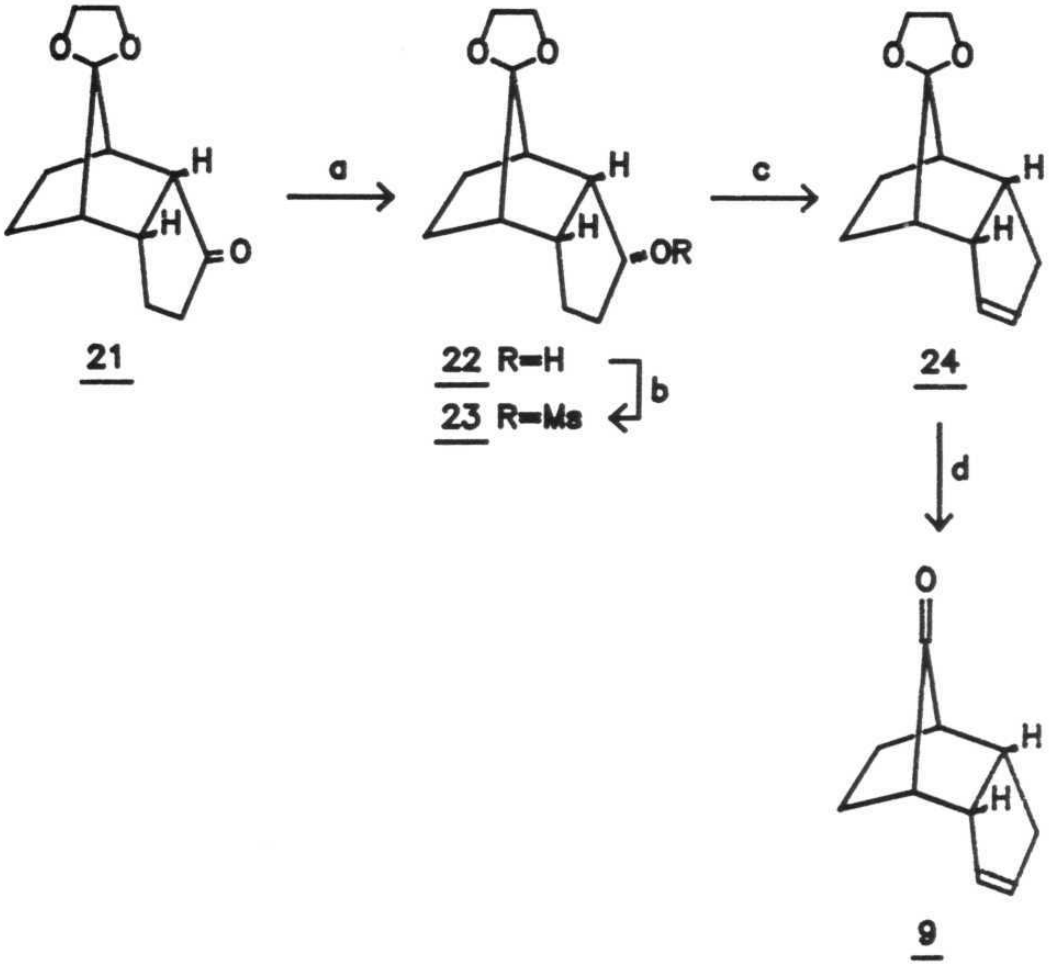
17 18 19 20 21

Reagent: a) $2Br_2$, dioxane, r.t., 3h, 60%; b) NaOMe, MeOH, reflux, 6h, 70%; c) dil.HCl, r.t., 1h, 80%; d) $Pd/C-H_2$, ethyl acetate, r.t., 15 min, 99%.

Tricyclic ketone ketal 21 smoothly underwent reduction to give alcohol 22. Alcohol 22 on mesylation to 23 followed by elimination using NaI and HMPA furnished 24 in 76% yield. The structure of 24 was revealed through its ^1H NMR, which showed resonances at δ 5.84-5.40 (m, 2H) corresponding to

the olefinic protons. Unsaturated ketal 24 on hydrolysis with 70% aq.H_2SO_4 in DCM provided tricyclo[5.2.1.$0^{2,6}$]dec-3-en -10-one 9 in 85% yield, **Scheme** 8. The structure of 9 is in agreement with its IR, ^{1}H and ^{13}C NMR spectral data (Fig II.3 and Fig II.4).

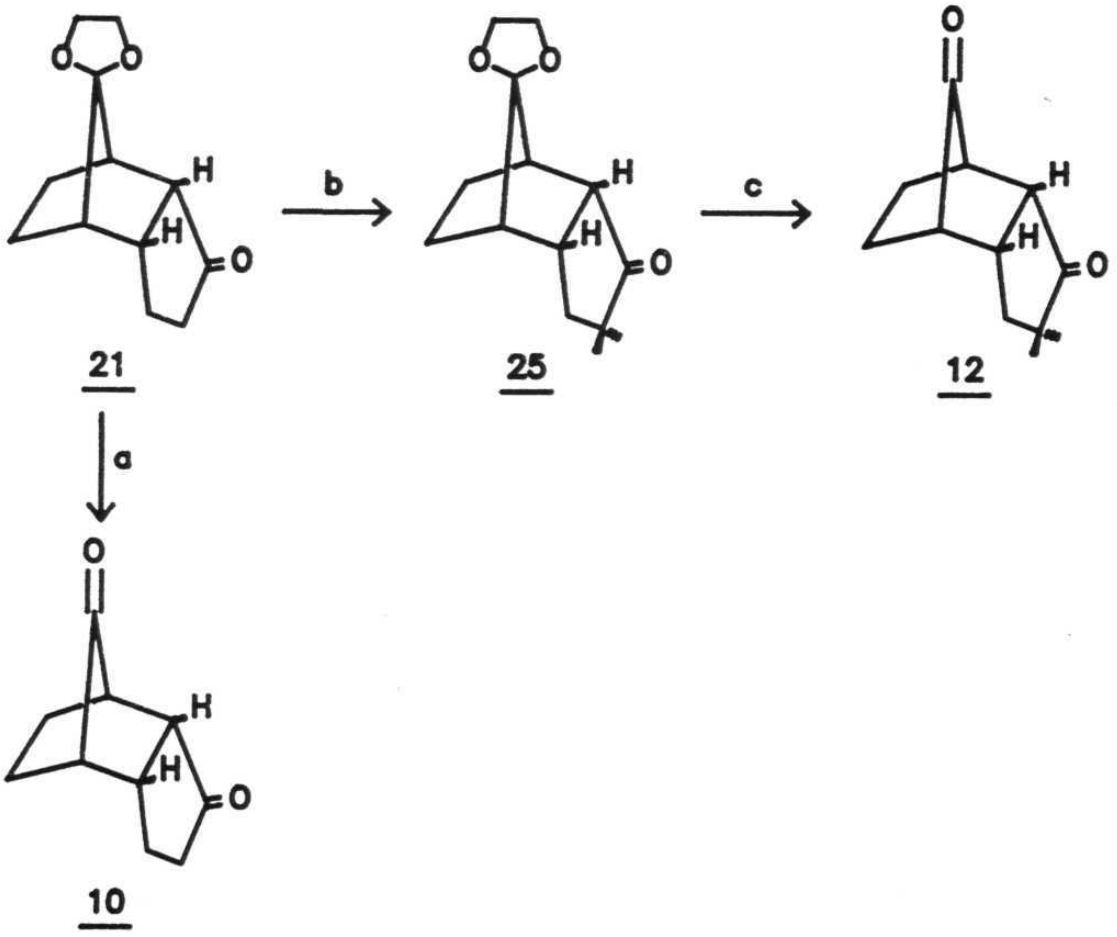
Scheme 8



Reagents: a) $NaBH_4$, MeOH, r.t., 30 min, 99%; b) MsCl, pyridine, r.t., 1h, 90%; c) NaI, HMPA, 120°C, 9h, 74%; d) 40% aq.H_2SO_4, DCM, r.t., 4h, 90%.

When ketone ketal 21 was subjected to hydrolysis with 80% aq.H_2SO_4 using DCM as the solvent, tricyclo[5.2.1.$0^{2,6}$]decan-3,10-dione 10 was obtained in 80% yield, **Scheme 9**. Diagnostic carbonyl absorptions at 1770, 1730 cm^{-1} in the IR spectrum and a 10 line ^{13}C NMR spectrum (Fig II.6) with carbonyl resonances at δ 219.9 and 211.7 confirmed the structure as 10.

Scheme 9



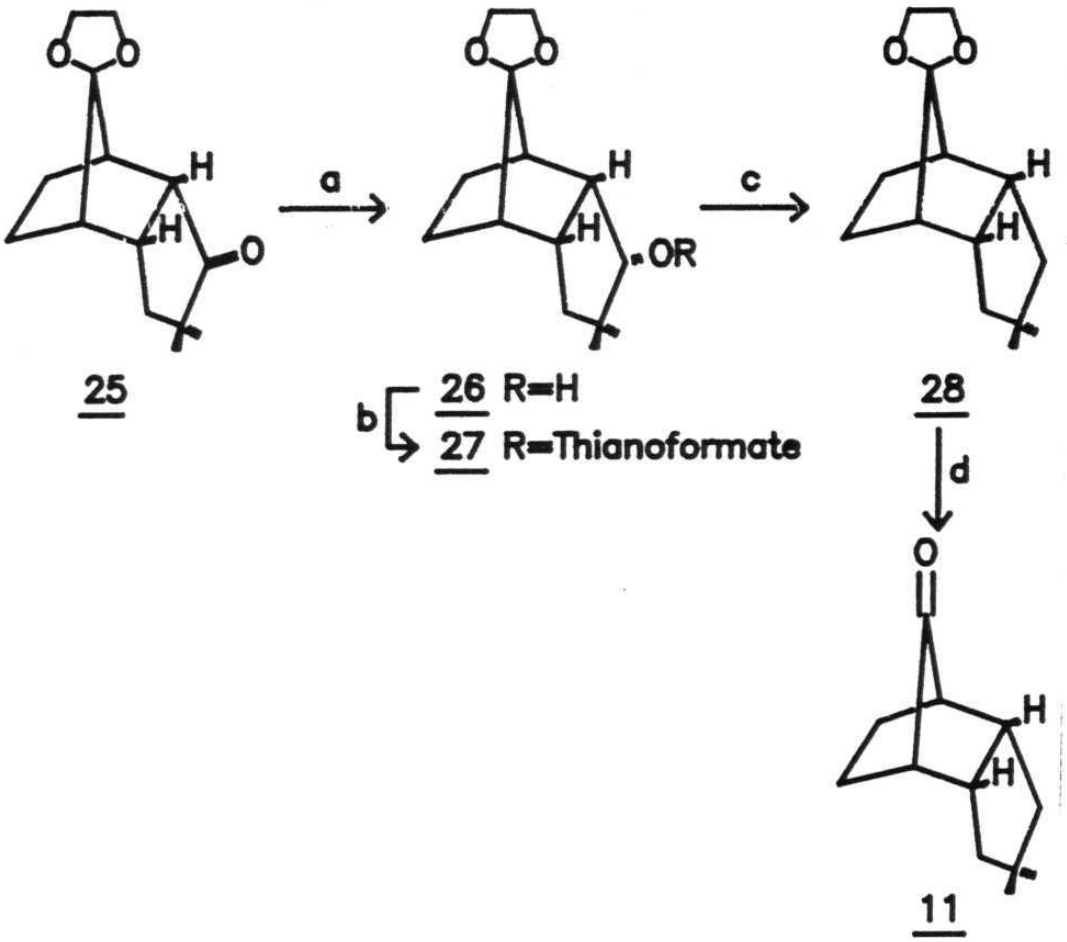
Reagents: a) 80% aq.H_2SO_4, DCM, r.t., 1h, 80%; b) $^{t}BuOK$, MeI, $^{t}BuOH$, reflux, 10h, 84%; c) 70% aq.H_2SO_4, DCM, r.t., 1h, 80%.

Dimethyl diketone 12 was synthesized from dimethyl ketone-ketal 25, prepared via gem-dimethylation of ketone-ketal 21 with potassium t-butoxide and excess methyl iodide. Hydrolysis of 25 with 70% aq.H_2SO_4 using DCM as a medium gave 12 in 80% yield, Scheme 9. Carbonyl absorptions at 1770 and 1730 cm^{-1} in the IR spectrum and two singlets of dimethyl at 1.08 and 1.04 in the ^1H NMR spectrum (Fig II.9) and a 12 line ^{13}C NMR spectrum (Fig II.10) with carbonyl resonances at δ 220.5, 211.3 fully supported the structure 12.

Synthesis of endo-tricyclodeca-4-bismethyl-10-one 11 initially gave some problems but a 4 step sequence involving alcohol 26 and thianoformate intermediate 27 furnished dimethyl ketone 11 in 90% yield, Scheme 10. The structure of this dimethyl ketone 11 was unambiguously confirmed by its IR, ^1H and ^{13}C NMR spectral data which showed characteristic carbonyl absorption at 1770 cm^{-1} in the IR spectrum. Two singlets at δ 1.26 and 1.08 in ^1H NMR spectrum (Fig II.7) and 8 line ^{13}C NMR spectrum (Fig II.8) with carbonyl resonance at δ 215.6 further confirmed its structure.

All the five tricyclodecanones 8-12 were subjected to carbonyl reduction with hydrides ($NaBH_4$, LAH and DIBAL-H) of varying size and reactivity and methylation with MeLi to furnish (E)-and (Z)-alcohols 16 & 29-45 in nearly quantitative yield, Scheme 11.

Scheme 10



Reagents: a) $NaBH_4$, MeOH, r.t., 10h, 99%; b) p-Tolyl chlorothianoformate, pyridine, r.t., 14h, 85%; c) $n\text{-}Bu_3SnH$, AIBN, benzene, reflux, 60h, 55%; d) 70% aq.H_2SO_4, DCM, r.t., 90%.

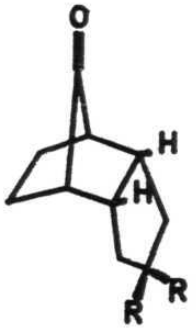
The diastereoselectivities and product ratios observed in the addition reactions are presented in **Table 1.**

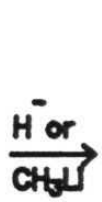
Table 1: Product ratios in the metal hydride and methyllithium addition to 8-12.

Substrate	E : Z ratios[a]			
	$NaBH_4$[b,c]	LAH[b,d]	DIBAL-H[e,f]	MeLi[b,d]
8	24 : 76 (16) (29)	25 : 75 (16) (29)	25 : 75 (16) (29)	14 : 86 (30) (31)
9	28 : 72 (36) (37)	27 : 73 (36) (37)	27 : 73 (36) (37)	19 : 81 (38) (39)
10	45 : 55 (40) (41)	-	-	-
11	37 : 63 (32) (33)	39 : 61 (32) (33)	40 : 60 (32) (33)	32 : 68 (34) (35)
12	56 : 44 (42) (43)	54 : 46 (42) (43)	-	53 : 47 (44) (45)

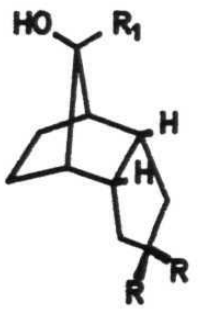
[a] Ratios based on ^1H NMR integration of the total mixture (± 5%). [b] Reductions were carried out at 0-10°C till the starting ketone was fully consumed. [c] In methanol. [d] In diethyl ether. [e] In dichloromethane. [f] Reaction carried out at -78°C.

Scheme 11





H^- or CH_3Li



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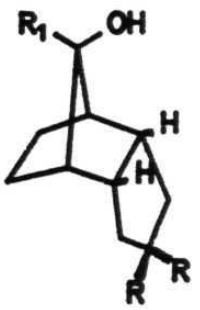


8 R=H

11 R=CH_3

(E)-16 R=R_1=H

30 R=H;R_1=CH_3

(E)-32 R=CH_3;R_1=H

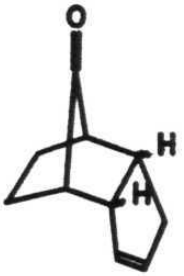
34 R=R_1=CH_3

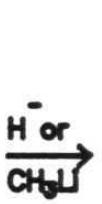
(Z)-29 R=R_1=H

31 R=H;R_1=CH_3

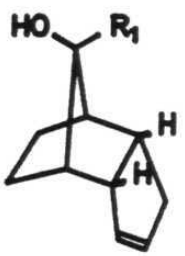
(Z)-33 R=CH_3;R_1=H

35 R=R_1=CH_3





H^- or CH_3Li



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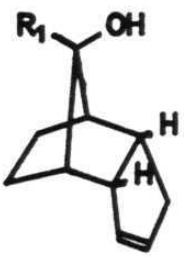


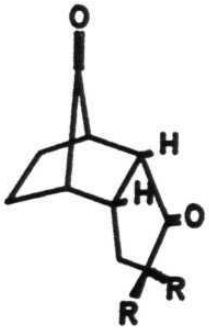
9

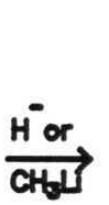
(E)-36 R_1=H

38 R_1=CH_3

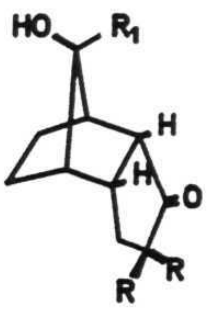
(Z)-37 R_1=H

39 R_1=CH_3





H^- or CH_3Li



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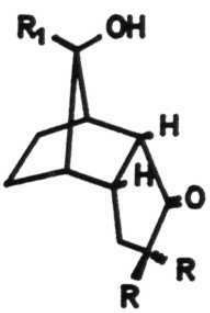


10 R=H

12 R=CH_3

(E)-40 R=R_1=H

(E)-42 R=CH_3;R_1=H

44 R=R_1=CH_3

(Z)-41 R=R_1=H

(Z)-43 R=CH_3;R_1=H

45 R=R_1=CH_3

The stereostructures of the diastereomers were unambiguously assigned on the basis of

a. the relative shielding of C_2,C_6-exo-protons in (Z)-alcohols compared to the (E)-alcohols confirmed by selective LIS studies

b. greater deshielding of the proton (Fig II.11-Fig II.25) and carbon attached to the hydroxyl group in the (Z)-series compared to (E)-series, , and

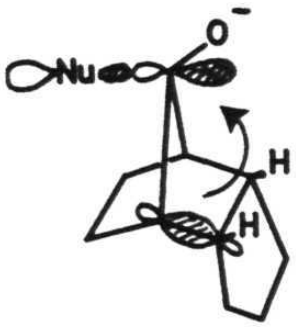
c. chemical correlation with some of the known compounds.

Several features of the results displayed in the Table 1 deserve comment, the parent tricyclodecanone 8 itself exhibits significant selectivity (3:1) in favour of the approach of nucleophiles from the face opposite to the endo-cyclopentane ring. Thus, endo-alkyl substituents seems to favour the approach to 7-norbornanone from the anti-face irrespective of the conformational rigidity (in 8) or mobility (in 6 R=Et) of these substituents.

Also, the (E):(Z) ratios reported here remain insensitive to the size of the hydride reducing agent. On the other hand, electronic perturbation in the endo-5 membered ring through introduction of electron withdrawing groups as in 9 and 10 results in an increase in syn-approach. Indeed, in 12 crossover is observed and the (E)-alcohol 42 from syn-approach predominates. The preferred formation of (Z)-product in 8 and progressive increase in

(E) product in the series 8 --> 9 --> 10 is a result that is best interpreted in terms of the Cieplak's transition state hyperconjugation model, **Scheme** 12, according to which delocalization of σ electron in electron rich antiperiplanar bond into the incipient σ^* orbital lowers the transition state energy.

Scheme 12



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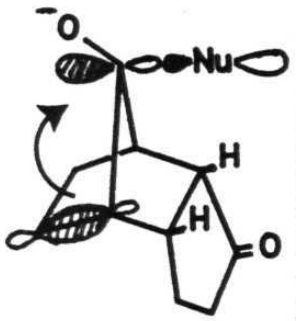

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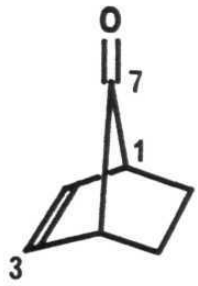
While the application of Cieplak's model to our systems 8-10 gave us a satisfactory rationalization but to counter the steric argument, that it is protons on C_4 that sterically hinder the approach of nucleophile and make the nucleophile to attack more from the anti side, we designed the systems 11 and 12 in which the protons on C_4 are replaced by more bulky methyl groups. Interestingly, the approach of nucleophile from anti side in 11 is decreased as compared to that in 8, the same effect is observed with 12. This clearly shows that it is only electronic factor and not steric factor which is controlling the face selectivity in the nucleophilic additions to the tricyclic system present in 8-12.

II.3.2. Nucleophilic additions to endo-tricyclo[5.2.1.$0^{2,6}$]-dec-8-en-10-ones:

7-Norbornenone 54 is an intrinsically interesting substrate that has served as an important stereoelectronic probe in diverse organic reactions. Initially it was believed that the homoconjugative interaction[23-25] between the endo cyclic double bond and the carbonyl group at C_7 will govern the face selectivity during nucleophilic additions to these system expect to result in a preferred approach of the reagent from the anti direction to give syn-alcohols as shown below.

Scheme 13



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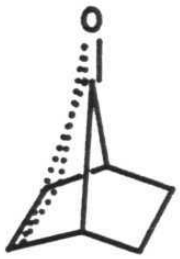

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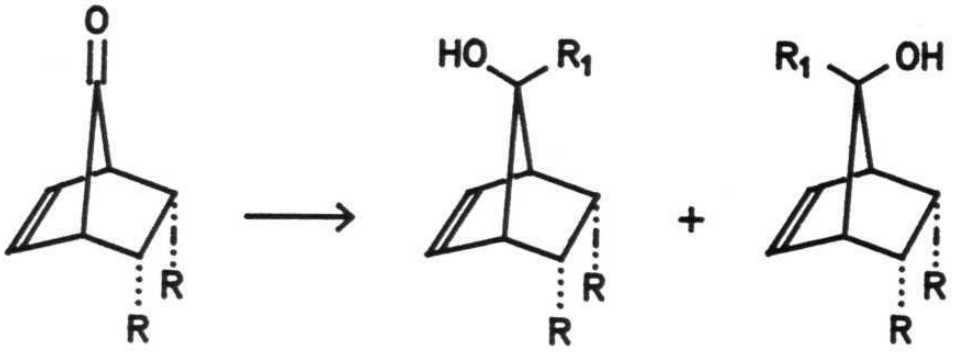
But the extensive study by Brown and Muzzio,[26] Erman[27], Warkentin[28] Gassman and O'Reilly[29] on face selectivity in nucleophilic additions to 48 showed that the hyperconjugative interaction as shown in 49, **Scheme 13**, does not seem to be playing any decisive role in controlling

reagent traffic at C_7.

Recent work in our lab showed altered or reversal in selectivity by the endo- substituents on 7-norbornanones, **Scheme 14.**[20]

Scheme 14

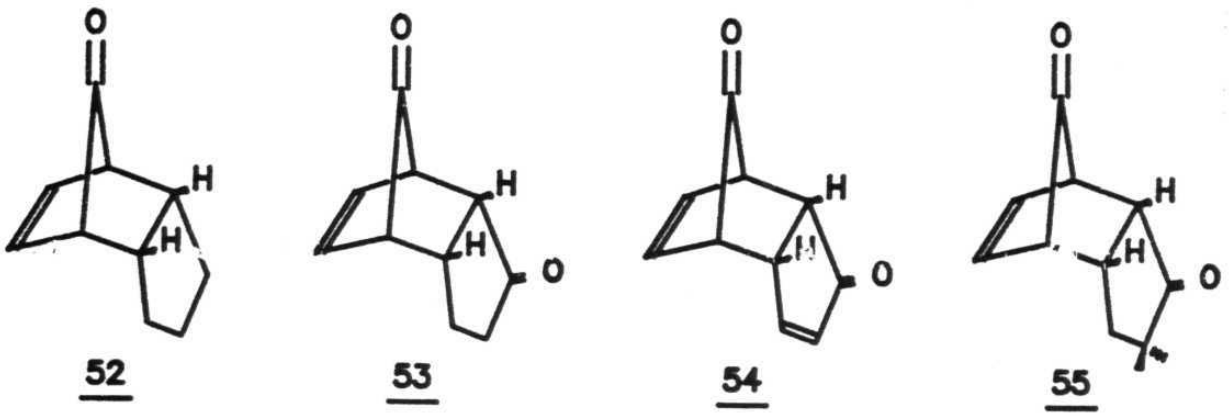


7	50	51
R=H	26	74
R=CO_2Me	90	10
R=CH_2OMe	26	74

The above results demonstrate significant variation in face-selectivity when the substituent is altered from CO_2Me ---> CH_2OMe.

The intriguing results discussed above prompted us to study face selectivity in endo-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-ones. For this purpose, we selected four substrates 52-55 with electron donating and electron withdrawing groups in the five membered ring, **Scheme 15.**

Scheme 15

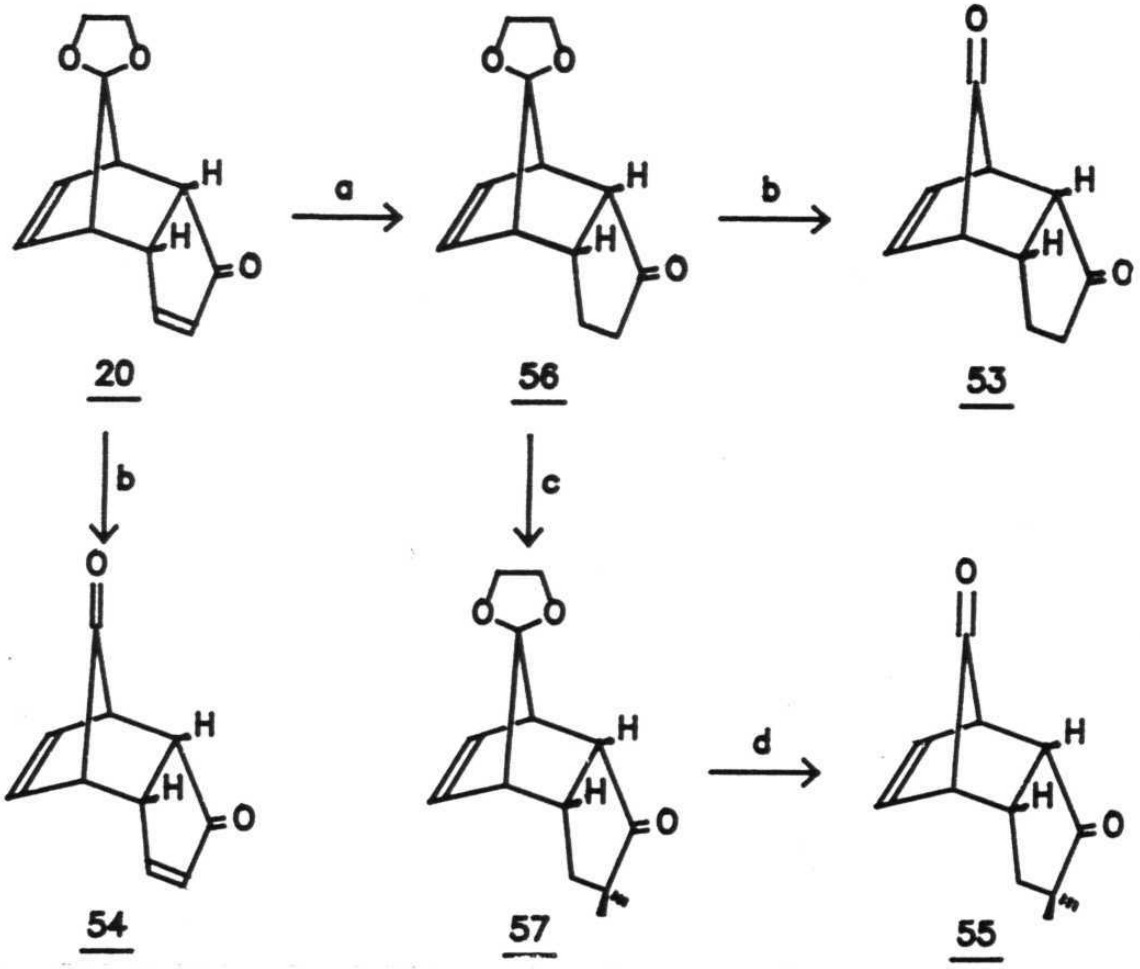


Except 52, all other substrates were synthesized from the readily and easily available starting materials as shown in **Scheme** 16.[31]

Hydrolysis of ketone ketal 56, obtained from 20 by 1,4-reduction using trimethoxy aluminum hydride[22d], with 70% aqueous sulfuric acid using DCM as a solvent furnished diketone 53 in 85% yield. Disappearance of the ketal peaks in the ^{1}H NMR spectrum (Fig I.1) and a 10 line ^{13}C NMR spectrum (Fig I.2) with carbonyl resonances at δ 200.3 and 218.5 confirmed its structure. The diketone 54 was obtained from the enone ketal 20 following the same procedure. The structure of the enone ketone 54 is in full agreement with its IR, ^{1}H and ^{13}C NMR spectral data (Fig II.28 and Fig II.29). The dimethyl diketone 55 was obtained when ketone ketal 57, synthesized from the ketone-ketal 56 by gem-

dimethylation using potassium t-butoxide and excess methyl iodide, stirred at room temperature for 24h using 40% aq.H_2SO_4 and DCM as solvent. Carbonyl adsorption in IR at 1770, 1730 cm^{-1} and 12 line ^{13}C NMR spectrum (Fig II.31) with carbonyl resonances at δ 219.9 and 200.9 further confirmed the structure as 55.

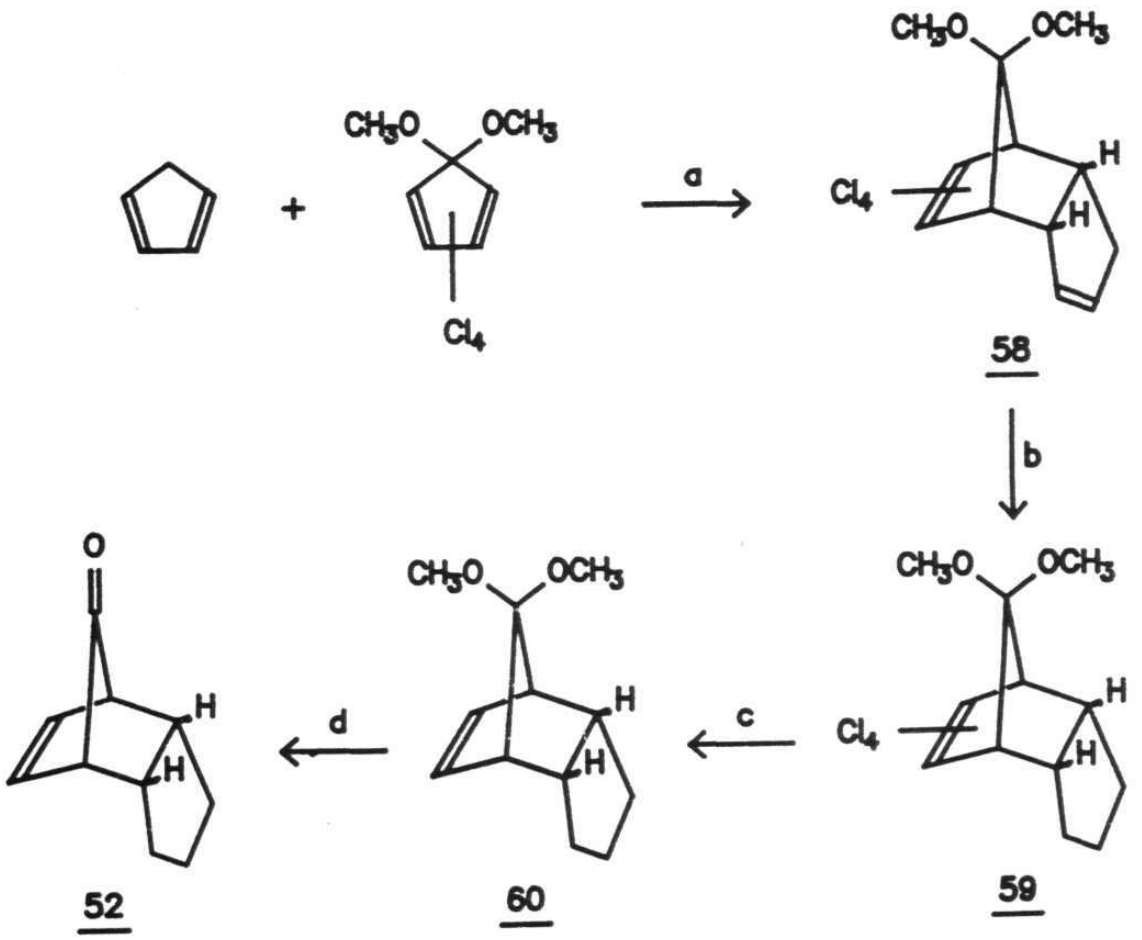
Scheme 16



Reagents: a) $LiAlH(OMe)_3$-THF, CuBr, -78°C, 30 min, 75%; b) 70% aq.H_2SO_4, DCM, r.t., 2h, 85%; c) $^{t}BuOK$, MeI, $^{t}BuOH$, reflux, 3h, 85%; d) 40% aq.H_2SO_4, DCM, r.t., 2h, 85%.

For the synthesis of 52, 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and cyclopentadiene were identified as abundantly available starting materials. Diels-Alder reaction between them furnished a single endo-adduct 58.[30]

Scheme 17



Reagents: a) Toluene, reflux, 24h, 70%; b) Pd/C-H_2, ethyl acetate, r.t., 8h, 70%; c) Na-Liq.NH_3, THF, ethanol, 20 min, NH_4Cl, 60%; d) Amberlyst-15, moist acetone, r.t., 6h, 80%.

Selective hydrogenation of the double bond in 58 gave mono-unsaturated compound 59 in 90% yield. A modified metal-NH_3 reduction procedure [31] was followed for reductive dehalogenation of the adduct 59 to furnish the unsaturated ketal 60 in 60% yield. Appearance of olefinic peaks in the ^1H NMR spectrum at δ 6.08 and a simple 8 line ^{13}C NMR spectrum indicated the structure 60. Hydrolysis of the ketal in 60 was effected by amberlyst resin in moist acetone to furnish the ketone 52 in 80% yield, **Scheme 17.** The IR spectrum showed characteristic carbonyl absorption at 1770 cm^{-1}. Disappearance of ketal protons in the ^1H NMR spectrum (Fig II.26) and 6 line ^{13}C NMR spectrum (Fig II.27) further supported the structure as 52.

All the four substrates 52-55 were subjected to hydride and alkyl lithium reductions to furnish a mixture of (E)- and (Z)- alcohols, 61-70 **Scheme 18,** whose ratios were determined from ^1H NMR spectral (Fig II.32-Fig II.39) integration of crude reaction mixture and GLC analyses. The diastereomers were separated by silica gel column chromatography and were fully characterized.

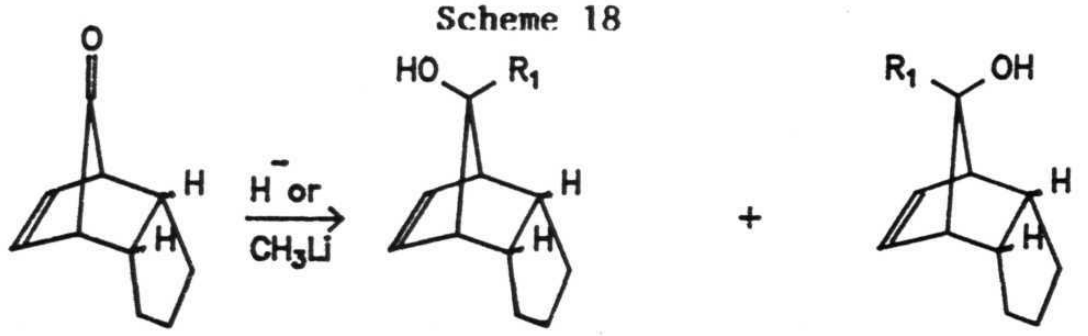
The diastereoselectivities and product ratios observed in the addition reactions are presented in **Table 2.**

Table 2: Product ratios in the metal hydride reduction and methyl lithium addition to 52-55.

Substrate	E : Z ratios[a]			
	$NaBH_4$[b,c]	LAH[b,d]	DIBAL-H[e,f]	MeLi[b,d]
52	6 : 94 (61) (62)	6 : 94 (61) (62)	5 : 95 (61) (62)	4 : 96 (63) (64)
53	25 : 75 (65) (66)	-	-	-
54	35 : 65 (69) (70)	35 : 65 (69) (70)	-	-
55	23 : 77 (67) (68)	23 : 77 (67) (68)	-	-

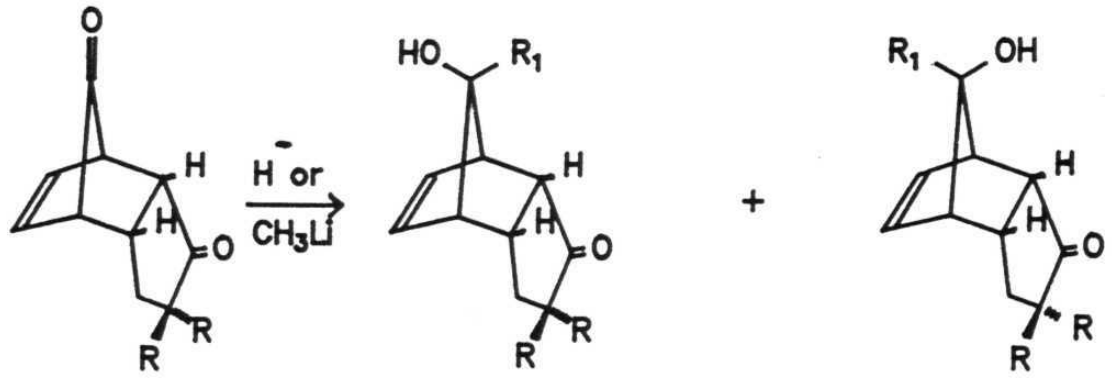
[a] Ratios based on ^1H NMR integration of the total mixture (± 5%). [b] Reductions were carried out at 0-10°C till the starting ketone was fully consumed. [c] In methanol. [d] In diethyl ether. [e] In dichloromethane. [f] Reaction carried out at -78°C.

Scheme 18



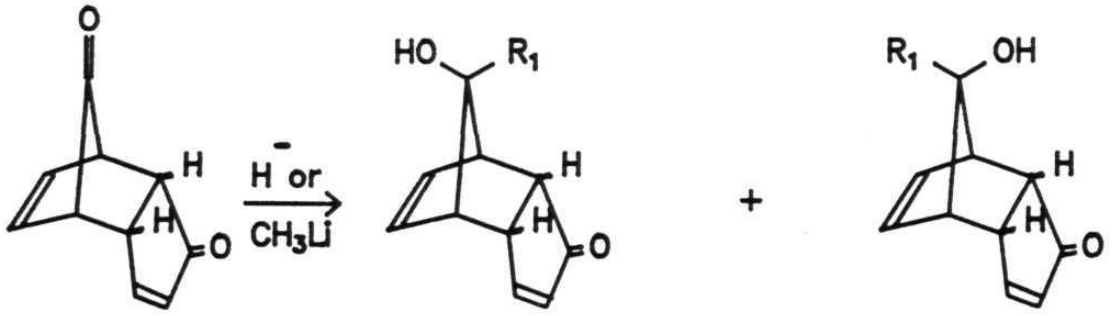
52 (E)–61 R_1=H (Z)–62 R_1=H

63 R_1=CH_3 64 R_1=CH_3



53 R=H (E)–65 R=R_1=H (Z)–66 R=R_1=H

55 R=CH_3 (E)–67 R=CH_3;R_1=H (Z)–68 R=CH_3;R_1=H



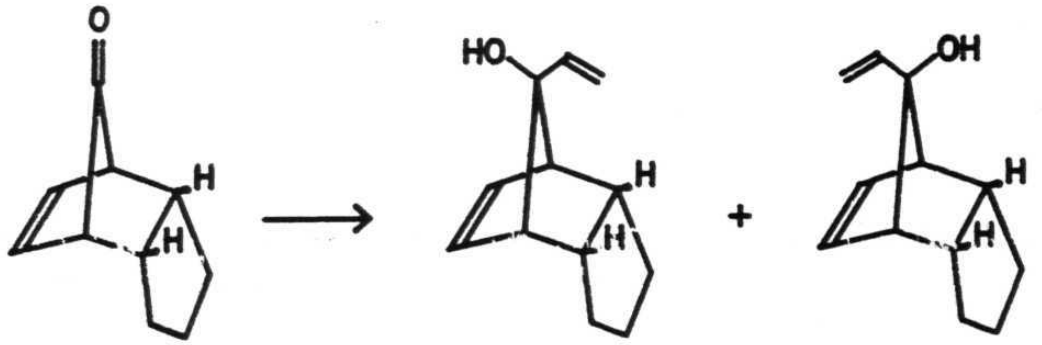
54 (E)–69 R_1=H (Z)–70 R_1=H

The results summarized in the **Table 2** demonstrate significant variation in the face-selectivity as one goes from 52, having both electron donating bonds, to 54, having election withdrawing bonds. The preferred formation of (Z)-alcohol in 52, similar to that observed to the endo-tricyclodecanones 8, and progressive increase in (E)-alcohol in the series 52 ---> 53 ---> 54 is a result that is best interpreted in terms of the Cieplak's model.[13,14]

The stereochemistry of the products in all the cases was determined unambiguously by the diagnostic deshielding effect of hydroxyl group on the exo-protons beneath it. The trends of these shifts are similar to those reported earlier for endo-tricyclodecanones 8-12. Further evidence for the stereochemistry was obtained by hydrogenating all the unsaturated alcohols individually and comparing them with the alcohols obtained in the tricyclodecanone series.

After our successful diastereoselective studies on tricyclo[5.2.1.$0^{2,6}$]decan-10-one systems we thought that the time had arrived to synthesize a suitable system for oxy-Cope rearrangement to deliver 5,6,5 fused system. When tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one 52 was subjected to addition reaction with vinyl magnesium bromide, it expectedly furnished syn-alcohol 72 (-OH towards five membered ring) as a major product, a system desired for oxy-Cope reaction, **Scheme 19.**

Scheme 19

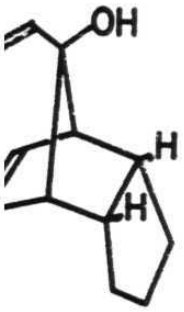


52 71 72

Among the various conditions reported in the literature[32] we preferred initially a milder condition, using KH and 18-Crown-6 in THF at room temperature, for oxy-Cope reaction. All our attempts to generate a 5,6,5 system from vinyl alcohol 72 were thwarted by the irrepressible side reactions.

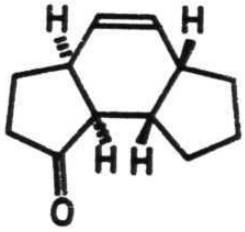
After some exploratory studies, change in conditions were called for. We found a solution through a drastic oxy-Cope reaction conditions, using $KN(SiMe_3)_2$ and 18-Crown-6 in THF and refluxing for 6 hr, where we have some indication of the product formation, Scheme 20. However, the product 73 could not be fully characterized. Further efforts towards realizing this objective are obviously called for.

Scheme 20



72

[3,3]



73

II.4. SUMMARY:

We have demonstrated that π-face selectivities in sterically neutral tricyclo[5.2.1.$0^{2,6}$]decanones can be modulated through electronic changes in the remote endo-five membered ring. These observations have a bearing on the currently debated models for diastereoselective nucleophilic additions to the carbonyl group. Efforts have been made to convert vinyl alcohol 72 into fused 5,6,5 system.

II.5. EXPERIMENTAL:

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

1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]decan-10-ol 16:

The alcohol 16 was prepared according to the procedure of Woodward[21] with some modifications. Freshly distilled dicyclopentadiene (186 g) was dissolved in 500 ml dioxane. Water (50 ml) and potassium dihydrogen phosphate (20 g) were added, and, while the solution was stirred and heated on a steam bath, selenium dioxide (80 g) was added. After 3 h the mixture was cooled, the precipitated selenium was filtered immediately with suction, and the precipitate was washed with ether. The filtrate was shaken with 1 l, of saturated NaCl solution. The aqueous solution was drawn off and washed with ether (3x300 ml). The combined organic solutions were then washed and dried. The solvent was removed at reduced pressure, and the residual oil was distilled (b.p. 67° at 0.1 mm) to yield 132 g (63%) of 14. When the alcohol 14 was heated to a temperature of 135-150°C in a seal tube, a ready isomerization takes place to furnish alcohol 15 in 60% yield (based on the recovery of the starting material). A solution of diene alcohol 15 (250 mg, 1.68 mmol) in dry ethyl acetate (4 ml) was stirred at room temperature under hydrogen atmosphere over Pt(IV)oxide. After 1 hr the catalyst was filtered and the solvent was evaporated to furnish the

saturated alcohol 16 (250 mg) in 100% yield.

IR (KBr) : 3300, 3000, 2900 cm^{-1}

^{1}H NMR (Fig II.12) : δ 4.12 (s, 1H), 2.30 (br s, 4H), 2.01 (m, 2H), 1.59 (br s, 9H).

^{13}C NMR : δ 81.7, 45.7 (2c), 41.6 (2c), 28.7, 27.1 (2c), 19.9 (2c).

Analysis : $C_{10}H_{16}O$ Calcd. : C, 78.89; H, 10.59
Found : C, 78.92; H, 10.49.

1α,2β,6β.7α-tricyclo[5.2.1.$0^{2,6}$]decan-10-one 8:

A solution of alcohol 16 (250 mg, 1.64 mmol) in dry dichloromethane was added to a mixture of PCC (528 mg, 2.46 mmol) and Celite (100 mg) in dry dichloromethane. After 4h the reaction mixture was filtered through a Celite pad and the solvent was evaporated to furnish ketone 8 (190 mg) in 77% yield.

m.p. : 63°C (Lit. : 65°C)

IR (KBr) : 3000, 2900, 1770, 1480 cm^{-1}

^{1}H NMR (Fig II.1) : δ 2.60-2.26 (br s, 2H), 2.30-1.86 (br s, 2H), 1.84-1.40 (m, 10H).

^{13}C NMR (Fig II.2) : δ 215.6, 43.5 (2c), 37.6 (2c), 28.1, 26.8 (2c), 16.9 (2c).

Analysis : $C_{10}H_{14}O$ Calcd. : C, 79.95; H, 9.39
Found : C, 79.82; H, 9.31.

10,10-(Ethylenedioxy)-1α,2β,6β.7α-tricyclo[5.2.1.$0^{2,6}$]deca-

4,8-diene-3-one 20:

For the procedure see experimental section of part 1.

10,10-(Ethylenedioxy)-1α,2β,6β.7α-tricyclo[5.2.1.$0^{2,6}$]decan-3-one 21:

A solution of enone 20 (1 g, 4.90 mmol) in dry ethyl acetate (10 ml) was stirred at room temperature under hydrogen atmosphere over 10% Pd/C (5 mg). After 15 min the catalyst was filtered and the solvent was evaporated to furnish saturated ketal 21 (1 g) in 99% yield.

IR : 3000, 2900, 1720, 1300 cm^{-1}

^{1}H NMR : δ 3.98 (s, 4H, ketal), 1.82-1.24 (series of m, 12H).

^{13}C NMR : δ 223.1, 122.1, 64.8 (2c), 50.8, 43.7, 42.4, 41.2, 38.7, 22.4, 20.7, 20.2.

10,10-(Ethylenedioxy)-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]decan-3-ol 22:

To a solution of ketone 21 (500 mg, 2.4 mmol) in dry methanol (10 ml) was added sodium borohydride (137 mg, 3.6 mmol) portionwise at ice temperature. After 30 min methanol was removed at room temperature under reduced pressure. Residue was diluted with water and extracted with ethyl acetate (3 x 25 ml). The combined extract was washed, dried and evaporated the solvent to furnish alcohol 22 (500 mg) in 100% yield.

IR : 3300, 3000, 2900 cm^{-1}

^{1}H-NMR : δ 3.98 (s, 4H, ketal), 3.20 (m, 1H), 2.24-1.16 (series of m, 13H).

10,10-(Ethylenedioxy)-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]deca-3-O-methylsulfonate 23:

To a solution of alcohol 22 (500 mg, 2.38 mmol) in pyridine (0.5 ml) at 0°C was added methylsulfonyl chloride (408 mg, 0.27 ml, 3.57 mm) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1h. Poured the reaction mixture in ice (10 g) and extracted the aqueous layer with ether (3 x 25 ml). The combined extract was washed, dried and the residue obtained after the evaporation of the solvent was filtered through a silica gel (10 g) column by eluting with 25% ethyl acetate-hexane to furnish 23 (617 mg) in 90% yield.

IR : 3000, 2900, 1300 cm^{-1}

^{1}H NMR : δ 5.28-4.92 (m, 1H, proton attached to OMs), 3.98 (s, 4H, ketal), 3.04 (s, 3H, methyl of OMs), 2.40-1.60 (m, 12H).

Analysis : $C_{13}H_{20}O_5S$ Calcd. : C,54.46; H,5.39

Found : C, 54.37; H, 5.31.

10,10-(Ethylenedioxy)-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-3-ene 24:

To a solution of mesylate 23 (500 mg, 1.73 mmol) in

freshly distilled dry HMPA (15 ml) was added activated sodium iodide (260 mg, 1.73 mmol) and the reaction mixture mixture was heated at 120°C for 9h. The reaction mixture was poured in ice water (10 ml) and extracted the aqueous layer with ether (3 x 25 ml). The combined extract was washed, dried and the residue obtained after the evaporation of the solvent was filtered through a silica gel (10 g) column by eluting with 15% ethyl acetate-hexane to furnish 24 (246 mg) in 74% yield.

IR : 3100, 3000, 2900, 1300 cm^{-1}

^1H NMR : δ 5.84-5.40 (m, 2H, olefinic), 3.98 (s, 4H, ketal), 3.40-1.16 (series of m, 10H).

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

Found : C, 74.86; H, 8.29.

1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-3-en-10-one 9:

To a cooled solution of 24 (200 mg, 1.04 mmol) in dichloromethane (5 ml) was added 40% aqueous sulfuric acid (0.5 ml) and stirred at room temperature for 4h. The reaction mixture was poured in ice water (10 ml) and extracted the aqueous layer with dichloromethane (3 x 25 ml). The combined extract was washed, dried and the residue obtained after the evaporation of the solvent was filtered thorough a silica gel (4 g) column by eluting with 15% ethyl acetate-hexane to furnish ketone 9 (138 mg) in 90% yield.

IR : 3100, 3000, 2900, 1770 cm^{-1}

^1H NMR (Fig II.3) : δ 6.06-5.88 (m, 1H, olefinic), 5.66-5.42 (m, 1H, olefinic), 3.40-3.04 (m, 1H), 2.90-2.60 (m, 1H), 2.60-2.36 (m, 2H), 2.16-1.80 (m, 2H), 1.64 (s, 4H).

^{13}C NMR (Fig II.4) : δ 214.2, 134.3, 130.2, 45.6, 43.5, 41.4, 34.1, 33.2, 19.0, 16.5.

Analysis : $C_{10}H_{12}O$ Calcd. : C, 81.04; H, 8.16
Found : C, 80.95; H, 8.08.

1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]deca-3,10-dione 10:

To a solution of ketal 21 (200 mg, 0.96 mmol) in dichloromethane (5 ml) at 0°C was added 80% aqueous sulfuric acid (0.5 ml) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured in ice water and extracted the aqueous layer with dichloromethane (3 x 15 ml). The combined extract was washed, dried and evaporated the solvent to furnish diketone 10 as crystalline solid (126 mg, 80%)

m.p. : 103°C

IR (KBr) : 3000, 2900, 1770, 1730 cm^{-1}

^1H NMR (Fig II.5) : δ 3.12-1.48 (series of m, 12H)

^{13}C NMR (Fig II.6) : δ 219.9, 211.7, 45.1, 43.2, 41.6, 40.0, 34.0, 20.8, 19.1, 16.8.

Analysis : $C_{10}H_{12}O_2$ Calcd. : C, 73.14; H, 7.37
Found : C, 73.10; H, 7.35.

4,4-Dimethyl-10,10-(ethylenedioxy)-1α,2β,6β,7α-tricyclo [5.2.1.$0^{2,6}$]decan-3-one 25:

To a solution of ketone 21 (500 mg, 2.4 mmol) in t-butanol (10 ml) was added freshly sublimed potassium t-butoxide (670 mg, 6 mmol) in t-butanol (10 ml) and excess methyl iodide (1 g = 0.5 ml; 7.2 mmol) under nitrogen atmosphere. The reaction mixture was refluxed for 10h. The reaction mixture was quenched with cold water and removed t-butanol under reduced pressure. The aqueous layer was extracted with ether (3 x 30 ml) and the combined extract was washed and dried. The residue obtained after the evaporation of the solvent was filtered through a silica gel (10 g) column by eluting with 25% ethyl acetate-hexane to furnish dimethyl ketone 25 (476 mg) in 84% yield.

IR : 3000, 2900, 1720, 1320 cm^{-1}

^{1}H NMR : δ 3.98 (s, 4H, ketal), 3.08-2.98 (m, 2H), 2.12-1.60 (m, 8H), 1.12 (s, 3H, methyl), 1.05 (s, 4H, methyl).

^{13}C NMR : δ 223.6, 122.0, 64.7 (2c), 49.9, 49.2, 42.6, 40.3, 35.9, 33.8, 27.1, 22.3, 22.2, 19.9.

Analysis : $C_{14}H_{20}O_3$ Calcd. : C, 71.16; H, 8.53
Found : C, 71.02; H, 8.46.

4,4-Dimethyl-10,10-(ethylenedioxy)-1α,2β,6β,7α-tricyclo [5.2.1.$0^{2,6}$]decan-3-ol 26:

A solution of ketone 25 (250 mg, 1.05 mmol) in dry methanol (5 ml) was cooled in an ice-bath and sodium borohydride (40 mg, 1.05 mmol) was added to it. The reaction mixture was stirred at room temperature for 10h. The reaction mixture was diluted with water (10 ml) and the aqueous layer was extracted with ethyl acetate (3 x 15 ml) The combined organic layer was washed, dried and the solvent was evaporated to furnish alcohol 26 (250 mg) in 99% yield.

IR : 3300, 3000, 2900, 1200 cm^{-1}

^1H NMR : δ 3.98 (s, 4H, ketal), 3.80-3.55 (m, 1H), 2.82-1.72 (m, 11H), 1.18 (s, 3H, methyl), 1.08 (s, 3H, methyl).

Analysis : $C_{14}H_{22}O_3$ Calcd. : C, 70.55; H, 9.31
Found : C, 70.42; H, 9.22.

4,4-Dimethyl-10,10-(ethylenedioxy)-1α,2β,6β,7α-tricyclo [5.2.1.$0^{2,6}$]deca-3-O-p-tolylthianoformate 27:

To a solution of 26 (250 mg, 1.05 mmol) in dry dichloromethane (4 ml) at 0°C was added pyridine (0.5 ml) and O-p-tolyl chlorothianoformate (196 mg, 0.16 ml) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 14h. Diluted the reaction mixture with dichloromethane (5 ml) and the combined organic layer was washed and dried. The residue obtained after evaporation of the solvent was filtered through a silica gel (5 g) column by eluting with 15% ethyl acetate-hexane to furnish o-

thianoformate 27 (223 mg) in 55% yield.

m.p. : 131°C

IR (KBr) : 3000, 2900, 1200 cm^{-1}

^1H NMR : δ 7.24-7.18 (m, 2H, aromatic), 7.00-.6.90 (m, 2H, aromatic), 5.34-5.28 (d, J = 6 Hz, 1H), 3.95 (s, 4H, ketal), 3.24-2.50 (m, 2H), 2.39 (s, 3H, aromatic methyl), 2.08-1.22 (m, 8H), 1.16 (s, 3H, methyl), 1.08 (s, 3H, methyl).

Analysis : $C_{22}H_{28}O_4S$ Calcd. : C, 68.01; H, 7.06
Found : C, 68.10; H, 7.00.

4,4-Dimethyl-10,10-(ethylenedioxy)-1α,2β,6β,7α-tricyclo [5.2.1.$0^{2,6}$]decane 28:

To a solution of o-thianoformate 27 (200 mg, 0.516 mmol) in dry benzene (10 ml) was added tri n-butyltin hydride (225 mg, 0.2 ml, 0.774 mmol) and catalytic amount of azobisisobutyronitrile. The reaction mixture was refluxed for 60h. The reaction mixture was cooled and washed with 1% ammonia solution, water, brine and dried. The residue obtained after evaporation of the solvent was filtered through alumina (4 g) column by eluting with 2% ethyl acetate-hexane to furnish the dimethyl ketal 28 (63 mg) in 55% yield.

IR : 3000, 2900, 1480 cm^{-1}

^1H NMR : δ 3.98 (s, 4H, ketal), 2.80-2.56 (m, 2H), 1.76-

1.20 (m, 10H), 1.12 (s, 3H, methyl), 1.00 (s, 3H, methyl).

Analysis : $C_{14}H_{22}O_2$ Calcd. : C, 75.63; H, 9.97
Found : C, 75.58; H, 9.95.

4,4-Dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]decan-10-one 11:

To a solution of ketal 28 (60 mg, 0.27 mmol) in dichloromethane (5 ml) at 0°C was added 70% aqueous sulfuric acid (1 ml) and stirred the reaction mixture at room temperature for 1h. Diluted the reaction mixture with dichloromethane (10 ml). The combined organic layer was washed, dried and evaporated the solvent to furnish ketone 11 (45 mg) in 95% yield.

IR : 3000, 2900, 1770 cm^{-1}
^1H NMR (Fig II.7) : δ 2.50-2.76 (m, 1H), 1.92-2.08 (m, 1H), 1.40-1.84 (m, 10H), 1.26 (s, 3H, methyl), 1.08 (s, 4H, methyl).
^{13}C NMR (Fig II.8) : δ 215.1, 43.8 (2c), 40.6, 39.5 (2c), 36.8 (2c), 28.6, 27.7, 16.5 (2c).
Analysis : $C_{12}H_{18}O$ Calcd. : C, 80.85; H, 10.18
Found : C, 80.75; H, 10.15.

4,4-Dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]deca-3,10-dione 12:

To a solution of ketal 25 (200 mg, 0.84 mmol) in dichloromethane (5 ml) at 0°C was added 80% aqueous sulfuric

acid (0.5 ml) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured into ice-water and extracted with dichloromethane (3 x 15 ml). The combined extract was washed, dried and the residue obtained after the evaporation of the solvent was filtered through a silica gel (4 g) column by eluting with 20% ethyl acetate-hexane ty furnish diketone 12 (130 mg) in 81% yield.

IR : 3000, 2900, 1770, 1730 cm^{-1}

^1H NMR (Fig II.9) : δ 2.96-2.60 (m, 2H), 2.24-1.20 (m, 8H), 1.08 (s, 3H, methyl), 1.04 (s, 3H, methyl)

^{13}C NMR (Fig II.10) : δ 220.5, 211.3, 46.7, 43.8, 42.3, 40.0, 35.5, 29.1, 26.5, 21.7, 18.3, 16.6.

Analysis : $C_{12}H_{16}O_2$ Calcd. : C, 74.97; H, 8.39
Found : C, 74.86; H, 8.35.

General procedure for $NaBH_4$ reduction of ketones:

A solution of ketone (0.2 mmol) in dry methanol (3 ml) was cooled in an ice-bath and sodium borohydride (0.2 mmol) was added to it. The reaction mixture was stirred for 15-30 min till the starting ketone was fully consumed. Reactions were continuously monitored by tlc. Methanol was removed at room temperature under reduced pressure and the residue diluted with water (5 ml). The aqueous layer was extracted with ethyl acetate (3 x 10 ml) and the combined organic layer was washed and dried. Removal of solvent gave a mixture of syn- and anti-alcohols in quantitative yield.

The product ratios were determined by ^1H NMR spectral analyses of the crude reaction mixture.

General procedure for $LiAlH_4$ reduction of ketones:

To a suspension of $LiAlH_4$ (0.1 mmol) in dry ether (5 ml) cooled in an ice-bath, the ketone (0.2 mmol) in ether (2 ml) was added under N_2. The reaction mixture was stirred for 15-20 min till the starting ketone was fully consumed. Reactions were continuously monitored by tlc. The reaction mixture was quenched with saturated sodium sulphate and extracted with ethyl acetate (3 x 20 ml). The combined extract was washed and dried. After evaporation of solvent, the crude mixture was analyzed using ^1H NMR spectroscopy.

General procedure for $(t\text{-BuO})_3LiAlH_4$ reduction:

Same as described above for $LiAlH_4$ reduction.

General procedure for DIBAL-H reduction:

To a solution of ketone (0.2 mmol) in dry dichloromethane cooled to -78^oC, DIBAL-H (0.2 ml of 1.2 M solution in toluene, 0.24 mmol) was added under N_2 and the reaction mixture was stirred for 15 min. The reaction was quenched with methanol, diluted with dichloromethane, washed and dried. Removal of solvent furnished a mixture of <u>syn</u> and <u>anti</u> alcohols (90-95%). The product ratios were determined by the ^1H NMR spectral analysis of the crude

reaction mixture.

General procedure for methyllithium addition:

To a cooled solution of ketone (0.2 mmol) in dry ether was added methyl lithium (0.3 ml of 1.4 M solution in ether) under N_2 and the reaction mixture was stirred for 15-30 min. The reaction mixture was diluted with ether, washed and dried. Removal of solvent furnished mixture of syn- and anti- tertiary alcohol (95%). The product ratios were determined by the ^{1}H NMR analysis of the crude reaction mixture.

General procedure for vinyl magnesium bromide addition:

To a solution of ketone (0.2 mmol) in dry THF was added vinyl magnesium bromide (0.2 mmol) under N_2 and the reaction mixture was refluxed for 1h. THF was removed, diluted with water and extracted with ethyl acetate (3 x 10 ml). The combined extract was washed and dried. Removal of solvent furnished mixture of syn and anti vinyl alcohols (95%). The product ratios were determined by the ^{1}H NMR analysis of the crude reaction mixture.

$NaBH_4$ Reduction of 8:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 16 : 29 (24:76) in quantitative yield.

$LiAlH_4$ Reduction of 8:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 16 : 29 (25:75) in quantitative yield.

DIBAL-H Reduction of 8:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 16:29 (25:75) in quantitative yield.

$(t\text{-BuO})_3LiAlH$ Reduction of 8:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 16 : 29 (26:74) in quantitative yield.

16: 29

IR : 3300, 3000, 2900 cm^{-1}

^1H NMR (Fig II.11) : δ 4.24 (s, 1H, H attached to OH), 4.12 (s, 1H, H attached to OH), 2.72 (br s, 2H), 2.30-2.01 (m, 6H), 1.81-1.18 (m, 20H).

^{13}C NMR : δ 85.0, 81.8, 45.7 (2c), 44.9 (2c), 42.2 (2c), 41.6 (2c), 29.7, 28.7, 27.1 (2c), 26.3 (2c), 20.4 (2c), 19.9 (2c).

Methyllithium addition to 8:

The reaction was performed as described in the general procedure to furnish alcohols 30 : 31 (14:86) in

quantitative yield, **Fig** II.13. The isomers could not be separated by column chromatography but the access to the individual isomers 30 and 31 was possible through hydrogenation of the corresponding unsaturated compounds 38 & 39 respectively, which were obtained by $NaBH_4$ reduction of 9.

30:

IR : 3350, 3000, 2900, 1200 cm^{-1}

^1H NMR : δ 2.40 (br s, 2H), 1.72-1.48 (m, 13H), 1.40 (s, 3H, methyl).

^{13}C NMR : δ 88.8, 48.6 (2c), 42.7 (2c), 29.2, 27.0 (2c), 21.4 (2c), 21.0.

Analysis : $C_{11}H_{18}O$ Calcd. : C, 79.46; H, 10.92
Found : C, 79.32; H, 10.86.

31:

IR : 3350, 3000, 2900, 1200 cm^{-1}

^1H NMR (**Fig** II.14) : δ 2.80 (br s, 2H), 1.44 (s, 3H, methyl), 1.72-1.48 (m, 13H).

^{13}C NMR : δ 88.8, 48.1 (2c), 43.7 (2c), 29.6, 26.6 (2c), 21.0, 20.8 (2c).

Analysis : $C_{11}H_{18}O$ Calcd. : C, 79.46; H, 10.92
Found : C, 79.39; H, 10.85.

$NaBH_4$ Reduction of 11:

The reaction was performed as described in the general

procedure to furnish a mixture of alcohols 32 : 33 (32:68) in quantitative yield.

$LiAlH_4$ Reduction of 11:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 32 : 33 (27:73) in quantitative yield.

DIBAL-H Reduction of 11:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 32 : 33 (33:67) in quantitative yield.

32 : 33

IR : 3300, 3000, 2900 cm^{-1}

^1H NMR (Fig II.20) : δ 4.40 (s, 1H, H attached to OH), 4.12 (s, 1H, H attached to OH), 3.01-2.60 (m, 2H), 2.52-2.20 (m, 2H), 2.04-1.16 (m, 11H), 1.14 (s, 3H, methyl), 1.13 (s, 3H, methyl), 1.06 (s, 3H, methyl), 0.96 (s, 3H, methyl).

^{13}C NMR : δ 85.9, 82.1, 45.3, 44.2, 43.0 (2c), 41.8 (2c), 41.0 (2c), 39.6 (2c), 38.9 (4c), 29.4, 29.2, 27.8, 27.6, 19.8 (2c), 19.3 (2c).

Methyllithium addition to 11:

The reaction was performed as described in the general procedure to furnish 34 : 35 (19:81) in quantitative yield.

34 : 35

IR : 3300, 3000, 2900 cm^{-1}

^1H NMR (Fig II.21) : δ 3.04-2.76 (m, 2H), 2.68-2.60 (m, 2H), 1.92-1.60 (m, 4H), 1.51 (s, 3H, methyl attached to OH),1.50 (s, 3H, methyl attached to OH), 1.46-1.16 (m, 9H), 1.24 (s, 3H, methyl), 1.14 (s, 6H, methyl), 1.04 (s, 3H, methyl).

^{13}C NMR : δ 89.5, 89.4, 46.9 (2c), 46.2 (2c), 44.3 (2c), 43.1 (2c),39.4 (4c), 29.4, 29.2, 27.9 (2c), 22.5 (2c), 20.6 (2c), 20.0 (2c).

$NaBH_4$ Reduction of 9:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 36 : 37 (37:63) in quantitative yield.

$LiAlH_4$ Reduction of 9:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 36 : 37 (39:71) in quantitative yield.

DIBAL-H Reduction of 9:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 36 : 37 (40:60) in quantitative yield.

36 : 37

IR : 3300, 3100, 3000, 2900 cm^{-1}

^1H NMR (Fig II.15) : δ 5.80-5.48 (m, 2H, olefinic), 4.28 (s, 1H, H attached to OH), 4.12 (s, 1H, H attached to OH), 3.42-3.20 (m, 1H), 3.12-2.80 (m, 1H), 2.42-1.80 (m, 6H), 1.28 (s, 4H).

^{13}C NMR : δ 132.3, 131.8 (2c), 131.1, 83.3, 80.9, 50.5, 49.5, 45.6, 44.5, 43.7, 43.4, 39.0, 37.9, 32.9, 31.7, 22.2, 22.0, 19.7, 19.5.

Methyllithium addition of 9:

The reaction was performed as described in the general procedure to furnish alcohols 38 : 39 (24:76) in quantitative yield (Fig II.16). The two isomers were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane.

38:

IR : 3300, 3100, 3000, 2900 cm^{-1}

^1H NMR : δ 5.76-5.60 (m, 1H, olefinic), 5.56-5.40 (m, 1H, olefinic), 3.20-2.86 (br s, 1H), 2.80-2.58 (br s, 1H), 2.36-2.16 (m, 2H), 1.84-1.64 (m, 3H), 1.60 (s, 4H), 1.52 (s, 3H, methyl).

^{13}C NMR : δ 132.3, 131.6, 86.3, 51.0, 48.7, 39.0, 32.9, 29.6, 23.6, 21.0, 20.5.

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

Found : C, 80.32; H, 9.80.

39:

IR : 3300, 3100, 3000, 2900 cm^{-1}

^1H NMR (Fig II.17 : δ 5.80-5.60 (m, 1H, olefinic), 5.60-5.44 (m, 1H, olefinic), 3.52-3.24 (br s, 1H), 3.24-2.84 (br s, 1H), 2.40-2.20 (m, 2H), 1.84-1.52 (m, 3H), 1.51 (s, 3H, methyl), 1.33 (s, 4H).

^{13}C NMR : δ 132.6, 131.4, 87.6, 52.1, 47.9, 46.6, 40.1, 32.7, 22.9, 21.9, 20.2.

$NaBH_4$ Reduction of 10:

The reaction was performed as described in the general procedure at -80 to -100°C to furnish a mixture of alcohols 40 : 41 (45:55) in quantitative yield (Fig II.18). The isomers could not be separated by column chromatography but the access to the individual isomers 40 and 41 was possible through hydrogenation of the corresponding unsaturated compounds 69 & 70 respectively, which were obtained by $NaBH_4$ reduction of 54.

40:

IR : 3300, 3000, 2900, 1730 cm^{-1}

^1H NMR : δ 4.08 (s, 1H, H attached to OH), 2.88-1.24 (series of m, 13H)

^{13}C NMR : δ 223.5, 80.9, 50.0, 46.1, 44.7, 40.5, 38.2, 22.3, 20.9, 19.9.

Analysis : $C_{10}H_{14}O_2$ Calcd. : C, 72.26; H, 8.49
Found : C, 72.17; H, 8.42.

41:

IR : 3300, 3000, 2900, 1730 cm^{-1}

^{1}H NMR (Fig II.19) : δ 4.32 (s, 1H, H attached to -OH), 3.44-1.24 (series of m, 13H)

^{13}C NMR : δ 224.8, 83.4, 51.6, 45.6, 45.3, 41.7, 39.4, 22.1, 20.2, 19.9.

Analysis : $C_{10}H_{14}O_2$ Calcd. : C, 72.26; H, 8.49
Found : C, 72.18; H, 8.45.

$NaBH_4$ Reduction of 12:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 42 : 43 (56:44) in quantitative yield (Fig II.22). The two isomers were separated by column chromatography using silica gel and elution with 20% ethyl acetate-hexane.

$LiAlH_4$ Reduction of 12:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 42 : 43 (54:46) in quantitative yield.

DIBAL-H Reduction of 12:

The reaction was performed as described in the general

procedure to furnish a mixture of alcohols 42 : 43 (55:45) in quantitative yield.

42:

IR : 3300, 3000, 2900 1730 cm^{-1}

^1H NMR (Fig II.23) : δ 4.08 (s, 1H, H attached to OH), 2.80-2.60 (m, 2H), 2.40-2.20 (br s, 1H), 2.20-2.04 (br s, 1H), 2.00-1.20 (m, 7H), 1.04 (s, 6H, methyl)

^{13}C NMR : δ 209.8, 81.3, 49.1, 48.9, 45.0, 43.6, 36.5, 33.4, 27.3, 22.2, 21.2, 19.5.

Analysis : $C_{12}H_{18}O_2$ Calcd. : C, 74.19; H, 9.34
Found : C, 74.12; H, 9.21.

43:

IR : 3300, 3000, 2900, 1730 cm^{-1}

^1H NMR : δ 4.40 (s, 1H, H attached to -OH), 3.28-3.18 (m, 2H), 2.36-2.18 (br s, 1H), 2.18-1.40 (m, 8H), 1.08 (s, 6H, methyl).

^{13}C NMR : δ 210.6, 84.2, 51.3, 51.1, 44.3, 42.6, 36.1, 34.6, 27.4, 23.5, 21.6, 20.0.

Analysis : $C_{12}H_{18}O_2$ Calcd. : C, 74.19; H, 9.34
Found : C, 74.05; H, 9.30.

Methyllithium addition of 12:

The reaction was performed as described in the general procedure to furnish 44 : 45 (53:47) in quantitative yield (Fig II.24). The two isomers were separated by column

chromatography using silica gel and elution with 20% ethyl acetate-hexane.

44:

IR : 3300, 3000, 2900 1730 cm^{-1}

^{1}H NMR (Fig II.25) : δ 2.90-2.74 (m, 2H), 2.04-1.52 (m, 9H), 1.48 (s, 3H, methyl attached to OH), 1.08 (s, 6H, dimethyl)

^{13}C NMR : δ 224.1, 86.3, 52.3, 50.5, 49.2, 47.3, 44.0, 36.6, 35.6, 34.5, 27.4, 23.5, 20.6.

Analysis : $C_{13}H_{20}O_2$ Calcd. : C, 74.96; H, 9.68
Found : C, 74.87; H, 9.59.

45:

IR : 3300, 3000, 2900, 1730 cm^{-1}

^{1}H NMR : δ 3.28-3.20 (m, 2H), 2.04-1.52 (m, 9H), 1.48 (s, 3H, methyl attached to OH), 1.12 (s, 6H, methyl).

^{13}C NMR : δ 225.6, 88.2, 52.3, 50.6, 49.3, 47.8, 46.3, 36.3, 35.6, 34.5, 27.4, 22.3, 21.7.

Analysis : $C_{13}H_{20}O_2$ Calcd. : C, 74.96; H, 9.68
Found : C, 74.82; H, 9.65.

10,10-Dimethoxy-1,7,8,9-tetrachloro-2β,6β-tricyclo-[5.2.1.$0^{2,6}$]deca-3,8-diene 58:

To a solution of dimethoxytetrachlorocyclopentadiene (10 g, 6.7 ml, 0.037 mmol) in dry toluene (25 ml) was added

cyclopentadiene (2.49 g, 3.1 ml, 0.037 mmol) under nitrogen atmosphere. The reaction mixture was refluxed for 24h. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish the adduct 58 (8.7 g) in 70% yield.

IR : 3100, 3000, 2900, 1600, 1200 cm^{-1}

^1H NMR : δ 5.84-5.64 (m, 1H, olefinic), 5.44-5.44 (m, 1H, olefinic), 3.60 (s, 3H, methyl), 3.54 (s, 3H, methyl), 3.26-3.06 (m, 1H), 2.42-2.20 (m, 3H).

10,10-Dimethoxy-1,7,8,9-tetrachloro-2β,6β-tricyclo-[5.2.1.$0^{2,6}$]dec-8-ene 59:

A solution of 58 (2 g, 6.06 mmol) in dry ethyl acetate (10 ml) was stirred at room temperature under hydrogen atmosphere over 10% Pd/C (10 mg). After 8h the catalyst was filtered and the solvent was evaporated to furnish 59 (1.4 g) in 70% yield.

IR : 3000, 2900, 1600, 1200 cm^{-1}

^1H NMR : δ 3.59 (s, 3H, methyl), 3.53 (s, 3H, methyl), 3.09-3.02 (m, 2H), 1.75-1.42 (series of m, 6H).

^{13}C NMR : δ 129.1 (2c), 115.0, 78.0 (2c), 53.7 (2c), 52.4, 51.5, 26.6, 25.7 (2c).

10,10-Dimethoxy-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene 60:

In a 250 ml two-necked R.B. flask fitted with a

^{1}H NMR (Fig II.28) : δ 7.48-7.36 (m, 1H, olefinic), 6.42-6.04 (m, 3H, olefinic), 3.64-3.32 (m, 2H), 3.32-3.16 (m, 1H), 3.00-2.82 (m, 1H).

^{13}C NMR (Fig II.29) : δ 212.0, 206.8, 161.5, 141.5, 129.8, 129.3, 50.1, 49.2, 43.2, 41.6.

Analysis : $C_{10}H_8O_2$ Calcd. : C, 74.99; H, 5.03
Found : C, 75.01; H, 5.05.

4,4,-Dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10- dione 55:

To a solution of dimethyl ketal 57 [for the preparation of this ketal see experimental section of part 1 (500 mg, 2.14 mmol)] in dichloromethane (10 ml) at 0°C was added 70% aqueous sulfuric acid and the reaction mixture was stirred at room temperature for 2h. Poured the reaction mixture in ice water and extracted with dichloromethane (3 x 10 ml). The combined organic layer was washed, dried and evaporated the solvent to furnish diketone 55 as a white solid (345 mg, 85%).

m.p. : 88-89°C

IR : 3000, 2900, 1770, 1730 cm^{-1}

^{1}H NMR (Fig II.30) : δ 6.56-6.24 (m, 2H, olefinic), 3.32-2.88 (m, 4H), 2.12-1.08 (m, 2H), 1.08 (s, 3H, methyl), 0.92 (s, 3H, methyl).

^{13}C NMR (Fig II.31) : δ 219.9, 200.9, 133.2, 131.4, 51.0, 47.8, 46.7,

46.4, 39.0, 31.3, 26.3, 21.1.

Analysis : $C_{12}H_{14}O_2$ Calcd. : C, 75.76; H, 7.42

Found : C, 75.62; H, 7.38.

$NaBH_4$ Reduction of 52:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 61 : 62 (6:94) in quantitative yield.

$LiAlH_4$ Reduction of 52:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 61 : 62 (4:96) in quantitative yield.

61 : 62

IR : 3300, 3000, 2900 cm^{-1}

^1H NMR (Fig II.32) : δ 5.99-5.92 (m, 2H, olefinic), 5.82-5.72 (m, 2H, olefinic), 3.88-3.80 (br s, 1H), 3.72-3.62 (m, 1H), 2.80-0.86 (series of m, 11H).

^{13}C NMR : δ 135.2 (2c), 134.8 (2c), 88.8, 88.5, 49.9 (2c), 44.6 (2c), 44.2 (2c), 30.7, 30.2, 27.9 (2c), 26.9 (2c).

Methyllithium addition of 52:

The reaction was performed as described in the general procedure to furnish 63 : 64 (4:96) in quantitative yield.

63 : 64

IR : 3300, 3000, 2900 cm^{-1}

^1H NMR (Fig II.33) : δ 6.20-6.12 (m, 2H, olefinic), 6.12-6.00 (m, 2H, olefinic),3.02-2.72 (m, 2H), 2.60-2.52 (m, 1H), 2.48-2.32 (m, 1H), 1.82-1.40 (m, 8H), 1.32 (s, 3H, methyl).

^{13}C NMR : δ 136.2 (2c), 135.9 (2c), 96.5, 96.4, 55.5 (2c), 54.3 (2c), 45.5 (2c), 44.0 (2c), 30.4 (2c), 28.7 (2c), 28.1 (2c), 21.6.

Vinylmagnesium bromide addition of 52:

The reaction was performed as described in the general procedure to furnish a mixture of vinyl alcohol 71 : 72 (5:95) in quantitative yield. The two isomers were separated by column chromatography using silica gel and elution with 10% ethyl acetate-hexane.

71:

m.p. : 120°C

IR : 3300, 31,00, 3000, 2900 cm^{-1}

^1H NMR (Fig II.35) : δ 6.07-6.04 (m, 2H, olefinic), 5.91-5.73 (m, 1H, $-C\underline{H} = CH_2$), 5.30-5.03 (m, 2H, $-CH = C\underline{H_2}$), 4.35-4.20 (m, 1H), 3.05-1.02 (series of m, 10H).

^{13}C NMR : δ 141.2, 126.2, 135.5, 114.2, 99.1, 72.8, 54.0,

51.6, 45.2, 45.0, 30.4, 28.1.

Analysis : $C_{12}H_{16}O$ Calcd. : C, 81.77; H, 9.15
Found : C, 81.65; H, 9.11.

72:

m.p. : 115°C

IR : 3300, 3100, 3000, 2900 cm^{-1}

^1H NMR (Fig II.34) : δ 6.38-6.24 (m, 1H, -CH = CH_2), 6.06-6.04 (m, 2H, olefinic), 5.27-5.02 (m, 2H, -CH = CH_2), 3.10-2.95 (m, 2H), 2.58-2.51 (m, 1H), 1.66-1.26 (m, 6H).

^{13}C NMR : δ 141.3, 135.5 (2c), 114.5, 97.8, 53.9 (2c), 45.6 (2c), 30.6, 27.8 (2c).

Analysis : $C_{12}H_{16}O$ Calcd. : C, 81.77; H, 9.15
Found : C, 81.62; H, 9.09.

$NaBH_4$ Reduction of 53:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 65 : 66 (25:75) in quantitative yield.

65 : 66

IR : 3300, 3000, 2900, 1730 cm^{-1}

^1H NMR : δ 6.21-6.16 (m, 1H, olefinic), 6.11-6.07 (m, 1H, olefinic), 3.94-3.91 (m, 1H), 3.20-2.79 (m, 4H), 2.25-2.15 (m, 1H), 1.93-1.81 (m, 1H), 1.26-1.13 (m, 3H).

$NaBH_4$ Reduction of 54:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 69 : 70 (36:64) in quantitative yield (Fig II.36). The two isomers were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane.

$LiAlH_4$ Reduction of 54:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 69 : 70 (35:65) in quantitative yield.

69:

IR : 3300, 3000, 2900 1400 cm^{-1}

^1H NMR : δ 7.44-7.36 (m, 1H, olefinic), 6.06-5.72 (m, 3H, olefinic), 4.04-3.96 (m, 2H), 3.44-3.20 (m, 1H), 3.16-3.00 (m, 11H), 2.84-2.68 (m, 1H), 2.44-2.20 (m, 1H).

^{13}C NMR : δ 211.7, 162.9, 138.2, 129.6, 129.2, 88.9, 50.5, 49.8, 45.8, 43.5.

Analysis : $C_{10}H_{10}O_2$ Calcd. : C, 74.05; H, 6.22
Found : C, 73.90; H, 6.17.

70:

IR : 3300, 3000, 2900, 1400 cm^{-1}

^{1}H NMR (Fig II.37) : δ 7.52-7.40 (m, 1H, olefinic), 6.08-5.72 (m, 3H, olefinic), 4.08 (br s, 1H), 3.84-3.60 (br s, 1H), 3.20-2.92 (m, 2H), 2.82-2.68 (br s, 1H), 2.44-2.24 (br s, 1H).

^{13}C NMR : δ 211.8, 164.7, 137.1, 131.5, 131.1, 88.9, 49.1, 48.1, 47.9, 46.0.

Analysis : $C_{10}H_{10}O_2$ Calcd. : C, 74.05; H, 6.22
Found : C, 73.86; H, 6.15.

$NaBH_4$ Reduction of 55:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 67 : 68 (24:96) in quantitative yield (Fig II.38). The two isomers were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane.

$LiAlH_4$ Reduction of 55:

The reaction was performed as described in the general procedure to furnish a mixture of alcohols 67 : 68 (24:76) in quantitative yield.

67:

IR : 3300, 3000, 2900, 1730 cm^{-1}

^{1}H NMR : δ 6.21-6.16 (m, 1H, olefinic), 6.11-6.07 (m, 1H, olefinic), 3.94-3.91 (m, 1H), 3.20-2.79 (m, 4H), 2.25-2.15 (m, 1H), 1.93-1.81 (m, 1H), 1.26-1.13

(m, 1H), 1.00 (s, 3H, methyl), 0.88 (s, 3H, methyl).

^{13}C NMR : δ 223.5, 134.0, 132.2, 88.6, 52.2, 50.6, 49.6, 49.4, 39.2, 33.2, 26.8, 21.5.

Analysis : $C_{12}H_{16}O_2$ Calcd. : C, 81.77; H, 9.15
Found : C, 81.68; H, 9.11.

68:

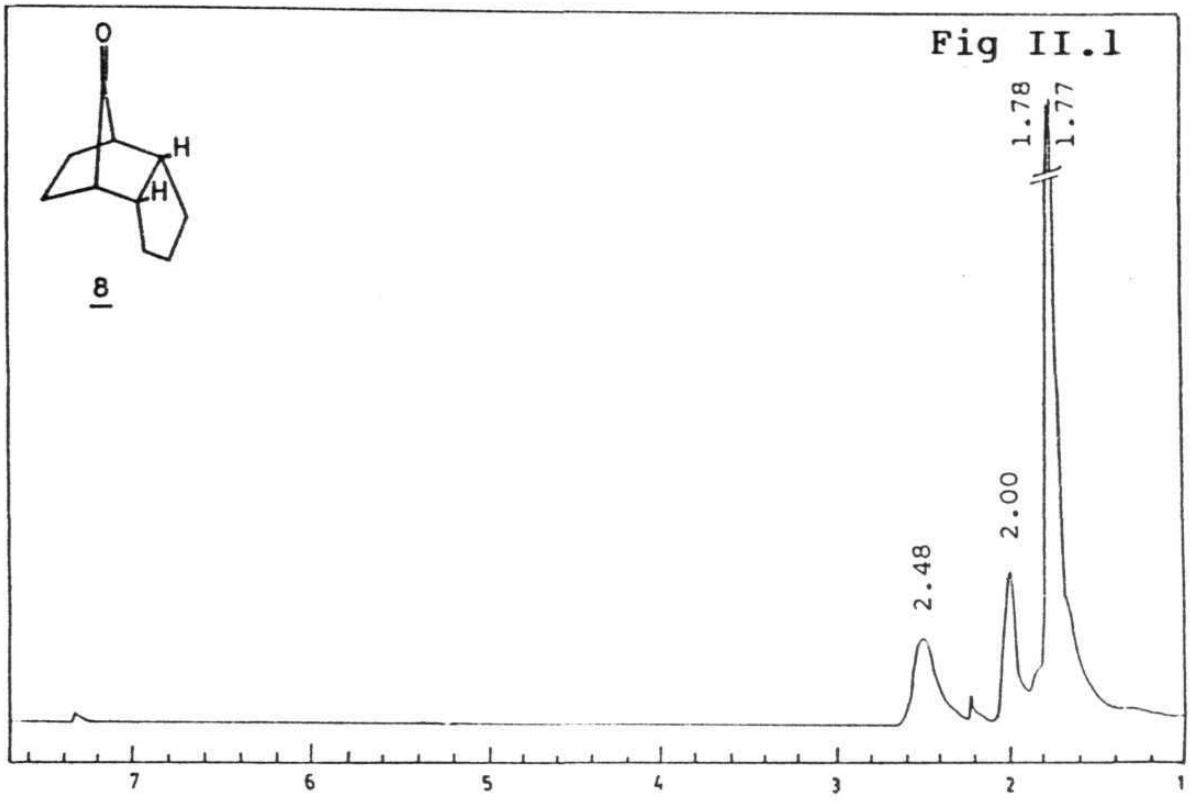
IR : 3300, 3000, 2900, 1730 cm^{-1}

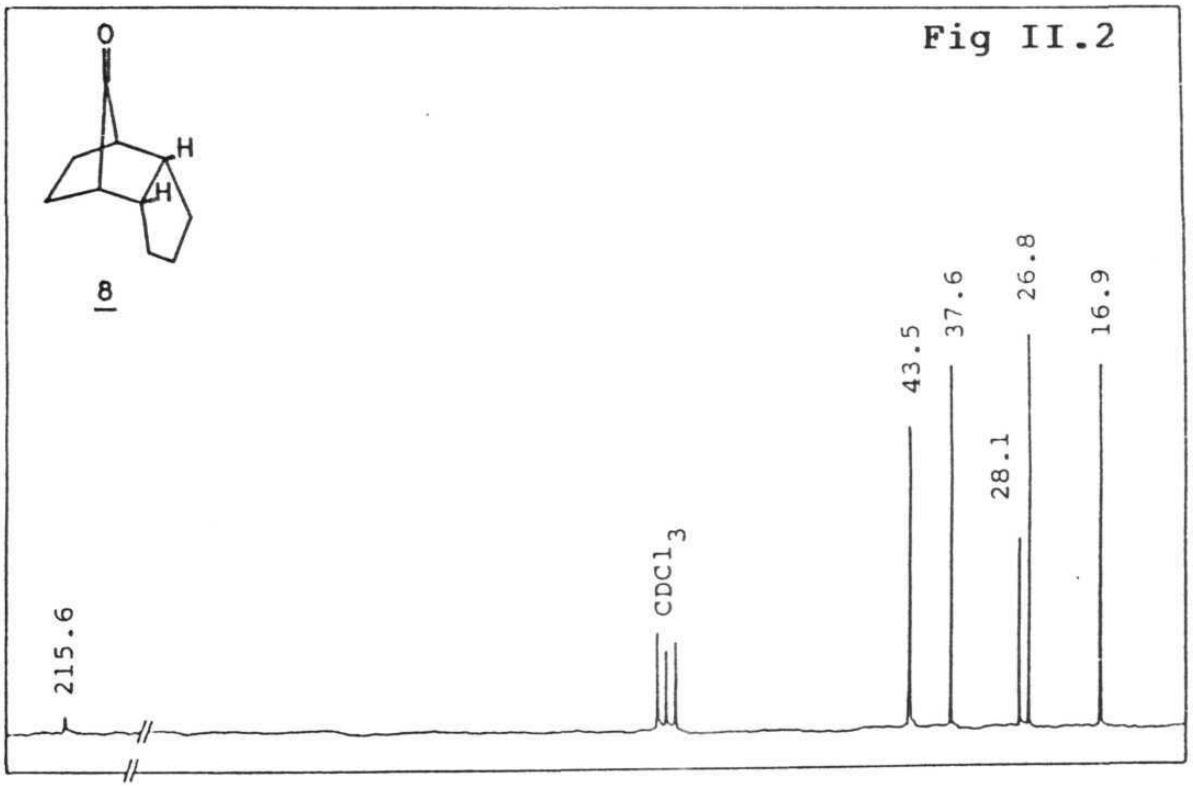
^{1}H NMR (Fig II.39) : δ 6.20-6.05 (m, 2H, olefinic), 3.92 (br s, 1H), 3.40-3.33 (m, 1H), 3.25-3.10 (m, 1H), 2.94-2.91 (m, 1H), 2.78-2.75 (m, 1H), 1.97-1.85 (m, 2H), 1.37-1.27 (m, 1H), 1.08 (s, 3H, methyl), 0.90 (s, 3H, methyl).

^{13}C NMR : δ 223.5, 135.2, 134.2, 87.3, 51.2, 50.7, 50.1, 48.4, 38.9, 34.5, 27.0, 21.9.

Analysis : $C_{12}H_{16}O_2$ Calcd. : C, 81.77; H, 9.15
Found : C, 81.66; H, 9.12.

II.6. SPECTRA:


O
H
H
8
Fig II.1
1.78
1.77
2.48
2.00
7
6
5
4
3
2
1


O
H
H
8
Fig II.2
215.6
CDCl3
43.5
37.6
28.1
26.8
16.9

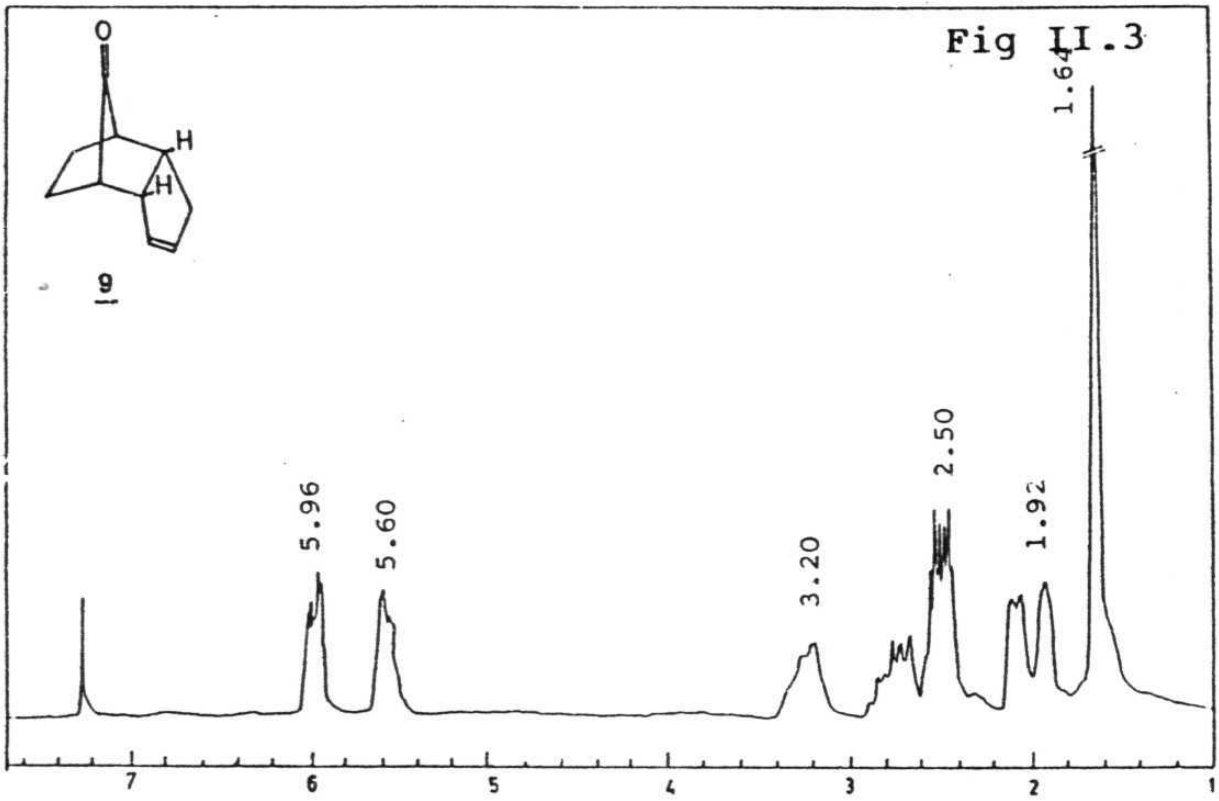


Fig II.3

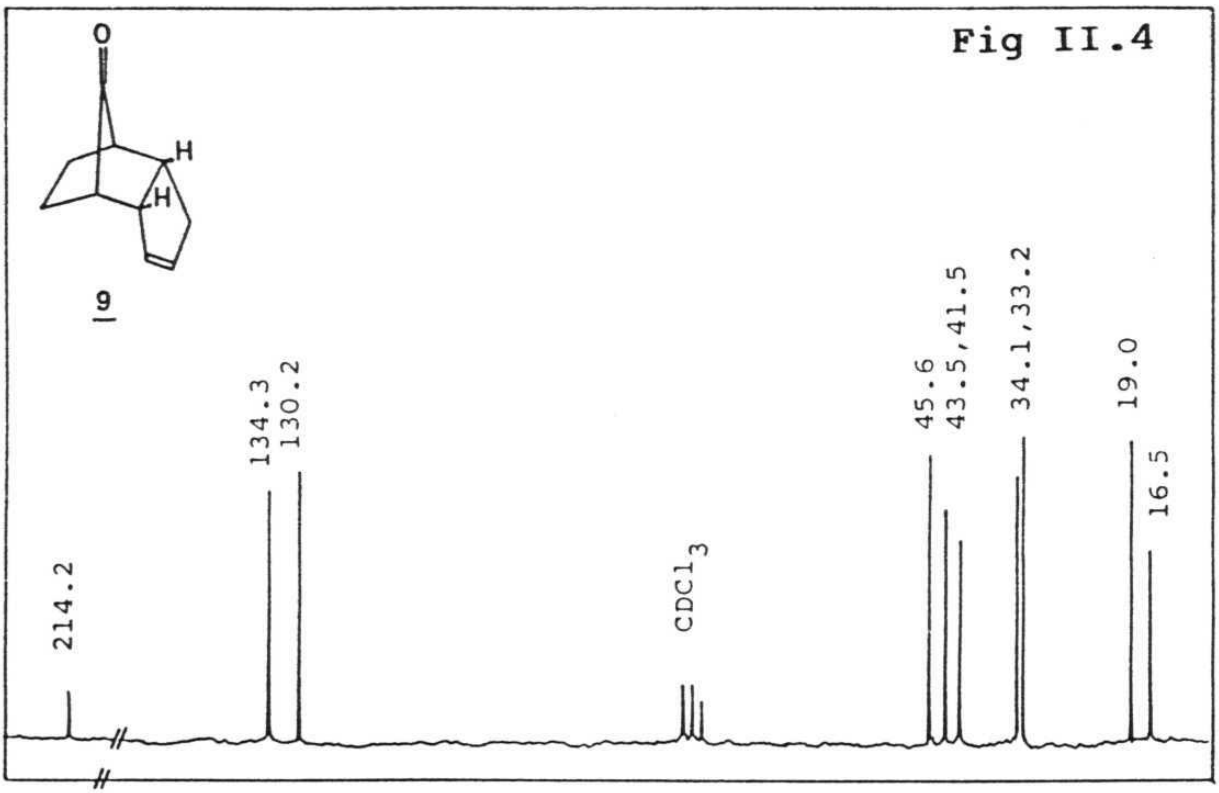


Fig II.4

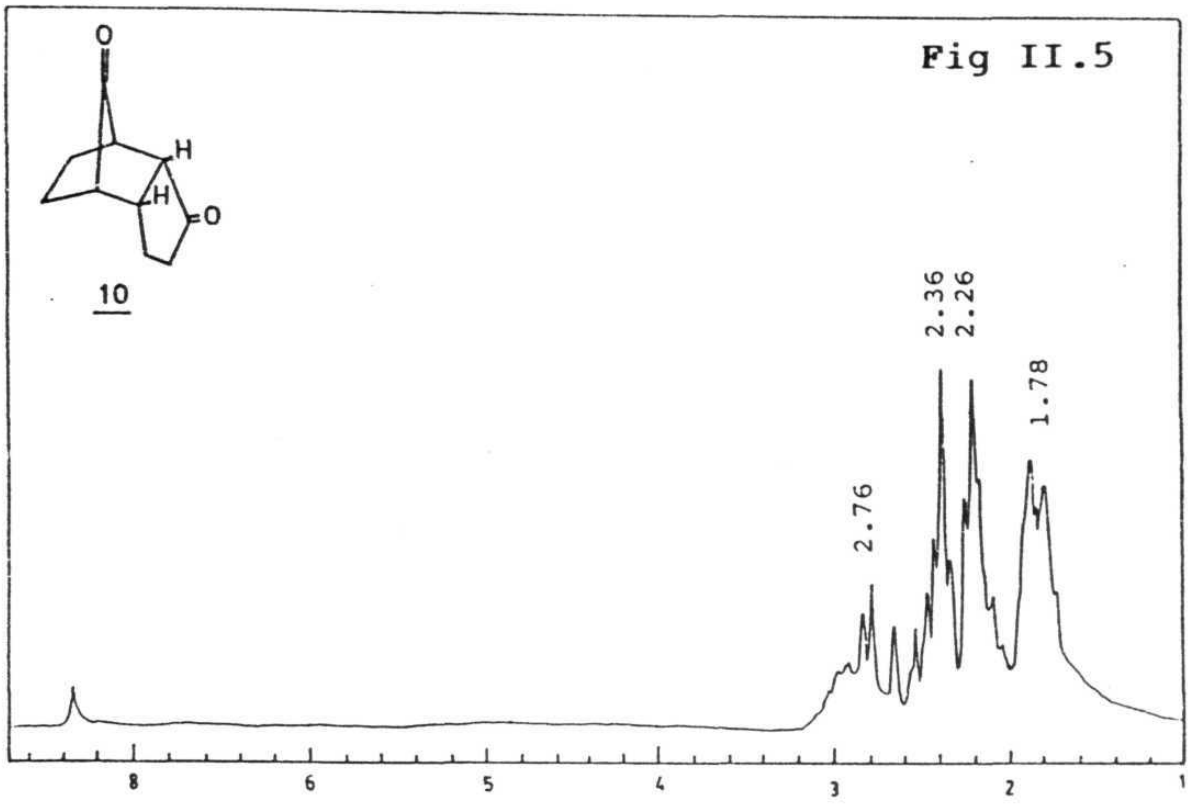


Fig II.5
O
H
H
O
10
2.36
2.26
1.78
2.76
8
6
5
4
3
2

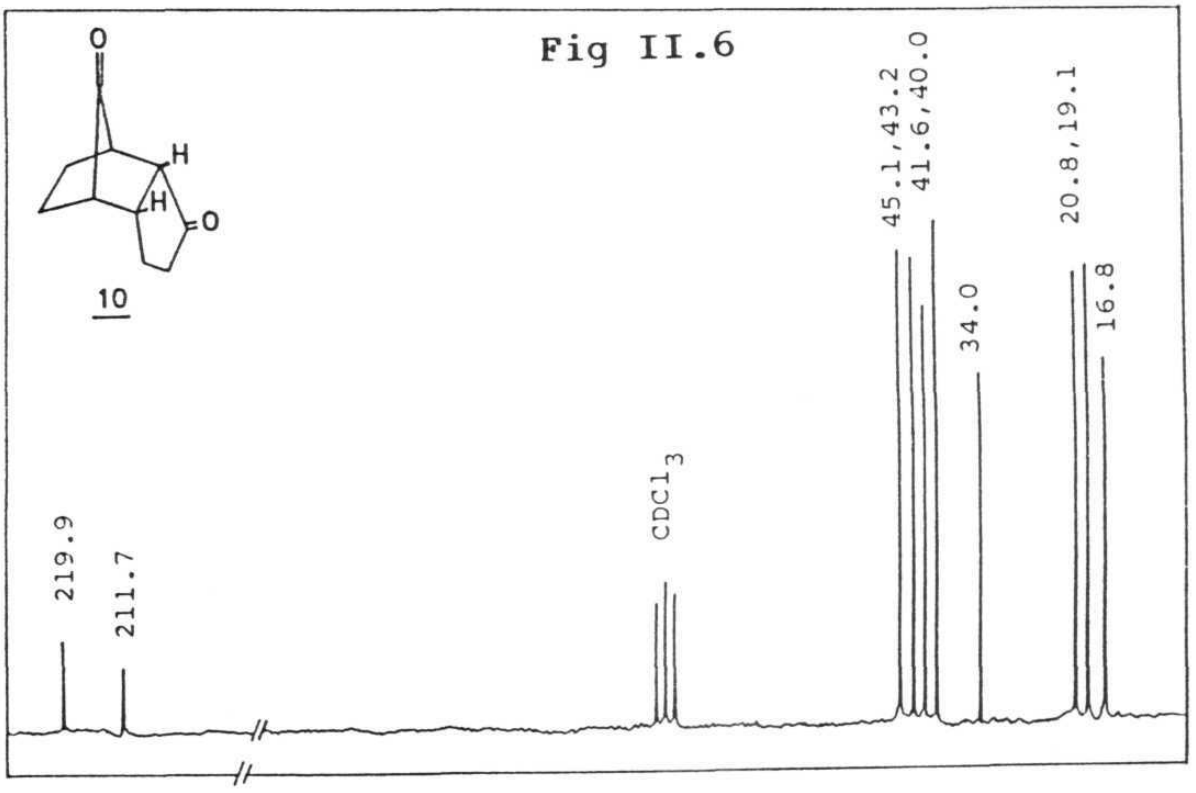


Fig II.6
O
H
H
O
10
45.1,43.2
41.6,40.0
34.0
20.8,19.1
16.8
CDCl3
219.9
211.7

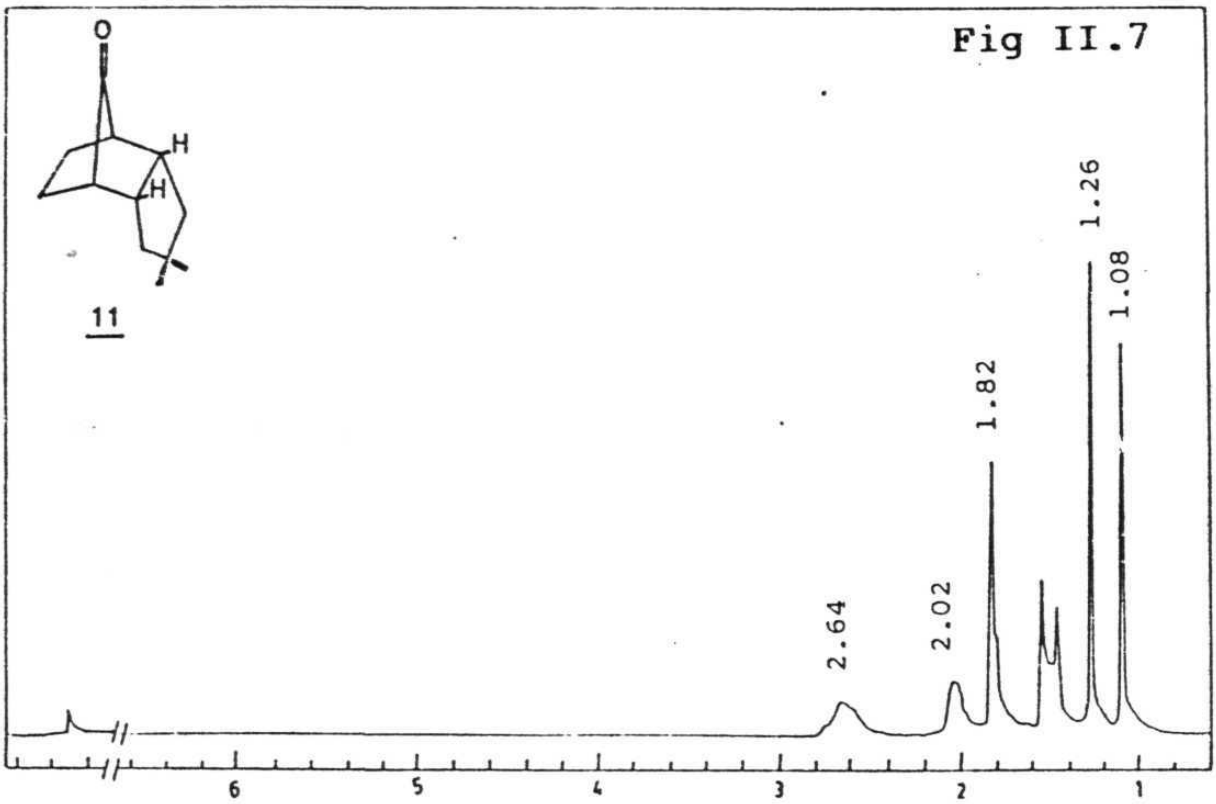


Fig II.7
O
H
H
11
2.64
2.02
1.82
1.26
1.08
6
5
4
3
2
1

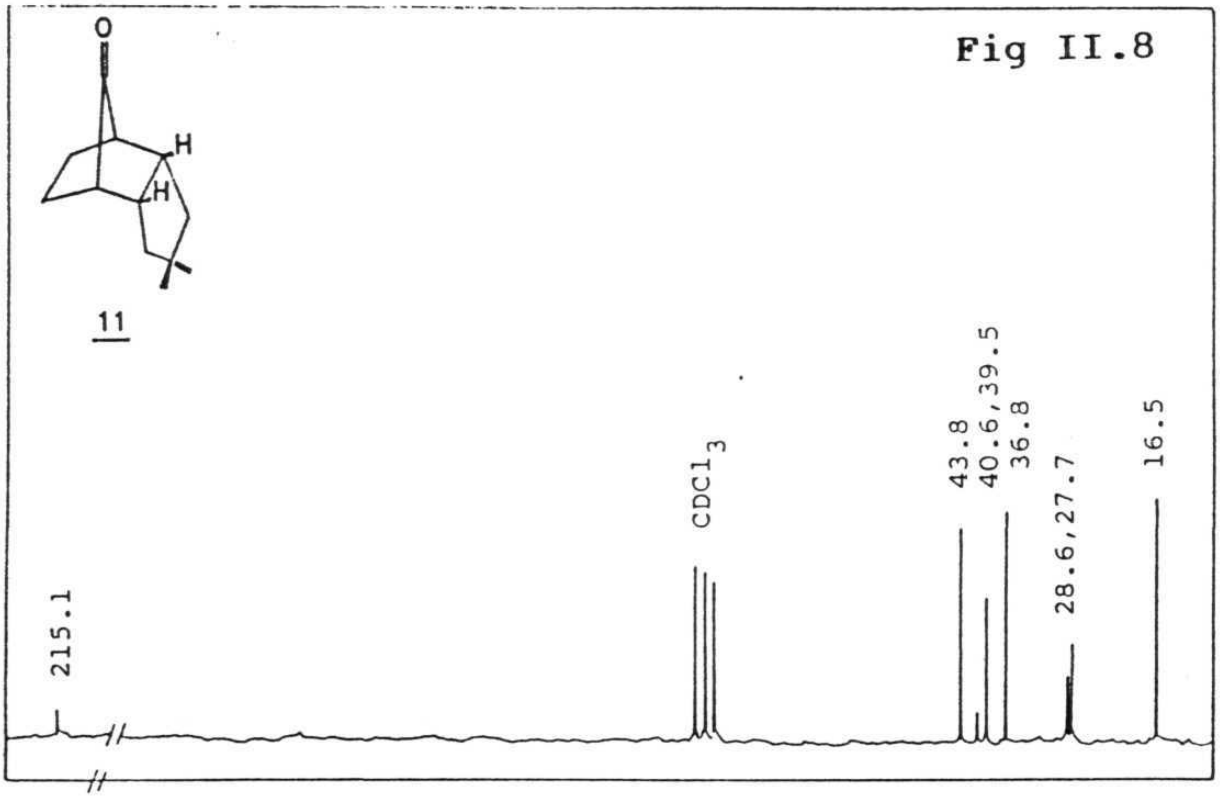


Fig II.8
O
H
H
11
215.1
CDCl3
43.8
40.6,39.5
36.8
28.6,27.7
16.5

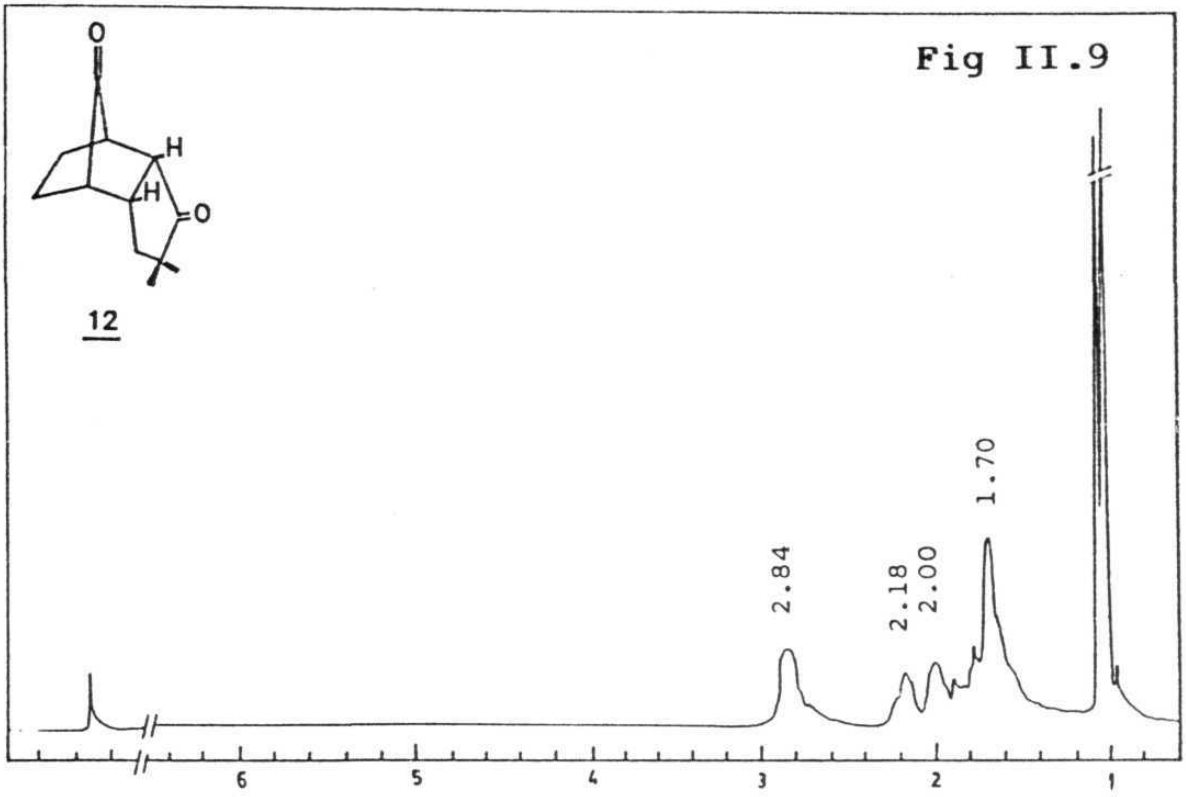


Fig II.9
12
2.84
2.18
2.00
1.70
6
5
4
3
2
1

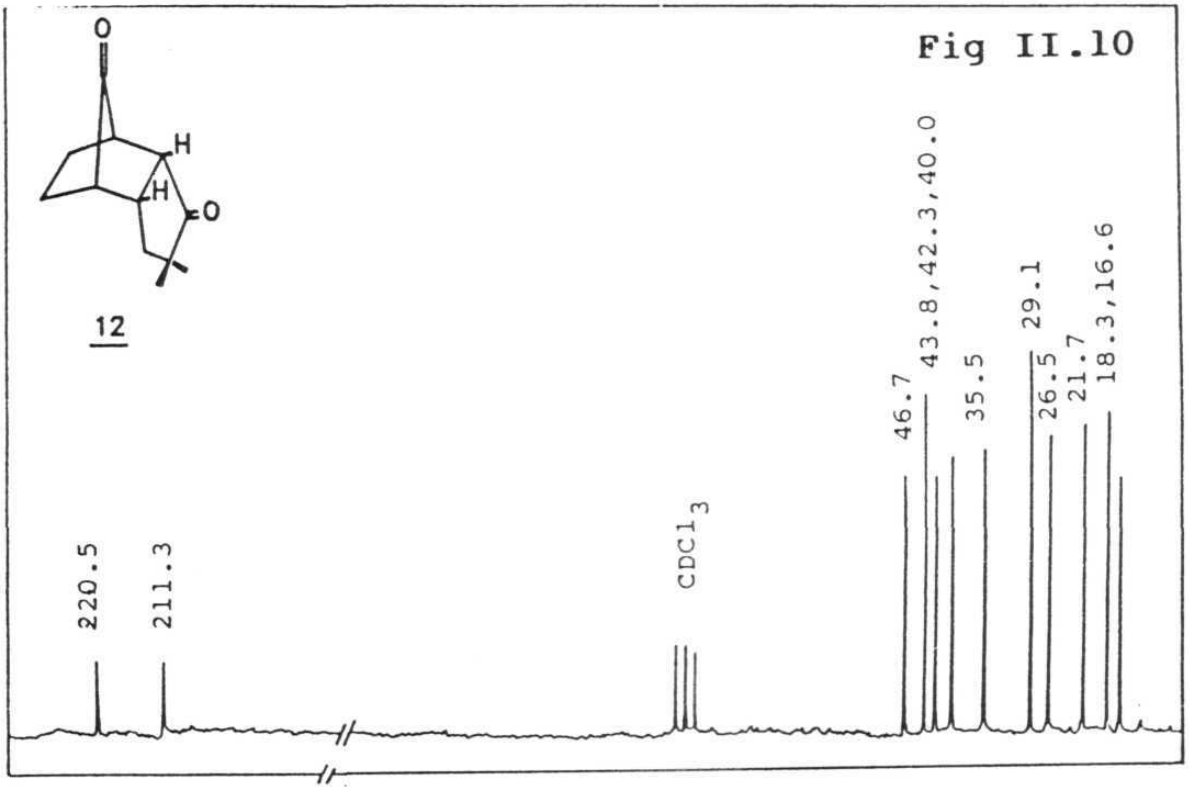


Fig II.10
12
220.5
211.3
CDCl3
46.7
43.8,42.3,40.0
35.5
29.1
26.5
21.7
18.3,16.6

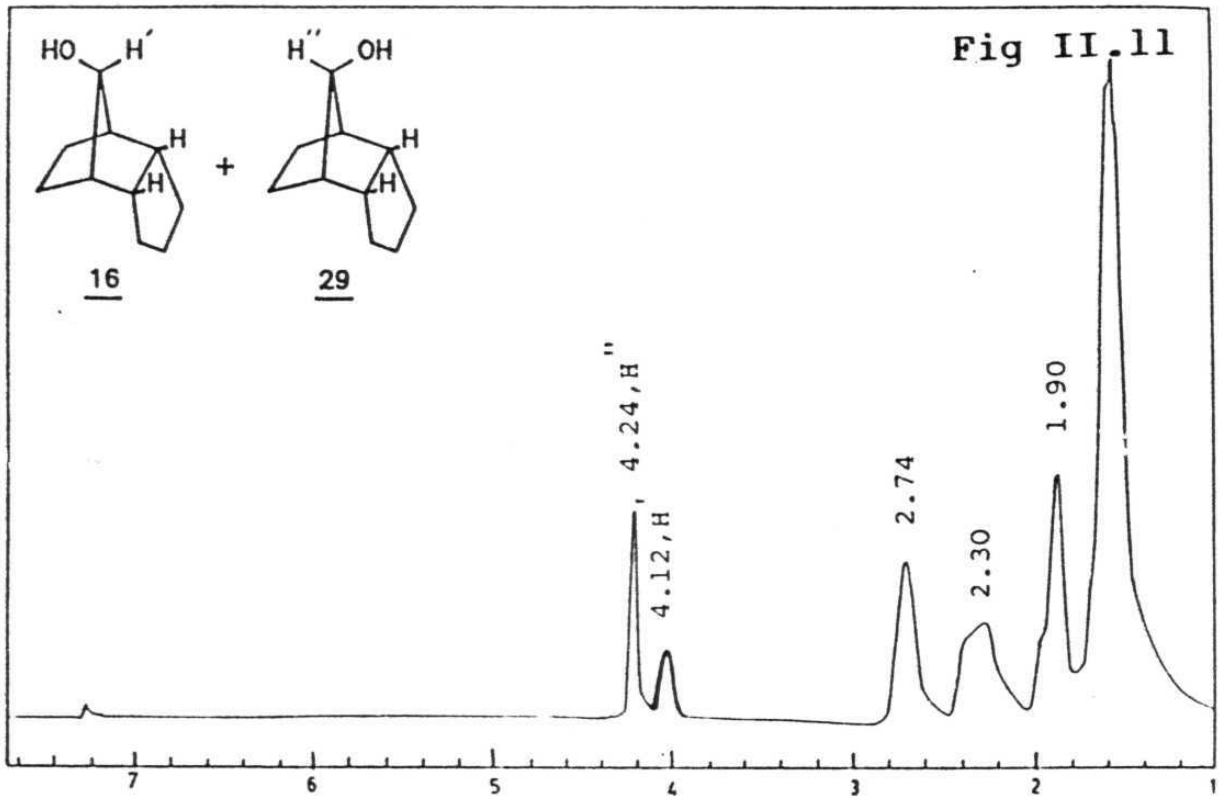


Fig II.11

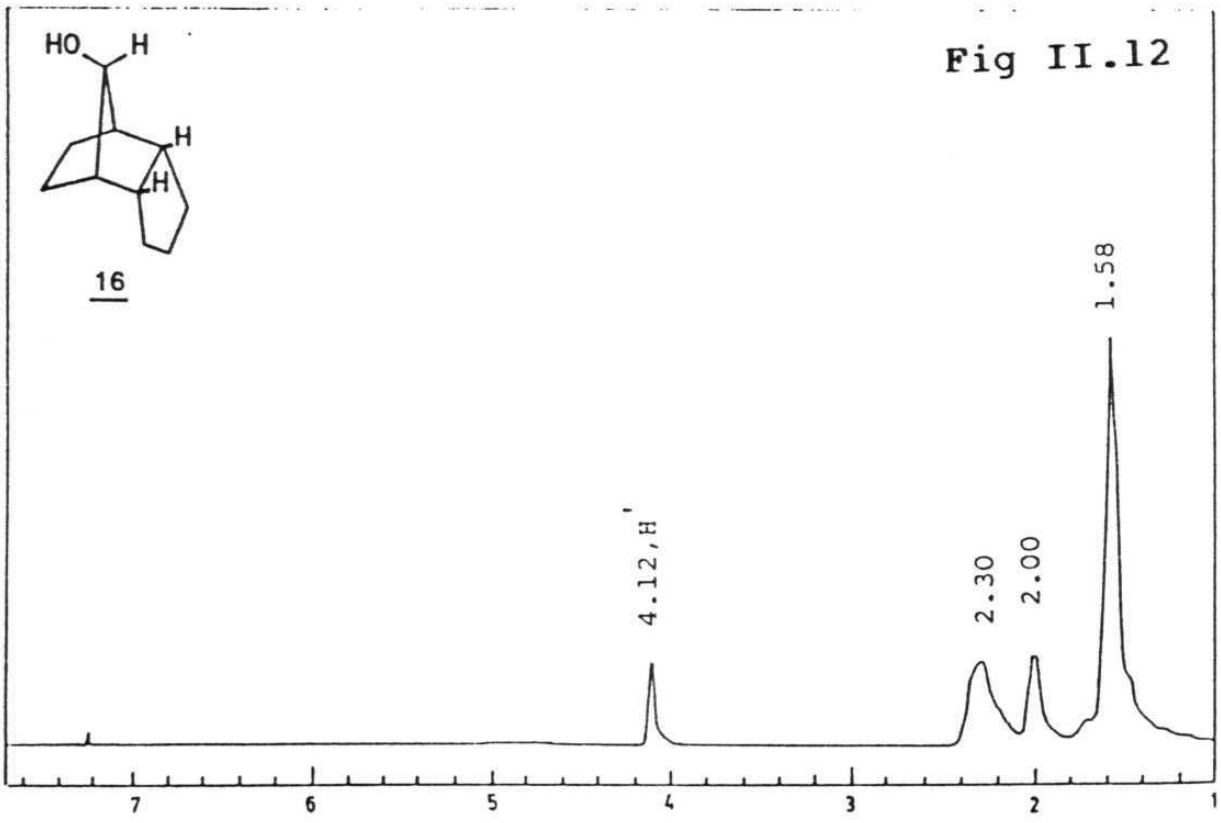
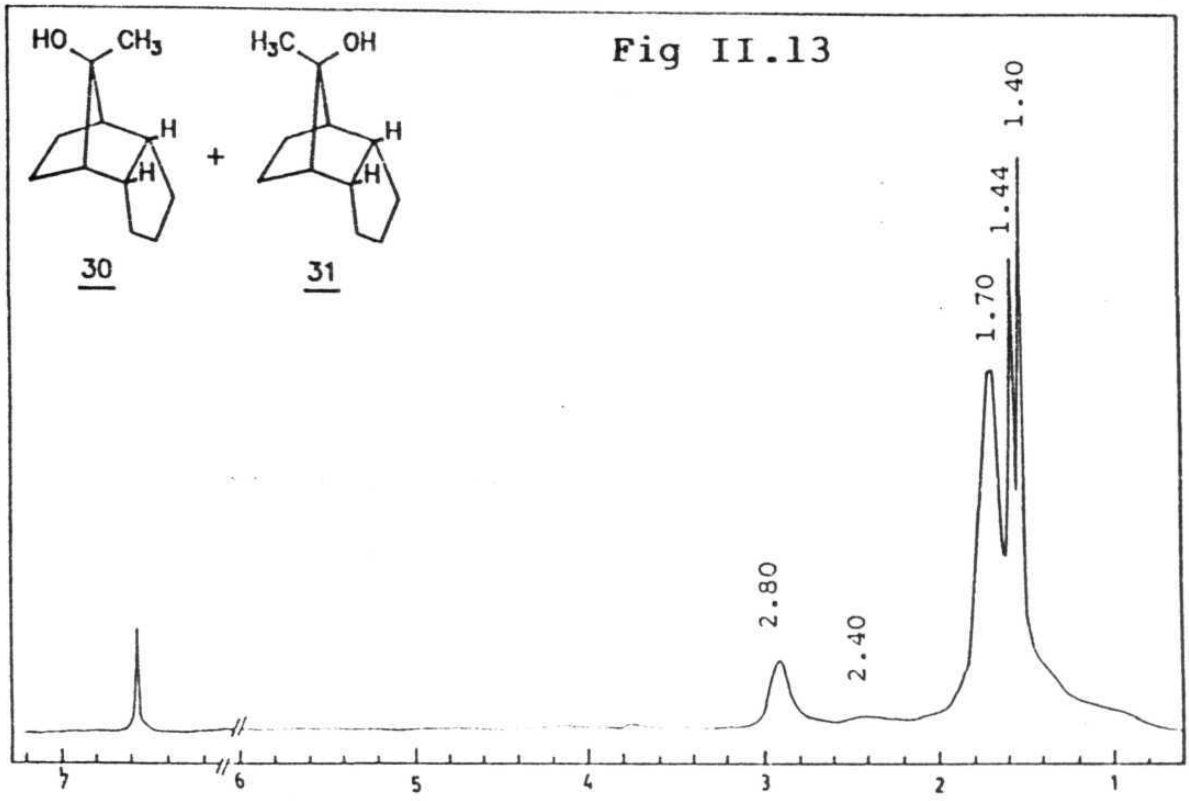
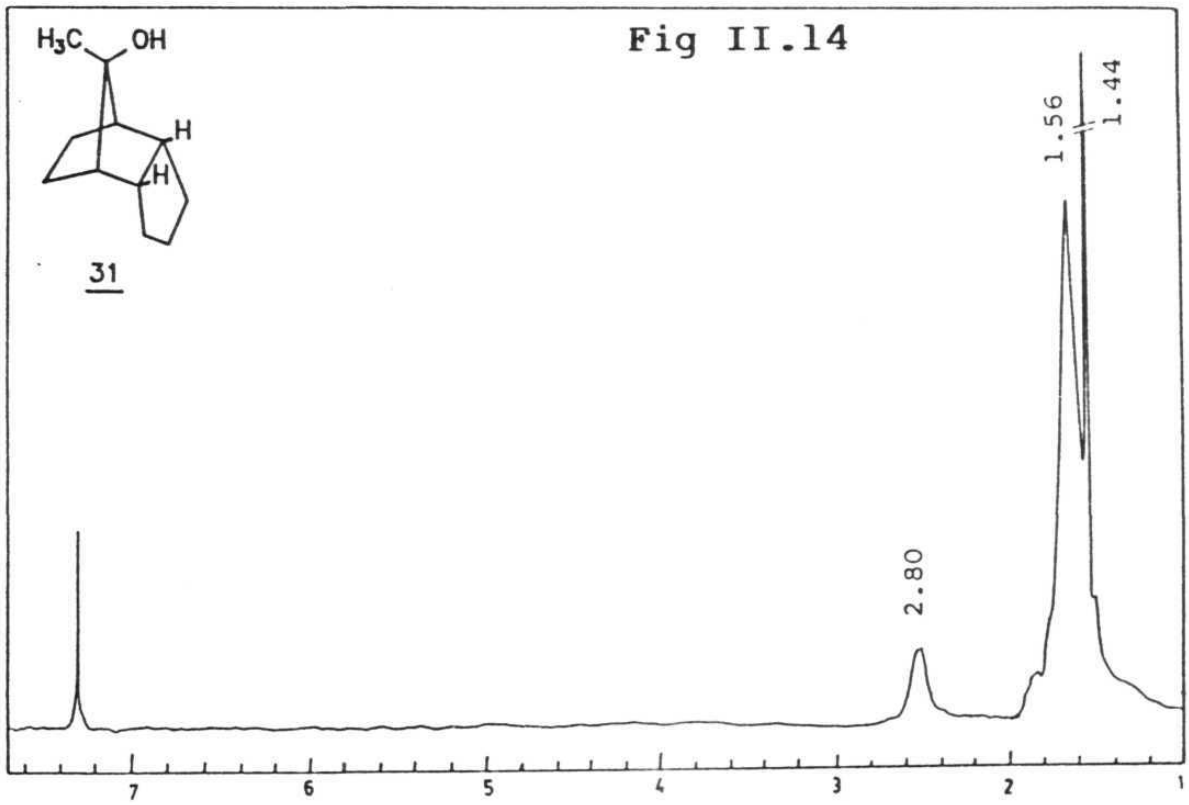
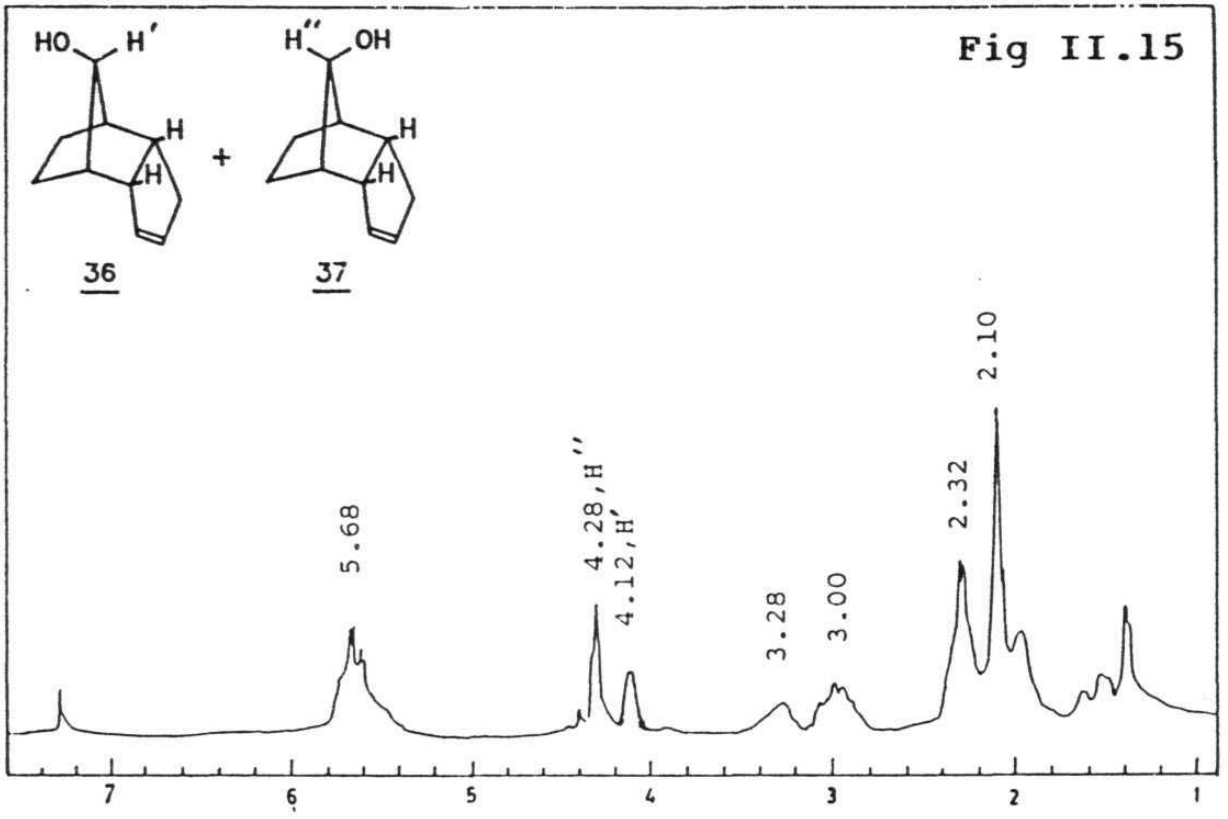
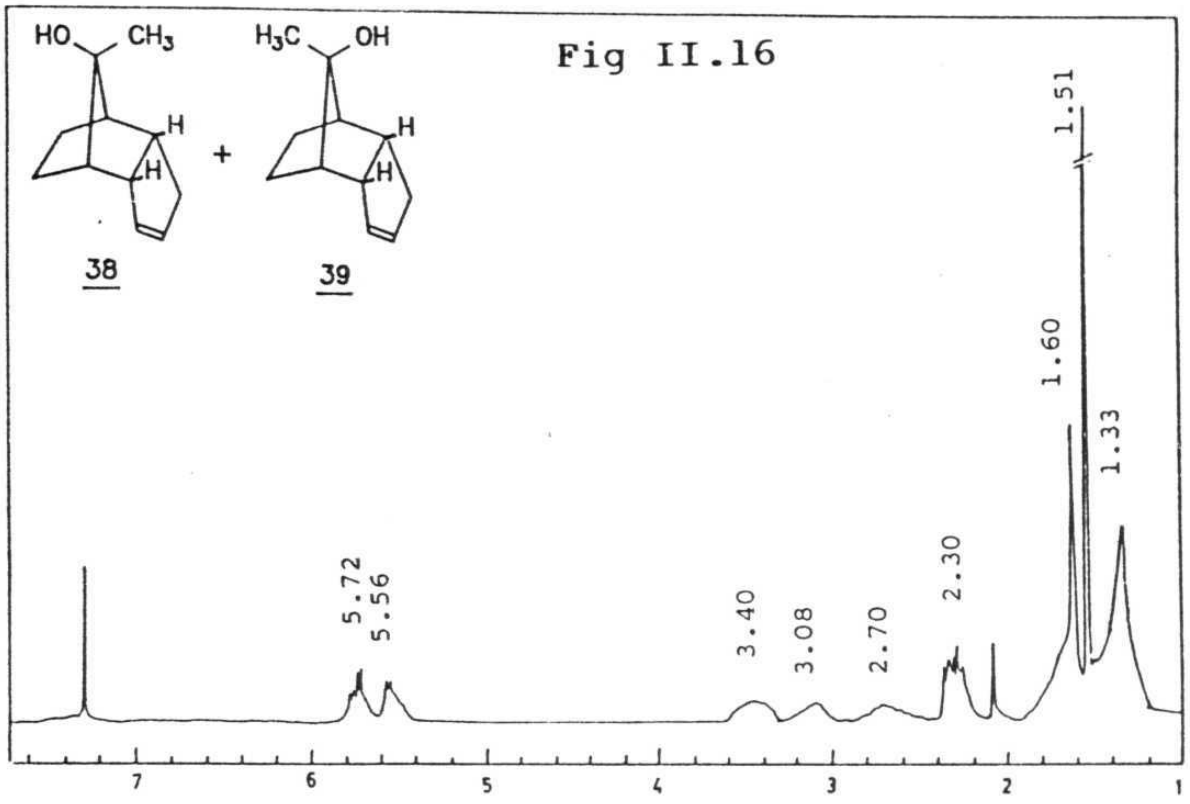


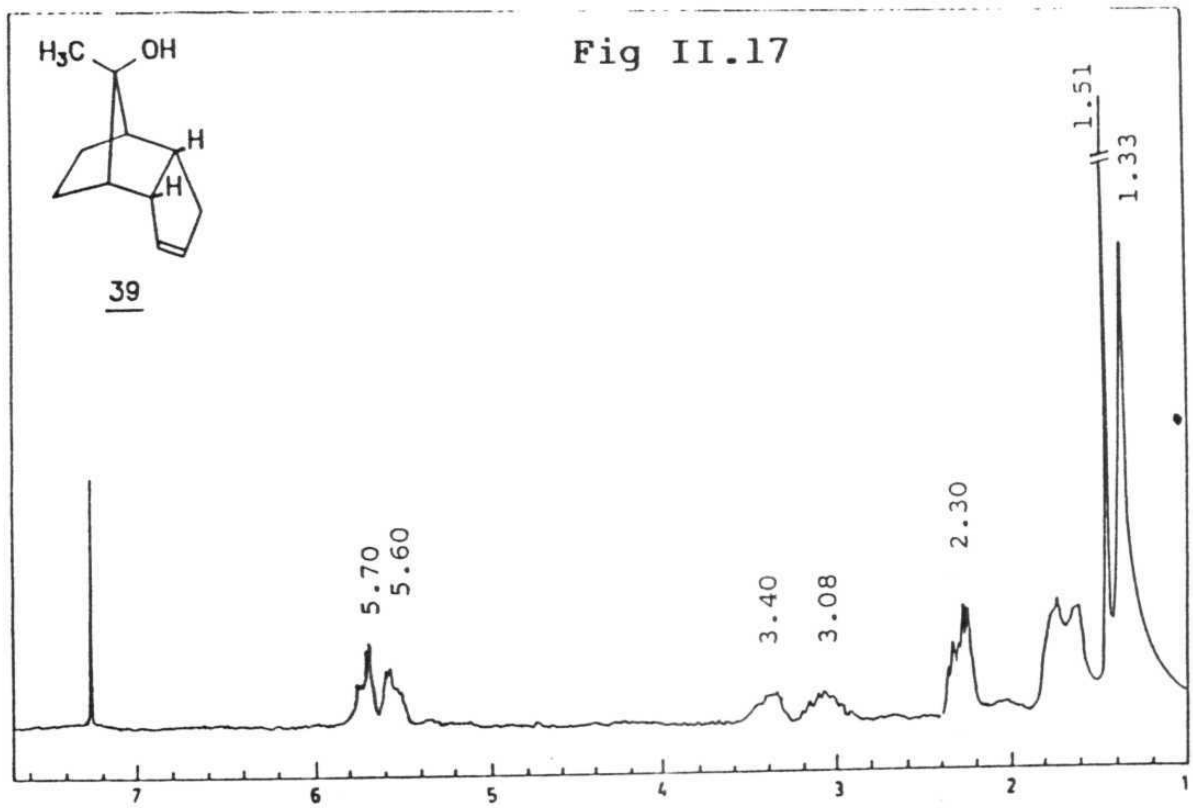
Fig II.12


HO
CH3
H3C
OH
H
H
+
30
31
Fig II.13
1.40
1.44
1.70
2.80
2.40
7
6
5
4
3
2
1


H3C
OH
H
H
31
Fig II.14
1.56
1.44
2.80
7
6
5
4
3
2
1


HO
H'
H
H
36
+
H''
OH
H
H
37
Fig II.15
5.68
4.28, H''
4.12, H'
3.28
3.00
2.32
2.10
7
6
5
4
3
2
1


HO
CH3
H
H
+
H3C
OH
H
H
38
39
Fig II.16
5.72
5.56
3.40
3.08
2.70
2.30
1.60
1.51
1.33
7
6
5
4
3
2
1


H3C
OH
H
H
39
Fig II.17
5.70
5.60
3.40
3.08
2.30
1.51
1.33
7
6
5
4
3
2
1

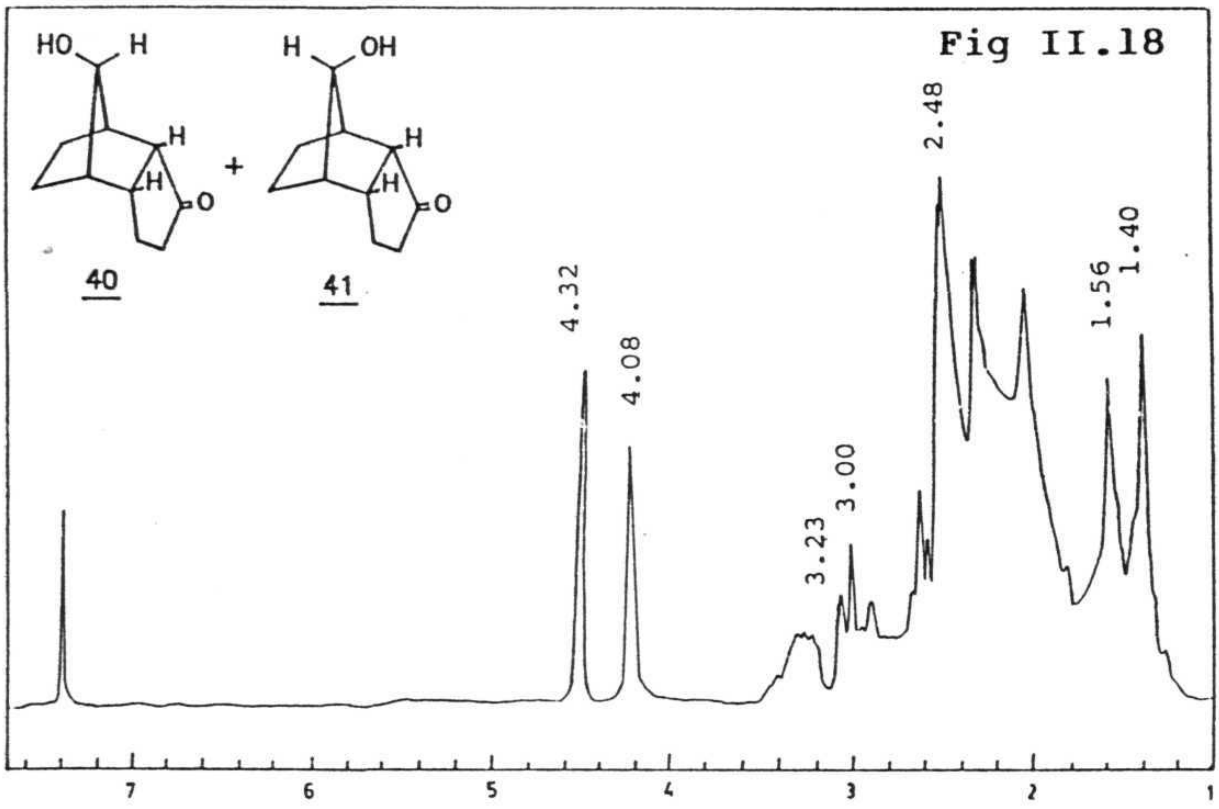


Fig II.18

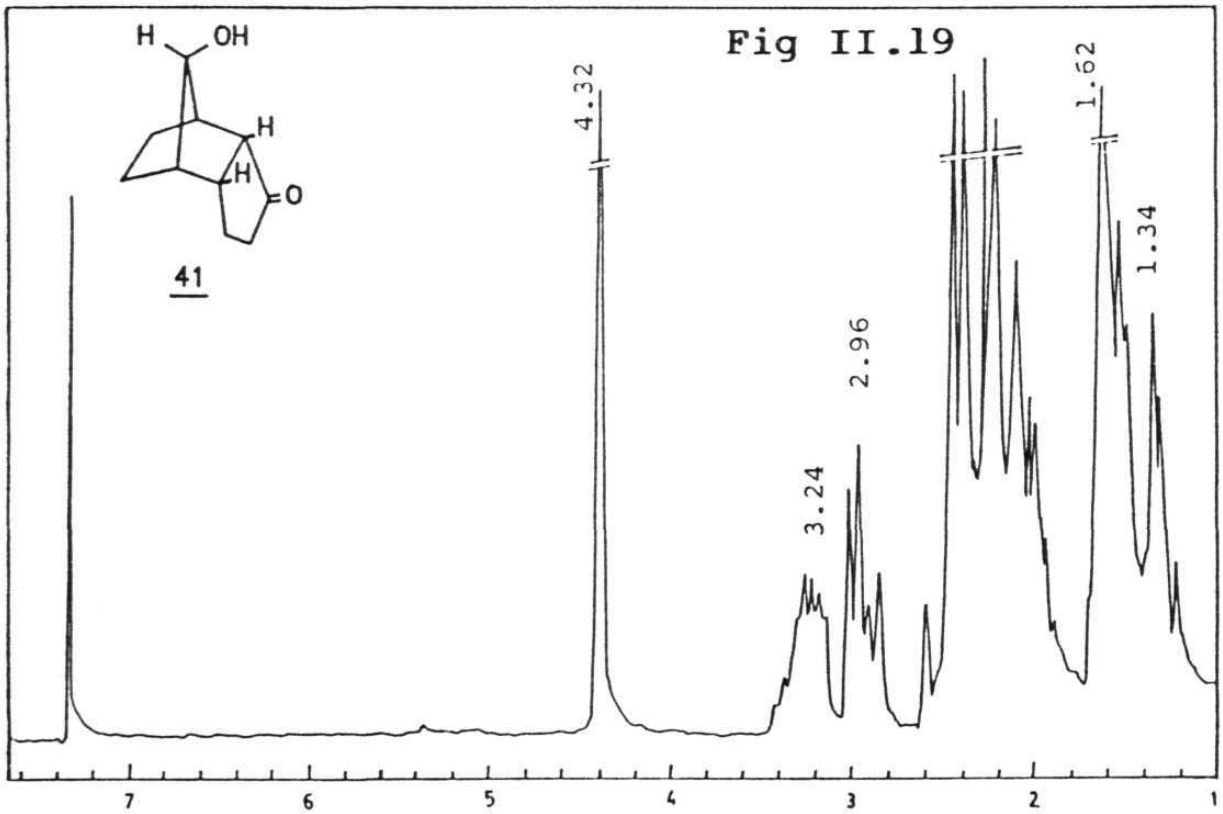
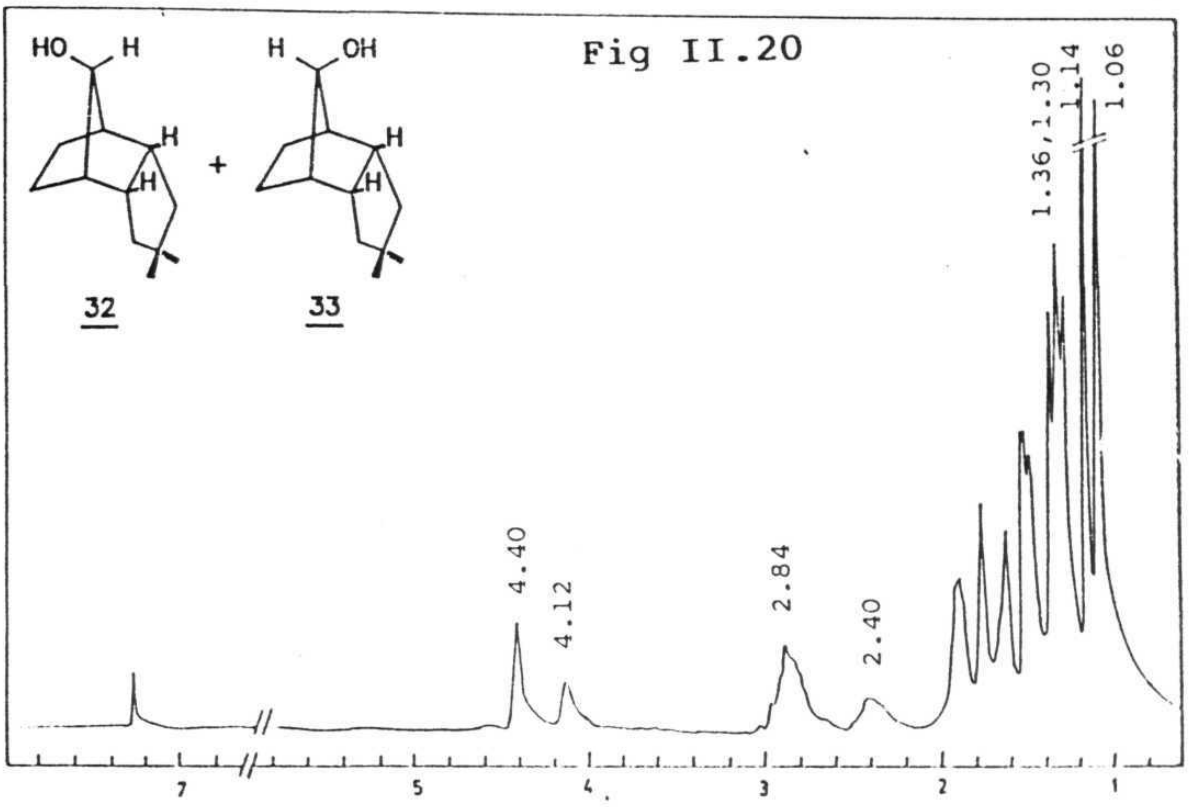


Fig II.19


HO H
H OH
H
H
H
H
+
32
33
Fig II.20
4.40
4.12
2.84
2.40
1.36,1.30
1.14
1.06
7
5
4
3
2
1

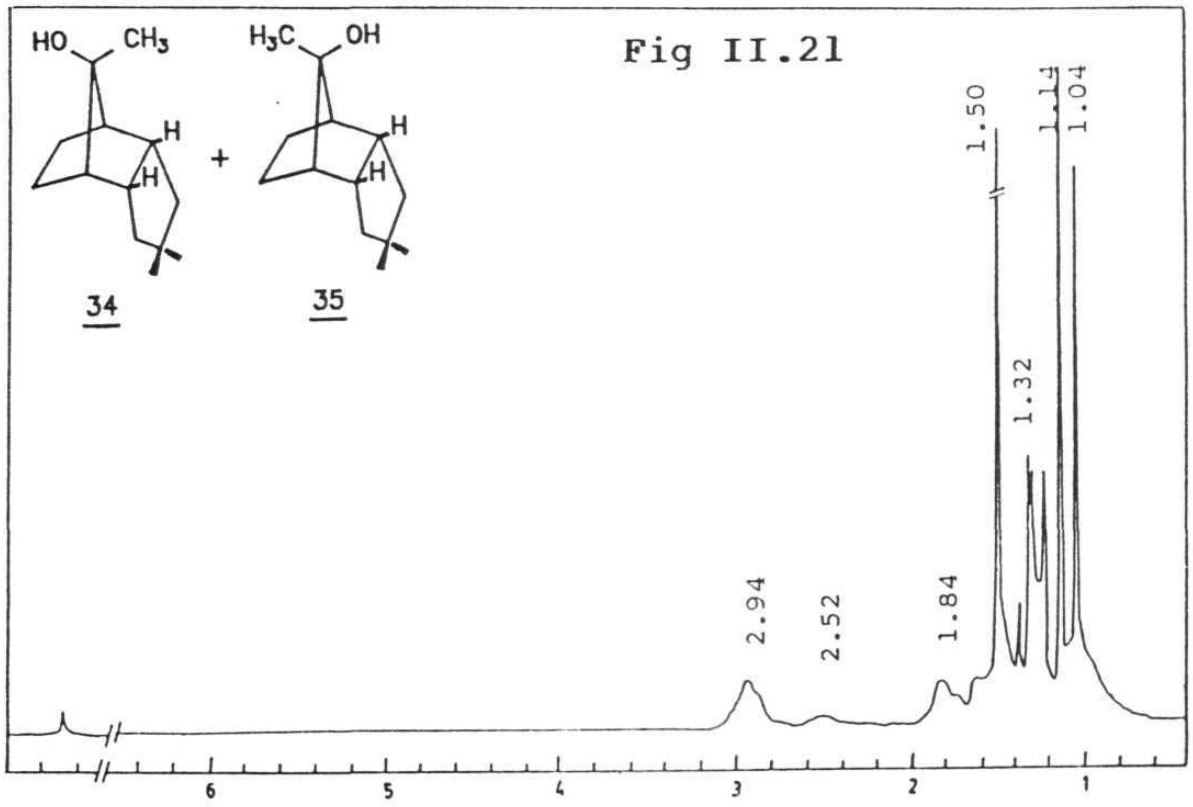

HO CH3
H3C OH
H
H
H
H
+
34
35
Fig II.21
2.94
2.52
1.84
1.50
1.32
1.14
1.04
6
5
4
3
2
1

Fig II.22

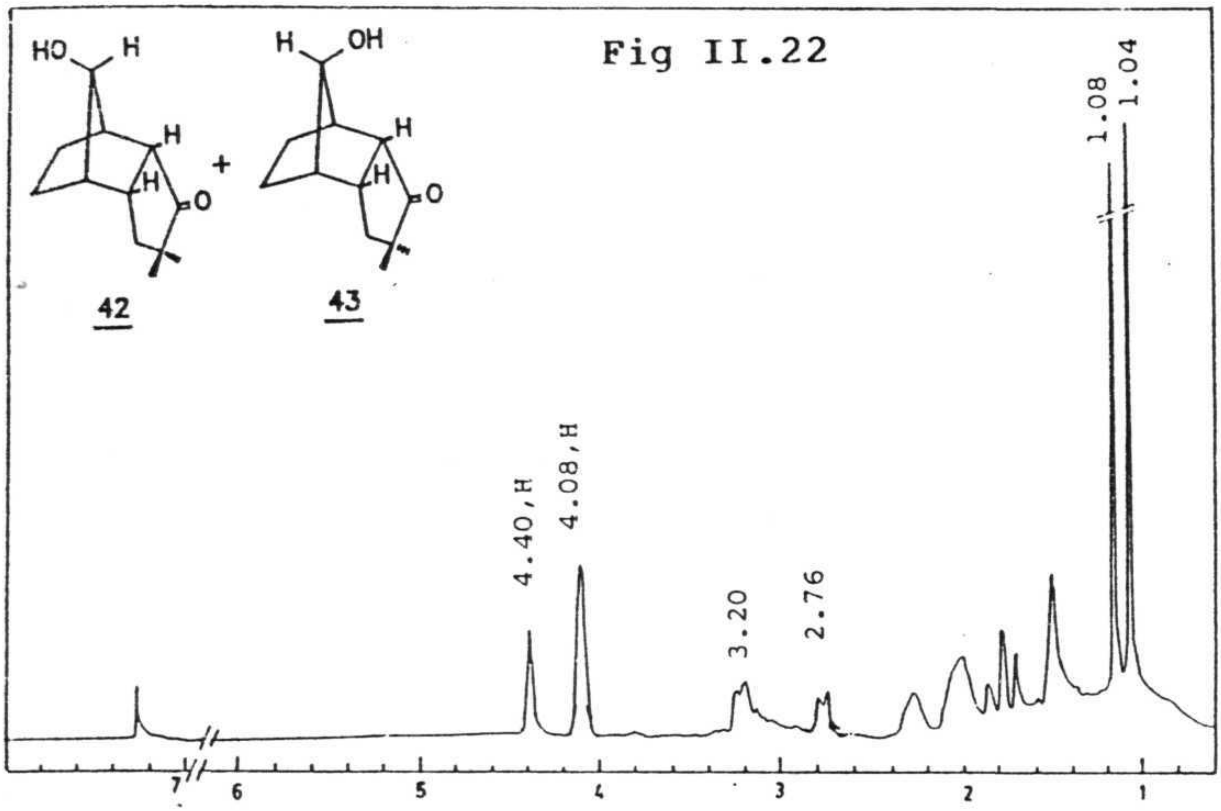
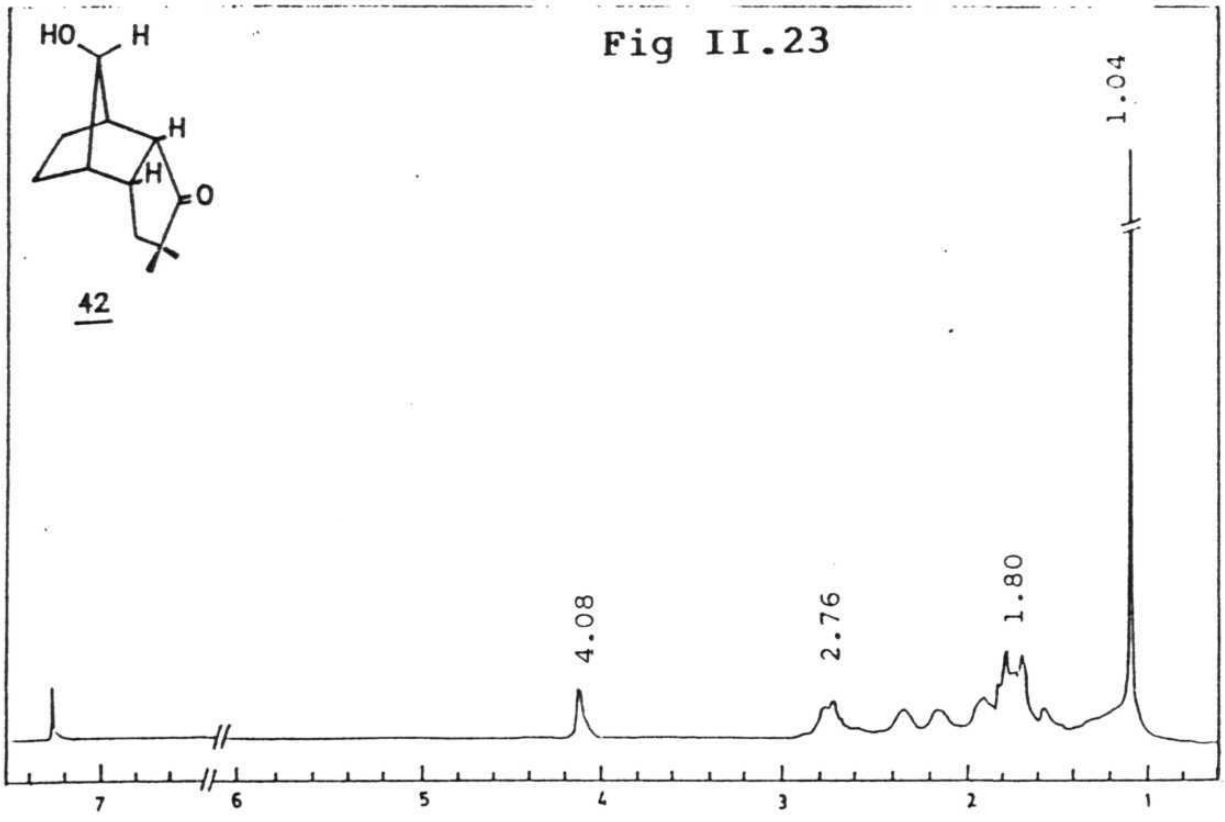


Fig II.23



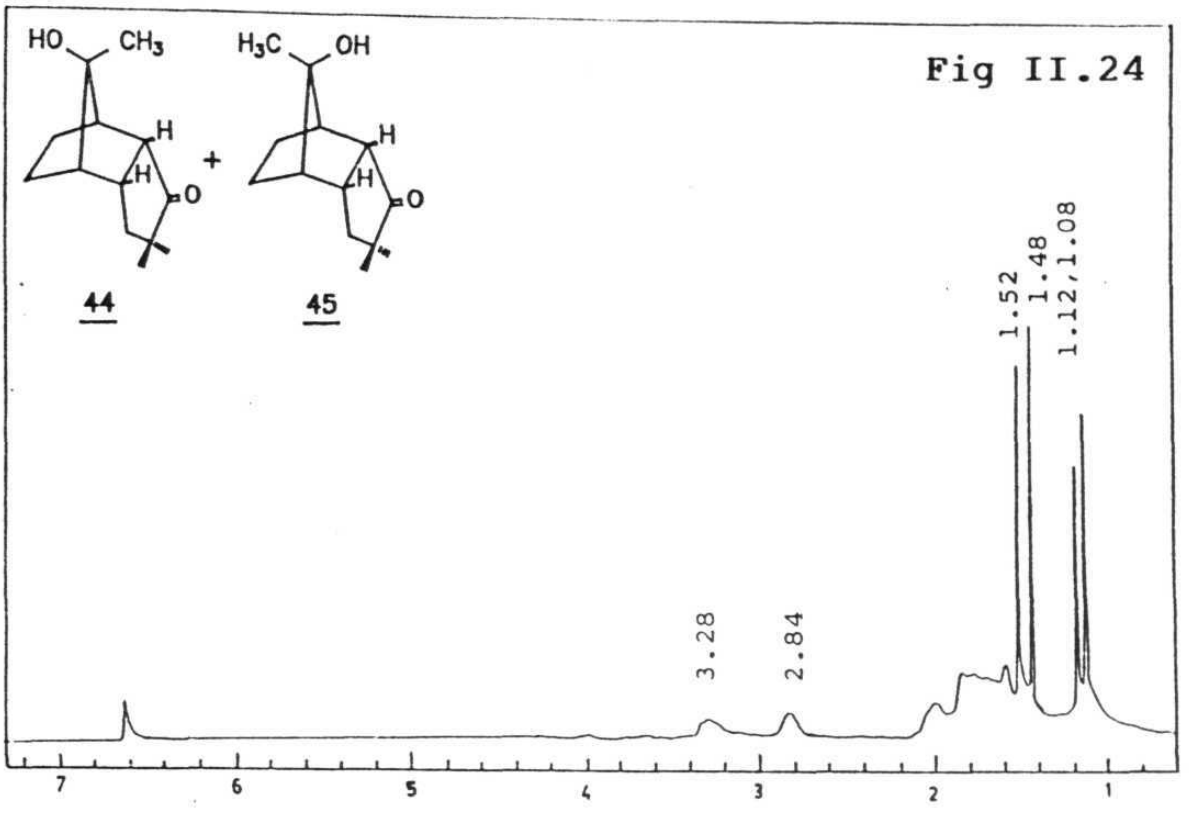


Fig II.24

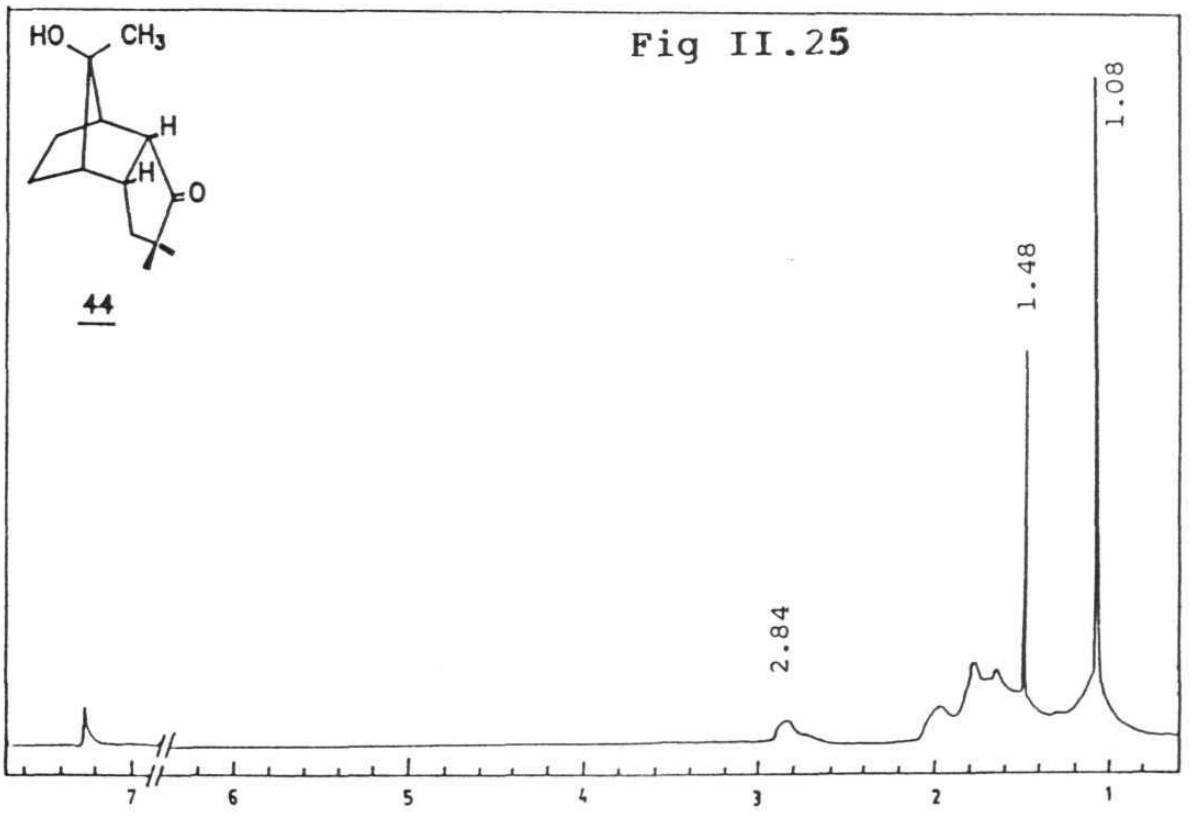


Fig II.25

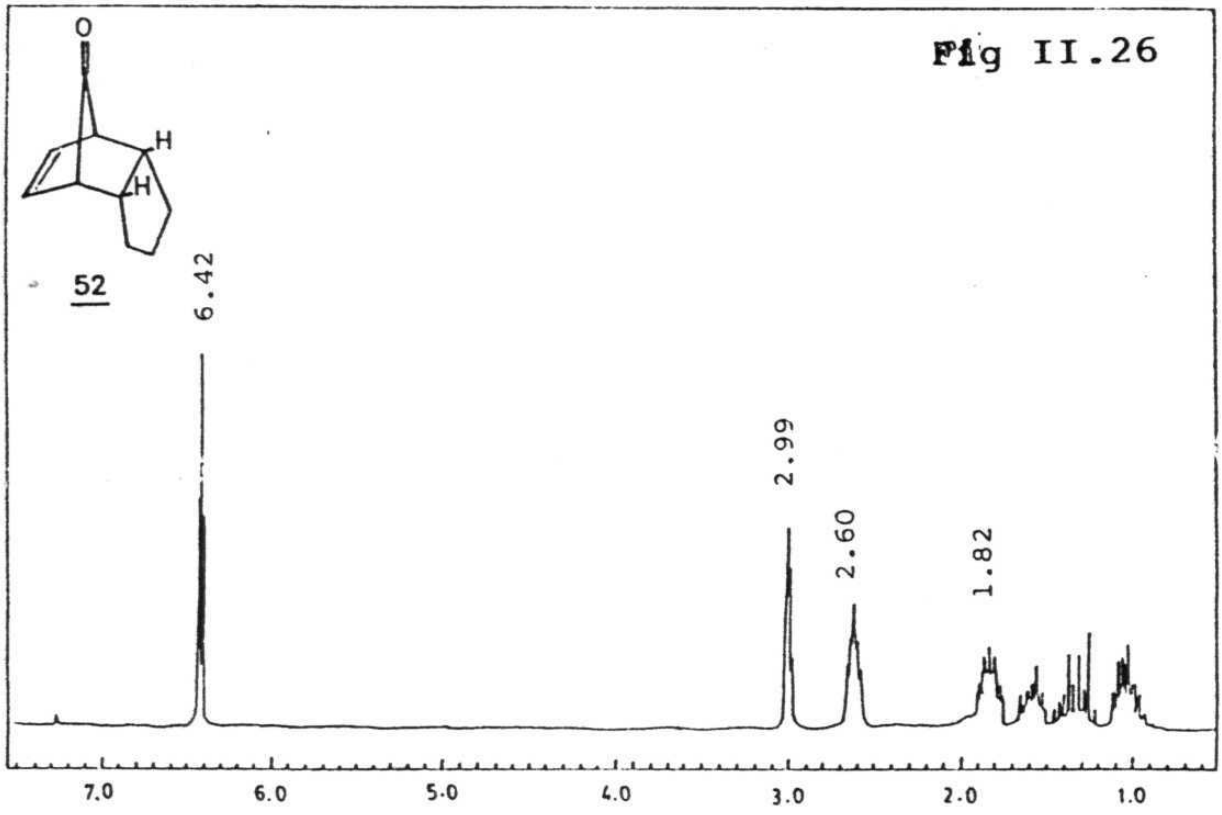


Fig II.26

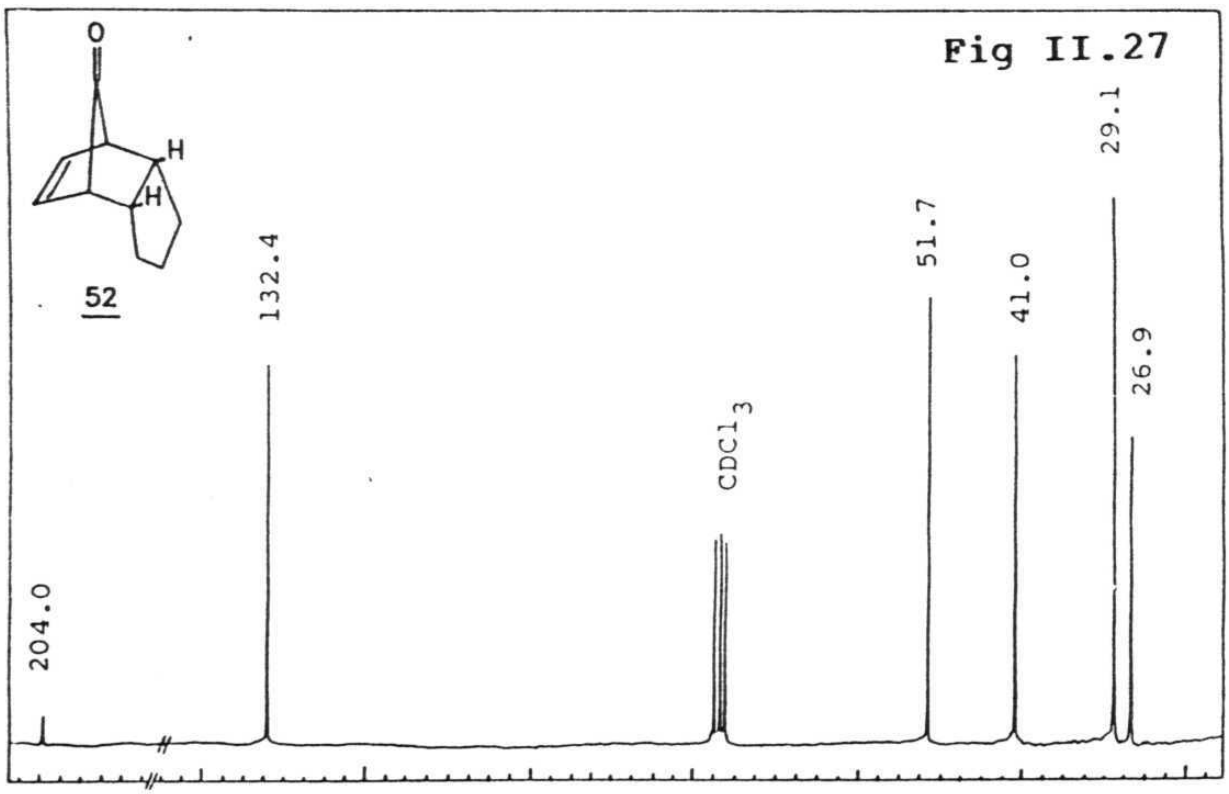


Fig II.27

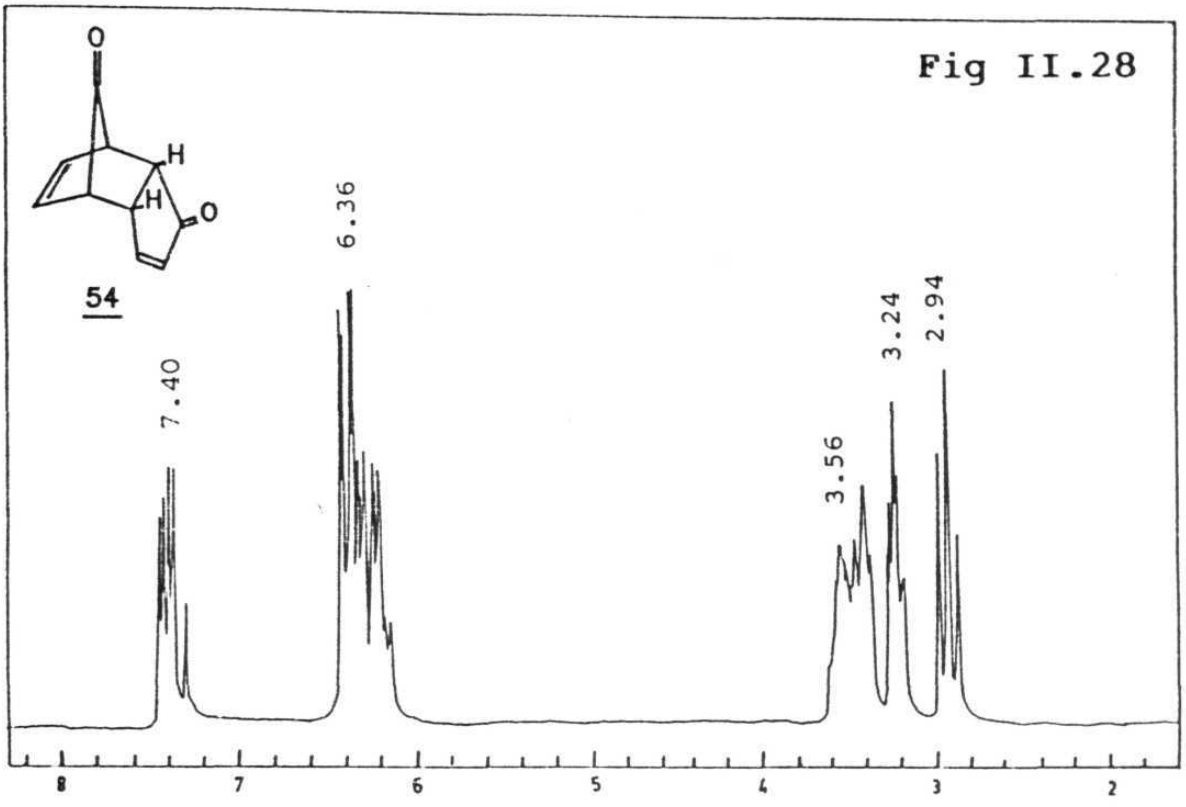


Fig II.28

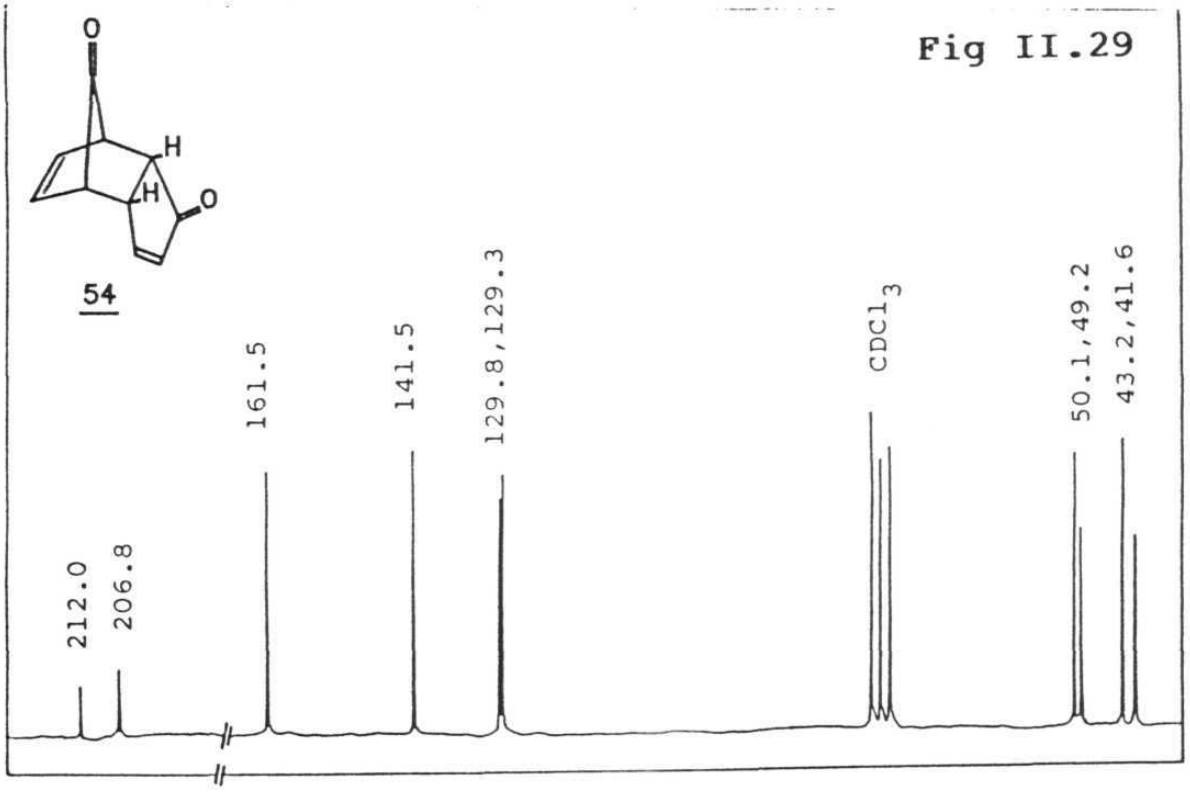


Fig II.29

Fig II.30

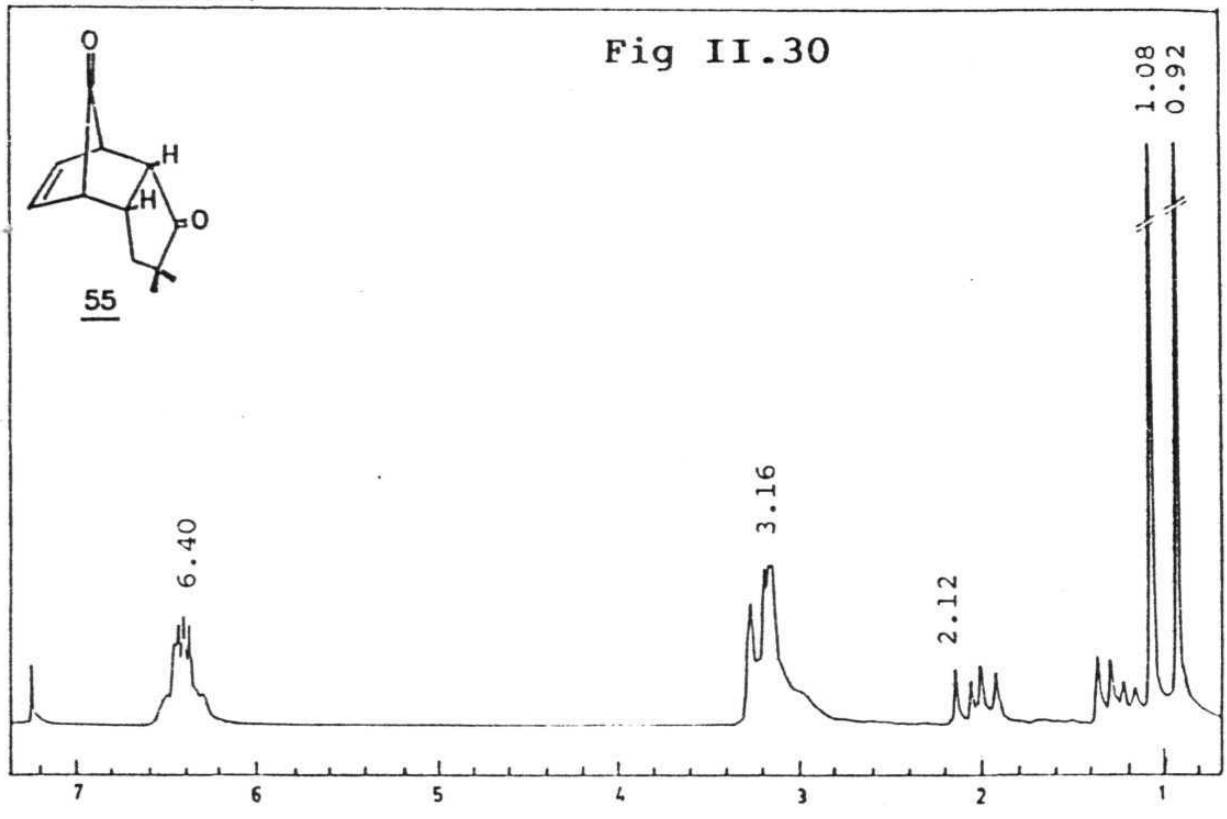
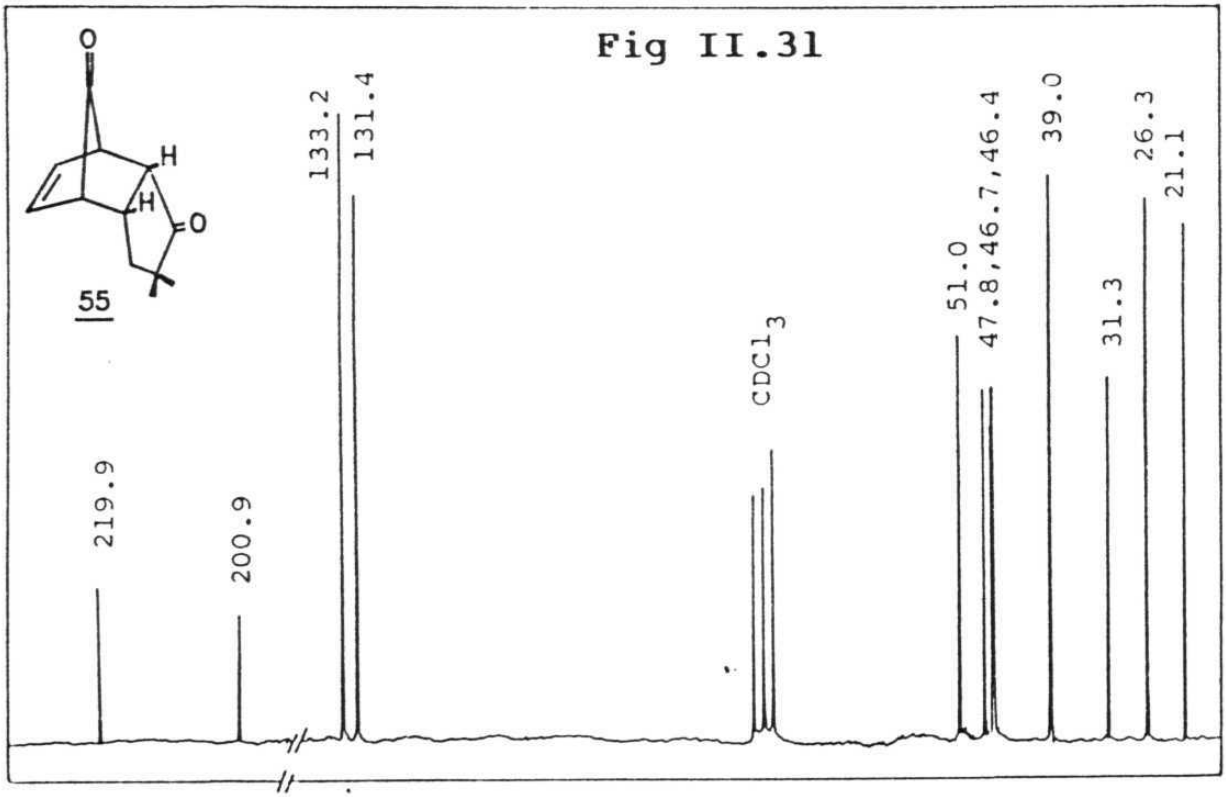


Fig II.31



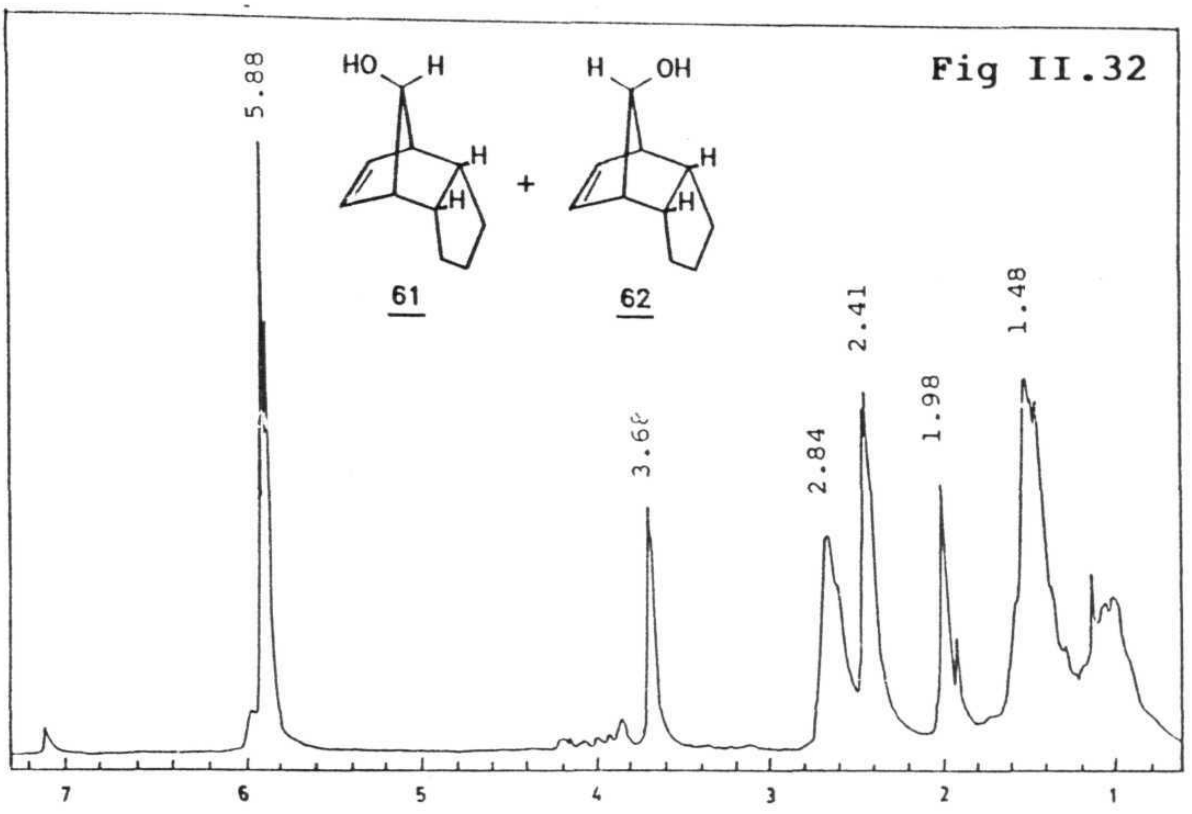


Fig II.32

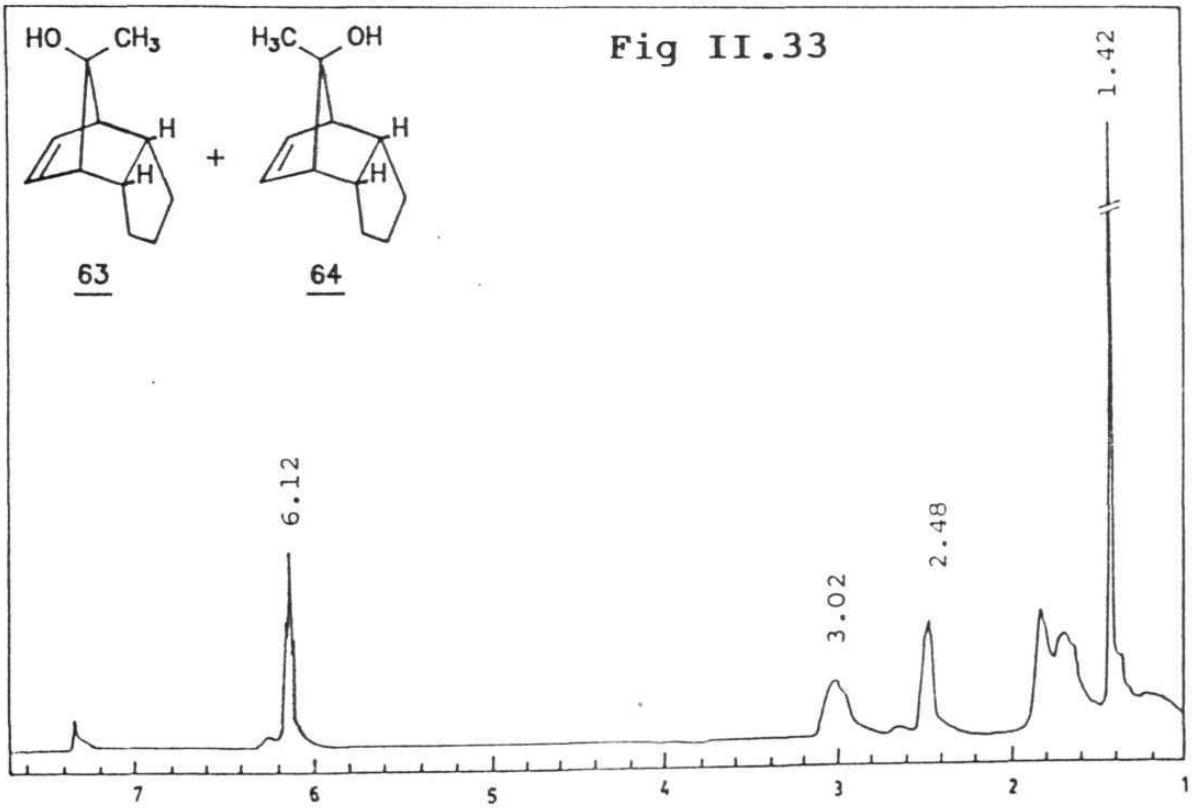


Fig II.33

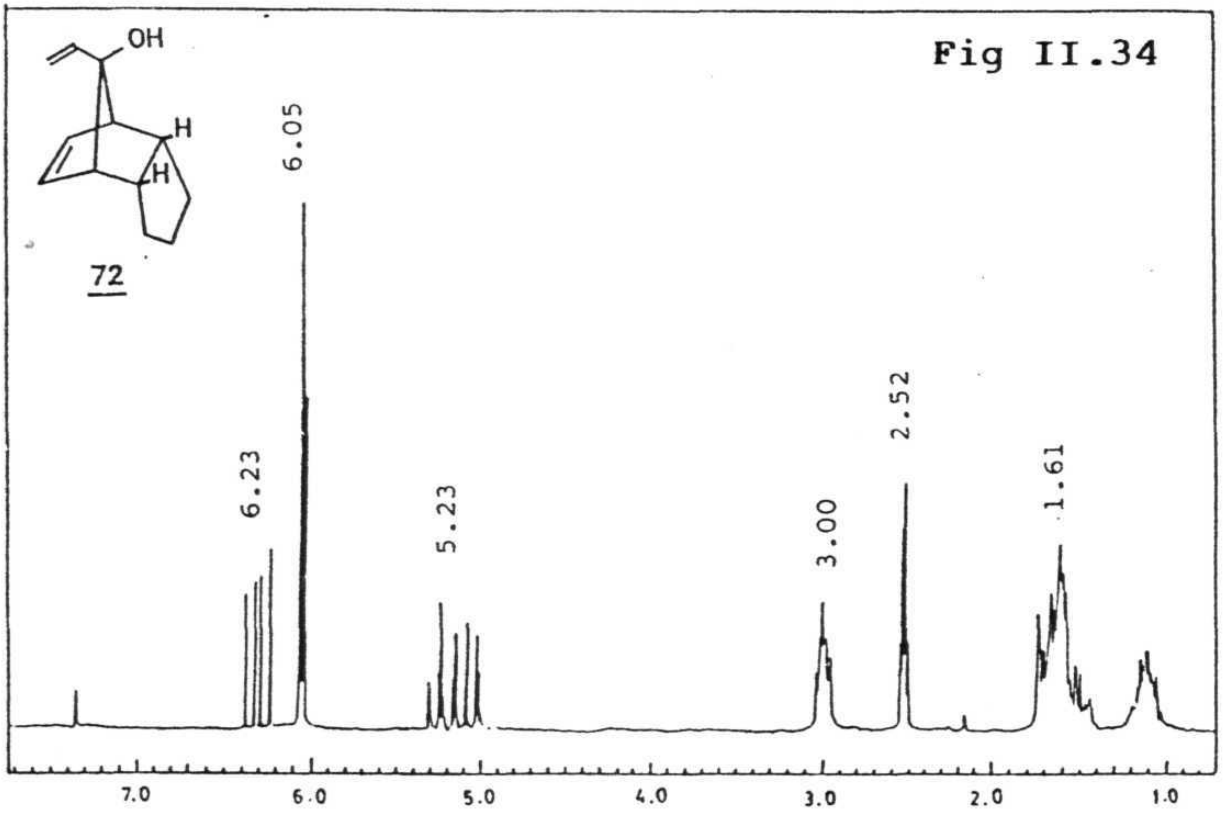


Fig II.34

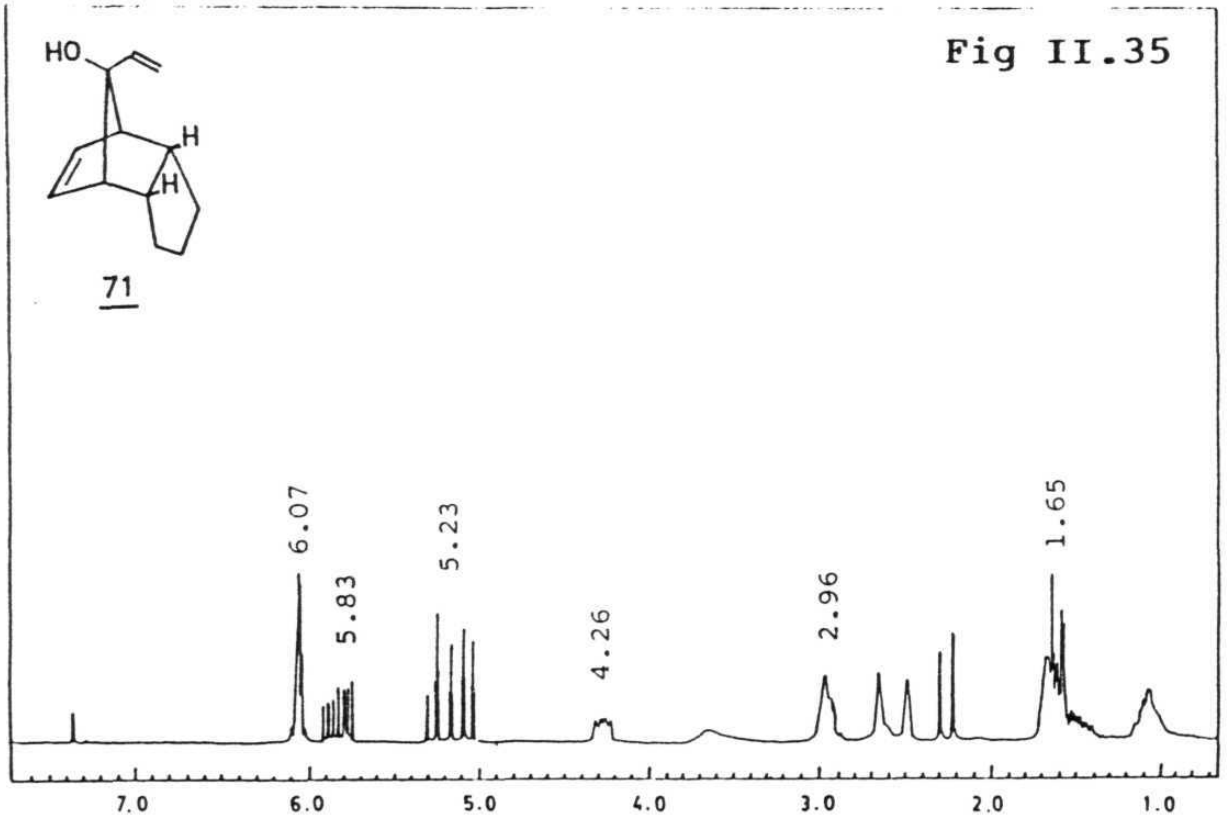


Fig II.35

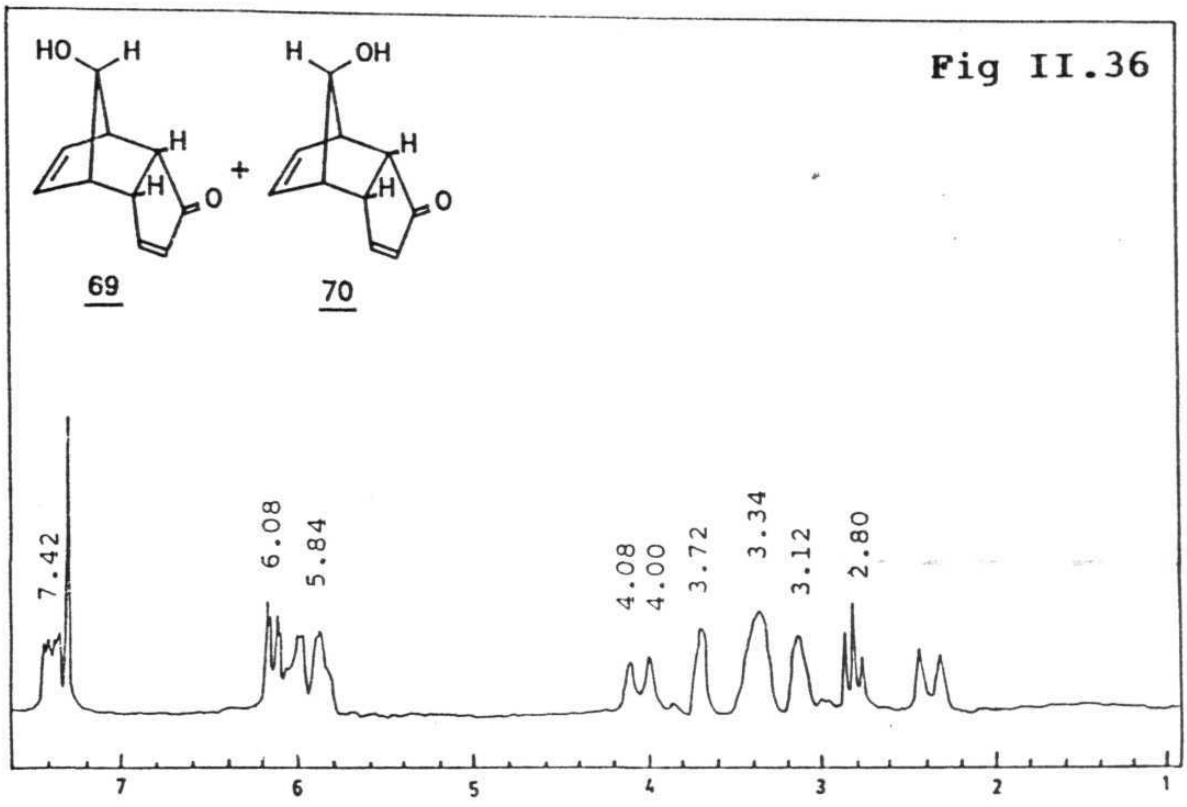


Fig II.36

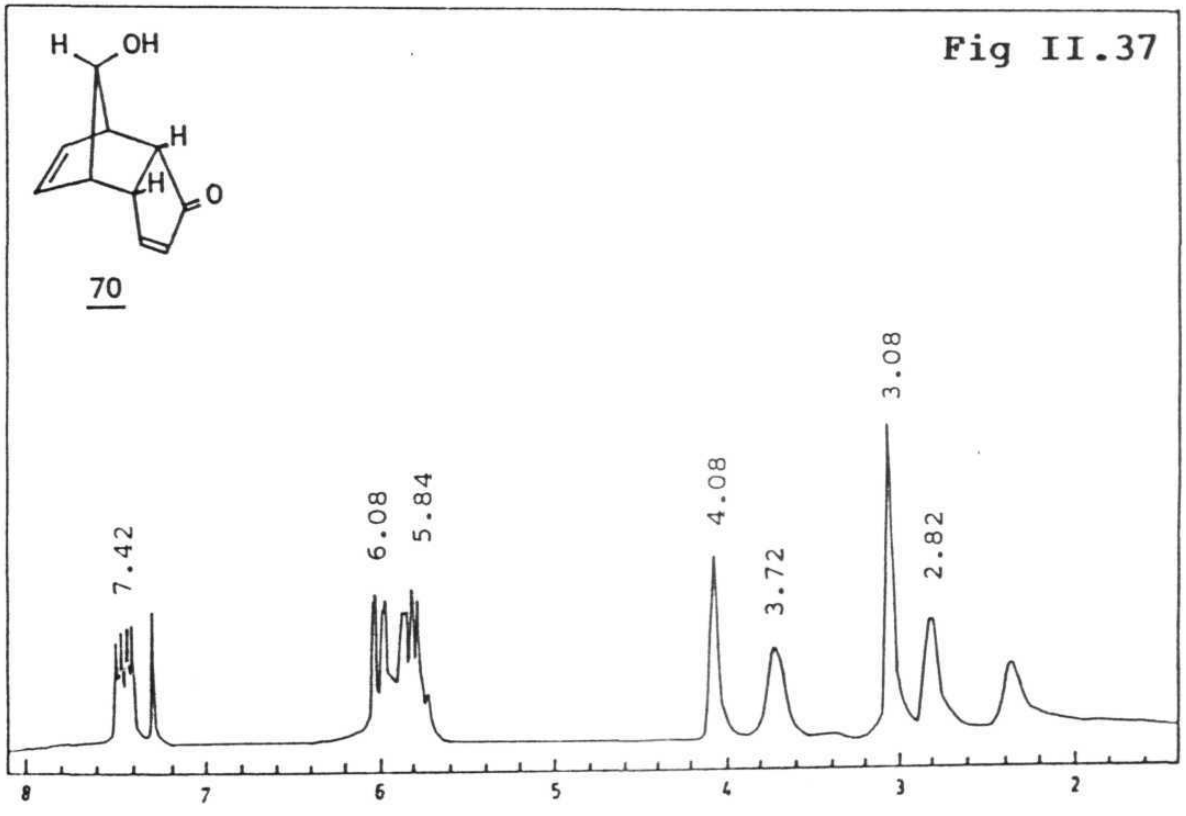
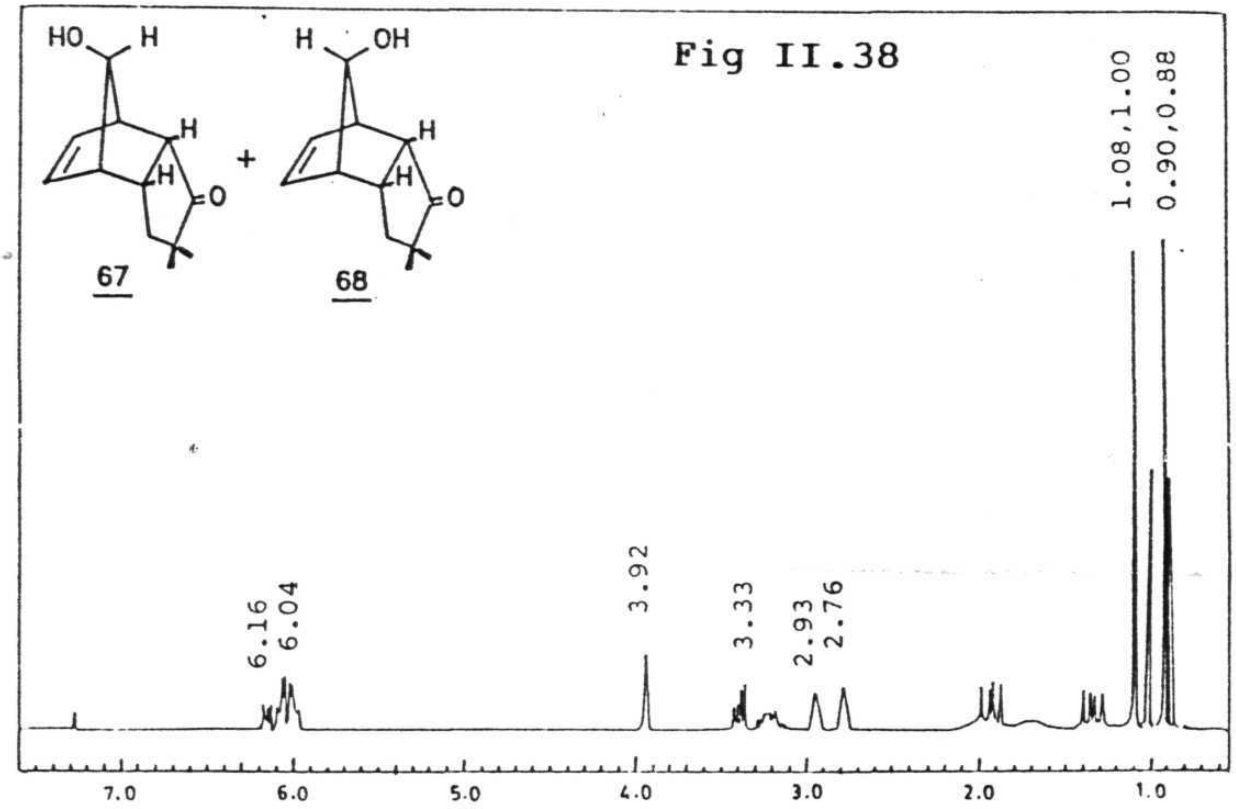
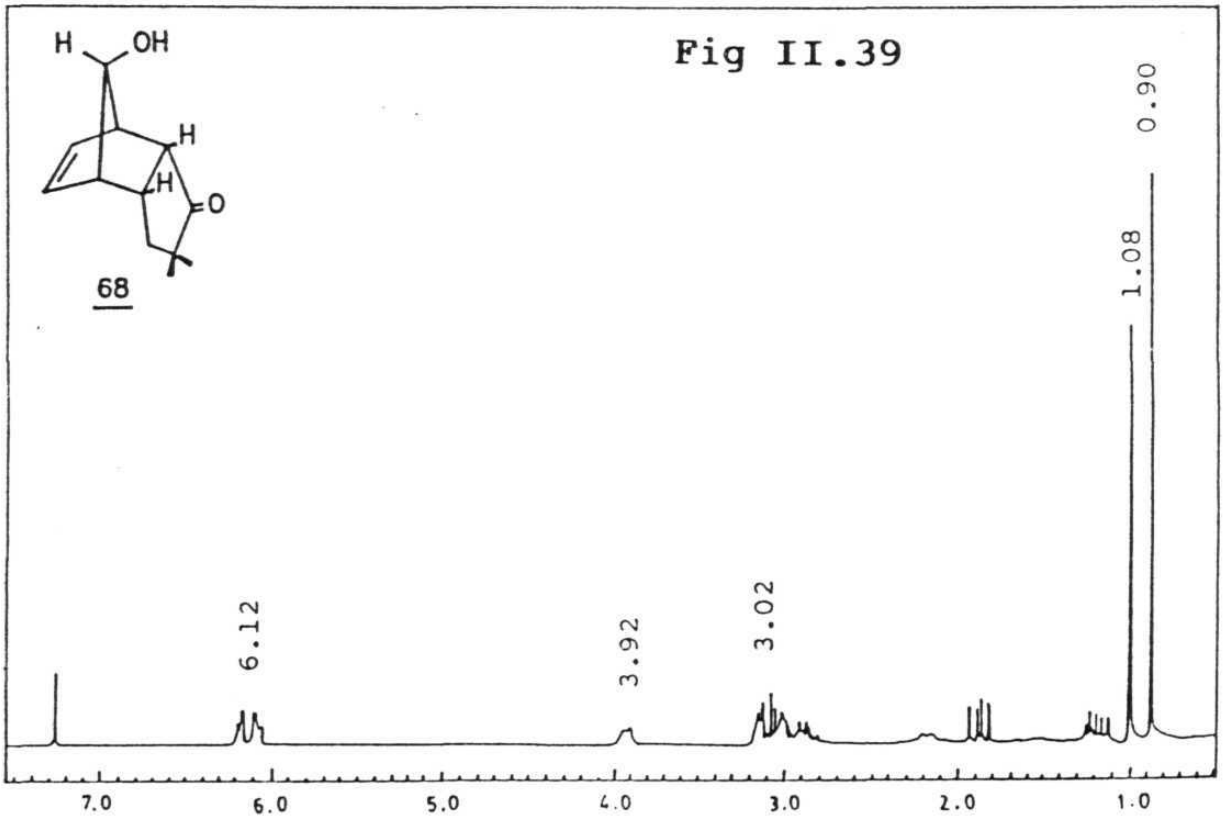


Fig II.37


HO
H
H
H
O
67
+
H
OH
H
H
O
68
Fig II.38
1.08,1.00
0.90,0.88
6.16
6.04
3.92
3.33
2.93
2.76
7.0
6.0
5.0
4.0
3.0
2.0
1.0


H
OH
H
H
O
68
Fig II.39
0.90
1.08
6.12
3.92
3.02
7.0
6.0
5.0
4.0
3.0
2.0
1.0

II.7. REFERENCES

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VITAE

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List of Publications:

1. Stereochemistry of nucleophilic additions to 2,3-endo,-endo-bridged-7-ketonorbornanes[tricyclo[5.2.1.$0^{2,6}$)-decan-10-ones]. Observation of long-range electronic effects, G. Mehta and **M. Praveen**, Tetrahedron Lett., 33, 1759, 1992.

2. Stereoselective route to functionalized cis-hydrindanes from tricyclo[5.2.1.$0^{2,6}$]decan-10-ones. A total synthesis of (±)-coronafacic acid, G. Mehta and **M. Praveen**, J. Chem. Soc. Chem. Commun., 1573, 1993.

3. Regioselective Haller-Bauer cleavage in tricyclo-[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione. A total synthesis of (±)-pumiliotoxin C, G. Mehta and **M. Praveen**, J. Org. Chem., 60, 279, 1995.

4. Role of Electrostatic Interactions in Fine-Tuning the π-Face selectivity in Nucleophilic Additions to 2-endo-Aryl-7-Norbornanones, G. Mehta, F.A. Khan, M. Praveen, I.N. Namboodri, B. Ganguly and J. Chandrashekar, Manuscript Submitted for Publication.