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Synthetic Approaches For Natural Product Lactones-Mintlactones And Artemisinin Derivatives

A thesis submitted to the

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for the degree of

Doctor of Philosophy
in

CHEMISTRY

PH-1072

By
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National Chemical Laboratory
Pune 411 008,INDIA

October 1996

DEDICATED

TO

MY PARENTS

TH-1072

CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Synthetic Approaches for Natural Product Lactones-Mintlactones and Artemisinin Derivatives"** submitted by **MR. VIJAY DATTATRAY DHONDGE** was carried out by the candidate under my supervision. Such material as has been obtained from other sources and has been duly acknowledged in the thesis.

October, 1996

Dr. T. RAVINDRANATHAN

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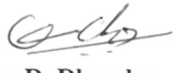
I would like to thank the Director NCL for allowing me to work in NCL and permitting to submit it as a thesis.

Finally thanks to CSIR, India for the financial support for this study which otherwise wouldn't have been possible.



October, 1996
NCL, Pune

Vijay D. Dhondge

Abbreviations

Ac	Acetyl
Ar	Aryl
BMS	Borane Dimethyl Sulfide Complex
B.P.	Boiling Point
CAN	Ceric Ammonium Nitrate
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DEAD	Diethyl Azodicarboxylate
DIBAL-H	Diisobutylaluminium Hydride
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
EtOAc	Ethylacetate
g	Gram/s
h	Hour/s
LDA	Lithium Diisopropylamide
m-CPBA	m-Chloroperbenzoic acid
mg	Milligram
Me	Methyl
Me_2SO_4	Dimethylsulfate
M.P.	Melting Point
M^+	Molecular Ion
MS	Mass Spectrum
NaH	Sodium hydride
NBS	N-Bromosuccinimide
NMO	N-methylmorpholine-N-oxide
NMR	Nuclear Magnetic Resonance
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
Ph	Phenyl
pTSA	p-Toluenesulfonic acid
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl Chloride
WHO	World Health Organisation

General Remarks

1. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

2. The compound numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.

3. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.

4. Organic layers were dried over anhydrous sodium sulfate (Na_2SO_4).

5. TLC analysis were carried out on glass plates using silica gel: GF-254 and the plates were analysed by keeping in iodine chamber.

6. In cases where chromatographic purifications were done, SiO_2 was used as a stationary phase.

7. The IR spectra were recorded on Perkin-Elmer infrared spectrophotometer model 683B or 1605 FTIR and IR absorptions are expressed in cm^{-1}.

8. The ^1H NMR and ^{13}C NMR spectra were recorded on Varian FT-80A (20 MHz) or Bruker WH 90 (22.63 MHz) or Bruker AC 200 (50 MHz) instrument. Figures in the parentheses correspond to ^{13}C frequencies. ^1H NMR and ^{13}C NMR spectra are reported in parts per million from internal standard (tetramethylsilane) on δ scale.

9. Optical rotations were recorded at room temperature on JASCO Dip-181 digital polarimeter using sodium vapour lamp.

10. Mass spectra were recorded at an ionization energy of 70eV on Finnigan MAT-1020, Automated GC/MS instrument, and mass values are expressed as (m/e).

11. GLC was carried out on Hewlett Packard 5890.

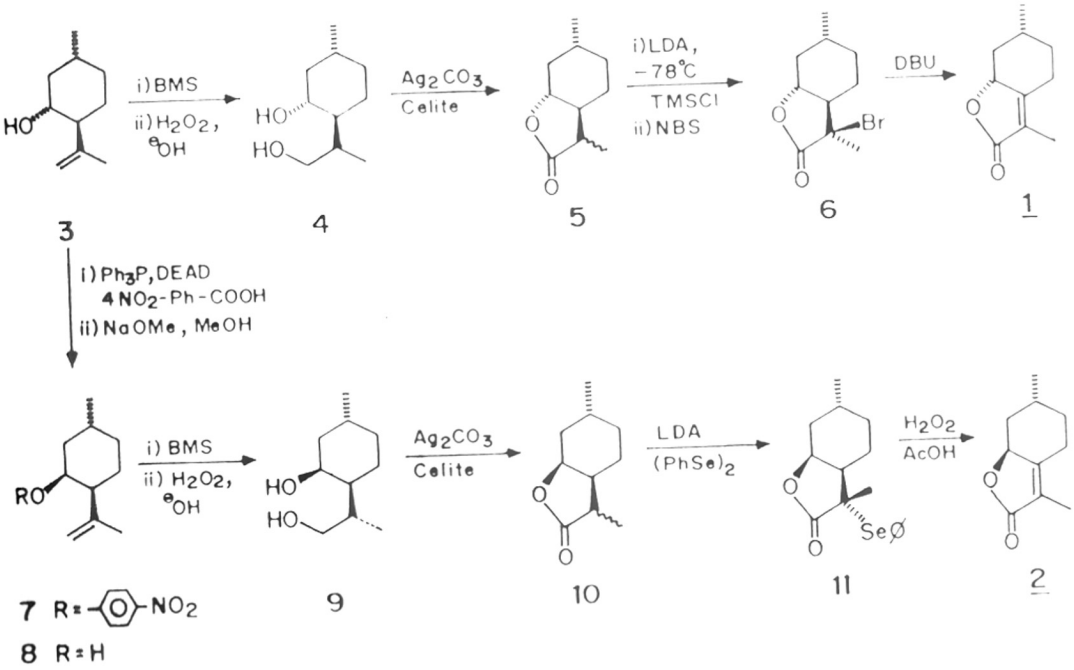
ABSTRACT

The thesis entitled **"Synthetic Approaches for Natural Product Lactones - Mintlactones and Artemisinin derivatives"** is divided into three chapters.

CHAPTER-I : Synthesis of Terpenic lactones and furans :

Section-A : A short and Efficient Synthesis of (-)-Mintlactone and (+)-Isomintlactone:

(-)-Mintlactone **1** and (+)-Isomintlactone **2**, minor components of commercially important flavouring essential oils are *Mentha pipertia L.* (pippermint oil) and *Spearmint oil.*[1] These monoterpene compounds possess a butenolide moiety as the essential component. The synthesis of (-)-mintlactone and (+)-isomintlactone has been achieved from common precursor viz. (-)-isopulegol **3**. The sequence involves oxidation of 1,4-diols **4** & **9** to the corresponding butyrolactones **5** & **10** as the key step followed by introduction of double bonds to furnish the desired **1** & **2** butenolides as shown in scheme-1.1.



Thus, very short, convenient and highly stereoselective synthesis of (-)-Mintlactone and (+)-isomintlactone has been achieved starting from a common precursor (-)-isopulegol.[2]

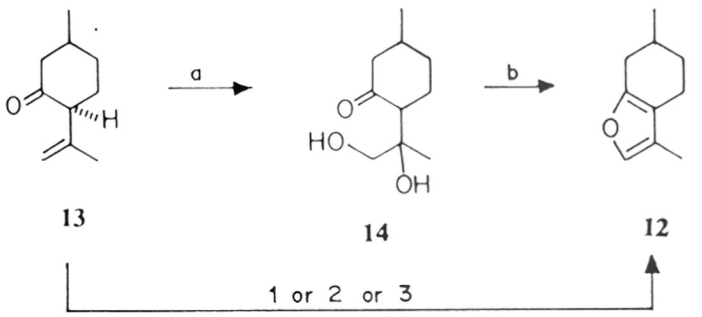
Section-B : Synthesis of R(+)-Menthofuran :

Menthofuran **12**, one of the most well known member of furanoterpenes was obtained by Charabot in 1904 from peppermint oil.[3] Menthofuran served not only as an important perfumery but also as a synthetic intermediate for other biologically related compounds e.g. Mintlactone and isomintlactone.

This section describes one pot, simple and practical synthesis of menthofuran from isopulegone **13** as shown in scheme-1.2.

According to this plan, osmylation of isopulegone **13** gave ketodiol **14** in good yield. The most economical and efficient method for conversion of ketodiol **14** to menthofuran **12** is the treatment with 10% HCl which furnished the menthofuran in 78% yield.

Scheme-1·2



a : OsO_4 , NMO, CH_3CN , R.T. b : 10 % HCl

1 : OsO_4 , NMO, CH_3CN , Δ 2 : NBS, MeOH : CH_2Cl_2 , R.T

3 : Br_2 , $CHCl_3$, R.T.

One pot conversion of isopulegone **13** into Menthofuran **12** was achieved by using three different reagents (scheme-1.2).

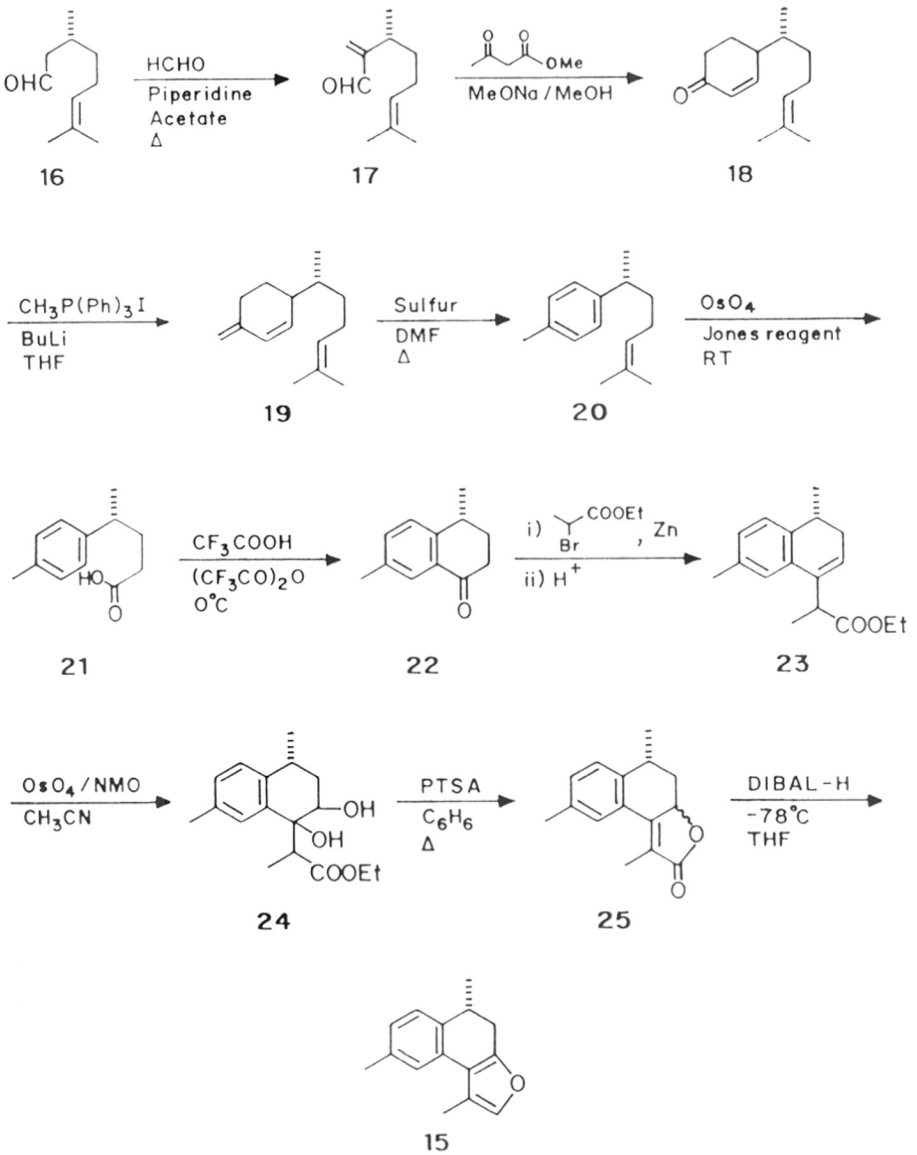
Isopulegone **13** was treated with OsO_4/NMO in acetonitrile under reflux to afford menthofuran in 50% yield and 30% ketodiol was recovered back. Isopulegone **13** was treated with NBS in CH_2Cl_2:MeOH (8:2) at room temperature to furnish the menthofuran in 71% yield. Bromination of isopulegone **13** in chloroform also afforded the menthofuran in 60% yield.

Thus, one pot, simple and practical synthesis of Menthofuran **12** has been achieved from isopulegone **13**.

Section-C : Studies towards total synthesis of (+)-Laevigatin :

Laevigatin **15**, a naturally occurring terpene having unusual skeleton was isolated from *Eupatorium laevigatum*.[4] In connection with the studies towards the synthesis of Heritol, Heritonin, and related compounds two convenient and efficient methodologies to generate butenolide were developed in these lab (1) *via* Osmylation of ß, γ-unsaturated esters (2) and direct oxidative conversion of ß, γ-unsaturated acid to butenolides by CAN at room temperature. This section describes application of above protocol for the synthesis of naturally occurring Laevigatin **15** as shown in scheme-1.3.

Scheme - 1·3

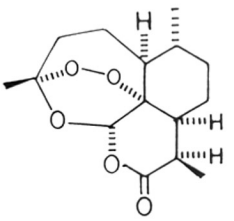


The key sequences involves the stereoselective synthesis of 4,7-dimethyl tetralone **22** from citronellal **16**, synthesis of butenolide **25** and its conversion to naturally occurring Laevigatin **15**.

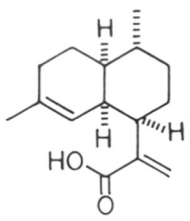
Thus, very simple, efficient route towards the synthesis of (+)-Laevigatin has been achieved from citronellal as a starting material.

CHAPTER-II : Synthetic Approaches Towards (+)-Artemisinin :

Since ancient times *Artemisia Annua L* has been used as a traditional Chinese herbal medicine for treating fever and malaria. The effective constituent was isolated by Chinese investigators in 1972 and shown to be a sesquiterpene lactone, named artemisinin **1**.[5] It was found to be a potent plasmocidal agent, and extensive clinical trials in China have revealed that artemisinin has considerable promise for the treatment of drug resistant malaria. This unusual compound has a peroxide grouping but lacks a nitrogen containing heterocyclic system which is found in most antimalarial compounds. The combination of an outstanding biological activity and an intriguing chemical structure having no precedent in the field of antimalarials was the key factor to develop a synthetic route towards this novel natural product. *Artemisia Annua L.* has been found to contain approximately 8-10 times more artemisinic acid **2** than artemisinin **1**. Recently, Roth and Acton[6] have converted artemisinic acid **2** into artemisinin in two steps.



1 (+)-Artemisinin



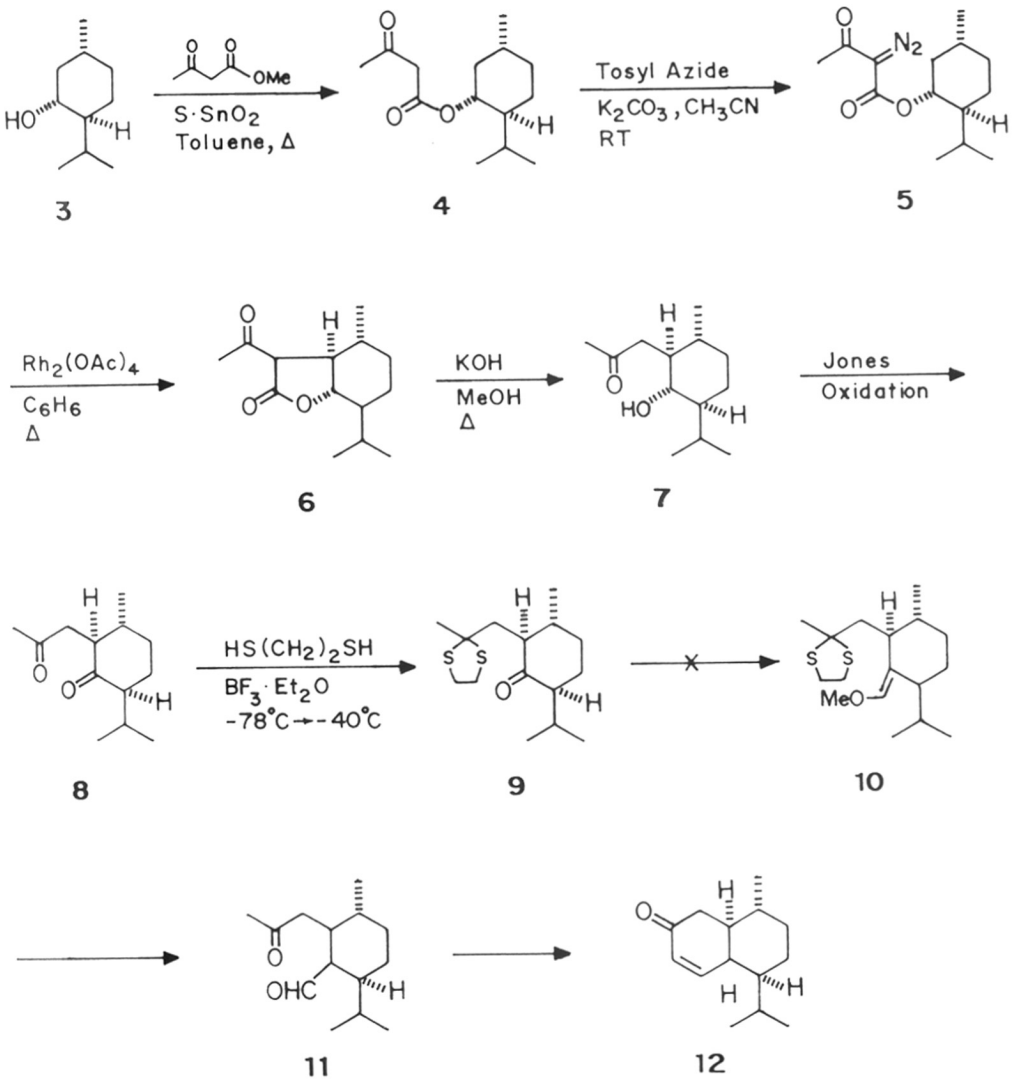
2 Artemisinic Acid

Artemisinin **1** could be synthesised by an intramolecular carbenoid C-H insertion approach (Route A) or an intramolecular ene reaction approaches (Route B) and (route C). The route A, B and C start with naturally occurring citronellal which is abundantly available in India.

Route-A : Intramolecular carbenoid C-H insertion approach :

The key reaction involves rhodium acetate catalysed decomposition of diazoesters **6** to form bicyclic-γ-lactone **6**. Lactone **6** incorporates methyl as well as isopropyl side chain in *trans*stereochemical disposition and trans ring fusion was well suited for conversion to dihydroartemisinic acid **2**. In order to study the feasibility of this route, studies were carried out on model scheme-2.1.

Scheme-2·1



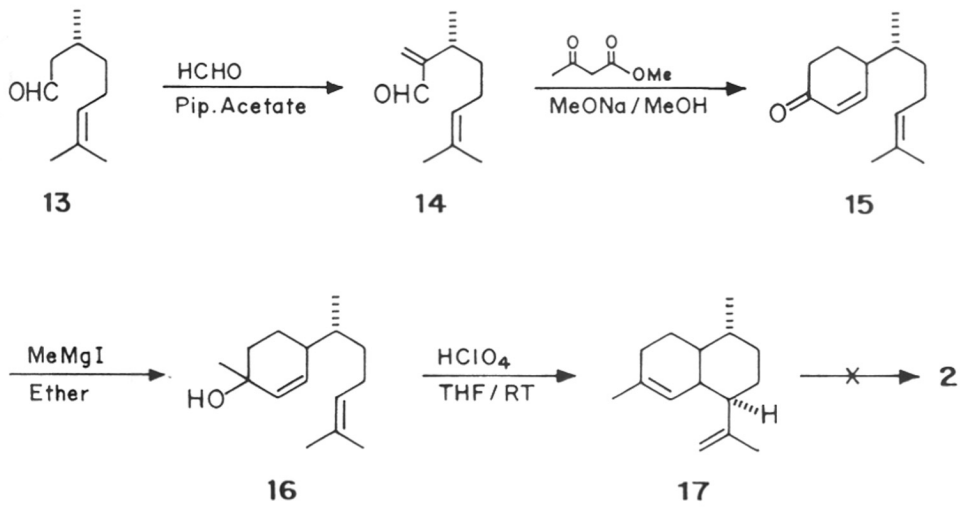
Methyl acetoacetate was treated with menthol **3** in presence of catalytic sulfated tin oxide in refluxing toluene to furnish transesterified ester **4** in excellent yield. Diazo compound **5** was prepared by diazo transfer reaction using tosyl azide. $Rh(OAc)_4$ catalysed decomposition azo compound **5** resulted in formation of bicyclic-γ-lactone **6** in 80% yield.

The hydrolysis of bicyclic-γ-lactone **6** followed by oxidation furnished the dione **8** in excellent yield. Selective protection of the side chain carbonyl group of dione with 1,2-ethanthiol furnished the protected compound **9** in good yields. All attempts for one carbon homologation by conventional methods like Wittig methoxymethylenation reaction, Wittig methylenation reaction, Grignard reaction, cyanohydrin formation, epoxidation reaction and Lambordo reaction were also unsucessful. The present study indicates that the carbonyl group was highly sterically hindered. To avoid the problem of steric hindrance many other synthetic transformations were attempted, without success are described in this section.

Route-B : Intramolecular Ene Reaction Approach :

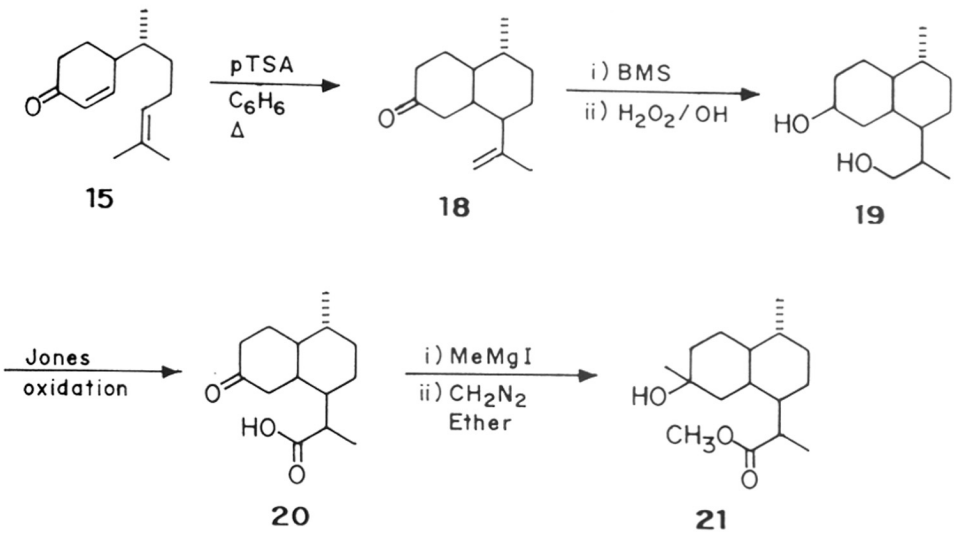
According to the plan, the key reaction involved is an intramolecular ene reaction of carbinol **16** to **17**. The carbinol **16** was prepared as shown in scheme-2.2.

Scheme-2·2



The carbinol **16** was treated with $HClO_4$ in THF at R.T. gave ene product **17**. Attempted regioselective conversion of isopropene unit into isopropionate unit by conventional methods like hydroboration by 9-BBN and SeO_2 allylic oxidation were unsuccessful.

In order to circumvent this problem following modification was attempted scheme 2.3.

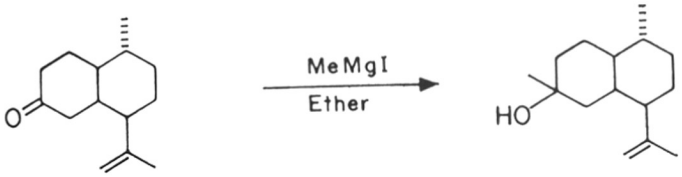


15 18 19 20 21

Here Key reaction involved is the intramolecular ene reaction of **15** to enone **18** and the conversion of isopropene unit to isopropionate by BMS complex. Intramolecular ene reaction of **15** gave enone **18** in good yield 80%. Hydroboration of enone **18** furnished the desired diol **19** in excellent yield 88%. Oxidation of **19** by Jones reagent afforded the keto acid **20** in 72% yield. Grignard reaction and esterification of **20** gave carbinol in 47% yield. Finally dehydration of **21** furnished the dihydro-artemisinate skeleton in 72% yield. All these reactions went very smoothly and mild conditions and in very good yields.

The resolution of enone **18** was achieved by nucleophillic addition reaction as shown in scheme-2.4.

Scheme-2·4

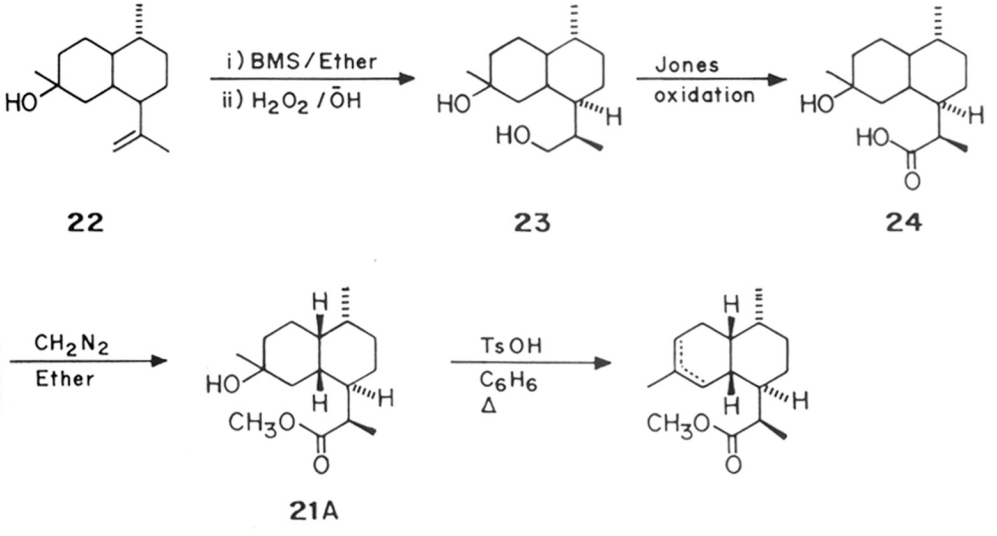


18 **22**

70 : 20 : 10

After Grignard reaction, three isomers were separated by column chromatography. The ratio of the three isomers was 70:20:10. The major isomer was converted to dihydroartemisinate as shown in scheme-2.5.

Scheme-2·5



22 **23** **24**

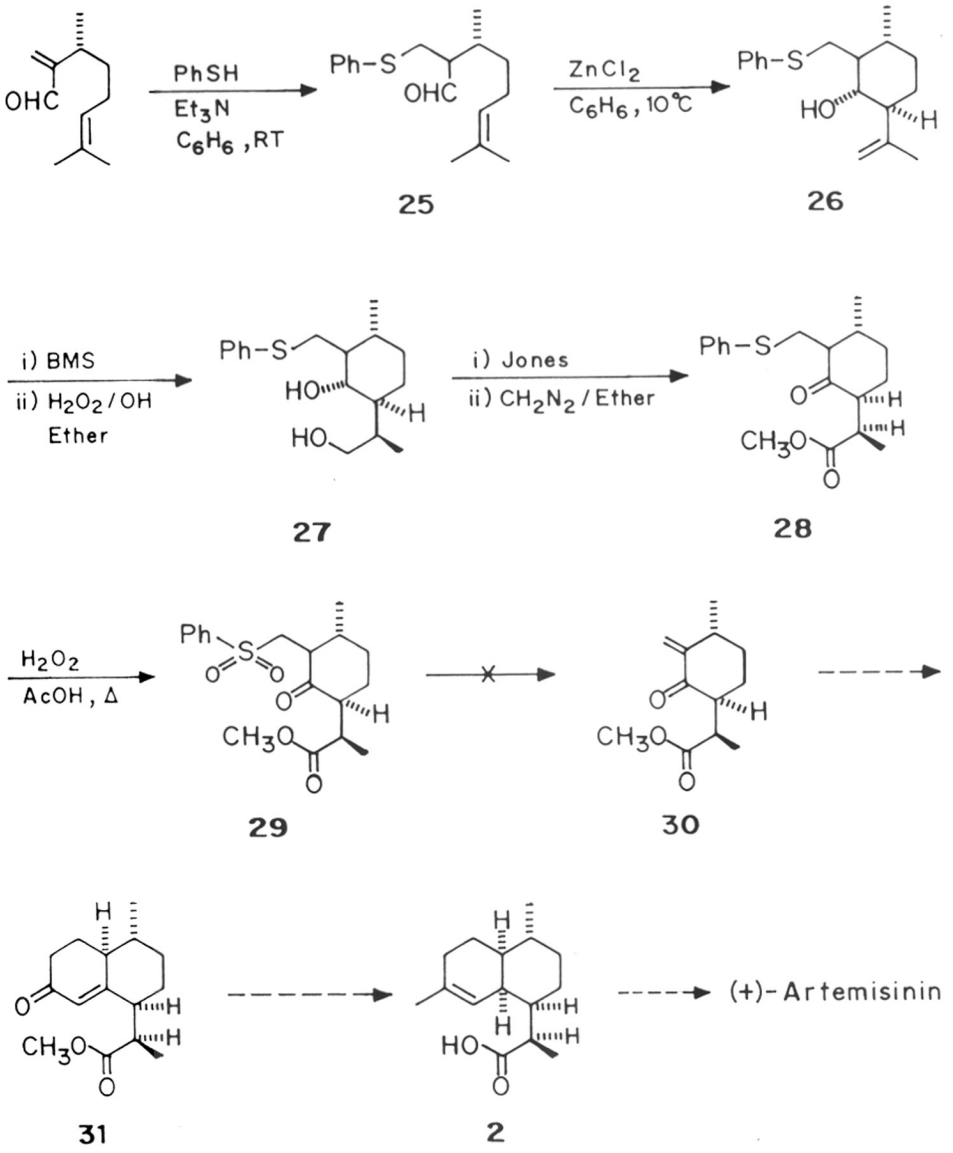
21A

Hydroboration of major isomer **22** furnished the diol **23** as a single diastereoisomer in 80% yield. Oxidation and esterification of diol **23** afforded the carbinol ester **21A** as a single diastereoisomer in 80% yield. The final of **21A** dehydration was achieved by refluxing in benzene in the presence of TsOH to furnish the dihydroartemisinate skeleton **2** in 72% yield as a mixture of regioisomers. The stereochemistry of the ring junction was confirmed to be cis by single crystal X-ray analysis, but unfortunately stereochemistry was the undesired one.

Route-C : Intramolecular Ene Reaction Approach :

According to the synthetic plan the key reaction involves an intramolecular ene rection of **25** to **26** based on the fact that an arylsulphonyl group is sufficiently good nucleofuge that an elimination reaction is possible under basic conditions as shown in scheme-2.6.

Scheme - 2·6

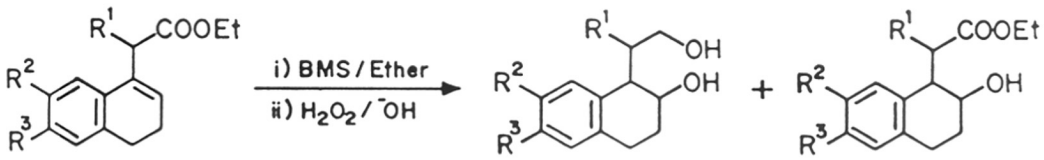


Aldehyde **25** was cyclized using $ZnCl_2$ to ene product **26** in good yield. Hydroboration of **26** gave diol **27** in excellent yield. The diol was converted to ketoester **28** in two steps. The oxidation of sulfur using H_2O_2/AcOH gave sulphone **29** in excellent yield. Attempts to convert the sulphone **29** to the α,ß-unsaturated ketone **30** has not been met with success so far.

CHAPTER-III : Assisted reduction of ß,γ-unsaturated esters by Boron Methyl Sulfide Complex

Normally esters are considered to undergo hydroboration very slowly at room temperature, even under reflux conditions.[7] This chapter describes a simple procedure which makes it possible the hydroboration of double bond followed by reduction of carboxylic ester with BMS complex at room temperature in very good yields shown in scheme 3.1.

Scheme-3·1



R^1 = -H, -Me, $-CH_2-CH_3$
R^2 = -H, -OH, -OMe
R^3 = H, -Me

Major Minor

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CHAPTER-I

Synthesis of Terpenic lactones and Furans

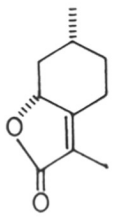
Section - 1 : A short and efficient Synthesis of (-)-Mintlactone and (+)-Isomintlactone

1.1.0 : Summary :

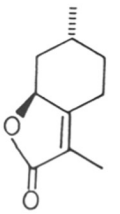
The present chapter concerns with the total stereoselective synthesis of (-)-mintlactone **1** and (+)-isomintlactone **2**. These monoterpenic compounds are minor components of commercially important flavouring essential oils like peppermint and spearmint oil. The short, convenient and highly stereoselective synthesis of (-)-mintlactone and (+)-isomintlactone has been achieved starting from a common precursor *viz* (-)-isopulegol.

1.1.1 : Introduction :

The essential oil of Mentha piperita L. (peppermint oil), one of the most important commercial flavouring materials, is produced in many countries. Its chemical composition has been thoroughly investigated. More than 300 components have been reported from the peppermint oil.



1



2

Among the minor constituents, the menthane derivatives (-)-mintlactone **1** and (+)-isomintlactone **2** were isolated by Takahashi et. al. from a sample of American peppermint oil in 1980.[1] The structure of the minor components was deduced and stereochemistry of **1** and **2** was established from spectroscopic data. Before their first description as natural products, the formation of these compounds in the course of synthetic processes[2-4] had been reported. Racemic **1** was also an intermediate in a total synthesis of menthofuran. These two monoterpenic compounds possess a butenolide moiety as the essential component.

1.1.2 : Synthesis of (-)-mintlactone and (+)-isomintlactone : Literature survey :

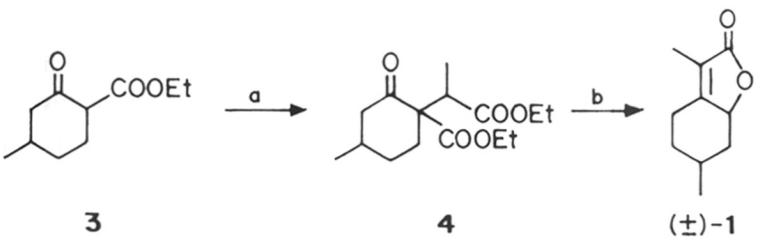
In order to provide an adequate background and to appreciate the problem involved in the synthesis, a brief survey of the reported racemic and optically pure synthesis of mintlactone and isomintlactone is presented.

Takeda's Approach[5] (Scheme - 1, 1980) :

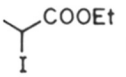
Takeda et. al. reported the first racemic synthesis of mintlactone as a precursor to menthofuran, one of the important aromatics. This synthesis comprises of 3 steps starting from 4-methyl-2-oxo-1-cyclohexane carboxylate **3**. Thus direct C-alkylation of **3** with 2-iodopropionate in DMF at 100°C gave the diester **4** in good yields. Hydrolysis of diester **4** with conc. HCl for 4 days at reflux temperature furnished the (±)-mintlactone **1** in 65% yields.

Although this route is short, it involves the use of strong base and reaction at elevated temperatures for extended periods of time.

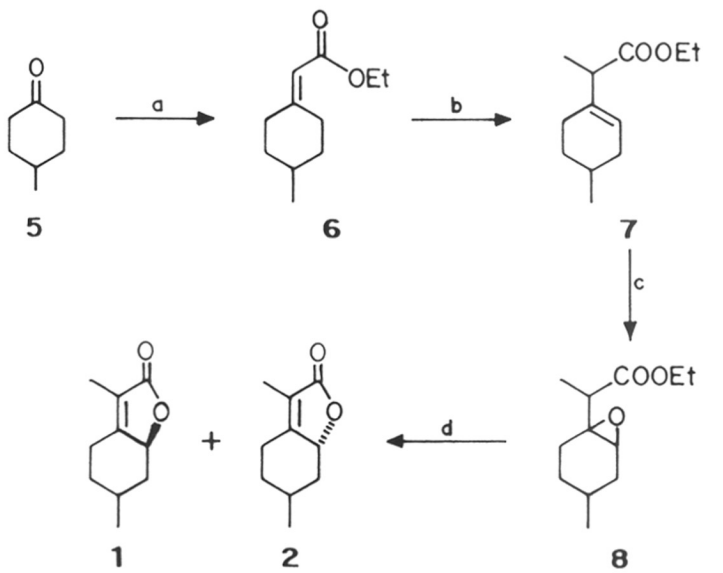
Scheme 1 (Takeda et.al. J. Org. Chem. 1980, 45, 1517)



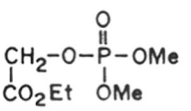
3 4 (±)-1

a:  , NaH, DMF, 100°C b: Conc. HCl, 4 days, Δ

Scheme 2 (Cory et. al, Tet. Lett. 1990, 31, 6789)



5 6 7 8 1 2

a:  , NaH b: LDA, MeI c: m-CPBA, CH_2Cl_2

d: LDA, HMPA, 18h

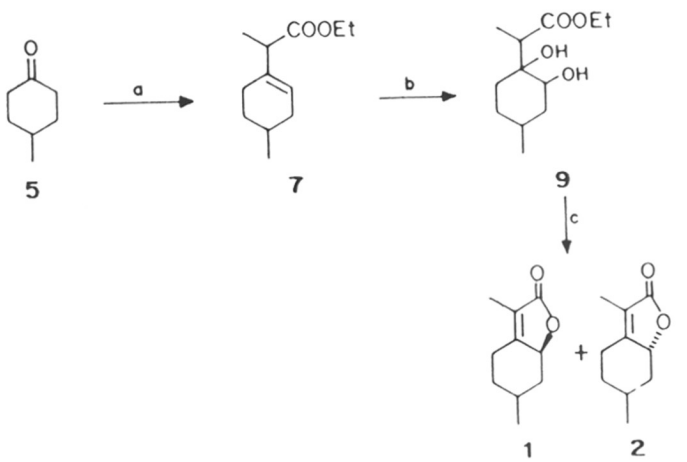
Cory's Approach[6] (Scheme - 2, 1990) :

Second racemic synthesis of mintlactone **1** was reported by Cory et. al. in 1990 employing a new methodology from 4-methyl cyclohexanone **5**. Thus, Wittig Horner reaction at ethyl-2(dimethylphosphono)acetate with 4-methyl cyclohexanone in benzene at 50°C afforded the α,ß-unsaturated ester **6** in 65% yield. Enolisation of the ester **6** with LDA and alkylation with methyl iodide yielded ß, Y-unsaturated ester **7** in 80% yield. Epoxidation of ester **7** with m-CPBA in CH_2Cl_2 furnished the epoxide **8** in 70% yield. Attempted acid catalysed rearrangement of epoxide **8** with trifluoroacetic acid gave a complex mixture of products. But the same reaction under basic conditions with LDA/HMPA (18 h, reflux) afforded a mixture of (±)-mintlactone and (±)-isomintlactone in the ratio of 10:1 in 68% yield. Presence of HMPA as the co-solvent is a perquisite for the success of this transformation. Although this route is novel, it involves the use of strong bases like NaH, LDA and stoichiometric amount of oxidant viz. m-CPBA. Moreover the conversion of **8** to **1/2** involves use of the strong base LDA in HMPA as the solvent at elevated temperatures for extended period.

Chavan's Approach[7] (Scheme - 3, 1992) :

Third racemic synthesis of (±)-mintlactone and (±)-isomintlactone by Chavan et. al. in 1992 employing a new methodology from 4-methylcyclohexanone **5**. Thus, 4-methyl cyclohexanone **5** when subjected to Reformatsky reaction furnished the corresponding alcohol, which on dehydration using thionyl chloride and pyridine furnished the ß,Y-unsaturated **7** in 72% overall yield. Catalytic dihydroxylation of **7** afforded **9** as a mixture of diastereoisomers.

Scheme 3 (Chavan et.al. Tet Lett. 1992, 33, 4605)



a: i) $\underset{Br}{\overset{COOEt}{\curlyvee}}$, Zn ii) $SOCl_2$, Py. b: OsO_4, NMO, CH_3CN

c: TsOH, C_6H_6, Δ

The conversion of diol **9** to butenolide was accomplished by refluxing it with pTSA in toluene (3 h) to afford (±)-mintlatone and (±)-isomintlactone in 80% yield as a mixture of diastereoisomers. This approach for butenolide synthesis is not only complementary to Cory's approach but superior in terms of yields, operational simplicity and efficiency.

Carda's Approach[8] (Schemes - 4 and 5, 1992) :

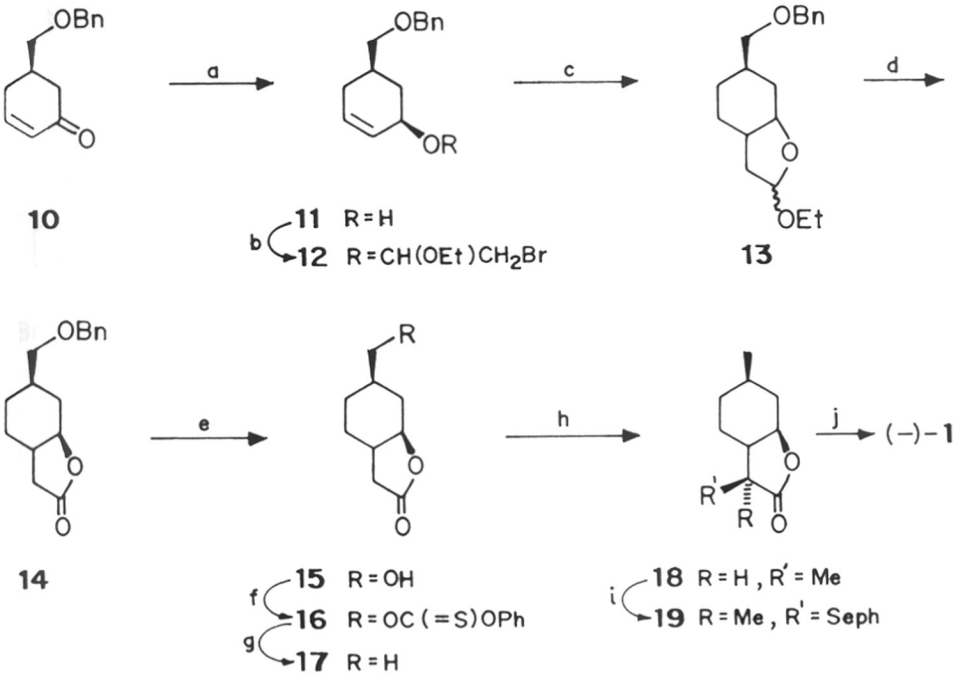
Carda et. al. reported the first stereoselective synthesis of (-)-mintlactone (+)-isomintlactone *via* intramolecular radical cyclisation as the key step in the synthesis. The chiral starting material enone **10** in turn was obtained by enzymatic hydrolysis in twelve steps. Hydride reduction of (-)-**10** gave allylic alcohol **11** which was then transformed into the bromo acetal **12** by reaction with NBS at -40°C in ethyl vinyl ether as the solvent. Tri-n-butyltin hydride promoted the ring closure under homolytic conditions to the acetal **13** as a diastereoisomeric mixture, which was then oxidised by Jones reagent to the stereochemically homogenous lactone **14**. Debenzylation to **15** was best performed by hydrogenolysis with $Pd(OH)_2$ as catalyst. Acylation of **15** with o-phenyl chlorothionoformate gave **16** which was then treated with tri-n-butyltin hydride and AIBN in refluxing toluene gave lactone **17**. Methylation of **17** *via* the enolate generated with LDA took place stereoselectively from the less hindered α-face, yielding **18** a dihydroderivative of (-)-mintlactone. Finally, dehydro selenation of **18** to **1** was performed in 33% overall yield *via* the phenylselenyl derivative **19**.

The synthesis of epimeric (+)-isomintlactone **2** was then executed alongside the same lines as **1** (Scheme - 5). Epimerization of cyclohexenol **11** was performed *via* Mitsunobu's procedure. This yielded the expected trans cyclohexanol **20** as the major product but also a small percentage of the *cis* isomer **21**. The authors carried out following steps with this isomeric mixture until lactone **24** which could be separated from its minor counterpart by HPLC. All the steps were performed in a way analogous to that in Scheme - 4 and proceeded with similar yields. The oxidative deselenation step furnished, however, not only the desired (+)-isomintlactone **2** but also its exocyclic double bond isomer **30**.

Thus first chiral synthesis of (-)-mintlactone & (+)-isomintlactone was achieved employing enzymatic resolution and radical cyclisation as the pivotal steps. However, the synthetic sequence is quite lengthy as well as suffers from the drawback of formation of unwanted isomer in appreciable amounts during formation of (+)isomintlactone.

Scheme 4 (Carda et. al . Tet. 1992 , 48 , 9789)

Synthesis of (-) – Mintlactone



a: $NaBH_4$, $CeCl_3$, EtOH, O°C b: NBS, excess EtO-CH=CH_2, -40°C

c: Bu_3SnH, AIBN, C_6H_6,Δ d: Jones Reagent e: H_2, $Pd(OH)_2$

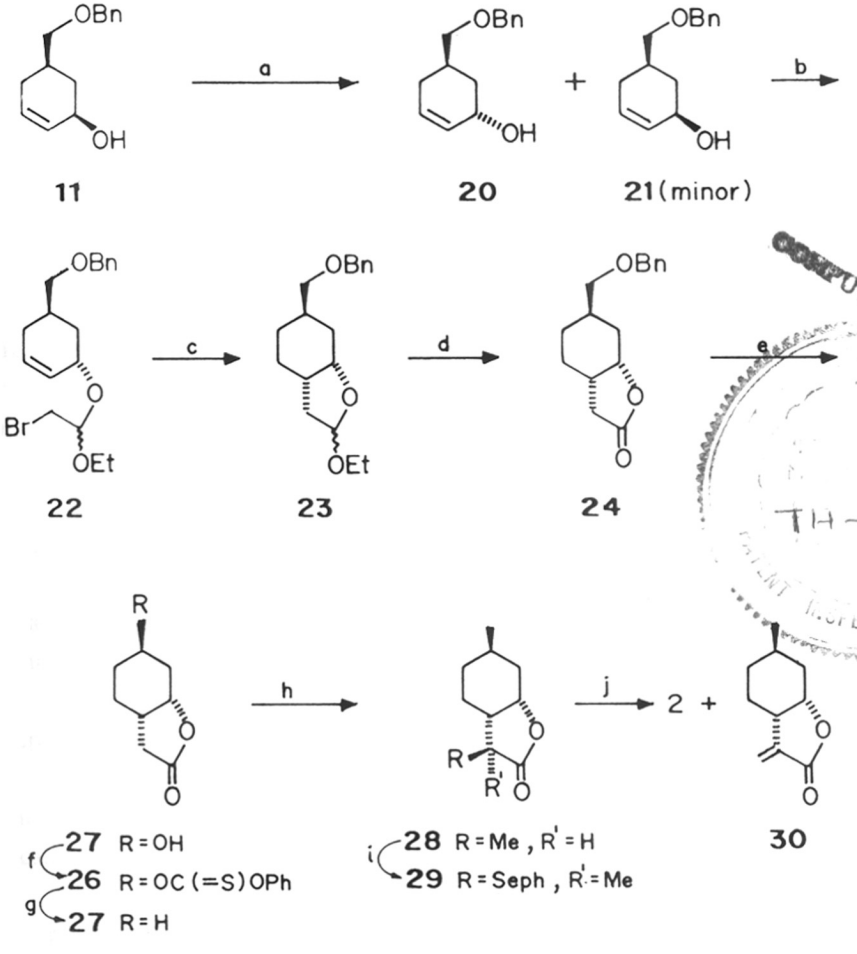
f: Cl-C(S)OPh, DMAP, MeCN, rt g: Bu_3SnH, AIBN, Tol, Δ

h: LDA, THF, -78°C,1h, then MeI, HMPA, THF, 1h at -78°Cto -50°C

i: LDA, THF, -78°Cthen PhSeCl, HMPA, THF, at -78°Cto -50°C

j: H_2O_2, THF, AcOH

Scheme-5 (Carda et. al. Tet. 1992, 48, 9789)
Synthesis of (+)-isomintlactone



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a: i) DEAD, PPh_3, PhCOOH, THF ii) NaOH, aq. MeOH

b: NBS, excess EtO-CH=CH_2, -40°C c: Bu_3SnH, AIBN, C_6H_6, Δ

d: Jones Reagent e: H_2, $Pd(OH)_2$ f: Cl-C(S)OPh, DMAP, MeCN, rt

g: Bu_3SnH, AIBN, Tol, h: LDA, THF, -78°C, 1h, then MeI, HMPA, THF, 1h

i: LDA, THF, -78°Cthen PhSeCl, HMPA, THF, at -78°Cand 40 min at -50°C

i· H_2O_2, THF, AcOH

RR
547-314·057(043)
DHO

Shishido's Approach[9] (Scheme - 6, 1992) :

Shishido and coworkers reported the second stereoselective synthesis of (-)-mintlactone and (+)-isomintlactone *via* a fused butenolide construction strategy based on an intramolecular [3+2] cycloaddition reaction of nitrile oxide. Thus, olefinic acetal **31** was ozonized and the resulting aldehyde was condensed with ethyl-2-(triphenylphosphoranylidene)propionate to unsaturated ester **32**. Acidic hydrolysis of **32** and subsequent oxime formation provided **33** in 57% yield. Treatment of **33** with 7% aqueous sodium hypochorite in CH_2Cl_2 at room temperature afforded a chromatographically separable diastereoisomeric mixture of isoxazolines **34** and **35** in a ratio of 20:1 in 84% yield. The key step was diasterioselective hydride reduction of the carbonyl group and subsequent assembly of fused butenolide. The treatment of **36** with tetramethylammoniumtriacetoxyborohydride in acetonitrile acetic acid at -40°C - room temperature for 6.5 h afforded corresponding 1,3-diol which was immediately treated with catalytic amount of pTSA to provide the hydroxylactones **38** and **39** in 88% yield as an easily separable mixture of diastereoisomers in ratio 30:1. Dehydration of **38** with phosphorous oxychloride in pyridine furnished the (-)-mintlactone in 92% yield. The minor isomer **39** was converted into (+)-isomintlactone in 93% yield. Synthesis of (+)-isomintlactone was achieved in better yield by treatment of **36** with zinc borohydride in ether at 0°C for 5 min. followed by acidic treatment to give a more favourable ratio of diastereoisomeric lactones **39** and **38** (6:1) in 47% yield.

Thus a 10 steps synthetic sequence involving intramolecular [3+2] nitrone cycloaddition as the key step has been established. The same intermediates could be converted to either (-)-mintlactone or (+)-isomintlactone efficiently.

Crisp's Approach[10] (Scheme - 7, 1995) :

After publication of present work Crisp *et. al.* reported the fourth (The third synthesis is ours) stereoselective synthesis of (-)-mintlactone **1**. The route is based on the synthesis of optically pure γ-butyrolactones using a combination of baker's yeast reductions of α-ketoesters to provide the chiral alcohol, trapping of a kinetic enolate by N-phenyltriflimide to provide vinyl triflate and a palladium catalysed carbonylation to assemble the γ-butyrolactone.

Thus, (±)-4-methyl-2-cyclohexanone-1-carboxylate **40** was reduced with baker's yeast to afford α-hydroxy ester (-)-**41** in 44% yield and 50% starting unreacted ester was recovered. α-Hydroxy ester (-)-**41** was initially protected as the tert-butyldimethylsilylether to afford **42** in 61% yield. DIBAL-H reduction of **42** to the corresponding aldehyde was not clean some ester remained unreacted and could not be separated from desired alcohol. Aldehyde ester mixture was subjected to Grignard reaction to form alcohols **45** as a diastereoisomeric mixture. Subsequent oxidation of the alcohol unit yielded methyl ketone **46** in 74% yield.

Regioselective triflation produced vinyl triflate **47** in excellent yield and followed by

palladium mediated carbomethoxylation affording acrylate **48** in 57% yield. Quantitative lactonization to **49** was followed by a rhodium-catalyzed double bond isomerization to yield (+)-mintlactone.

Although the synthesis of 9 steps from **40**, overall yield is low and it involves use of expensive and toxic reagents.

1.1.3 : Present work :

The present chapter primarily concerns with the stereoselective synthesis of (-)-mintlactone and (+)-isomintlactone, minor components found in commercially important flavouring essential oils such as peppermint oil and spearmint oil. Interest in butenolides has led to development of a general methodology for butenolides synthesis and synthesis of (+) mintlactone and (-) isomintlactone.[7,11]

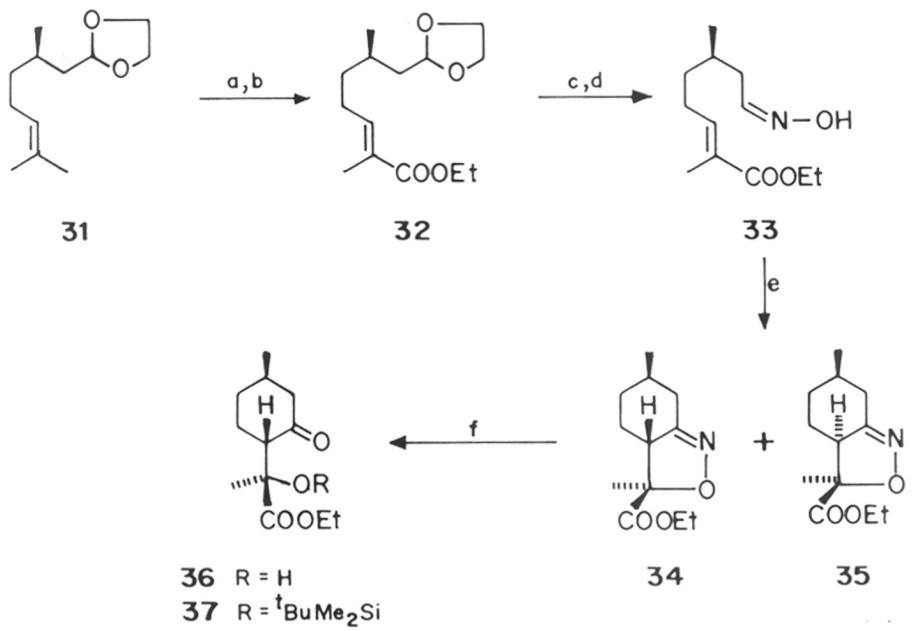
When the present work was under taken in 1992, there was no report on the synthesis of optically pure **1** and **2** following its isolation by Takahashi et. al. in 1980.[1] During the course of development of butenolide methodology, Carda et. al.[8] reported the first stereoselective synthesis of (-)-mintlactone **1** and (+)-isomintlactone **2** *via* intramolecular radical cyclisation as the key step comprising of more than twelve steps. The chiral starting material in turn was obtained by enzymatic hydrolysis in twelve steps. Later, Shishido et. al.[9] have also reported the total synthesis of (-)-**1** and (+)-**2** involving an intramolecular [3+2] cycloaddition reaction to generate the butenolides as the key step comprising more than ten steps. The present work describes very short (4 and 6 steps) and highly convenient stereoselective synthesis of (-)-**1** and (+)-**2** from (-)-isopulegol a common starting material which is superior to Carda's approach (12 steps) and Shishido's approach (10 steps).

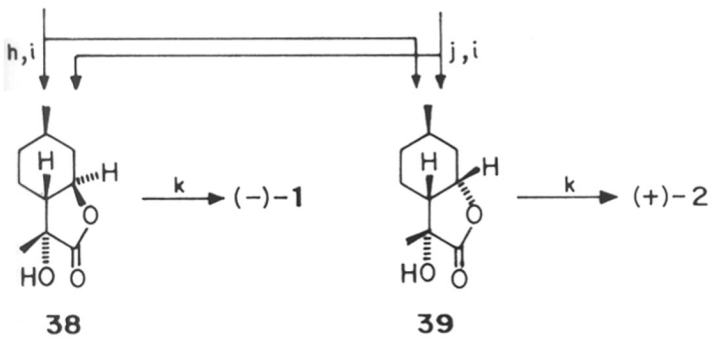
1.1.4 : Results and Discussions :

The present strategy (**scheme - 8**) was to convert the triols **51** and **55** into hydroxylactones **52** and **56** and then dehydration to (-)-mintlactone **1** and (+)-iso-mintlactone **2**.

The osmylation[20] of (-)-isopulegol **50** furnished the desired triol **51** in excellent yield 88%. The IR spectrum of triol **51** showed absorption at 3050-3350 cm^{-1} for the hydroxyl groups. The ^{1}H-NMR spectrum showed disappearance of signals at δ 4.9 (m, 2H) and δ 1.6 (s, 3H) of olefinic protons and methyl protons while appearance of signals at δ 3.8-3.9 (m, 2H) and δ 1.2 (d, 3H) for -$\underline{CH_2}$-OH and ethyl protons. M^+ at 188 (10%) and fragmentations observed in the mass spectrum confirmed the assigned structure as **51**. Selective oxidation of primary alcohol in **51** & **55** in preference to the secondary alcohol with Ag_2CO_3/celite in refluxing benzene failed to furnish the desired lactones **52** and **56**. It gave the corresponding

Scheme-6 (Shishido et. al. Tet. Lett. 1992, 4589)



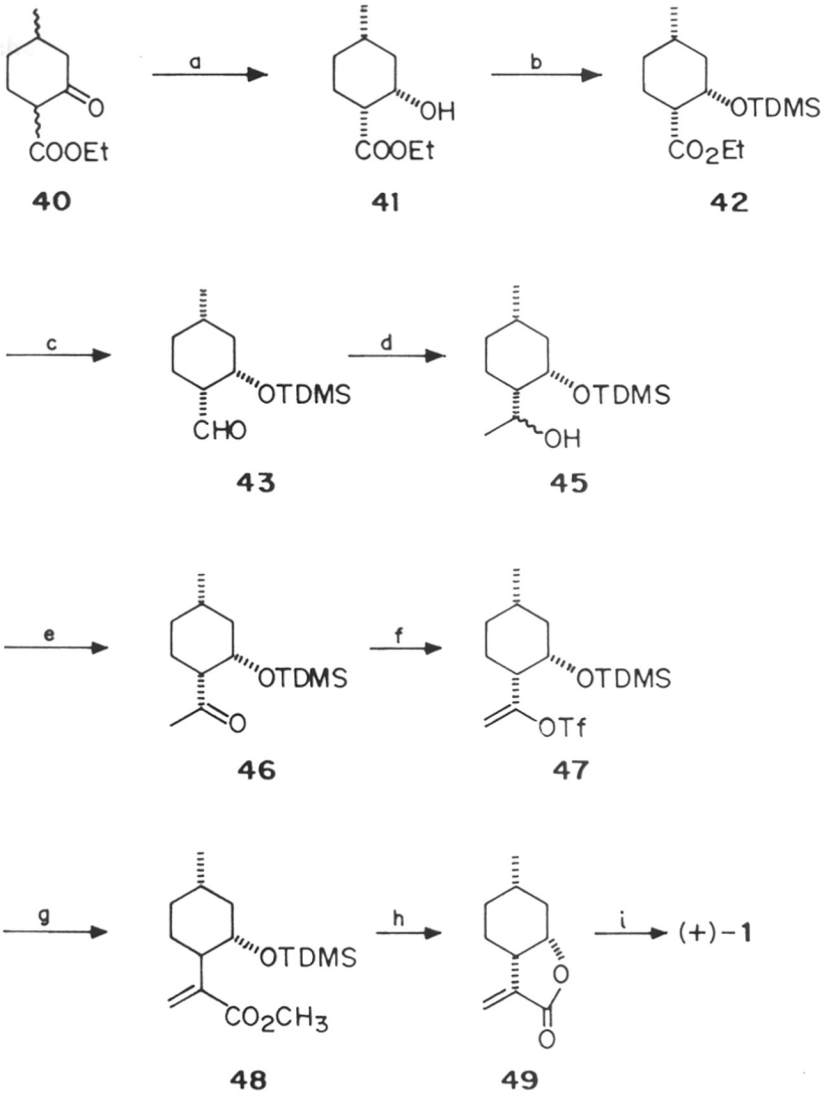


a: O_3, Me_2S b: $Ph_3P{=}C(Me)COOEt$ c: 5% HCl d: $NH_2.OH.HCl$, AcONa

e: 7% NaOCl f: H_2, Raney Ni, $B(OMe_3)$ g: t-$BuMe_2SiOTf$, 2,6-lutidine

h: $Me_4NBH(OAc)_3$ i: p-TsOH j: $Zn(BH_4)_2$ k: $POCl_3$, Pyridine

Scheme-7 (Crisp et.al, Tet. 1995, 51, 5831)



a: Baker's Yeast, Sucrose, H_2O, $MgSO_4$, KH_2SO_4, $CaCO_3$, 35°C,5 days

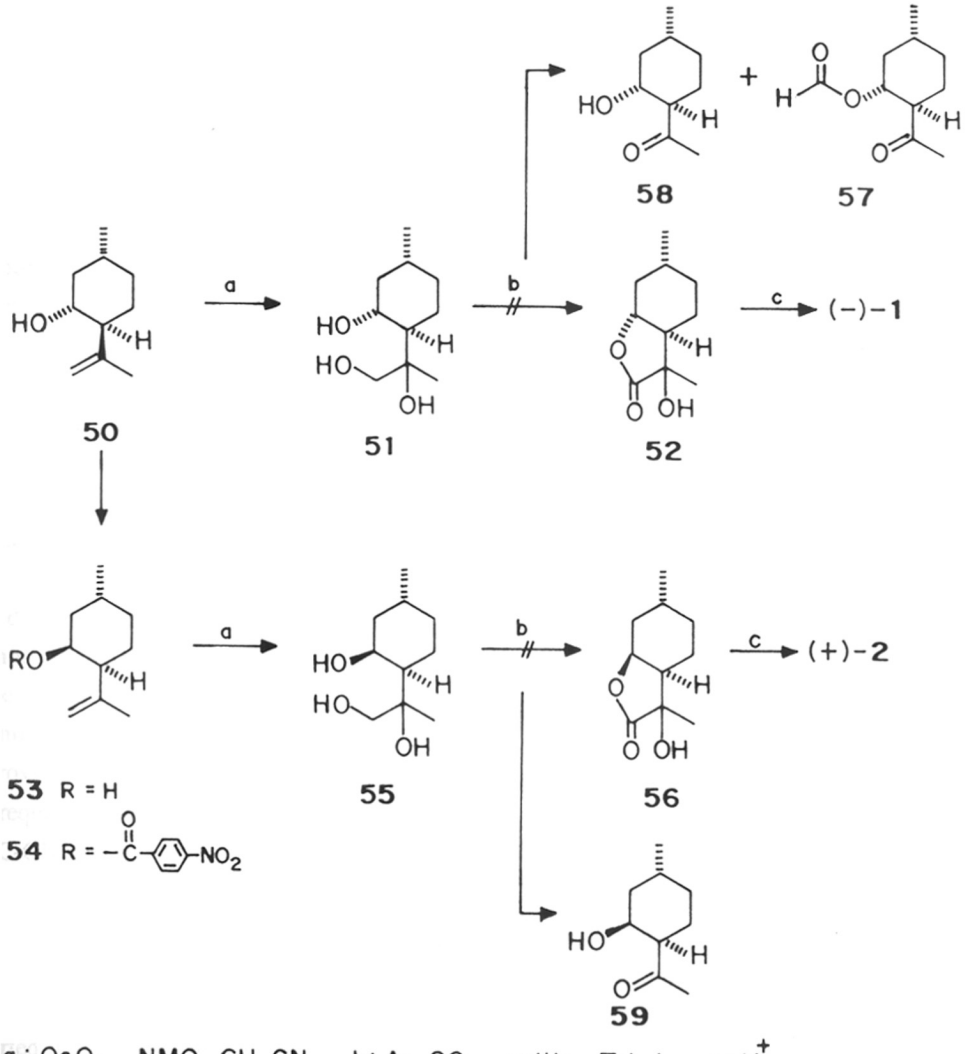
b: TDMSCl, DMF, imidazole, rt c: DIBAL-H, -78°C d: MeMgI, H^+

e: PCC f: i) KHMDS, THF ii) Tf_2NPh

g: $Pd(PPh_3)_4$, CO(1atm), CH_3OH, n-Bu_3N, CH_3CN

h: TFA, CH_2Cl_2, rt i: $HRh(PPh_3)_3CO$

Scheme-8


HO
H
50
a
HO
HO
OH
51
b
58
+
O
H
O
57
O
OH
52
c
(-)-1
RO
53 R = H
54 R = -C(=O)-C6H4-NO2
55
56
(+)-2
59
a : OsO4 , NMO , CH3CN
b : Ag2CO3 , celite , Tol. Δ
c : H+

1,2-diol cleavage products **57**, **58**, and **59** in 70% yield. The keto alcohol **58** was fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy (**Fig.1**). The IR spectrum displayed absorption at 3550 and 1710 cm^{-1} for the hydroxy and carbonyl functionalities respectively. ^{1}H-NMR spectrum showed disappearance of signals at δ 3.8-3.9 (m, 2H) and δ 1.2 (d, 3H, J = 4.4 Hz) while appearance of signals at δ 2.1 (s, 3H) was indicative of acetyl group. The mass spectrum exhibited M^+ at 156 (10%). The ^{13}C-NMR showed 9 signals corresponding to 9 carbon atoms among them 213.32 (s) and 70.75 (d) was characteristic of carbonyl carbon and secondary alcohol bearing carbon.

IR spectrum of **57** showed absorption at 1710 cm^{-1} and 1730 cm^{-1} indicating that the presence of ketone carbonyl and ester carbonyl groups. In the ^{1}H-NMR spectrum (**Fig.2**), signals at δ 7.9 (s, H) for aldehydic proton. In the ^{13}C-NMR analysis signals at 208.69 (s), 160.04 (d) and 73.04 (d) could be accounted for ketone carbonyl carbon, aldehyde carbonyl carbon and CH-O carbon. Further confirmation of the structure was obtained from mass spectral data which revealed M^+ peak at 184 (4%).

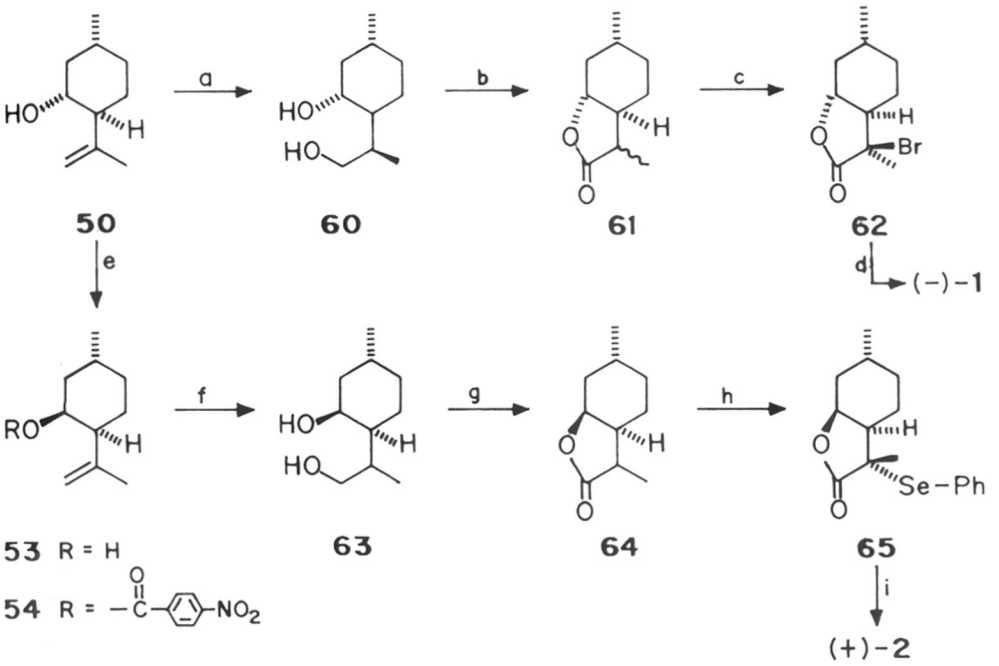
IR spectrum of **59** showed absorption at 3500 cm^{-1} and 1710 cm^{-1} indicating the presence of hydroxy and ketone groups. The ^{1}H-NMR spectrum showed disappearance of signals at δ 3.8-3.9 (m, 2H) and δ 1.2 (d, 3H, J = 4.4 Hz) of -$\underline{CH_2}$O and methyl protons while appearance of signals at δ 2.1 (s, 3H) of acetyl group. THe ^{13}C-NMR showed a signals corresponding 9 carbons among them 208 (s) and 66.55 (d) responsible for carbonyl carbon and secondary alcohol bearing carbon. Mass spectrum of **59** exhibited M^+ at 156 (4%).

In an another approach (**Scheme - 9**) The strategy was to obtain dihydromintlactone **61** and dihydroisomintlactone **64**, which inturn could be prepared from (-)-isopulegol **50** as the common starting material and introduce the double bonds to furnish (-)-**1** and (+)-**2** respectively. It was realised that (-)-isopulegol **50** would be an ideal starting material for both (-)-mintlactone **1** as well as (+)-isomintlactone **2** as it incorporates a methyl as well as a hydroxy group in a *cis* stereochemical disposition, well suited for conversion to (-)-**1** whereas, the required *trans*-stereochemistry for (+)-**2** could be easily obtained by a simple inversion at the C-OH centre.

Hydroboration[13] of isopulegol **50** furnished the desired diol **60** in excellent yield (98%) as a viscous liquid. The diol **60** was characterized by ^{1}H-NMR and optical rotation. The spectral data of diol **60** was found to be identical in all respects to the data reported in the literature[13]. The optical rotation $[\alpha]_D$ = -17° (c = 5.8, $CHCl_3$) is in good agreement to that reported in literature $[\alpha]_D$ = -18°.

The 1,4-diol **60** thus obtained was smoothly transformed to the butyrolactone **61** using Ag_2CO_3/celite[14] in high yields (83%) as a mixture of diastereoisomers (88:12), $[\alpha]_D$ = + 63.3° (c = 11.7, $CHCl_3$). The structural assignment of **61** was based on its IR, ^{1}H-NMR ^{13}C-NMR and Mass spectroscopy (**Fig.3**).

Scheme-9



a: i) BMS ii) H_2O_2, ^-OH b: Ag_2CO_3, Celite, C_6H_6,

c: i) LDA, -78°C ii) NBS d: DBU, C_6H_6, Δ

e: Ph_3P, DEAD, $4NO_2$-Ph-COOH ii) MeOH, MeONa

f: Ag_2CO_3, Celite, Tol, Δ g: LDA, -78°C, $(PhSe)_2$

h: H_2O_2, AcOH

The IR spectrum of **61** showed disappearance of hydroxyl groups while absorption at 3350 cm^{-1} and at 1770 cm^{-1} confirmed the presence of the five membered lactone functionality. In the ^{1}H-NMR spectrum the protons on the carbon bearing oxygen atom of the lactone appeared at δ 4.05 (ddd, 1H, J = 3.78, 11.1 Hz) while disappearance of signal at δ 3.7 (m, 2H) which was responsible for -$\underline{CH_2}$OH protons also confirmed the formation of lactone. ^{13}C-NMR showed 10 signals correspoding to the 10 carbons. The mass spectrum showed M^+ at 168 (7%).

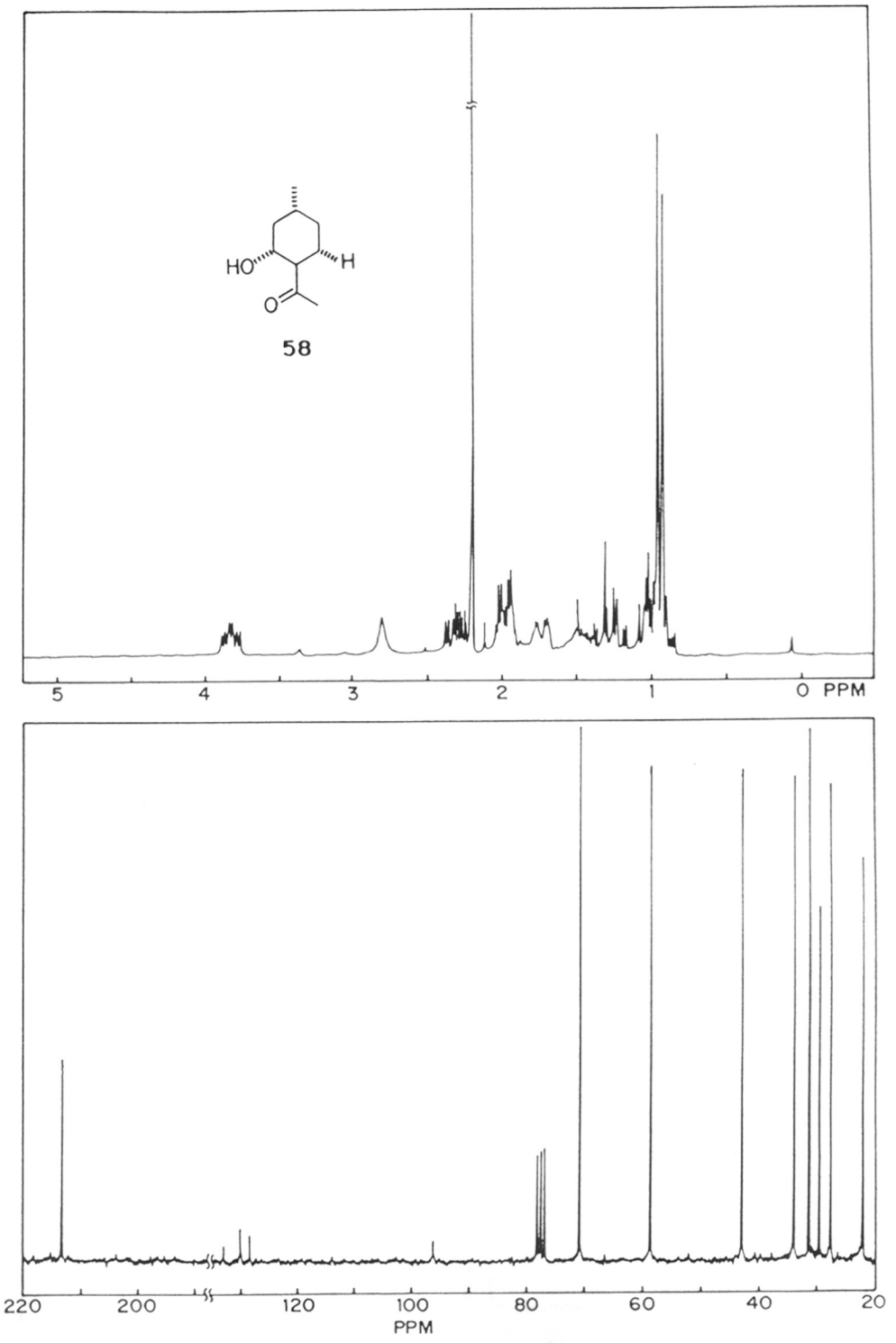


FIG. 1

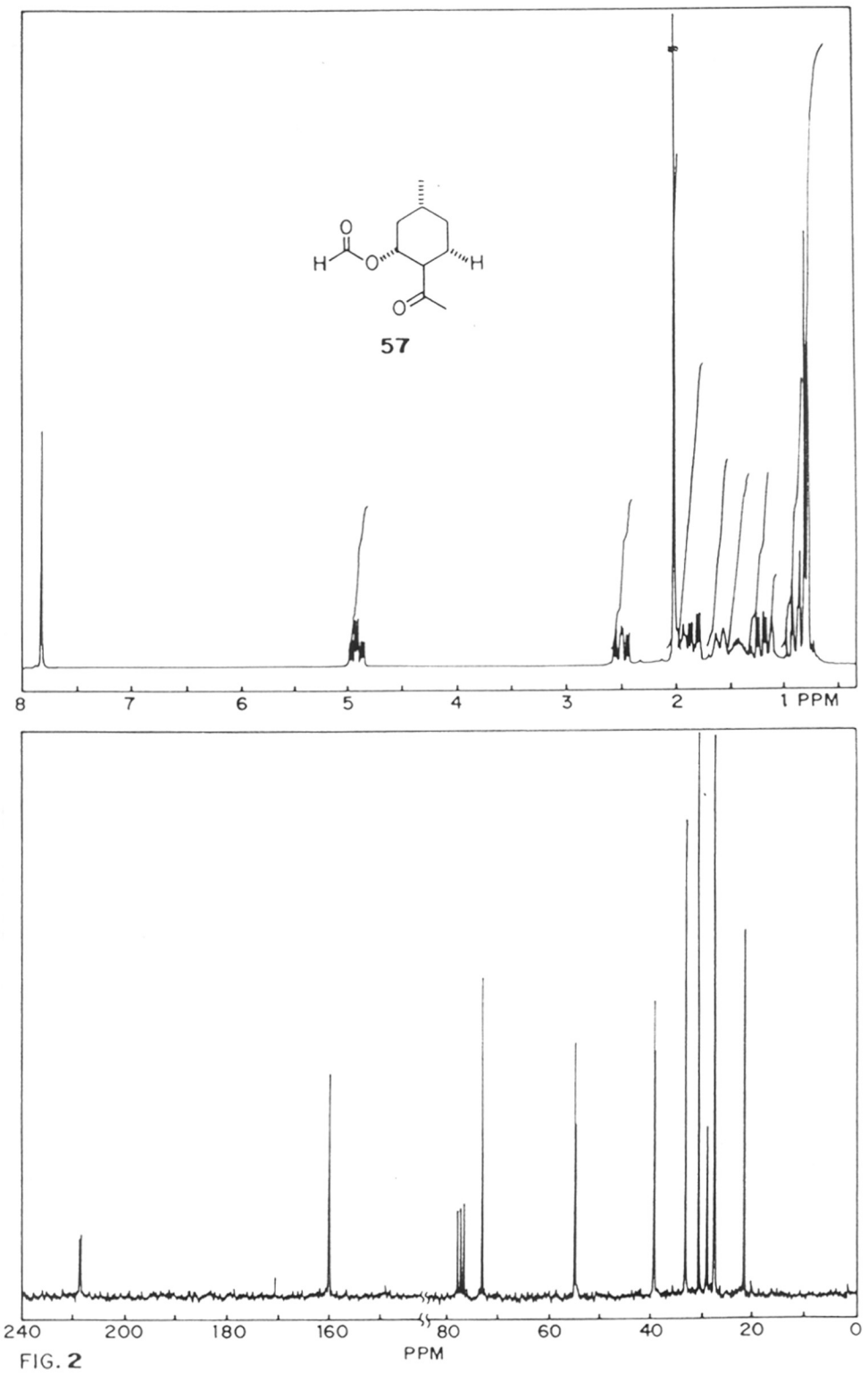


FIG. 2

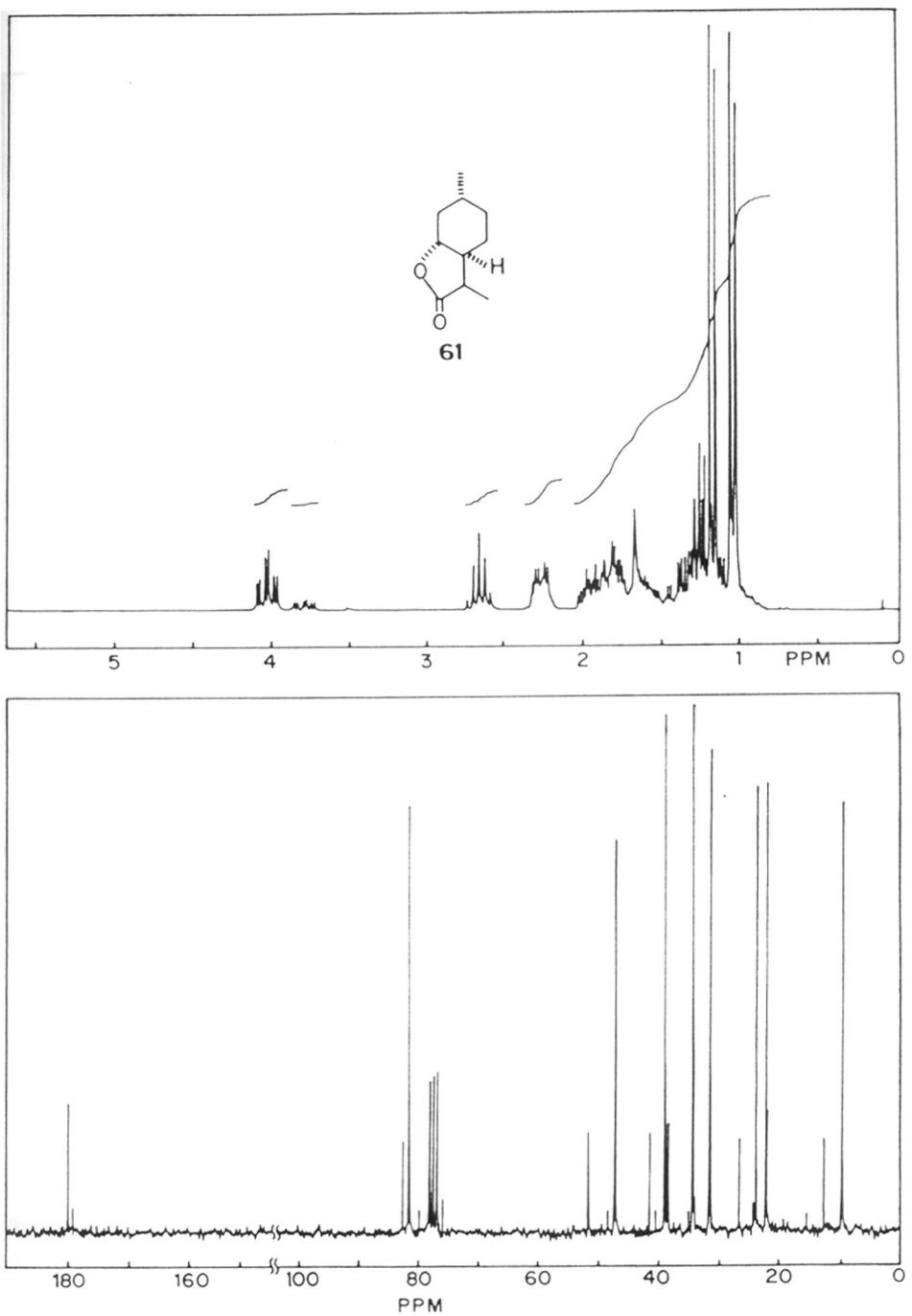


FIG.3

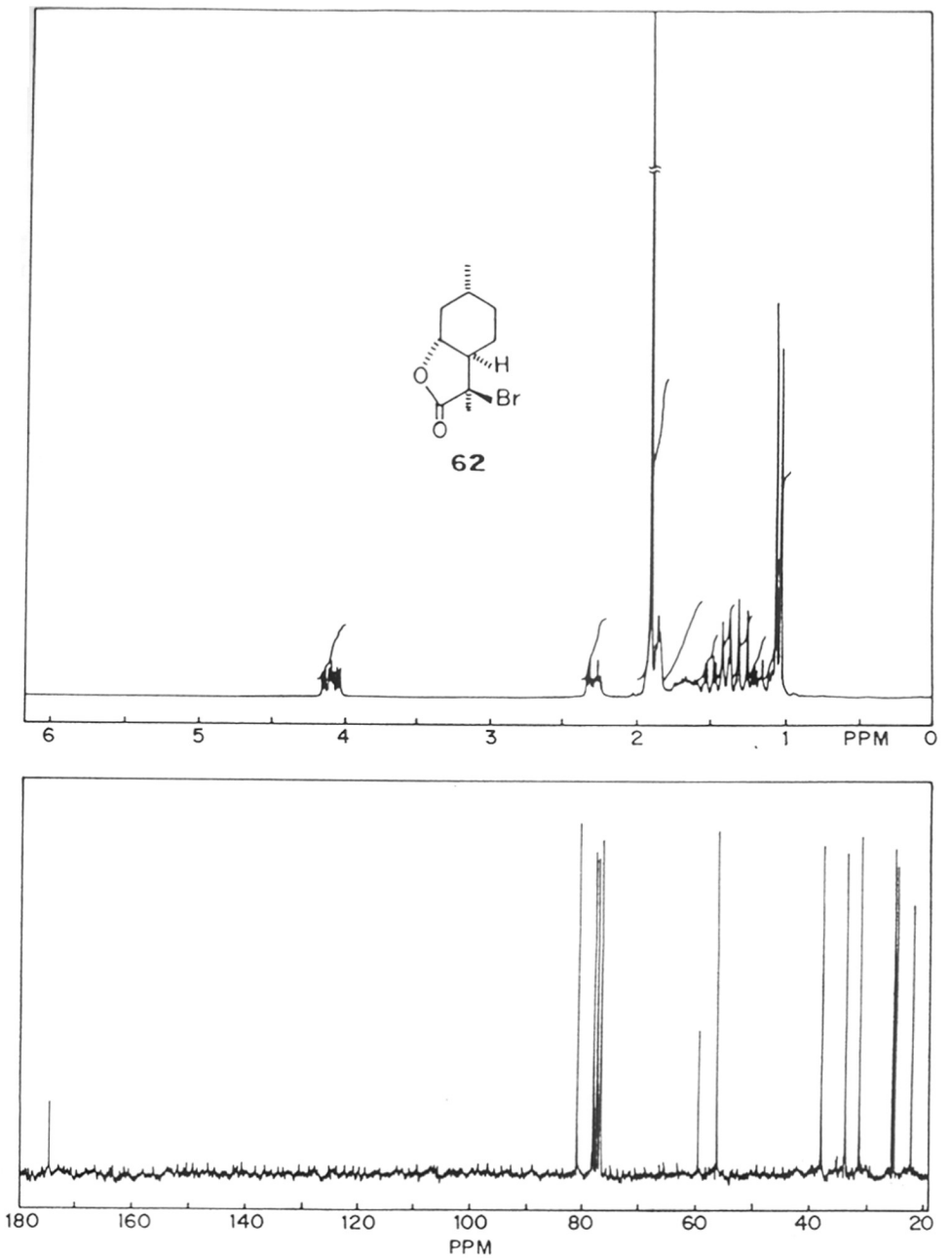


FIG. 4

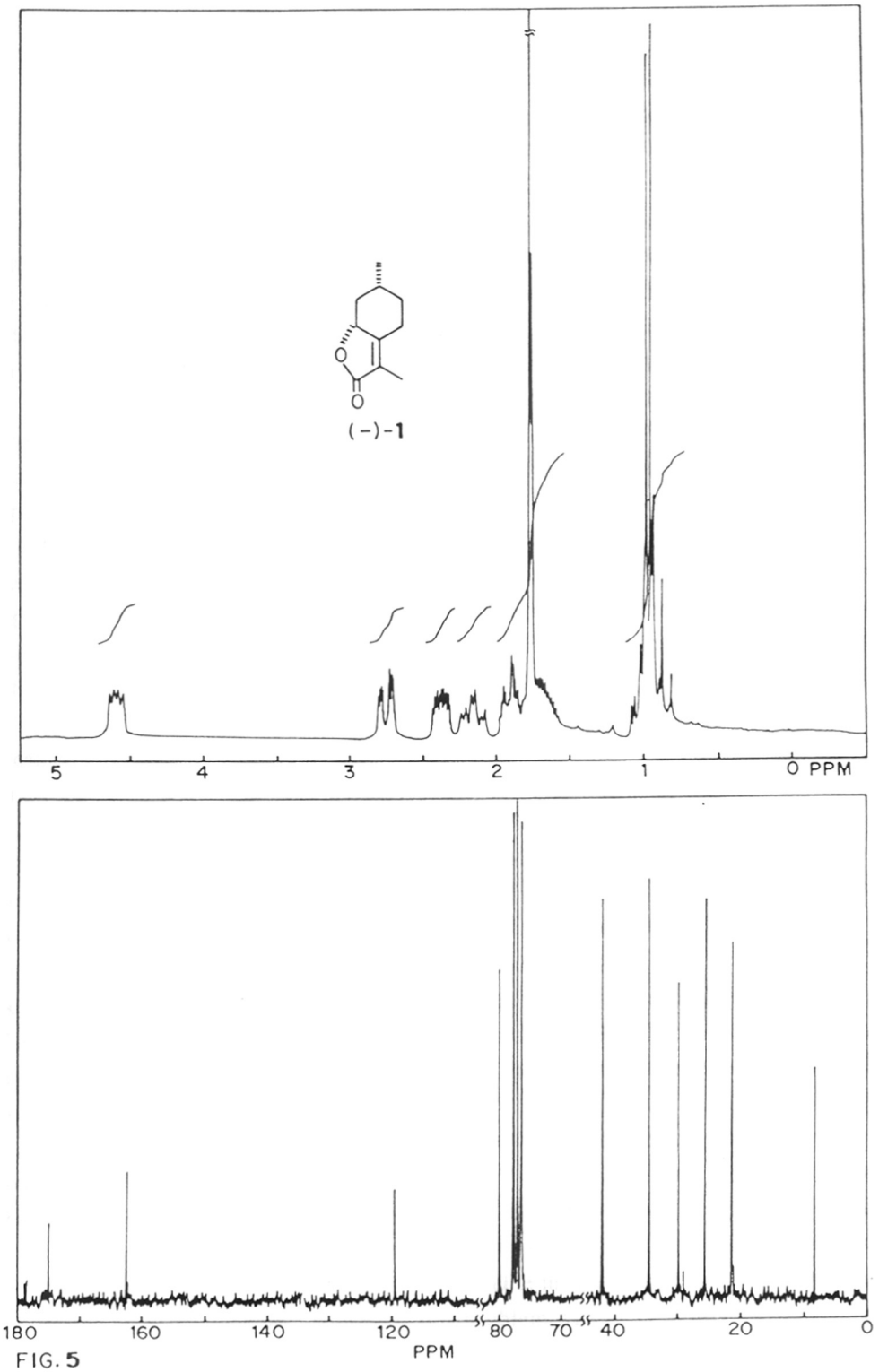


FIG. 5

Having constructed dihydromintlactone **61**, the next task was to introduce the double bond. This was accomplished as follows. Treatment of butyrolactone **61** with LDA at -78°C and subsequent treatment of resultant enolate with chlorotrimethyl silane and NBS[15] in one pot furnished the bromolactone **62** in 95% yield as a colourless solid. M.P. = 107-110°C, $[\alpha]_D$ = + 16.8° (c = 1.5, $CHCl_3$). The structure of bromolactone **62** was fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy (**Fig.4**). IR spectrum showed absorption at 1780 cm^{-1} for five membered lactone ring. ^{1}H-NMR spectrum showed disappearance of signal at δ 1.25 (d, 3H, J = 6.4 Hz) and appearance of a new signal at δ 1.95 (s, 3H) for the methyl protons. ^{13}C-NMR interpretation indicated singlet at 174.5 (s) and 80.7 (s) for carbonyl group and bromo carbon. Mass spectral analysis confirmed the assigned structure **62** (247, M^+).

The final dehydrohalogenation of bromolactone **62** was smoothly achieved by refluxing in benzene in presence of DBU[16] to furnish the (-)-mintlactone **1** in 76% yield. The spectral data and physical data of (-)-mintlactone **1** thus obtained were found to be identical in all respects with the data reported in literature[1,8] for natural **1**. Additionally the optical purity of (-) **1** was also confirmed by GC analysis on chiralsel val. column. The IR spectrum showed a strong absorption at 1760 cm^{-1} which is characteristic of butenolide moiety. ^{1}H-NMR spectrum (**Fig.5**) besides showing the expected signal for the compound was conspicous by the presence of a signal at δ 4.66 (dd, 1H, J = 6.0, 11.0 Hz) for the methine proton, on the carbon bearing lactone oxygen atom (-CH-O). ^{13}C-NMR spectrum displayed 10 signals for the presence of 10 carbons and in particular the signals at 174.86 (s), 162.62 (s) and 119.85 (s) for the presence of carbonyl and α,ß-unsaturated double bond confirmed the structure of (-)-mintlactone. The optical rotation was found to be $[\alpha]_D$ = -56.6° (c = 2·2, EtOH), lit.[1,8] $[\alpha]_D$ = -51.8° (c=10, EtOH). The mass spectrum showed occurrence of M^+ at 166 (100%).

The synthesis of the epimeric (+)-isomintlactone **2** was then executed alongside the same lines as (-)-**1**. The stereochemistry at C-OH centre was inverted by employing a modified Mitsunobu conditions.[17] Thus (+)-neo-isopulegol **53** was obtained from (-)-isopulegol **50** through its 4-nitrobenzoate **54** followed by hydrolysis in 83% overall yield. IR spectrum of 4-nitrobenzoate **54** presented absorption at 1750 cm^{-1} thus confirming the presence of ester group. ^{1}H-NMR analysis of **54** revealed multiplet at δ 8.1 for four aromatic protons and shift of signal from δ 3.5 (td, 1H) for -CH-OCOAr proton. Mass spectrum (M^+, 303) confirmed the assigned structure.

Having obtained (+)-neoisopulegol **53** with desired stereochemistry as required in (+)-isomintlactone **2**. It was subjected to hydroboration[13] to furnish the diol **63** in excellent yield (98%). The spectral data and optical rotation of diol **63** was found to be identical in all respects to the data reported in the literature.[13] Selective oxidation of primary alcohol in preference to the secondary alcohol with Ag_2CO_3/celite in refluxing benzene failed to furnish the desired butyrolactone **64**. However, this problem was successfully circumvented by

performing the reaction at elevated temperature employing toluene as the solvent and under these conditions the lactone **64** was obtained in 70% yield. m.p. = 41-45°C, $[\alpha]_D$ = -36° (c = 2.6, $CHCl_3$). The structure of the butyrolactone **64** was fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy (**Fig.6**). IR spectrum showed disappearance of alcohol absorption at 3350 cm^{-1} while absorption at 1770 cm^{-1} carbonyl confirmed the presence of 5-membered lactone functionality. ^{1}H-NMR spectrum of **64** showed following features at δ 4.7 (dd, 1H, J= 3.4, 7.0 Hz) for methine proton, on the carbon bearing lactone oxygen (-CH-O). ^{13}C-NMR showed 10 signals corresponding to the 10 carbons. The mass spectrum exhibited M^+ peak at 168 (2%).

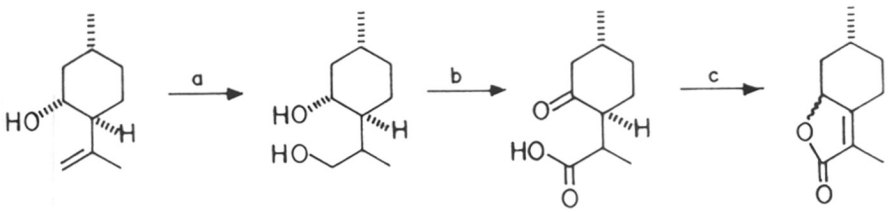
Having constructed dihydroisomintlactone **64** the next task was to introduce the double bond. To introduce the double bond. in **64** a different strategy that employed for (-)-mintlactone **1** had to be adopted. Thus, treatment of **64** with LDA followed by quenching the anion with diphenyl diselenide furnished the selenolactone **65** as a colourless soild. m.p. = 140°C $[\alpha]_D$ = + 40.5° (c = 2.2, $CHCl_3$). The structure was confirmed by the analysis of IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy (**Fig.7**). IR spectrum showed absorption at 1770 cm^{-1} characteristic of five membered lactone ring. In the ^{1}H-NMR spectrum, disappearance of signal at δ 1.3 (d, 3H), corresponding to the methyl group and appearance of new signals at δ 1.55 (s, 3H) for methyl protons and δ 7.7-7.3 (m), for aromatic protons. ^{13}C-NMR showed 16 signals corresponding to 16 carbons among them signals at 129.87 (d), 129.26 (d), 138.19 (s) responsible for the aromatic carbons. The mass spectrum was in agreement with the structure (M^+, 323, 64%).

The oxidative deselenylation of **65** with H_2O_2[18,19] furnished the (+)-isomintlactone **2** as a colourless solid in 73% yield. m.p. = 78-79°C. The IR spectrum of **2** showed absorption at 1760 cm^{-1} and 1690 cm^{-1} for the carbonyl group and double bond of butenolide. In the ^{1}H-NMR spectrum (**Fig.8**), the proton on the carbon bearing oxygen atom of the lactone appeared at δ 4.8 (dd, 1H, J = 6, 11 Hz) for (+)-isomintlactone whereas it appeared at δ 5.1 (dd, J = 3.5, 6.9 Hz) for selenolactone. Methyl group of lactone ring appeared at δ 1.8 (t, 3H, J = 1.5 Hz) for (+)-isomintlactone while at δ 1.55 (s, 1H) for selenolactone. The ^{13}C-NMR showed 10 signals corresponding to the 10 carbons among them 175.11 (s), 163.20 (s) and 119.56 (s) was characteristic of butenolide moiety. The mass spectrum exhibited M^+ peak at 166 (95%). Optical rotation $[\alpha]_D$ = + 79° (c = 0.7, $CHCl_3$), lit.[1,8], $[\alpha]_D$ = +76.9° (C = 5, EtOH). Optical purity of (+)-isomintlactone **2** was also confirmed by GC analysis on chirasil val. column temperature. The spectral data and physical properties of (+)-isomintlactone were in perfect agreement with those reported[18] for (+)-**2** obtained from natural sources.

γ-ketoacids continue to be main source of butenolides. Aliphatic keto acids and aromatic ketoacids may be lactonized by heating with acetic anhydride, polyphosphoric acid and benzenesulfonic acid.[21] Employing above methodology synthesis of (±)-mintlactone and

(±)-isomintlactone was achieved in three steps (**Scheme - 10**).

Scheme-10



50 **60** **66** **67**

a : BMS, H_2O_2, ^-OH b : Jones reagent c : TsOH, C_6H_6, Δ

Oxidation of isopulegol diol **5** with Jones reagent furnished the γ-ketoacid **66** in 60% yield. The structure of ketoacid **66** was fully confirmed by IR, ^{1}H-NMR and mass spectroscopy. The IR spectrum of ketoacid **66** showed absorption at 3450 cm^{-1} and 1700 cm^{-1} indicating the presence of -COOH group. The ^{1}H-NMR spectrum showed disappearance of signal at δ 2.7 (m, 2H) for -$\underline{CH_2}$-OH protons while appearance of new signal at δ 1.00 (d, 3H, J = 6.5 Hz) and δ 2.2 (1H) for the side chain methyl and $\underline{CH}$-COO protons respectively. The mass spectrum was in perfect agreement with the assigned structure (M^+, 184).

The acid catalysed cyclisation of the ketoacid **66** with catalytic amount of pTSA in refluxing benzene afforded the corresponding butenolide (±)-mintlactone and (±)-isomintlactone in the ratio of 9:1 in 82% yield. The spectrum showed a characteristic frequency at 1760 cm^{-1} along with 1670 cm^{-1} for the presence of α,ß-unsaturated -γ-lactone moiety. Further, the ^{1}H-NMR spectrum besides showing the expected signal at δ 4.6 (ddq, 1H, J = 2,6 and 11 Hz) for the methine proton, on the carbon bearing lactone oxygen atom (-$\underline{CH}$OCO). The mass spectrum showed occurance of M^+ at 166 (100%). The diastereoisomer ratio was determined from the integration of signals at δ 4.6 and δ 4.7 to be 9:1 and was confirmed by g.l.c. analysis. The above spectral data were in good agreement with those reported in the literature.[5,7]. This is a simple synthesis of (±) **1** and (±) **2** . The easy availability of starting material (-)-isopulegol, makes the overall process a method of choice for relatively large scale preparation of (±)-mintlactone and (±)-isomintlactone.

In conclusion, synthesis of optically pure (-)-mintlactone and (+)-isomintlactone have been achieved in a short, convenient and highly stereoselective fashion from common precursor *viz.* (-)-isopulegol.[12]

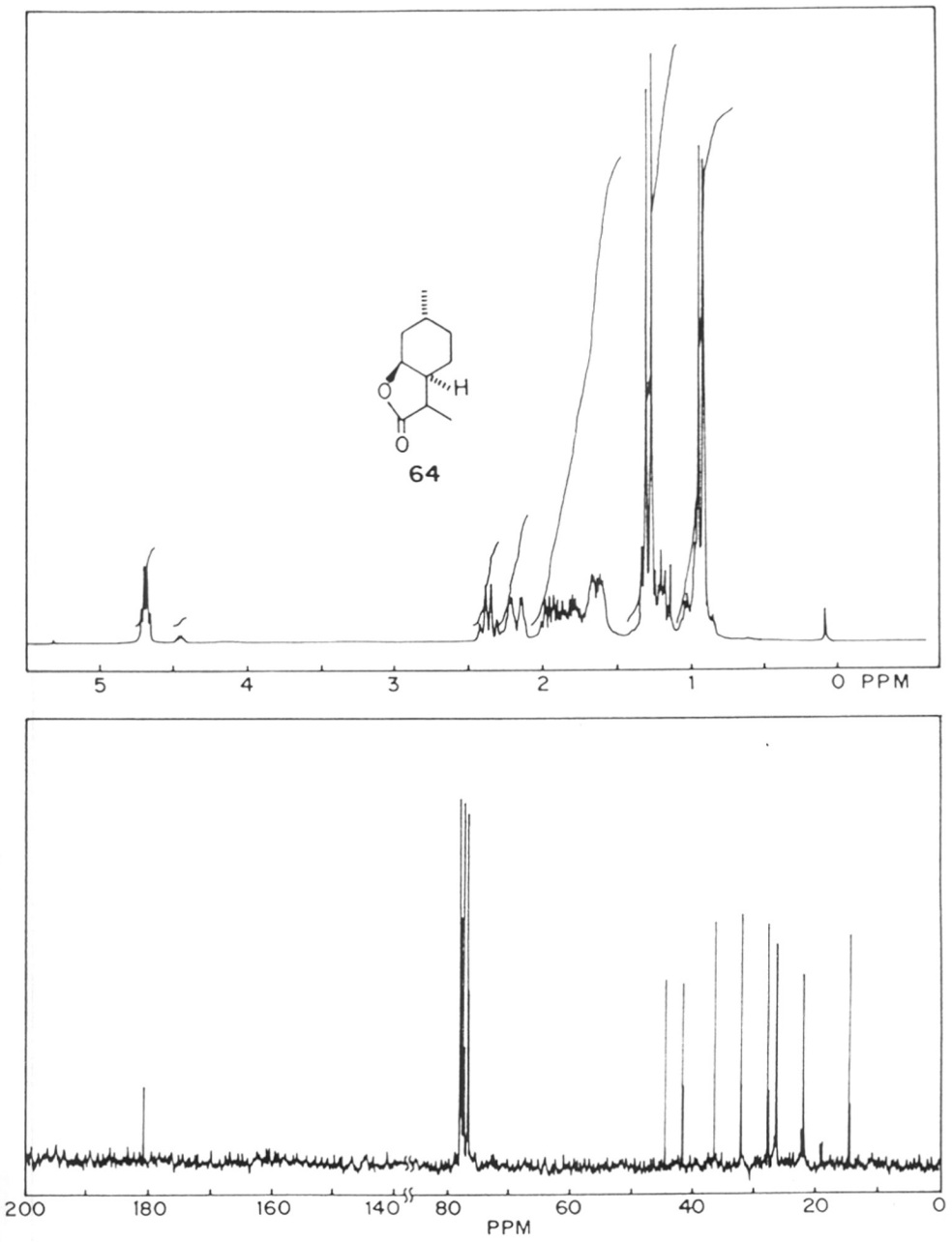


FIG.6

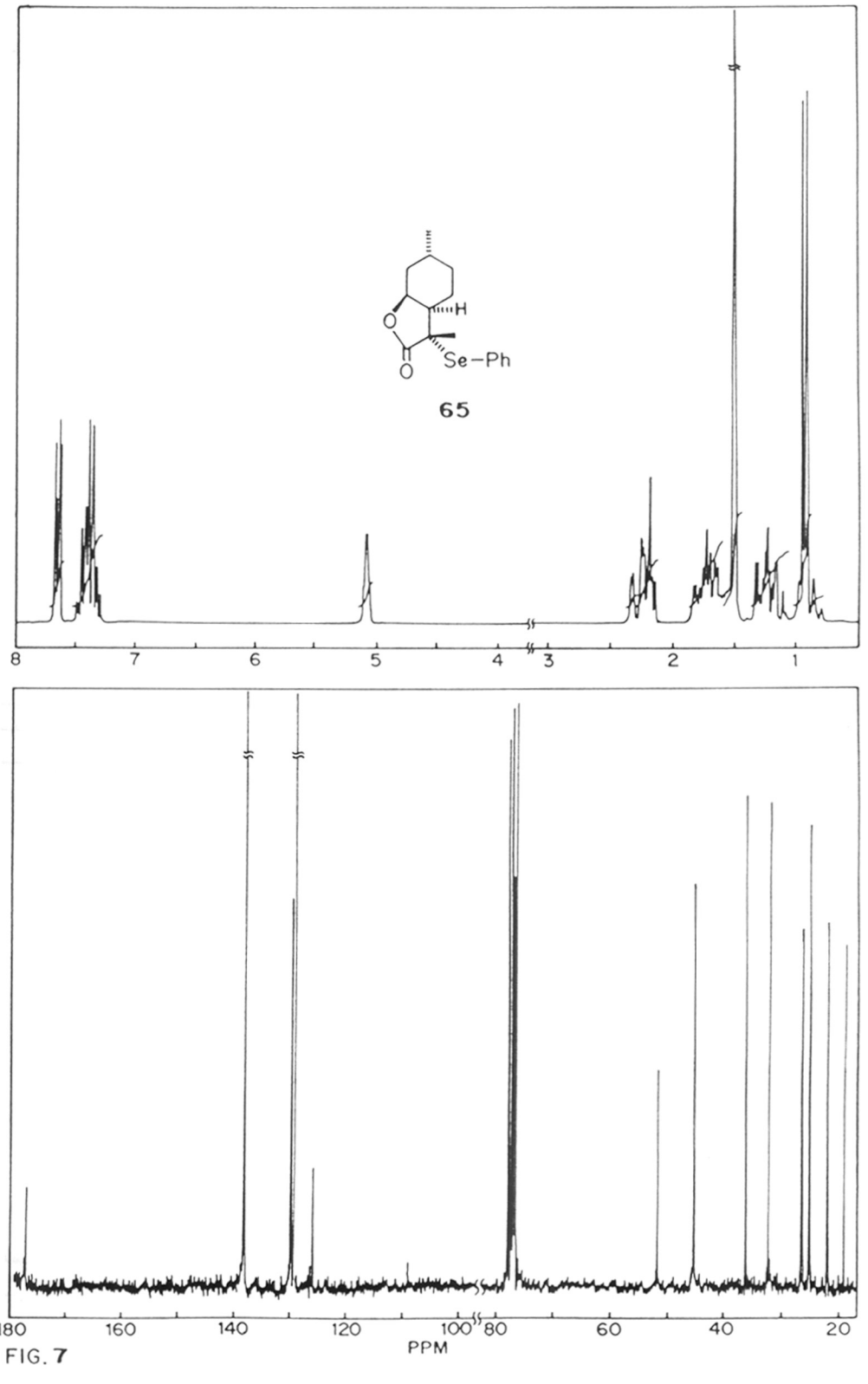


FIG. 7

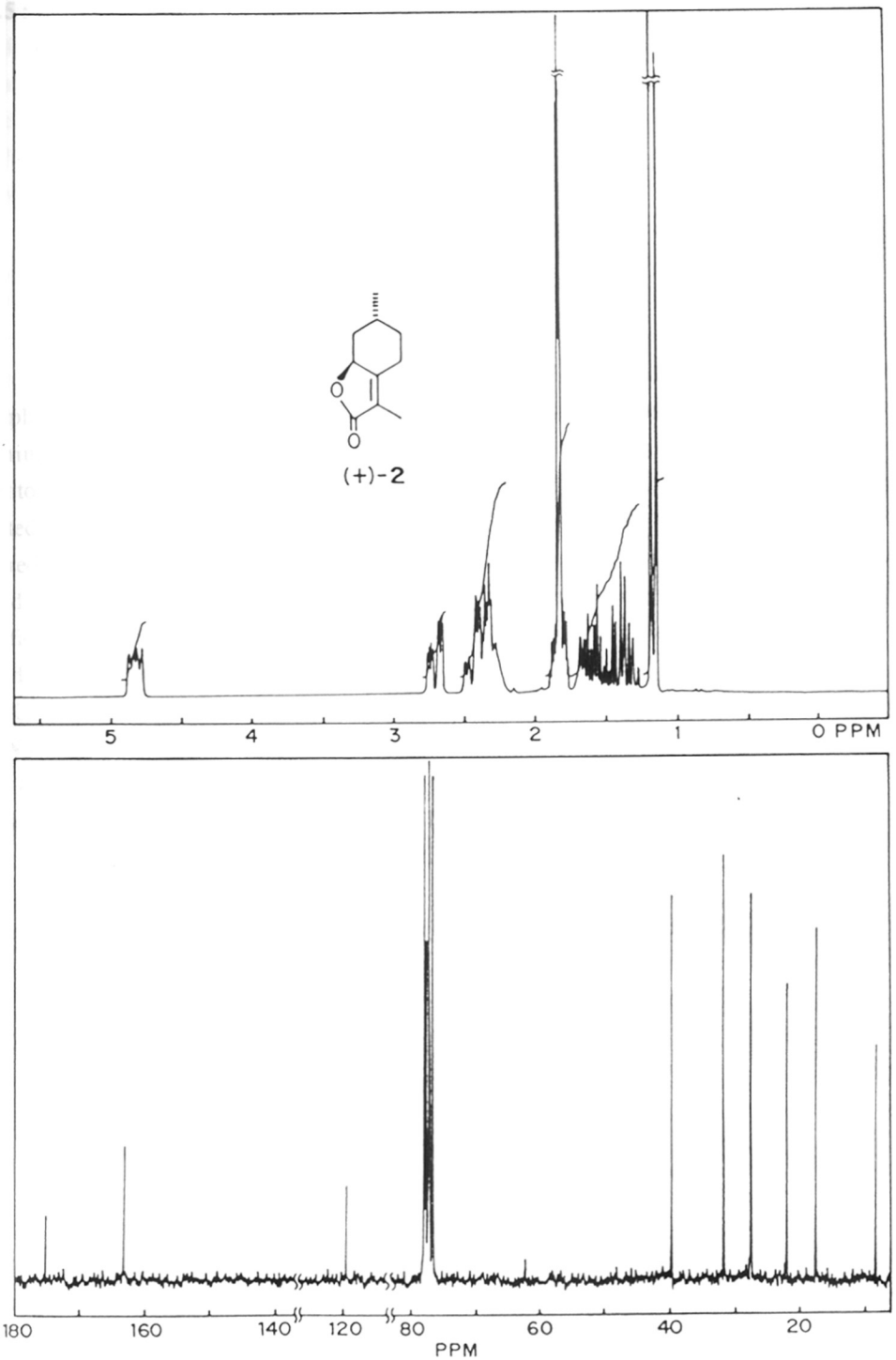
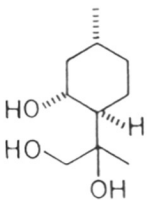


FIG.8

1.1.5 : Experimental :

(1S, 3S, 8RS)-p-Menthone-3,8,9-triol (51) :



A 20 ml tube charged with (-)-isopulegol (2.5 g, 16.02 mmol) and N-methyl morpholine N-oxide (2.848 g, 24.34 mmol) in acetonitrile (2 ml). Catalytic amount of Osmium tetroxide (0.005 M, 0.1 ml) solution in toluene was injected. The reaction was monitored by t.l.c. After being stirred for 12h at room temperature, the resulting solution was treated with sodium metabisulphite ($Na_2S_2O_5$) (0.5 gm) for 0.5 h. The reaction mixture was filtered and solid was washed repeatedly with dichloromethane. The combined washings were dried over anhydrous sodium sulphate and evaporated to afford a viscous oil, which on purification by column chromatography (SiO_2) furnished the triol **51** as a viscous oil.

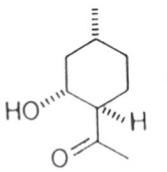
Yield : 2.5 gm, 90%

IR ($CHCl_3$) : 3450, 2900

^{1}H-NMR ($CDCl_3$, 80 MHz) : δ 0.95 (d, 3H, J = 6.4 Hz), 1.2 (d, 3H, J = 3.2 Hz), 1.2 - 1.9 (m, 9H), 3.6-4.00 (m, 2H).

Mass (m/z) : 188 (M^+, 10%), 183 (5), 169 (3), 153 (97), 140 (45), 123 (20), 109 (46), 95 (28), 81 (100), 75 (52), 71 (41), 67 (39), 55 (35).

(1R, 2R, 4S) 1-Acetyl-2-hydroxy-4-methyl-cyclohexane (58) :



58

The solution of triol **51** (0.3 g, 16 mmole) in dry benzene was taken in two necked flask (50 ml) fitted with Dean-Stark apparatus. To this solution Ag_2CO_3/celite (10 eqvi) was added and the reaction mixture was refluxed for 24 hours. The reaction mixture was cooled,

filtered and benzene was removed under reduced presssure to furnish a residue which was purified by column chromatography (SiO_2) to afforded the formate ester **57** (5%) and ketoalcohol **58** as a colourless oil.

Yield : 166 mg, 67%.

IR (Neat) : 3550, 1710 cm^{-1}

^{1}H-NMR ($CDCl_3$,200 MHz) : δ 1.00 (s, 3H, J = 4.4 Hz), 1.00-1.1 (m, 2H), 1.15-1.3 (m, 2H), 1.4-1.6 (m, 2H), 1.6-1.8 (m, 2H), 1.9-2.1 (m, 2H), 2.2 (s, 3H), 2.2-2.3 (m,1H), 2.8 (br.s, -OH D_2O exchangeable), 3.8 (ddd, 1H, J = 4.4 Hz).

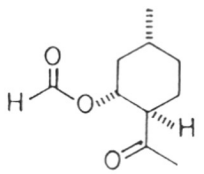
^{13}C-NMR ($CDCl_3$, 50 MHz) : 213.32 (s), 70.75 (d), 58.59 (d), 42.84 (t), 33.88 (t), 31.26 (d), 29.65 (q), 21.7 (t), 22.16 (q).

Mass (m/z) : 156 (M^+), 138 (88), 131 (6), 123 (100), 109 (24), 105 (6), 95 (6), 81 (24), 67 (54), 55 (22).

Analysis : Calculated for $C_9H_{16}O_2$: C, 69.23; H, 10.25%

Found : C, 68.9 ; H, 9.8%

1-Acetyl-4-methyl-2-cyclohexane formate (57) :



Yield : 5%

IR (Neat) : 1730, 1710, 1200 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 6.5 Hz), 1.00 (t, 2H, J = 11.68 Hz), 1.2 (ddd, 1H, J = 3.4, 13 Hz), 1.5 (m, 1H), 1.6 (m ,1H), 1.8-1.9 (m, 2H), 2.1 (s, 3H), 2.5 (ddq, 1H, J = 3.8, 10.63, 12.5 Hz), 4.9 (ddd, 1H, J = 4.48, 10.79 Hz), 7.9 (s, 1H).

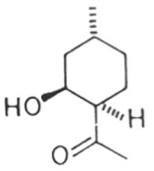
^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 208.69 (s), 160 (d), 73.04 (d), 55.03 (d), 39.33 (t), 33.24 (t), 30.75 (d), 28.99 (d), 27.67 (t), 21.60 (q).

Mass (m/z) : 184 (M^+, 4%), 138 (22), 123 (10), 96 (54), 89 (4), 81 (100), 71 (8), 67 (30), 54 (32).

Analysis : Calculated for $C_{10}H_{16}O_3$: C, 65.20; H, 8.69%

Found : C, 65.00; H, 8.69%

(1S, **4R, 2S)-1-acetyl-2-hydroxy-4-methyl cyclohexane (59)** :



Yield : 70%

IR (Neat) : 3500, 1710 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 4.4 Hz), 1.1-1.3 (m, 3H), 1.4-1.6 (m, 1H), 1.75-2.00 (m, 6H), 2.2 (s, 3H), 2.4 (m, 1H), 3.3 (bs, 1H, D_2O exchangeable), 4.3 (d, 1H).

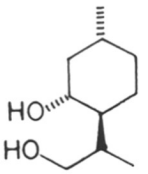
^{13}C-NMR ($CDCl_3$, 50 MHz) : 208 (s), 66.51 (d), 54.04 (d), 40.83 (t), 34.61 (t), 29.02 (d), 25.62 (d), 23.11 (t), 22.29 (q).

Mass (m/z) : 156 (0), 138 (80), 131 (2), 123 (100), 109 (24), 105 (5), 95 (0), 81 (20), 67 (50), 55 (15).

Analysis : Calculated for $C_{10}H_{16}O_3$: C, 65.20; H, 8.69%

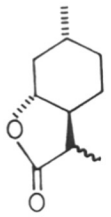
Found : C, 65.00; H, 8.10%

(-)-(**1R, 3R, 4S, 8R)-p-Menthane-3,9-diol (60)** :



The diol **60** was obtained by the hydroboration oxidation of (-)-iso-pulegol **50** as described Schulte-Elte et. al.[13]. This material was sufficiently pure by NMR and optical rotation ($[\alpha]_D$ = -17°, c=5.8 $CHCl_3$, lit.[13] $[\alpha]_D$ = -18°) for use in the next reaction.

(3R, 6R, 7aR, 8S) 3,6-dimethyl hexahydro-2(3H) benzofuranone (61) :



The solution of diol **60** (0.520 g, 3.0 mmol) in dry benzene (10 ml) was taken in two necked (50 ml) flask fitted with a Dean Stark apparatus. To this solution reaction Ag_2CO_3/celite (2.499 g, 9.06 mmol) was added and the reaction mixture was refluxed 24 hours. The reaction mixture was cooled and filtered. Benzene was removed under reduced pressure to furnish a residue which was purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish saturated lactone **61** (0.420 g, 83%) as a mixture of stereoisomers (88:12) as a viscous oil.

Yield : 420 mg, 83%

IR (Neat) : 1770, 1460, 1000 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.25 (3H, d, J = 6.4 Hz); 1.15 (3H, d, J = 7.5 Hz); 1.25 (m, 5H); 1.5 -1.7 (m, 1H); 1.6-2.05 (m, 1H); 2.2 (m, 1H); 2.55 (q, 1H); 4.05 (ddd, 1H, J = 3.78, 11.1 Hz).

^{13}C-NMR ($CDCl_3$) : 180 (s), 81.3 (d), 47.1 (d), 38.7 (d), 38.18 (t), 31.24 (t), 31.36 (t), 23.78 (t), 22 (q), 9.56 (q).

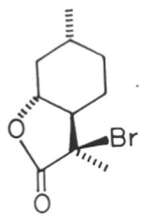
Mass m/z : 168 (M^+, 7%), 113 (100), 85 (88), 81 (82), 95 (77), 67 (71), 109 (63), 124 (58), 156 (51), 56 (31), 139 (6).

Optical rotation : (mixture) $[\alpha]_D$ = +63.3°, (c= 11.7, $CHCl_3$).

Analysis : Calculated for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52%

Found : C, 71.4; H, 9.48%

(3R, 6R, 7aR, 8S) 3,6 dimethyl 3-bromo hexahydro-2(3H) benzofuranone (62) :



Saturated lactone **61** (0.4 g, 2.3 mmol) in dry THF (5 ml) was added to the solution of

lithium diisopropylamide [prepared from diisopropylamine (0.280 g, 2.7 mmol) and butyllithium (0.2 g, 3.1 mmol) in dry THF 7 (ml) at 0°C under argon atmosphere] at -78°C. After 30 minutes chlorotrimethylsilane (0.333 g, 3.0 mmol) was added. To the resultant solution , NBS (0.550 g, 3.0 mmol) was added after a further 15 minutes. The reaction mixture was stirred at -78°C and warmed to room temperature and stirred overnight. Water was added and the residue thus obtained by usual work up was further purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish bromolactone **62** as a colourless solid.

Yield : 560 mg, 95%

M.P. : 107-110°C

IR ($CHCl_3$) : 1780, 1460, 1400, 1230, 1100, 1010 cm^{-1}.

^{1}H-NMR ($CDCl_3$) : δ 1.05 (3H, d, J = 7 Hz); 1.1-1.5 (m, 6H); 1.7 (m, 1H); 1.95 (s, 3H); 2.3 (m, 1H); 4.1 (ddd, 1H, J = 4.1, 9.4, 13.4 Hz).

^{13}C-NMR ($CDCl_3$) : 174.5 (s), 80.7 (s), 59.56 (d), 56.26 (d), 37.85 (t), 33.63 (t), 31.24 (d), 25.33 (t), 24.91 (q), 22.15 (q).

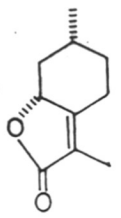
Mass (m/z) : M^+ (247, 0%), 81 (100), 67 (4), 123 (51), 55 (81), 95 (14), 41 (10).

Optical rotation : $[\alpha]_D$ = +16.8° (c = 1.5, $CHCl_3$).

Analysis : Calculated for $C_{10}H_{15}BrO_2$: C, 48.78; H, 6.09%

Found : C, 48.60; H, 6.43%

(6R, 7aR) 3,6 dimethyl-5,6,7,7a tetrahydro-2 (4H) benzofuranone (1) :



To a solution of bromolactone **62** (0.240 g, 0.9 mmol) in benzene (10 ml), DBU (0.148 g, 0.9 mmol) was added. The reaction mixture was refluxed for 45 min, filtered and solvent was removed under reduced pressure to furnish a residue. Purification of the residue by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent afforded (-) mintlactone **1**.

Yield : 122 mg, 76%

IR (Neat) : 1760, 1700 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.00 (d, 3H, J = 6.5 Hz); 1.1-1.5 (m, 2H); 1.75 (m, 1H);

1.8 (t, 3H, J = 1.4 Hz); 2.00 (m, 1H); 2.25 (m, 1H); 2.45 (m, 1H); 2.8 (ddd, 1H, J = 1.9, 4.6, 14.0 Hz); 4.66 (dd, 1H, J = 6.0, 11.0 Hz).

^{13}C-NMR ($CDCl_3$) : δ 174.86 (s), 162.62 (s), 119.85 (s), 80.24 (d), 42.27 (t), 34.82 (t), 29.19 (d), 25.75 (t), 21.45 (q), 8.38 (q).

Mass m/z : 166 (M^+, 100%), 137 (60), 109 (53), 67 (50), 81 (47.5), 95 (42), 123, 53 (17.5), 77 (10), 51 (8), 91 (7), 63 (3).

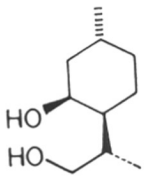
Optical rotation : $[\alpha]_D$ = -57° (c = 2.4 $CHCl_3$), $[\alpha]_D$ = -56.6° (c = 2.2, EtOH), lit.[1,3a] $[\alpha]_D$ = 51.8° (c = 10, EtOH).

Analysis : Calculated for $C_{10}H_{14}O_2$: C, 72.28; H, 8.43%

Found : C, 72.02; H, 8.08%

Chiral GC : Chiral val. column temperature 120°C, split ratio (1:100), retention time 9.12 min.

(+)-(1R, 3S, 4S, 8S)-p-menthane-3,9 diol (63) :



Isopulegol (4.647 g, 3 mmol), triphenyl phosphine (9.48 g, 3.6 mmol) and p-nitrobenzoic acid (6.030 g, 3.6 mmol) were dissolved in dry benzene (40 ml) in a two necked flask (100 ml) under nitrogen atmosphere. Diethyl azodicarboxylate (6.3 g, 3.6 mmol) was added dropwise at 0°C. The clear yellow reaction mixture was stirred at R.T. for 3 hours. The reaction mixture was filtered and benzene was removed under reduced pressure to furnish a residue. The residue was purified by column chromatography (SiO_2) using pet ether as a eluent to furnish benzoate **54** as a yellow solid.

Yield : 7.655 g, 84%

M.P. : 92°C,

IR (Neat) : 1750, 1460, 1400, 1340, 1140, 1160, 1240 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 90 MHz) : δ 0.8 (d, 3H, J = 8 Hz); 1.15 (m, 6H); 4.66 (s, 1H); 5.4 (s, 1H); 8.1 (m, 4H).

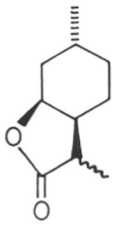
Mass (m/z) : 303, (M^+, 20%), 150 (100), 136 (91), 104 (55), 121 (54), 93 (44), 76 (22), 69 (10), 55 (9).

Optical rotation : $[\alpha]_D$ = +53° (c = 4.9, $CHCl_3$).

Benzoate **54** (4.822 g, 1.5 mmol) was added to a solution of MeONa/MeOH [prepared from sodium (0.726 g, 3.1 mmol) and MeOH (30 ml)] at room temperature, and the reaction mixture was stirred at room temperature for 30 minutes. Water was added, extracted with ether and the ether layer was washed with water (2 x 30 ml). The ether was removed under reduced pressure to furnish Neo-isopulegol **53** (2.360 g, 97%) as a oil. Spectral data and physical data of Neo-isopulegol (**53**) were found to be identical in all respects with data reported in literature[13].

The diol **63** was obtained by the oxidative hydroboration, of (+)-Neo-isopulegol **53** as described Schulte-Elte et. al.[13]. This material was sufficiently pure by NMR and optical rotation for use in the next reaction.

(3S, 6R, 7aS, 8S)-3,6 dimethyl hexahydro -2(3H) benzofuranone (64) :



The solution of diol **63** (1.752 g, 10.1 mmol) in dry toluene (20 ml) was taken in two necked (50 ml) flask fitted with a Dean-Stark apparatus. To this solution Ag_2CO_3/Celite (9.6 g, 34 mmol) was added and the reaction mixture was refluxed for 24 hrs. The reaction mixture was cooled and filtered, and toluene was removed under reduced pressure to furnish a residue. The residue was purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish saturated lactone **64** as a mixture of stereoisomers (92:8).

Yield : 1.186 g, 70%

M.P. : 41-45°C

IR ($CHCl_3$) : 1770, 1460, 1210, 1180 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, 3H, J = 6.4 Hz); 1.3 (d, 3H, J = 7.2 Hz); 1.05-1.25 (m, 2H); 1.55-1.75 (m, 3H); 1.75-2.05 (m, 2H); 2.1-2.3 (m, 1H); 2.4 (q, 1H); 4.7 (dd, J = 3.4, 7 Hz).

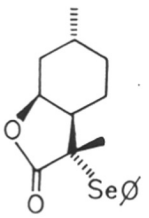
^{13}C-NMR ($CDCl_3$) : 180.66 (s), 77.66 (d), 44.32 (d), 41.5 (d), 36.18 (t), 31.85 (t), 27.54 (t), 26.23 (d), 21.70 (q), 14.32 (q).

Mass (m/z) : 168 (M^+, 2%), 95 (100), 67 (71), 81 (60.5), 55 (40.5), 109 (26.5), 124 (22).

Optical rotation (mixture) : $[\alpha]_D$ = - 36° (c = 2.6, $CHCl_3$).

Analysis : Calculated for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52%
Found : C, 71.83; H, 9.66%

(3S, 6R, 7aS, 8S)-3,6 dimethyl-3-phenyl seleno-2 (3H) benzofuranone (65) :



Saturated lactone **64** (0.3 g, 1.78 mmol) in dry THF (5 ml) was added to the solution of LDA [prepared from diisopropyl amine (0.2 g, 1.98 mmol), butyllithium (0.150 g, 2.3 mmol) in dry THF (7 ml) at 0°C under argon atmosphere] at -78°C. After 30 minutes diphenyl diselenide (0.555 g, 1.78 mmol) was added, the reaction mixture stirred at -78°C for 60 minutes, warmed to RT and stirred overnight. The reaction mixture was quenched with water and extracted with ether. Drying and evaporation of solvent furnished a residue which was purified by column chromatography (SiO_2) using 5% ethyl acetate in pet ether as eluent to furnish selenolactone **65** as a colourless solid.

Yield : 479 mg, 83%

M.P. : 140°C.

IR ($CHCl_3$) : 1770, 1540, 1251, 1209, 1097 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, 3H, J = 6.5 Hz); 1.1-1.3 (m, 3H); 1.55 (s, 3H); 1.75 (m, 3H); 2.25 (m, 2H); 5.1 (dd, 1H, J = 3.5, 6.9 Hz); 7.7-7.3 (m, 5H).

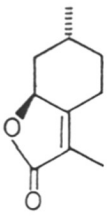
^{13}C-NMR ($CDCl_3$) : 177.18 (s), 138.19 (s), 129.87 (d), 129.26 (d), 125.8 (d), 76.951 (s), 51.83 (d), 45.46 (d), 36.312 (t), 32.305 (t), 26.58 (d), 25.29 (t), 22.04 (q), 19.06 (q).

Mass (m/z) : 323 (M^+, 64%), 167 (100), 149 (88), 93 (57), 121 (50), 81 (50), 55 (51), 158 (41), 77 (41), 111 (16), 139 (16).

Optical rotation : $[\alpha]_D$ = +40.5° (c=2.2, $CHCl_3$),

Analysis : Calculated for $C_{16}H_{20}O_2Se$: C, 59.44; H, 5.84%
Found : C, 59.27; H, 6.19%

(6R,7aS) 3,6-dimethyl-5,6,7,7a tetrahydro-2(4H) benzofuranone (2) :



To a solution of α-phenyl selenolactone **65** (0.2 g, 0.6 mmol) in THF (10 ml) containing 0.1 ml of CH_3COOH cooled to 0°C, was added 30% H_2O_2(0.14 ml). The reaction mixture was stirred for 30 minutes at 0°C, then poured into cold saturated sodium bicarbonate solution and extracted with ether. The ether was removed under reduced pressure to furnish a residue which was purified by column chromatography over silica gel,eluting with 5% ethyl acetate in pet ether as eluent to afford (+)-*iso* mintlactone (**2**) (0.074 g, 73%) as a colourless solid.

Yield : 74 mg, 73%

M.P. : 78-79°C.

IR ($CHCl_3$) : 1760, 1690, 1460, 1410, 1260 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.15 (d, 3H, J = 7.3 Hz); 1.37 (ddd, 1H, J = 11.9, 4.5 Hz); 1.59 (ddd, 1H, J = 13.3, 4.6 Hz); 1.8 (t, 3H, J = 1.5 Hz), 1.8 (m, 1H), 2.2-2.5 (m, 3H), 2.7 (ddd, 1H, J = 14.4, 4.9, 2.1 Hz); 4.8 (dd, 1H, J = 11.2, 6 Hz).

^{13}C-NMR ($CDCl_3$) : δ 175.11 (s), 163.20 (s), 119.56 (s), 77.64 (d), 39.77 (t), 31.85 (t), 27.55 (q), 21.97 (t), 17.45 (d), 8.35 (q).

Mass (m/z) : 166 (M^+, 95%), 81 (100), 67 (89), 95 (85), 109 (82), 137 (73), 123 (37), 55 (35), 91 (18), 73 (8), 60 (7), 151 (3).

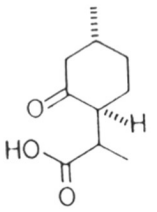
Optical rotation : $[\alpha]_D$ = +79° (c = 0.7, EtOH) lit.[1] $[\alpha]_D$ = +76.9° (c=5, EtOH).

Analysis : Calculated for $C_{10}H_{14}O_2$: C, 72.2; H, 8.43%

Found : C, 72.17; H, 8.39%

Chiral GC : Chiral val. column temperature 120°C, split ratio (1:100), retention time 12.67 min.

γ-Keto acid (66) :



The diol **51** (0.7 g, 4 mmol) was dissolved in acetone (20 ml) and was cooled to 0°C. To this solution Jones reagent was added dropwise until the colour of reagent persists. The reaction mixture was stirred at room temperature for another 2 hours. The reaction mixture was quenched by addition of isopropanol, usual workup gave a residue which was purified by column chromatography (SiO_2) furnished the γ-ketoacid **66** as a viscous oil.

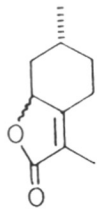
Yield : 450 mg, 60%

IR (Neat) : 3450, 1700, 1440, 1200, 920 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.00 (d, 6H, J = 6.5 Hz), 1.2 (m, 2H), 1.4-1.8 (m, 2H), 1.8-2.00 (m, 1H), 2.00 (q, 1H), 2.4 (m, 2H).

Mass (m/z) : 184 (M^+), 182 (2), 159 (2), 151 (6), 143 (15), 138 (6), 125 (30), 115 (10), 109 (19), 97 (21), 91 (7), 86 (14), 81 (52), 73 (33), 69 (95), 60 (100), 55 (90).

(±)-3,6-dimethyl-5,6,7,7a-tetrahydro-2(4H)-benzofuranone (67) :



The mixture of ketoacid **66** (0.150 g, 0.8 mmol) and p-toluene sulfonic acid (catalytic) in 10 ml dry benzene was refluxed under nitrogen atmosphere. After 2 hours reaction mixture was cooled, washed with aqueous $NaHCO_3$, brine and concentrated in vacuo gave a residue, which is chromatographed on silica gel (5% ethyl acetate in pet. ether) furnish (±) mintlactone and (±)-isomintlactone **67** as a mixture of diastereoisomers (9:1).

Yield : 110 mg, 81.5%

IR (Neat) : 1755, 1684, 1654, 1636, 1576, 1558, 1540 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200MHz) : δ 0.95 (d, J = 6 Hz, 3H), 1.8 (t, 3H, J = 2Hz), 2.3 (m, 7H), 4.6 (ddq, 1H, J = 2.6, 11Hz).

^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 174.53 (s), 162.28 (s), 119.45 (s), 79.82 (d), 42.16 (d), 39.6 (d), 34.6 (t), 31.6 (t), 29.7 (t), 27.3 (t), 25.4 (t), 21.7 (t), 21.14 (t), 17.23 (q), 7.99 (q).

Mass (m/z) : 166 (M^+, 100%), 157 (15), 137 (62), 123 (28), 109 (58), 95 (60), 81 (80), 67 (82), 55 (88).

Analysis : Calculated for $C_{10}H_{14}O_2$: C, 72.2; H, 8.4%

Found : C, 71.98; H, 8.12%

1.1.6 **References :**

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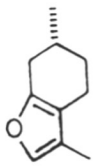
Section-2 : Synthesis of R(+)-Menthofuran

1.2.1 : Summary :

The present section concerns with the synthesis of (+)-menthofuran, one of the most well known member of furanoterpenes, was first obtained by Charabot in 1904 from peppermint oil. One pot, simple and practical synthesis of (+)-menthofuran has been achieved from a common precursor (-)-isopulegol.

1.2.2 : Introduction :

Menthofuran **1** one of the most well known members of furanoterpenes, was first obtained by Charabot in 1904 from peppermint oil[1], *Mentha piperita Vulgaris S.* subsequently, Wienhause[2] deduced the structure by a series of chemical experiments and the confirmation of it was made by a combination of the synthesis from pulegone and some chemical techniques by Treibs[3].



1

Menthofuran **1** has served not only as an important perfumery, but also as a synthetic intermediate for the other biologically related natural products e.g. mintlactone and isomintlactone.[4]

1.2.3 : Synthesis of Menthofuran : Literature survey

Several synthesis of menthofuran **1** (Racemic and natural) are reported in literature. A brief survey of the reported synthesis of menthofuran is presented.

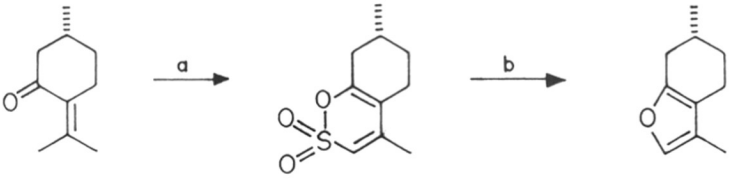
Treib's Approach[3] (Scheme - 1, 1937) :

Treib reported the first synthesis optically pure of menthofuran **1**. This synthesis involves two steps starting from pulegone **2**. Thus, pulegone **2** when treated with acetic anhydride-sulfuric acid mixture gave sulfonic ester **3** in good yield. When sulfonic ester 3 was heated with an inert filler such as zinc oxide to afford the menthofuran in 20% yield. Although this route is short, it involves very high temperature reaction (280-290°C) and also poor yield of **1**.

Stetter's Approach[5] (Scheme - 2, 1960) :

Stetter et. al. reported the first racemic synthesis of menthofuran **1**. Furan moiety was generated by treatment of α-haloester **5** with 1,3-diketone **4** as the key step. Further elaboration to menthofuran was done by decarboxylation and reduction of carbonyl. This is a 4 step sequence and required the preparation of starting materials 4 and 5.

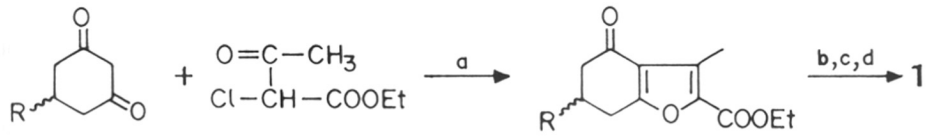
Scheme-1 (Treib, W. Ber. 1937, 70B, 85)



2 3 1

a : Ac_2O, H_2SO_4 b: Δ, 280-290°C

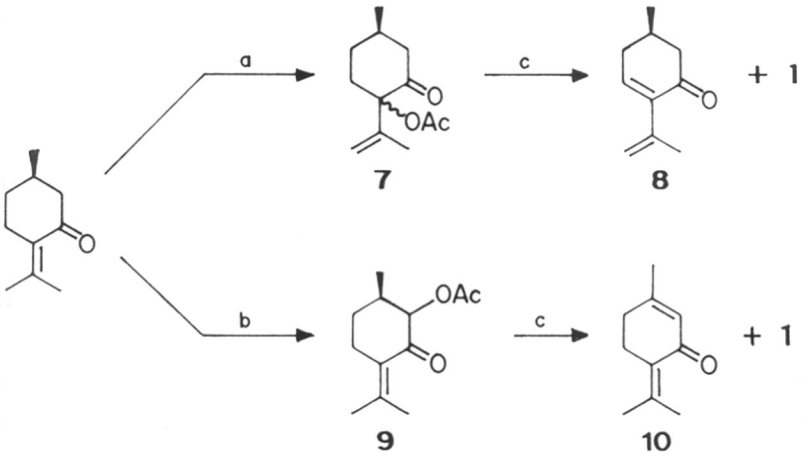
Scheme 2 (Stetter et al, Chem. Ber., 1960, 603, 1960)



4 5 6

a : Base b: KOH, MeOH, Δ c: Ts-NH-NH_2, Py
d: $NaBH_3CN$, THF

Scheme-3 (Zalkow et al, J. Org. Chem, 1964, 29, 2626)



7 8 9 10

a : $Pb(OAc)_4$, C_6H_6, Δ b: $Hg(OAc)_2$, CH_3COOH c: Δ

Zalkow's Approach[6] (Scheme - 3, 1964) :

In this approach, pulegone **2** on treating with $Pb(OAc)_4$ in benzene gave a mixture of *cis* and *trans* 4-acetoxy isopulegone **7** which on heating furnished the 56% of the expected pyrolysis product **8** and 44% of menthofuran. In an another approach, treatment of **2** with mercuricacetate afforded the 2-acetoxyisopulegone **9** which was pyrolysed to afford the expected pyrolysis product **10** and menthofuran in 43% yield. The disadvantage of this method is that formation of unwanted compounds **8** and **10**.

Magnus's Approach[7] (Scheme No - 4, 1977) :

Magnus et. al. reported in 1977 a new general route for the synthesis of furans from endoperoxides using this methodology synthesis of menthofuran have been achieved.

The transformation involves, isopulegol **11** was converted in thiobenzoate **12** and on pyrolsis to furnished the diene **13**. Photooxygenation of **13** gave a clean conversion into the endoperoxides **14**. Treatment of **14** with LDA at -78°C followed by p-toluenesulfonyl chloride afforded menthofuran in 70% yield. This four step sequence involves high temperature pyrolysis/photochemical transformation followed by strong base mediated formation of furan.

Wenkert's Approach[8] (Scheme - 5, 1977) :

Wenkert's et. al. reported in 1977 a new method for the synthesis of ß-methyfurans. The method involves thermal interaction of enolether with α-diazo-ß-dicarbonyl compounds over trimethoxyphosphinecopper(I)iodide to afford the diester. The diester was converted into ß-methyl furans. Although conceptually elegant, this synthesis had drawbacks. The starting material preparation posed problem of separation of the possible enolethers and low yields were obtained in the carbene reactions.

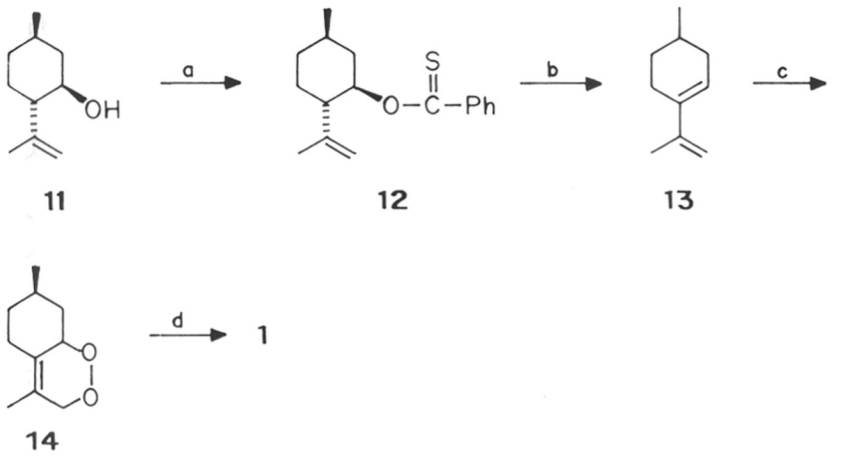
Dhar's Approach[9] (Scheme - 6, 1980) :

In this approach, one pot conversion of pulegone **2** and isopulegone **18** to menthofuran was achieved via **19** mediated by base in low yields (25-32%). This one pot conversion is a very convenient preparation of menthofuran.

Takeda's Approach[10] (Scheme - 7, 1980) :

Takeda et. al. reported the synthesis of (±)-menthofuran in about 45% overall yield in a three steps from ß-keto ester **20** Thus, direct C-alkylation of ß-ketoester **20** with 2-iodopropionate in DMF at 100°C gave diester **21** in good yields. Hydrolysis of diester **21** with conc. HCl for 4 days at reflux temperature furnished the mintlactone **22** in 65% yields. Reduction of mintlactone **22** with DIBAL-H afforded (±)-menthofuran in 75% yield.

Scheme-4 (Magnus et.al , Synth.Comm., 1977, 119)

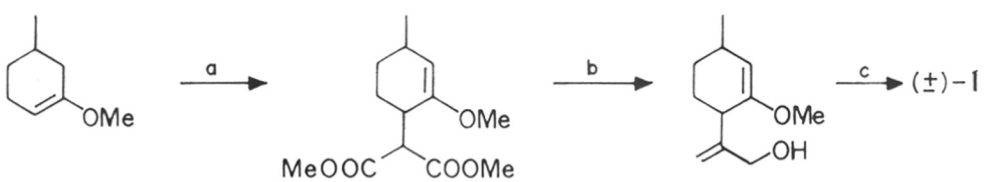


11 12 13

14

a : i) PhCN, $HCl_{(g)}$ ii) K_2CO_3 , H_2S , Py, 0°C b: 110°C / 10mm
c : hν, O_2 , Rose Bengal, MeOH d : LDA, −78°C , pTsCl

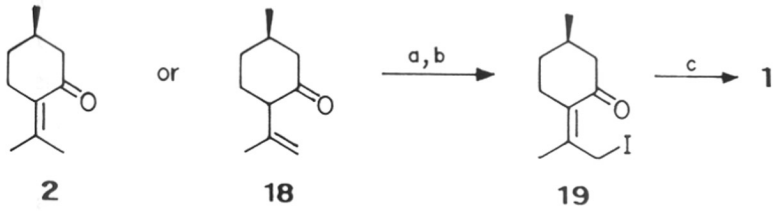
Scheme-5 (Wenkert et.al , J. Am. Chem. Soc. 1977, 99, 4778)



15 16 17

a : $N_2C(COOMe)_2$, $(MeO)_3PCuI$, 100°C b: NaH, EtOH, LAH, ether, R.T.
c : Amberlite IR-120-H resin

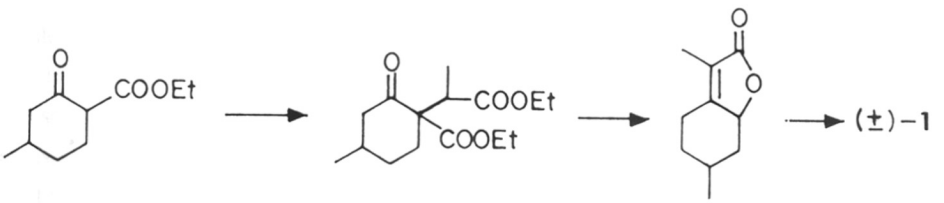
Scheme-6 (Dhar et. al , Ind. J. Chem. (Sect-B), 1980, 19B, 714)



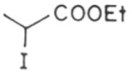
2 18 19

a : NaOH, MeOH b: I_2 , KI c : NaOH

Scheme 7 (Takeda et. al , J. Org. Chem., 1980, 45, 1517)



20 21 22

a :  , NaH , DMF b : Conc. HCl , Δ c : DIBAL-H , THF

Masaki's Approach [11] (Scheme - 8, 1981) :

Masaki et. al. reported the synthesis of optically pure (+)-menthofuran in 9 steps starting from methylcitronellate **23**. The key step in the synthetic sequence is the formation of endoperoxides to construct the furan ring of (+)-menthofuran.

Thus, R(+)-citronellate **23** was transformed to endoperoxide **27** in 50% overall yield as follows. Allylic chlorination of **23** which was converted to the sulfide **25**. Olefination was carried out by oxidation of sulfur followed by heating the sulfoxide **26** in toluene under reflux in the presence of $NaHCO_3$ and oxidation of diene providing endoperoxides **27** was affected by photosensitized oxygenation as the key step in 50% overall yield.

Treatment of **27** with t-BuOK at -70°C furnished the furan ester **28** in 42% yield. Cyclization of furan ester **28** was achieved by treatment of the corresponding acid with PCl_5 and $SnCl_4$ to furnish the optically active evodone **29** in good yields. This led to optically pure (+)-menthofuran via reduction of tosylhydrazone with $NaBH_3CN$ in good yields. It is a very lengthy process comprising 11 steps.

Kittagawa's Approach[12] (Scheme - 9, 1983) :

In this approach, key steps was synthesis of butenolide **22** and its conversion into furan. The butenolide was synthesized by catalytic hydrogenation of **30** which is derived from plant origin to give dihydro derivative **31** in good yield. Ruthenium tetroxide oxidation of **31** furnished a γ-lactone derivative **32** in excellent yields and methyl group and double bond was introduced by Trost's procedure in 80% yield. DIBAL-H reduction of butenolide **22** provided **1** in 77% yield.

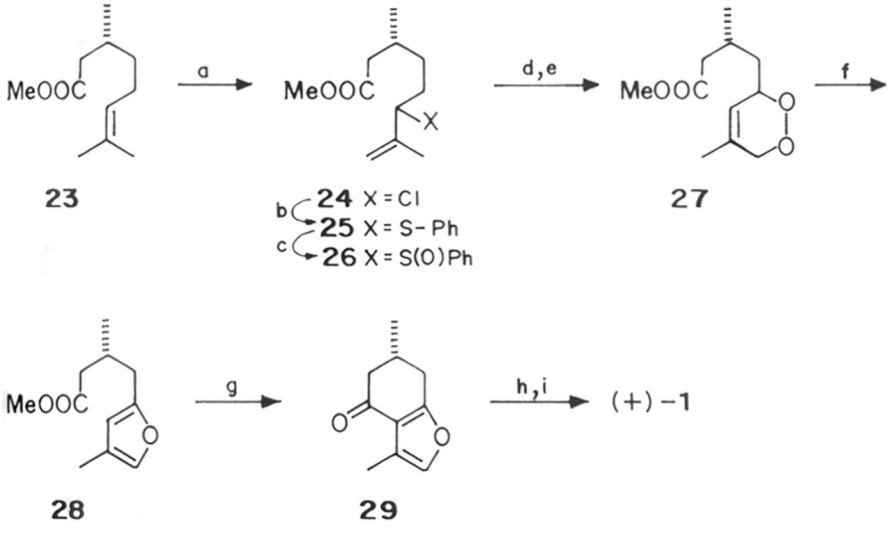
Wolinsky's Approach[13] (Scheme - 10, 1985) :

In this approach (+)-menthofuran was prepared from (+)-pulegone via the chloroisopulegone **33**. Thus, treatment of pulegone **2** with one equivalent of HOCl afforded 4-chloroisopulegone **33** as a mixture of stereoisomers in good yield. Dehydrochlorination of **33** was affected by refluxing in triethylamine afforded menthofuran in good yield. Alternatevely, treatment of **33** with anhydrous $AlCl_3$ in CH_2Cl_2 produced (+)-menthofuran in high yields. This two step protocol is highly efficient and concise.

Ho's Approach[14] (Scheme - 11, 1989) :

Ho et. al. reported the practical synthesis of (+)-menthofuran in 1989 from isopulegol in three steps. Epoxidation of isopulegol **11** with either a peracid or the acetonitrile H_2O_2 system to furnish isopulegol oxide **34** in excellent 94% yield. The epoxide **34** was converted to isopulegone epoxide **35** by oxidation with chlorine pyridine complex. Isopulegone oxide **35** was isomerized to menthofuran **1** by treatment with 9% HCl. This sequence besides being short is highly efficient and can be scaled up readily.

Scheme-8 (Masaki et.al, Chem. Lett, 1981, 9, 1283)



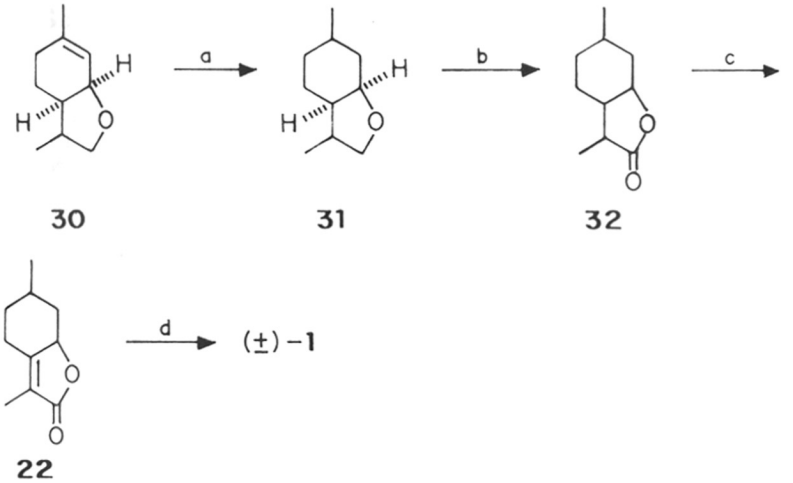
a: SO_2Cl_2, Py, CCl_4, O°C b: PhSNa, DMF, O°C c: H_2O_2, AcOH

d: $NaHCO_3$, Tol, Δ e: hν, O_2 f: t-BuOK, THF, -70°C

g: Hydrolysis, PCl_5, $SnCl_4$, CH_2Cl_2, -5°C to O°C

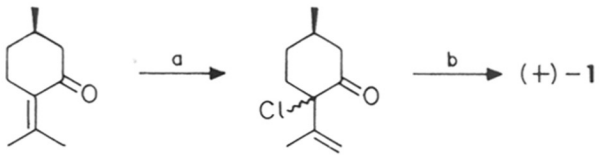
h: $TsNHNH_2$, Py i: $NaBH_3CN$, THF, AcOH, 15°C

Scheme-9 (Kittagawa et. al, Chem. Pharm. Bull. 1983, 31, 2639)



a : H_2, PtO_2 b : RuO_4 c : LDA, $(MeS)_2$, $NaIO_4$, Δ d : DIBAL-H, THF, -78°C

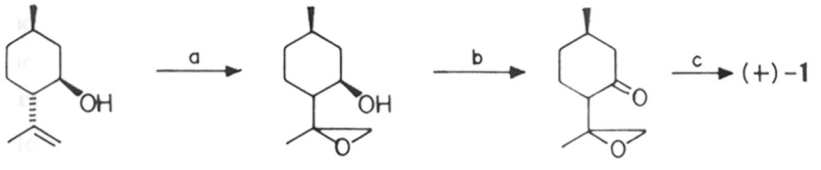
Scheme-10 (Wolinsky et.al, J.Org.Chem. 1985, 50, 894)



33

a: HOCl b: $Et_3\ddot{N}$ or $AlCl_3$, CH_2Cl_2

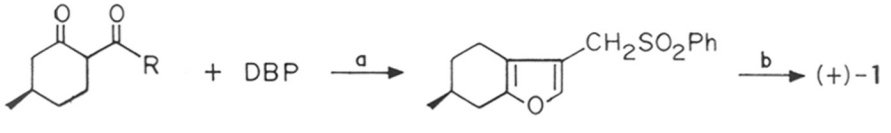
Scheme-11 (Ho et.al, Synth. Commun. 1989, 19, 813)



11 34 35

a: H_2O_2, CH_3CN, K_2CO_3 b: Chlorine-Py complex c: 9% HCl

Scheme-12 (Padwa et.al, J. Org. Chem. 1990, 55, 4241)



a: MeOH, MeONa b: Na(Hg)

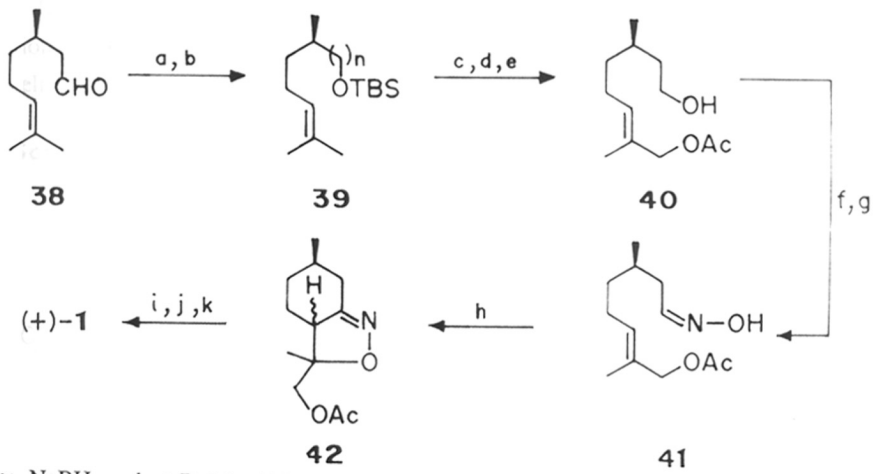
Padwa's Approach[15] (Scheme - 12, 1990) :

Padwa and coworkers reported a novel method for the synthesis of 2,4-disubstituted and 2,3-fused bicyclic furans. The method involves, treatment of 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP) with various ß-dicarbonyl compounds in the presence of sodium methoxide affords 2,4-disubstituted and 2,3-fused bicyclic furans in high yields. This methodology was employed for total synthesis of (+)-menthofuan. The menthofuran precursor **37** was prepared by same fashion. Furan **37** was treated with sodium amalgam to afford (+)-menthofuran in 85% overall yield.

Shishido's Approach[16] (Scheme - 13, 1993) :

In this approach, a fused furan assembling strategy based on an intramolecular [3+2] dipolar cycloaddition reaction of nitrile oxide has been applied to a total synthesis of (+)-menthofuran **1**. Earlier the authors have utilised same strategy for the synthesis of mint & isomintlactones. The key cycloaddition substrate **41** are prepared via straight forward route starting from (+)-citronellal. The cycloaddition reaction generated 10:1 mixture diastereo-isomeric isoxazolines **42** in good yields. The isooxazolines thus obtained were converted to (+)-menthofuran by sequential alkaline hydrolysis and reductive hydrolysis followed by acidic treatment to furnished the (+)-menthofuran **1** in 77% yield. Although this route is novel it involves the use of complex reagents and the scheme is lengthy (11 steps).

Scheme 13 (Shishido et.al , Heterocycles , 1992 , 33 , 73)



38 **39** **40** **41** **42**

a: $NaBH_4$, b: t-$BuMe_2SiCl$, imidazole, DMF c: SeO_2, t-BuOOH

d: Ac_2O, Pyridine e: n-Bu_4NF f: $(COCl)_2$, DMSO, Et_3N

g: $NH_2OH.HCl$, AcONa h: 7% NaOCl CH_2Cl_2 i: $LiOH.H_2O$, THF, H_2O

j: H_2, Raney Ni, $(MeO)_3B$, MeOH

K: p-TsOH, CH_2Cl_2

1.2.4 : Present work :

The present section primarily concerns with practical synthesis of (+)-menthofuran **1**. Menthofuran is a minor but essential component of peppermint oils. Although a large number of synthetic routes[3-16] to menthofuran are now available many of them are uneconomical or unattractive because exotic reagents are employed or involve multistep synthetic transformations with low yields.

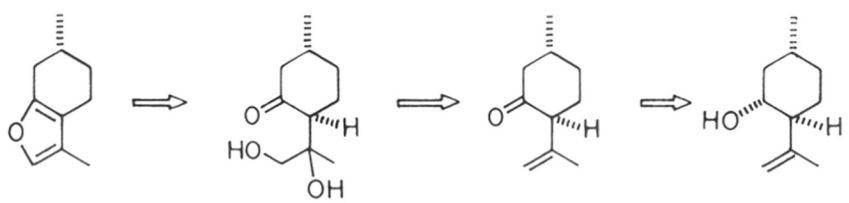
Trieb's et. al.[3] obtained (+)-menthofuran from pulegonol sulfonic ester in 20% yield. Zalkow et. al.[6] prepared optically pure (+)-menthofuran from pulegone in a two step sequence in 20% yield. Wenkert et. al.[8] synthesized (1)-menthofuran in about 18% overall yield in five steps. Masaki et. al.[11] prepared optically pure (+)-menthofuran from methyl citronellate by a 9 step sequence in 30% overall yield. K. Shishido et. al.[16] reported synthesis of (+)-menthofuran from citronellal by a 11 steps sequence in 31% overall yield.

Because of menthofuran characteristic organoleptic properties which are extremely difficult to duplicate by other compounds and it's limited supply a practical synthesis of menthofuran is highly desirable. The work described herein makes use of isopulegone as the starting material for menthofuran. Although a few methods existed for pulegone to menthofuran conversion involved in these protocols , were unacceptable because of low yields. The present work describes practical synthesis of (+)-menthofuran in two steps. One pot conversion of isopulegone to menthofuran in high yields.

1.2.5 : Results and discussions :

In order to have a still better and more practical synthesis of (+)-menthofuran, attention was focussed isopulegone **18** which is the intramolecular ene reaction product of citronellal.

Scheme-14 Retrosynthetic plan

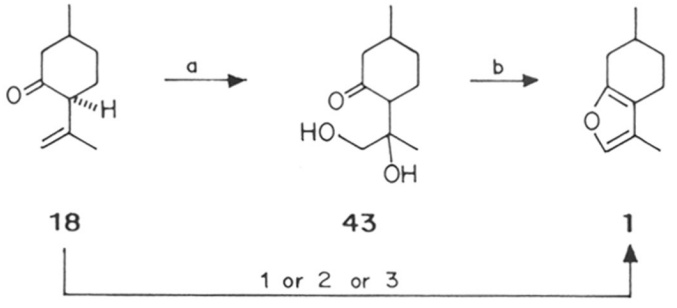


1 **43** **18** **11**

In accordance with planned retrosynthesis (Scheme - 14), isopulegol was converted isopulegone in 71% yield using Corey's procedure[17]. The structure isopulegone **18** was fully confirmed by IR, ^{1}H-NMR, mass spectroscopy and optical rotation measurements. The spectral data was found to be identical with those reported for isopulegone in the literature.[17]

The dihydroxylation[18] of isopulegone **18** with catalytic osmium tetroxide/N-methyl morpholine N-oxide in acetonitrile water mixture afforded the Keto-diol **43** as a mixture of diastereoisomers in 81% yield. The structure of ketodiol was confirmed by IR, ^{1}H-NMR and mass spectroscopy(**Fig.1**). The IR spectrum showed broad absorption at 3450 cm^{-1} and 1710 cm^{-1} indicating the presence of hydroxy and keto groups. In the ^{1}H-NMR spectrum displayed disappearance of signals at δ 4.6 (d, 1H), 4.9 (d, 1H) and 1.6 (s, 3H), corresponding to olefinic and methyl protons, and appearance of a new signals at δ 4.00 (m, 2H) which was assigned to $\underline{CH_2}$-CH proton. Further confirmation was obtained from mass spectral data, which revealed a base peak at 39 and molecular ion peak at 186.

Scheme-15



a : OsO_4 , NMO, CH_3CN , R.T. b : 10 % HCl
1 : OsO_4 , NMO, CH_3CN , Δ 2 : NBS, MeOH : CH_2Cl_2 , R.T
3 : Br_2 , $CHCl_3$, R.T.

The acid-catalysed cyclisation of the ketodiol **43** with hydrochloric acid (10%) in small amount of dichloromethane at room temperature afforded the menthofuran in good yield (78%) as a colourless oil. The IR spectrum of menthofuran displayed absorption at 1630, 1550 cm^{-1} indicating the aromatic character of compound with disappearance of absorption at 3450 cm^{-1} and 1710 cm^{-1} for hydroxy and keto groups. The ^{1}H-NMR spectrum (**Fig.2**) showed signal at δ 7.04 (s, 1H) and δ 2.1 (s, 3H) corresponding to aromatic proton and aromatic methyl group with disappearance of signals at δ 4.00 (m, 2H) and δ 1.8 (d, J = 1.5 Hz) for $\underline{CH_2}$-OH and

methyl protons. ^{13}C-NMR spectrum displayed 10 signals corresponding to 10 carbons among them signals at 150 (s), 136.9 (d), 119.74 (s) and 117.53 (s) were characteristics of aromatic carbons. Mass spectrum of menthofuran exhibited M^+ at 150 (25%). The optical rotation observed was $[\alpha]_D$ = +90.5° (c=3.5, $CHCl_3$), literature $[\alpha]_D$ = +93.3°. The above spectral data and other physical properties of menthofuran **1** thus, obtained were found to be identical in all respects with data reported in literature for natural menthofuran **1**.

In an alternate approach, one pot conversion of isopulegone **18** to menthofuran **1** was achieved by using three different reagents (Scheme -15). Isopulegone **18** was treated with OsO_4/NMO in acetonitrile under reflux to afford menthofuran **1** in 50% yield and 30% ketodiol was recovered back. Alternately, isopulegone **18** was treated with NBS[19] in CH_2Cl_2:MeOH (8:2) at room temperature to furnish the menthofuran in 71% yield. Even bromination[20] of isopulegone **18** in chloroform also afforded the menthofuran in 60% yield. The spectral data and physical properties of menthofuran **1** obtained from above three different methods was found to be identical in all respects with data reported by above method and in literature for natural menthofuran.

In conclusion, as part of the programme of work, practical synthesis of R(+)-menthofuran has been achieved in short, one pot and in high yielding steps. Because of the ease of availability of the efficient reagents utilised are easily available , the present synthesis is highly efficient and therefore highly attractive.

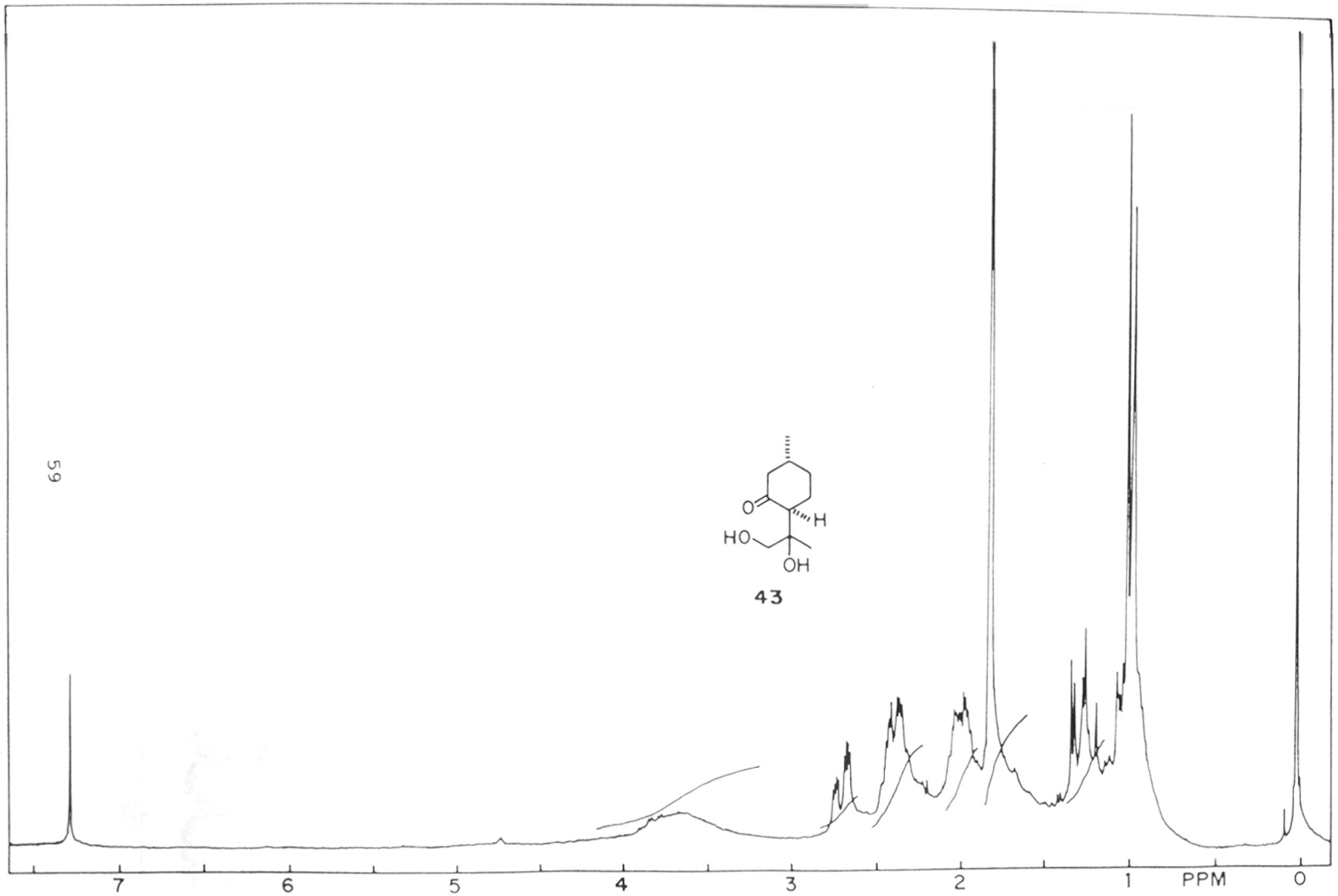


FIG.1

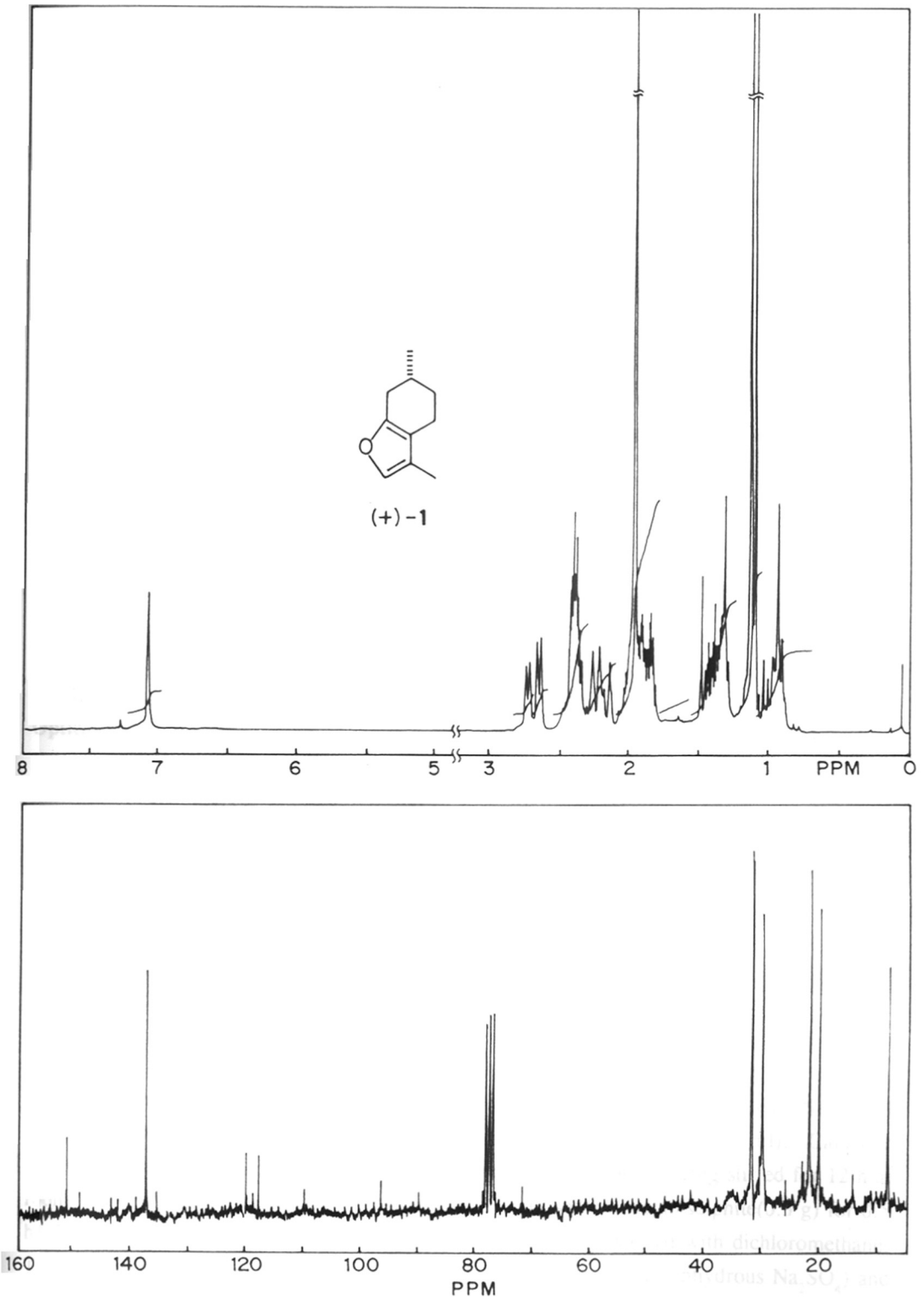
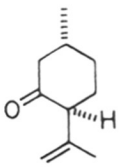


FIG. 2

1.2.6 : Experimental :

5-Methyl 2-(1-methyl ethylene)cyclohexa-1-one (isopulegone) (18) :



Pure citronellal (5 g) was converted to the isopulegone **18** according to the procedure of E.J. Corey[17] to give 3.5 gm (71%) of isopulegone. This material was sufficiently pure by NMR,IR and optical rotation for use in the next reaction.

Yield : 71%

B.P. : 52-54/0.7 mm

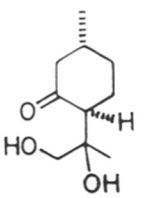
IR (Neat) : 1720, 1650, 1450, 1400, 1500, 1150, 910 cm^{-1}

^{1}H-NMR ($CDCl_3$, 80 MHz) : δ 1.00 (d, 3H, J = 6Hz), 1.2-1.5 (m, 3H), 1.7 (s, 3H), 1.75-2.00 (m, 2H), 2.4 (m, 2H), 3.00 (m, 1H), 4.6 (d, J = 1.7), 4.9 (d, 1H, J = 1.5)

Mass (m/z) : 152 (M^+, 2%), 123 (24), 119 (1), 109 (60), 93 (56), 82 (55), 79 (18), 91 (9), 68 (100), 65 (13), 53 (32), 41 (33).

Optical rotation : $[\alpha]_D$ = + 3.16° (c = 1.5 $CHCl_3$) Lit.[21] $[\alpha]_D$= +4.33° c = 2.5, EtOH.

p-menthane-3-one 8,9-diol (ketodiol) (43) :



A 20 ml test tube was charged with isopulegone **18** (3 g, 19.7 mmoles), N-methyl morpholine N-oxide (2.5 g, 21.36 mmoles) and acetonitrile: water (9:1, 5 ml). Catalytic amount of Osmium tetraoxide solution in toluene was injected. After being stirred for 12 h at room temperature, the resulting solution was treated with sodium metabisulphite(0.5 g) for 0.5 h. The reaction mixture was filtered and solid was repeatedly washed with dichloromethane. The combined organic extracts were washed with brine, water, dried (anhydrous Na_2SO_4) and evaporated to afford the viscous liquid which on purification by chromatography (SiO_2)

furnished the ketodiol **43** as a mixture of diastereoisomers.

Yield : 81%, 2.95 g

IR (Neat) : 3500, 2960, 1705, 1500, 1400 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.00 (d, 3H, J = 6.4 Hz), 1.05-1.4 (m, 2H), 1.8 (d, 3H, J = 1.5 Hz), 1.9 - 2.1 (m, 2H), 2.2-2.55 (m, 2H), 2.7 (dd, 1H, J = 2.1, 4.4 Hz), 3.7 (m, 2H).

^{13}C-NMR ($CDCl_3$, 50 MHz) : 200 (s), 107.83 (s), 81.87 (t), 79.50 (t), 52.71 (d), 43.54 (t), 33.03 (t), 29.52 (d), 26.84 (t), 26.54 (t), 22.26 (d), 21.84 (s), 20.21 (q).

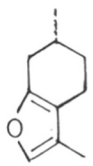
Mass (m/z) : 186 (M^+), 166 (37), 154 (32), 149 (18), 137 (31), 123 (15), 109 (28), 99 (18), 95 (26), 91 (6), 81 (50), 77 (21), 67 (46), 55 (50), 60 (7), 43 (98), 39 (100).

Analysis : Calculated for $C_{10}H_{16}O_3$: C, 64.5; H, 9.6%

Found : C, 64.9; H, 7.88%

Optical rotation $[\alpha]_D$ = -16° (c=0.9, $CHCl_3$)

(3R)-Benzofuran 4,5,6,7-tetrahydro-3,6-dimethyl (1) :



1) **From ketodiol (43)** : To a magnetically stirred solution of ketodiol (1 g, 5.37 mmol) in small amount of CH_2Cl_2, 10% HCl (30 ml) was added. After being stirred at the same temperature for 5 hours under argon atmosphere, it was extracted with ether, dried (anhydrous Na_2SO_4) and removal of solvent under reduced pressure furnished a residue. The residue which was purified on column chromatography (pet ether) to afforded (+)-menthofuran as a colourless oil.

Yield ; 0.6 g, 78%

IR (Neat) : 1681, 1550, 1108, 754, 732 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.08 (d, 3H, J = 4Hz), 1.35 (dddd, 2H), 1.83 (dddd, 1H), 1.93 (ddddq, 1H), 2.00 (d, 3H, J = 1.3 Hz), 2.16 (dddd, 1 H), 2.39 (m,1H), 2.65 (dd, 1H, J = 5.5, 10.5 Hz), 7.05 (s, 1H).

^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 150.79 (s), 136.9 (d), 119.74 (s), 117.53 (s), 31.64 (t), 31.52 (t), 29.78 (d), 21.63 (q), 20.02 (t), 8.1 (q).

Mass (m/z) : 150 (M^+), 108 (100%), 79, 39.

Optical rotation $[\alpha]_D$ = +90.5° (c = 3.5, $CHCl_3$). lit. $[\alpha]_D$ = + 93.3°

2) From Isopulegone (18) :

a) **OsO_4/NMO/CH_3CN/Δ** : A solution of isopulegone (1 g, 6.57 mmol), N-methyl morpholine N-oxide (1 g, 8.5 mmol) in 10 ml acetonitrile : water (9:1). Catalytic amount of Osmium tetraoxide solution in toluene was injected. The reaction mixture was heated at reflux temperature under argon atmosphere for 5 hours. After usual work-up furnished the residue which was purified on column chromatography to (pet.ether) to afford menthofuran (50%) as a colourless oil and ketodiol (30%) as a viscous liquid. The spectral data and and physical properties of menthofuran **1** and ketodiol **43** were found to be identical with data reported by above method (from ketodiol) and in literature[13] for natural menthofuran **1**.

b) **NBS/MeOH : CH_2Cl_2/RT** : To a magnetically stirred solution of isopulegone **18** (0.5 g, 3.2 mmol) in 10 ml MeOH: CH_2Cl_2 (2:3), NBS (0.585 g, 3.2 mmol) was added. The mixture was stirred at room temperature for 5 hours under argon atmosphere. The blue coloured solution was diluted with CH_2Cl_2 (20 ml), washed with water, brine, dried (anhydrous Na_2SO_4) and removal of solvent under reduced pressure furnished the residue. The residue which was purified by column chromatography (SiO_2) afforded menthofuran (0.380 g, 71%) as a colourless oil. The spectral data and physical properties of menthofuran was found to be identical with data reported by above method (from ketodiol) and in literature[13] for natural menthofuran **1**.

c) **Br_2/$CHCl_3$/RT** : To solution of isopulegone (0.5 g, 3.2 mmol) in pyridine (5 ml) at RT, bromine was added till the colour of bromine ceased to disappear. After half an hour the solution was heated at the reflux temperature for 2 hours under argon atmosphere. The solution was cooled and diluted with equal amount of water and extracted with ethyl acetate. Most of pyridine was washed off with water and brine, dried, evaporated to give residue which was chromatographed on silica gel (pet.ether) to afforded menthofuran (0.370 g, 75%) as a colourless oil. The spectral data and physical properties of (+)-menthofuran was found to be identical in all respects with reported by above methods and literature[13] for natural menthofuran.

1.2.7 : References :

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Section-3: Studies towards total synthesis of (+)-Laevigatin

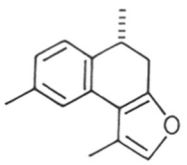
1.3.1 : Summary :

The present section concerns with the total synthesis of (+)-laevigatin, a novel sesquiterpene furan isolated from *Eupatorium laevigatum*. The simple, efficient route towards the synthesis of (+)-laevigatin has been achieved from citronellal as a starting material.

1.3.2 : Introduction :

(+)-Laevigatin **1** was isolated by two different groups. There exists confusion regarding its name as it has been coined as by Bohlmann et. al.[1a] and by Filho et. al.[1b] groups for the sake of convenience and to avoid confusion . The name laevigatin has been used for **1** throughout this thesis.

In 1978 Filho et. al.[1b] reported the isolation of a novel sesquiterpene furan laevigatin **1** from the *Eupatorium Laevigatum*. It has a novel sesquiterpene skeleton containing a furan ring which is not generally encountered in cadinane family.



1

Laevigatin

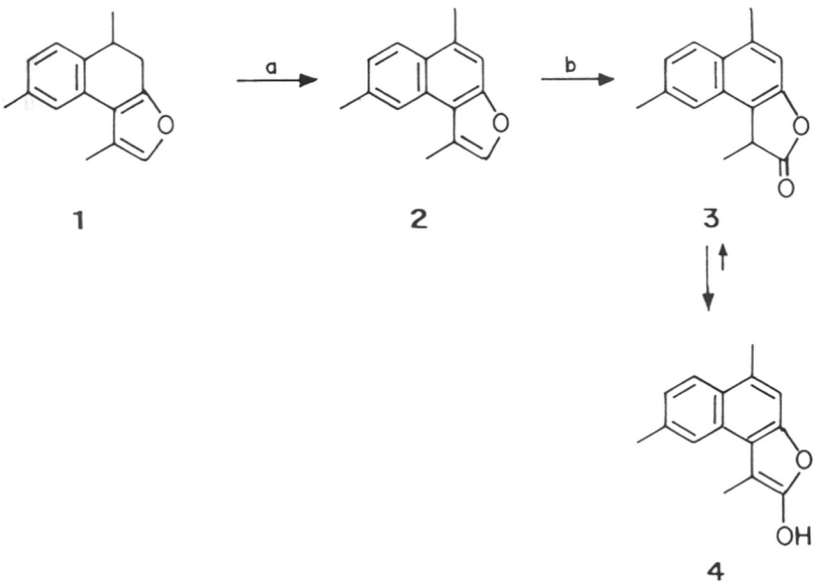
1.3.3 : Structure :

Filho et. al. determined the structure and stereochemistry of laevigatin **1** from spectroscopic data and chemical transformations. It was crystallized out from essential oil as a white solid, m.p. 65-66°C $[\alpha]_D$ = +88°. Molecular formula $C_{15}H_{16}O$ was indicated by high resolution mass spectrometry, 212.1201 calculated, Found 212.1253. The IR spectrum revealed the absorption at 1623, 1604, 1553, 1500, 1100, 809 cm^{-1} indicating the presence aromatic character as well as the absence of hydroxyl or carbonyl groups. This was supported by uv absorption at 276, 290 sh, 302 6h nm characteristic of aromatic character. The ^{1}H-NMR spectrum of **1** exhibited signals of two aromatic methyl groups at δ 2.3 and 2.33, a methyl group inserted in a secondary carbon atom at δ 1.25 (d, 3H, J = 7.0 Hz), four aromatic protons at δ 6.9 - 7.4 (m) and three benzylic protons at 2.25-3.30. The ^{13}C-NMR of **1** revealed three methyl groups at δ 10.74, 21.56 and 21.56, one methylene at δ 29.97, one non-aromatic at δ 34.57, four aromatic at δ 123.41, 126.43, 127.13 and 138.75 methine resonances and six quarternary aromatic carbons signals at δ 118.03, 125.00, 128.00, 135.50, 136.00 and 153.00.

Dehydrogenation of laevigatin **1** (Scheme-1) with DDQ-C_6H_6 at reflux temperature gave furano cadalene **2** characterized by its m.p. 98-100°C, UV, IR, mass, ^{1}H-NMR and ^{13}C-NMR and by direct comparison with an authentic sample.

Oxidation of furanocadalene **2** with m-CPBA afforded the lactone **3**. m.p. 187-188°C. The IR spectrum of **3** showed absorption at 1795 cm^{-1} characteristic of five membered lactone ring. The signal at δ 7.98 in the ^{1}H-NMR spectrum of furanocadalene **2** was assigned to the isolated peri-proton at C_5 but it should be assigned to the α-hydrogen on the furan ring. This signal is clearly absent in the spectrum of the lactone **3** which in $CDCl_3$ solution is mostly in the enol form **4** as is evidenced by the singlet at δ 2.13 due to methyl group on the heterocyclic ring. On the basis of above spectroscopic data and chemical transformation reactions, the structure **1** was assigned to Laevigatin.

Scheme-1



a : DDQ , C_6H_6 , Δ b : m-CPBA , $CHCl_3$

1.3.4 : Synthesis of (+)-Laevigatin : Literature survey :

Under this subheading Kano's, Herz's and Chavan's approaches for the synthesis of (±)-laevigatin, reported in the literature are covered. There is no report on optically pure synthesis of laevigatin **1** in the literature.

Kano's Approach[2] (Scheme - 2, 1980) :

Kano et. al. reported the first racemic synthesis of Laevigatin employing a new methodology for synthesis butenolides and its reduction into furans. Condensation of 1-phenyl-2-azetidin-2-one with 4,7-dimethyltetralone **5** gave alkylidene azetidin-2-one **6** in

excellent yield. Treatment of **6** with LDA in THF at 0°C yielded the isomerized product **7** in quantitative yield as mixture of diastereoisomers. Epoxidation of **7** with m-CPBA and its further treatment with methanesulfonic acid in refluxing benzene afforded butenolide **9** in good yield. Reduction of butenolide **9** with DIBAL-H (2.2 eq) in toluene in formation of furan **10** in quantitative yield. Hydrogenolysis of **9** over 10% Pd/C in ethanol at room temperature furnished (±)-laevigatin **1** in 75% yield. This six step synthesis of (±)**1** from **5** proceeds in good overall yields but requires the use of strong bases and expensive reagents in stoichiometric amounts.

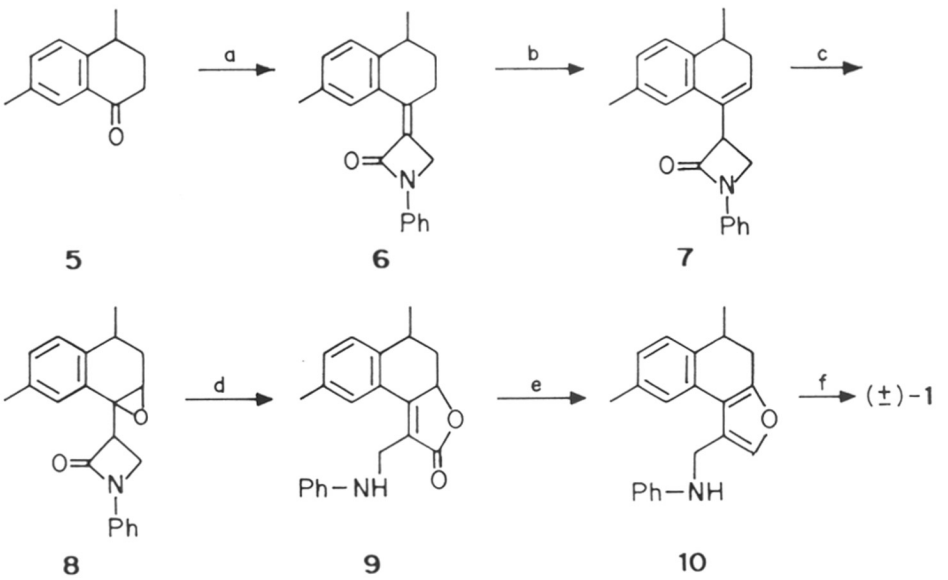
Herz's Approach[3] (Scheme - 3, 1983) :

Herz's et. al. reported the second racemic synthesis of (±) laevigatin in 1985, employing a new and general approach for the synthesis of furans, by photooxygenation of dienes to endoperoxides and its treatment with $FeSO_4$ to furnish furans. Thus, diene **11** was prepared by addition of the 4,7-dimethyltetralone **5** to isopropylmagnesium bromide followed by dehydration with $POCl_3$/pyridine. Photooxygenation of diene **11** at -78°C in acetone afforded 31% of endoperoxides **12** which was a mixture of diastereoisomers. $FeSO_4$ treatment of endoperoxides **12** in aqueous THF afforded the corresponding furan derivative (±)-laevigatin in 92% yield. This four step sequence is short and efficient to get (±)-laevigatin.

Chavan's Approach[4] (Scheme - 4, 1994) :

Like the other two approaches the starting material was the same tetralone **5**. Reformatsky reaction with ethylbromo propionate furnished the ß,γ-ester[13] in 78% yield. Here two different approaches developed in the lab were attempted. Thus, catalytic osmylation of the ß,γ-ester **13** provided diol **14** which was efficiently converted to butenolide. Alternately, the ß,γ-ester **13** was converted to the corresponding acid and CAN oxidation of acid furnished the butenolide **15** in 74% yield. DIBAL-H reduction of this furnished (±)-laevigatin in 77% yield. Thus a highly efficient and convenient methodology for the synthesis of (±)-laevigatin has been developed.

Scheme-2 (Kano et.al., Heterocycles, 1980, 14, 43):

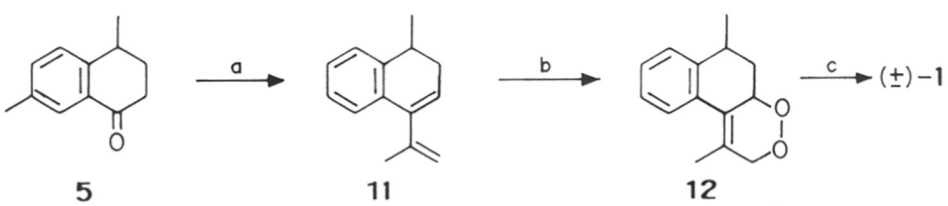


a: LDA, 1-phenyl-β-lactam b: LDA, THF, 0°C c: m-CPBA, CH_2Cl_2, R.T.

d: $MeSO_2H$, C_6H_6, Δ e: DIBAL-H, Toluene, -78°C

f: 10% Pd/C, H_2, EtOH, R.T.

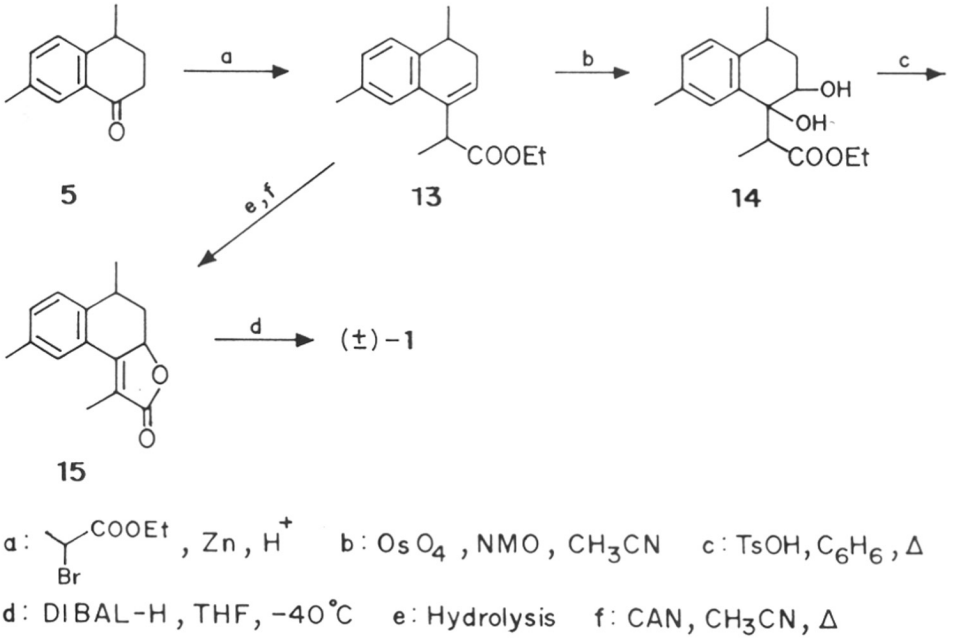
Scheme-3 (Herz et.al. J.Org.Chem. 1985, 50, 700):



a: i) $(CH_3)_2CHMgBr$, ii) $POCl_3$, Pyridine

b: O_2, Acetone, rose bengal, -78°C c: $FeSO_4$, THF, R.T.

Scheme - 4 (Chavan et.al, IUPAC, Bangalore, 1994, P-THU-26)



1.3.5 : Present work :

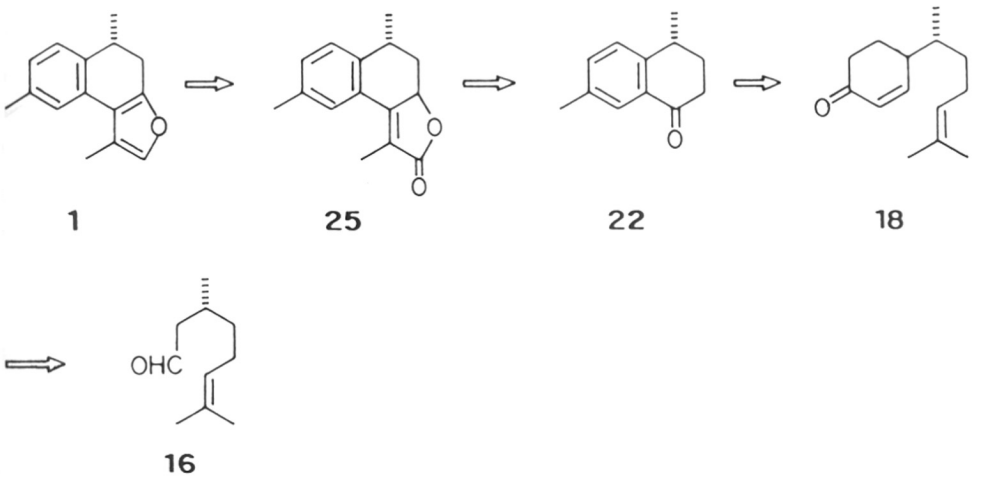
The present section primarily concerns with the stereoselective total synthesis of (+)-laevigatin, a naturally occurring terpene having unusual skeleton was isolated from *Eupatorium Laevigatum*.[1]

In connection with the interest in the synthesis of Heritol, Heritonin and related compounds. Two convenient and efficient methodologies to generate butenolides have been developed (1) *via* osmylation of ß,γ-unsaturated esters[5] (2) direct oxidative conversion of ß,γ-unsaturated acids to butenolides by CAN at room temperature.[6] The above protocol has been used for synthesis of butenolides and its conversion into naturally occurring laevigatin. The prime reason for undertaking the synthesis of laevigatin was that there is no report on optically pure synthesis of laevigatin in the literature, and also because of its unique structural features like presence of a furan ring which is not generally encountered in cadinane family. The present work describes stereoselective synthesis key intermediate 4,7-dimethyl tetralone, construction of butenolide moiety *via* osmylation of ß,γ-unsaturated esters and its conversion into naturally occurring (+)-laevigatin.

1.3.6 : Results and Discussions:

Retrosynthetic analysis (Scheme - 5) reveals that, laevigatin could be obtained from the butenolide **25** which in turn could be obtained from the key intermediate 4,7-dimethyltetralone **22**. The key intermediate optically pure 4,7-dimethyl tetralone **22** was obtained in good yields by following series of reactions.

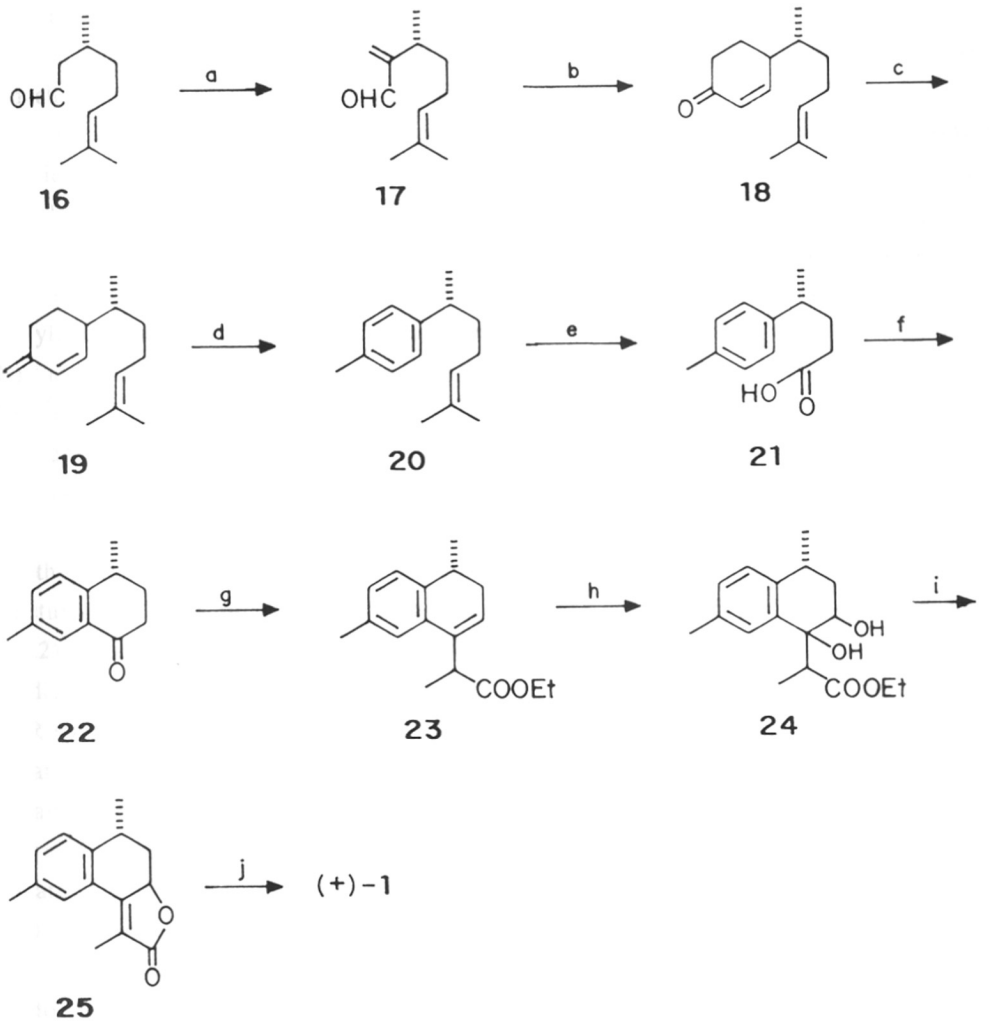
Scheme - 5 Retrosynthetic plan



In connection with the total synthesis of antimalarial artemisinin (discussed in chapter II) the enone **18** was also required. It was therefore felt that the same key synthon could be utilised for the synthesis of (+)-laevigatin as well as dihydroartemisinic acid which is a key intermediate for the synthesis of artemisinin. Thus, citronellal **16** was converted to enone **18** by reported procedures[7] (Scheme - 6). The spectral data and physical properties of exo-methylene compound **17** and enone **18** were in good agreement with those reported in the literature.[7] Wittig methylenation[8] of **18** gave triene **19** in good yield 80%. The IR spectrum of triene **19** showed absorption at 1450, 1390 cm^{-1} for double bonds and disappearance of absorption at 1690 cm^{-1} of α,β-unsaturated carbonyl group. ^{1}H-NMR spectral analysis of **19** exhibited singlet at δ 4.75 for terminal double bond protons. M^+ at 204 (58%) confirmed the assigned structure of triene **19**.

The aromatization[9] of **19** was achieved by refluxing in DMF in the presence of sulfur to furnish the aromatic compound **20** in 70% yield as a colourless oil. $[\alpha]_D$ = -25° (c=9.8 $CHCl_3$). IR spectrum of **20** revealed the absorptions at 1520, 1450, 1390 cm^{-1} indicating the

Scheme - 6



a : HCHO, Piperidine acetate, Δ

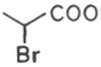
b :  , MeOH , MeONa

c : $(Ph)_3P$ CH_3I, BuLi, THF, 0°C

d : Sulfur, DMF, Δ

e : OsO_4 (Cata), Jones reagent, R.T.

f : TFA, TFAA, 0°C

g :  , Zn, H^+

h : OsO_4, NMO, CH_3CN

i : TsOH, C_6H_6, Δ

j : DIBAL-H, THF, -40°C

presence of aromatic character as well as absence of alkene groups. ^{1}H-NMR spectrum (**Fig.1**) of **20** displayed signals at δ 7.2 (s, 4H) and δ 2.4 (s, 3H) for aromatic protons and aromatic methyl group respectively. ^{13}C-NMR displayed 15 signals corresponding to 15 carbons, among them signals at δ 144.75, 135.19, 131.27, 129.19, 127 and 124.90 were characteristic of six aromatic and two olefinic carbons.

Oxidative cleavage of double bond with Jones reagent in the presence of Osmium tetroxide (catalytic) *via* diol to acid[10] in one operation afforded acid **21** in 84% yield as a colourless oil. $[\alpha]_D$ = -14° (c=4.4, $CHCl_3$). The IR spectrum of **21** showed absorption at 2900 cm^{-1} and 1700 cm^{-1} indicative of the presence of -COOH functionality. The ^{1}H-NMR spectrum showed following features δ 2.00 (m, 2H) and 2.25 (t, 2H) for the two side chain methylene groups. Further, ^{1}H-NMR spectrum showed disappearance of signals at δ 5.2 (t, 1H) and signal at δ 1.6 (s, 3H), 1.8 (s, 3H) for olefinic proton and two methyl group protons. The ^{13}C-NMR showed signal at 180.33 for -COOH carbon. Rest of carbons displayed expected splittings and chemical shifts. Mass spectrum [M^+, 192, (20%)] and fragmentations confirmed the assigned structure **21**.

Cyclization of acid **21** by using trifluoroacetic anhydride[11] gave optically pure 4,7-dimethyltetralone **22** as a colourless oil in 80% yield. $[\alpha]_D$ = +9° (c=7.0, $CHCl_3$). The structure of **22** was fully confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy (**Fig.2**). The IR spectrum showed absorptions at 1680 cm^{-1} for the benzylic carbonyl group and disappearance of absorptions at 1700 cm^{-1} and 2900 cm^{-1} of the -COOH group. The ^{1}H-NMR spectrum showed disappearance of methylene signal $\underline{CH_2}COO$ at δ 2.25 (t, 2H) and appearance of signal at δ 2.42-2.9 (m, 2H) for the $\underline{CH_2}$-CO protons. Aromatic protons were displayed at δ 7.2 (d, 1H), 7.3 (d, 1H) and 7.9 (s, 1H) thus confirming the ortho trisubstitution pattern of the benzene nucleus. The ^{13}C-NMR also confirmed the presence of benzylic carbonyl carbon at 197.8 (s). Mass spectral analysis confirmed the assigned structure **22** (M^+, 174, 77%).

Having achieved the synthesis of chiral teralone **22**, the next task was straight forward transformation of **22** to butenolide **25** developed in this laboratory and its further conversion to (+)-laevigatin.

Accordingly, Reformatsky reaction[12] on 4,7-dimethyl tetralone **22** with ethyl 2-bromopropionate in ether followed by acidic workup afforded the ß,γ-unsaturated ester **23** in 78% yield as a sole product. The ester **23** was well characterized by IR, ^{1}H-NMR and mass spectroscopy. The IR spectrum of **23** showed absorption at 1740 cm^{-1} for the ester carbonyl group indicating it to be isolated ester as against α,ß-unsaturated ester which would absorb at a lower frequency. The ^{1}H-NMR spectrum revealed a triplet at δ 5.3 (t, 1H) for Ar-CH=$\underline{CH}$ proton and doublet at δ 1.4 for $\underline{CH_3}$-CH-COOEt. The mass spectrum confirmed the structure which showed M^+ at 258 and base peak 157.

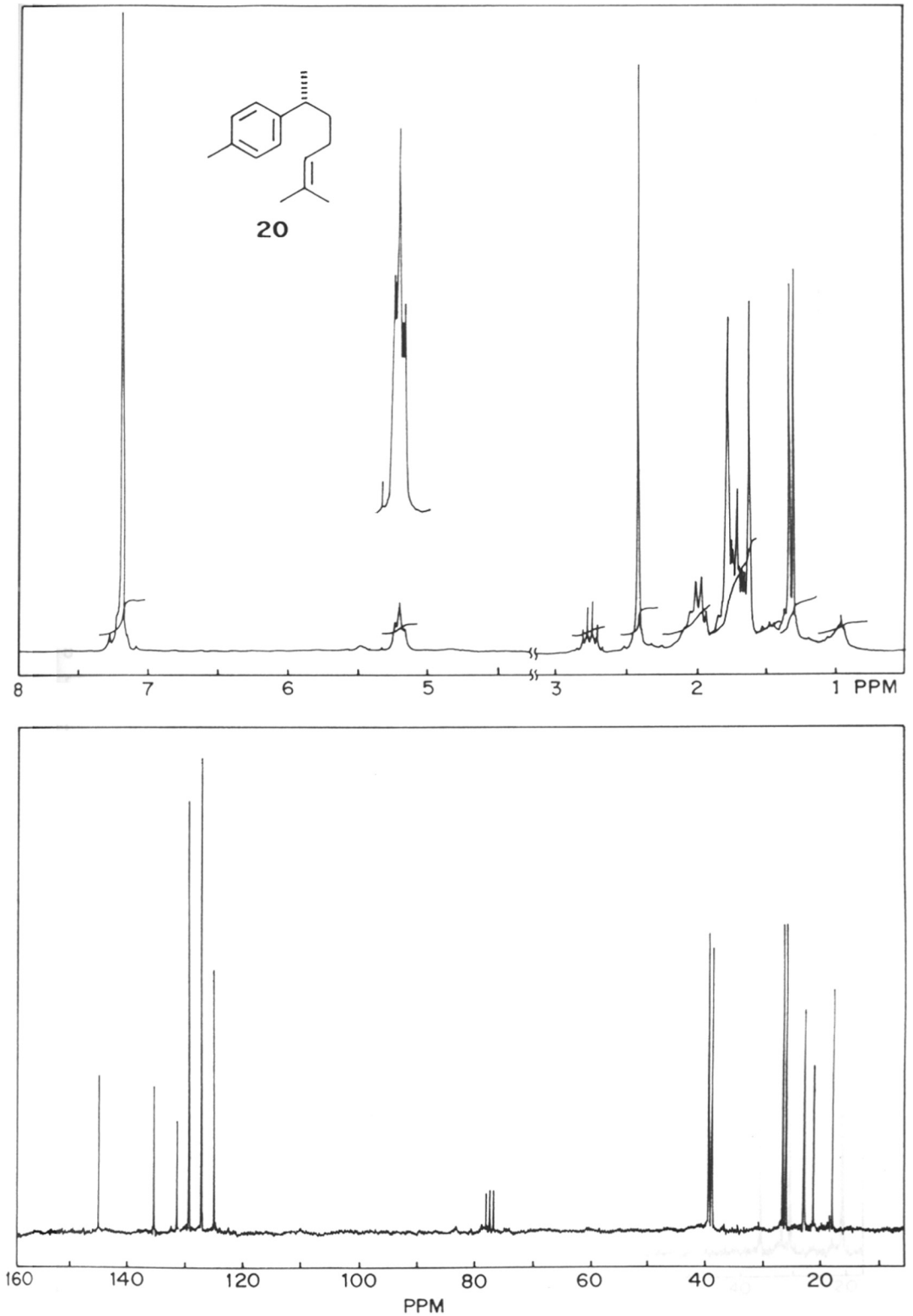


FIG.1

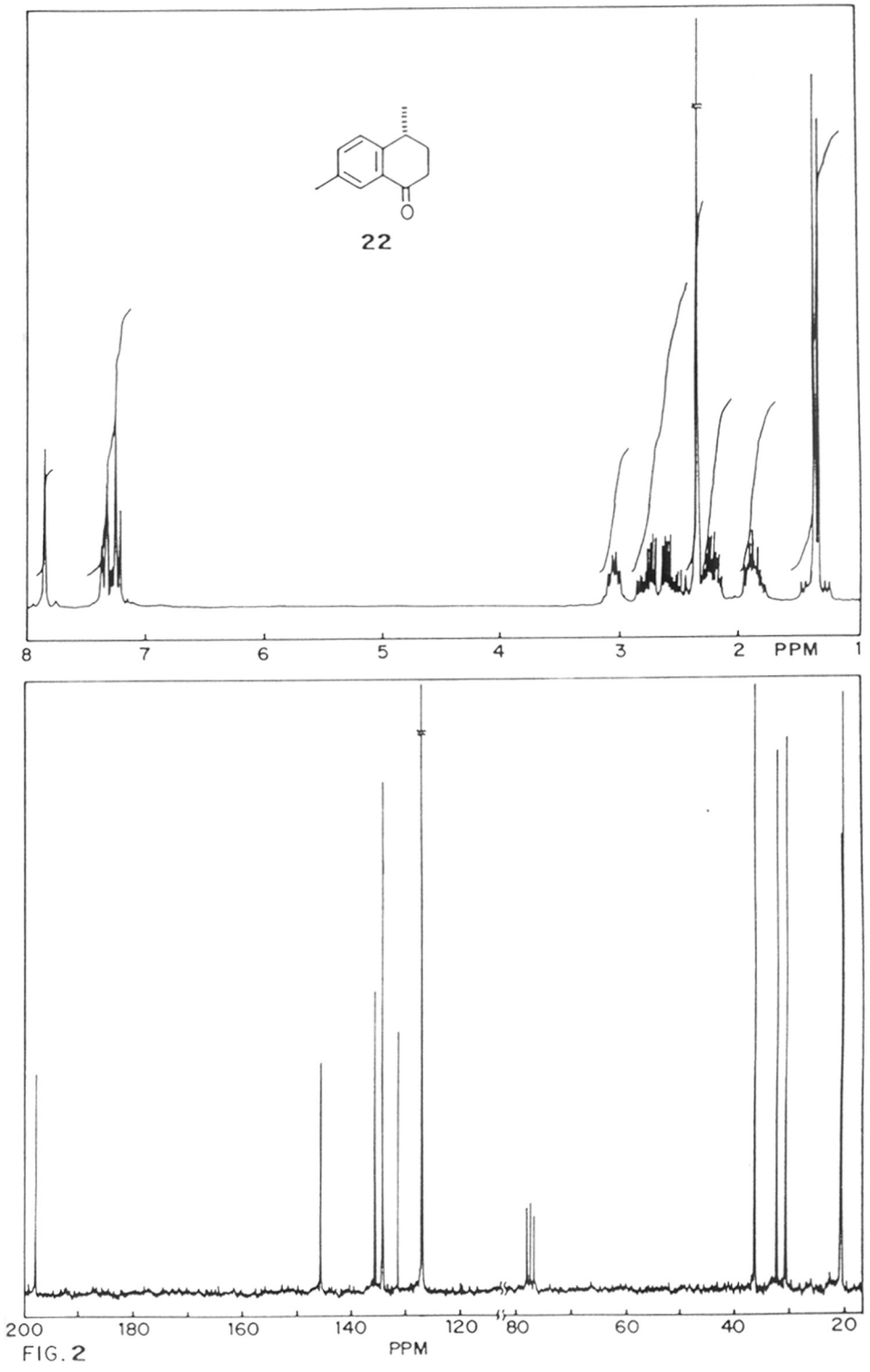


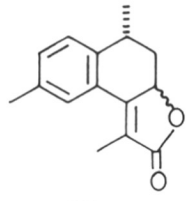
FIG. 2

Dihydroxylation[13] of the ß,Y-unsaturated ester **23** with catalytic osmiumtetroxide/N-methylmorpholine N-oxide in acetonitrile : water mixture afforded the diol **24** as a mixture of diastereoisomers in 80% yield. The IR spectrum showed absorption at 3450 cm^{-1} indicating the presence of hydroxyl groups. In the ^{1}H-NMR spectrum, the triplet centered at δ 5.9 for the olefin proton was absent and multiplet appeared at δ 4.1, which was assigned to Ar-CH-OH proton. Further confirmation was obtained from the mass spectral data, which revealed a base peak at m/z 145 and a molecular ion peak at m/z 214 ($-H_2O$).

The acid catalysed cyclization of the diol **24** with catalytic amount of p-TsOH in refluxing benzene afforded the corresponding butenolide **25** in 73% yield.[5] (m.p. 125°C). The structure of butenolide **25** was fully confirmed by IR, ^{1}H-NMR and mass spectroscopy (**Fig.3**). The IR spectrum displayed a characteristic carbonyl frequency at 1760 cm^{-1} for the presence of butenolide moiety with disappearance of absorption at 3450 cm^{-1} and 1740 cm^{-1}. The ^{1}H-NMR spectrum showed disappearance of signals at δ 4.2 (q, 2H), $-CH_2$-O, 4.1 (m, 3 H), CH-OH, 1.5 (d, 3H), CH_3-CH and exhibited following salient features δ 2.1 (s, 3H), CH_3-C, 5.1 (ddq, 1H) and 7.3-7.6 (m, 3H) aromatic protons. The aromatic protons showed downfield shift as compared to the diol **24**, due to the deshielding imposed on them by the butenolide moiety. M^+ at 228 (100%) confirmed the assigned structure of butenolide **25**.

Reduction of butenolide **25** with diisobutyl aluminum hydride (DIBAL-H)[14,15,16] in THF provided a furan compound (+)-laevigatin in 77% yield as a white solid. m.p. 66°C, $[\alpha]_D$ = +89° (c=2.3, $CHCl_3$). The IR spectrum showed absorption at 1620, 1604, 1553, 1550 cm^{-1} revealed its aromatic character. The ^{1}H-NMR spectrum (**Fig.4**) of (+)-laevigatin showed signals at δ 2.3, 2.33 of two aromatic methyl groups with disappearance of signal at δ 4.9 (ddq, 1H), of methine proton on the carbon bearing lactone oxygen atom. The mass spectrum exhibited M^+ peak at 212 (100%). The above spectral data and physical properties was found to be identical with those reported for laevigatin **1**[1b] obtained from the natural sources.

Thus first synthesis of (+)-laevigatin has been achieved from easily available citronellal. All the steps involved in the formation of dimethyltetralone are simple, efficient and convenient. Further conversion of to (+) laevigatin was done by a methodology developed in this lab.



25

FIG.3

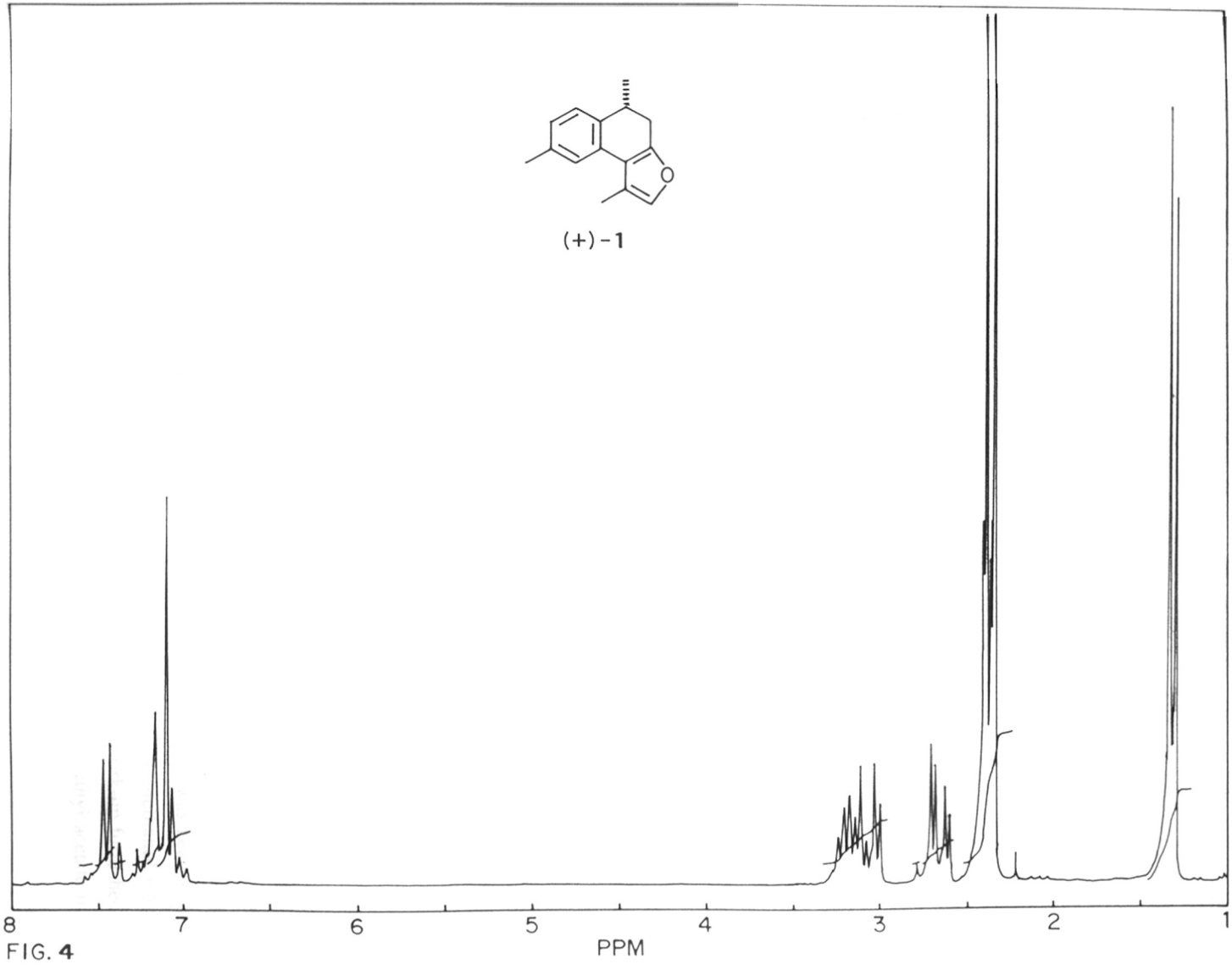
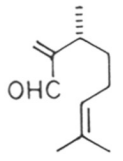


FIG. 4

1.3.7: Experimental :

α-Methylene-3,7-dimethyl-6-octanal (17) :



This was prepared from citronellal **16** accroding to reported procedure.[7]

Yield : 90%

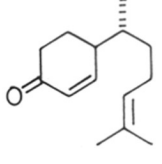
IR (Neat) : 1730, 1600, 1450, 1400, 1100, 1040 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.1 (d, 3H, J = 6.5 Hz), 1.3-1.5 (m, 2H), 1.55 (s, 3H), 1.6 (s, 3H), 1.8-2.00 (q, 2H), 2.7 (quintet, 1H), 5.1 (t, 1H), 6.0 (s, 1H), 6.2 (s, 1H), 9.5 (s, 1H).

Mass (m/z) : 166 (M^+, 8%), 151 (8), 133 (6), 123 (12), 109 (76), 105 (8), 95 (37), 93 (20), 91 (10), 83 (37), 81 (42), 79 (16), 77 (11), 69 (86), 67 (76), 65 (11), 63 (2), 59 (6), 55 (100), 53 (32), 51 (10).

Optical rotation : $[\alpha]_D$ = -67° (c=2.47, $CHCl_3$).

Enone (18) :



To a stirred solution of methyl acetoacetate (1.397 g, 12.00 mmol) in distilled methanol (10 ml) was added MeONa (catalytic) and reaction mixture was stirred at room temperature for 0.5 hours. Next a solution of α-methylene compound **17** (2 g, 12.00 mmol) in methanol (5 ml) was added and stirring was continued at the same temperature for 2 hours. It was heated at 60°C (oil bath temperature) for 4 hours and then refluxed for 5 hours. The methanol was removed in vacuo and water was added to the reaction mixture. After usual work-up furnished viscous liquid which was purified by column chromatography (SiO_2) with 5% ethyl acetate in pet ether afforded enone **18** as a colourless viscous liquid.

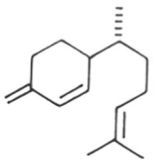
Yield : 1.15 g, 47%

IR (Neat) : 1690, 1600, 1466, 1385, 1250, 1143, 961 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 90 MHz) : δ 0.9 (d, 3H, J = 6Hz), 1.00 (d, 3H, J = 6Hz), 1.2-1.5 (m, 4H), 1.6 (s, 3H), 1.7 (s, 3H), 1.6-1.7 (m, 2H), 2.00 (m, 2H), 2.5 (m, 2H), 5.00 (t, 1H), 5.9 (dd, 1H, J = J_2 = 1.5 Hz), 6.9 (m, 1H).

Mass (m/z) : 206 (M^+, 20%), 191 (6), 179 (7), 162 (8), 149 (8), 136 (10), 123 (58), 109 (20), 94 (25), 79 (25), 69 (100), 55 (53).

Triene (19) :



2N Hexane solution of BuLi (3.675 g, 58.5 mmol, 30 ml) was added to a suspension of methyl triphenyl phosphonium iodide (28 g, 58.43 mmol) in 50 ml dry THF under nitrogen atmosphere at 10°C. The clear yellow coloured solution was stirred for 15 min. and then solution of enone **18** (12 g, 58.25 mmol) in THF (20 ml) was added. The colour of reaction mixture changed from yellow to orange. The reaction mixture was further stirred at R.T. for 5 hours. The thick precipitate was filtered off and washed thoroughly with ether (3 x 50 ml) and combined organic extracts was washed with water, brine, dried and solvent was removed in vacuo to furnish a residue. The residue oil was chromatographed on silica gel with pet-ether as the eluent to triene **19** as a colourless oil.

Yield : 9.65 g, 81.22%

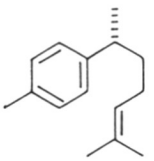
IR (Neat) : 1450, 1390, 880, 830 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5Hz), 1.1-1.4 (m, 2H), 1.4-1.6 (m, 3H), 1.65 (s, 3H), 1.7 (s, 3H), 1.85-2.15 (m, 2H), 2.3-2.6 (m, 3H), 4.75 (s, 2H), 5.1 (t, 1H), 5.7 (t, 1H), 6.2 (d, 1H, J = 5 Hz).

^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 143.860 (s), 135.19 (d), 133.98 (d), 131.30 (s), 130.16 (d), 129.80 (d), 125.07 (d), 110.203 (t), 110.13 (t), 41.32 (d), 40.88 (d), 36.91 (d), 36.80 (d), 34.56 (t), 34.19 (t), 30.77 (t), 30.63 (t), 26.63 (t), 26.33 (t), 24.770 (t), 17.84 (q), 16.68 (q), 16.14 (q).

Mass (m/z) : 204 (M^+, 204, 58%), 189 (6), 173 (3), 161 (100), 147 (15), 133 (76), 120 (53), 109 (36), 105 (26), 93 (44), 82 (9), 77 (13), 69 (12), 57 (2).

6-p-Tolyl-2,6-dimethyl Hept-2-ene (20) :



A homogeneous solution containing sulfur (0.480 g, 15 mmol) and triene **19** (1 g, 4.95 mmol) in 10 ml dry DMF was heated under reflux for 30 min. The reaction mixture was cooled, extracted with pet-ether (3 x 20 ml), washed with water, brine and dried. Rotary evaporation of solvent furnished the residue, which was purified by column chromatography (SiO_2, pet ether) afforded aromatic compound **20** as a colourless oil.

Yield : 700 mg, 71%

IR (Neat) : 1520, 1450, 1390, 820 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.3 (d, 3H, J = 5Hz), 1.6 (s, 3H), 1.8 (s, 3H), 1.6-1.7 (m, 2H), 2.9-2.11 (m, 2H), 2.4 (s, 3H), 2.8 (q, 1H), 5.2 (t, 1H), 7.2 (s, 4H).

^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 144.75 (s), 135.19 (s), 131.27 (s), 129.19 (d), 127.08 (d), 124.9 (d), 39.34 (q), 38.79 (t), 26.48 (t), 25.89 (q), 22.71 (d), 21.14 (q), 17.80 (q).

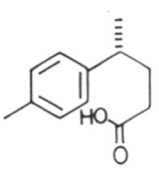
Mass (m/z) : 202 (M^+, 45%), 187 (4), 174 (4), 159 (7), 145 (30), 132 (87), 119 (100), 105 (55), 91 (32), 77 (15), 69 (24), 55 (26).

Optical rotation : $[\alpha]_D$ = -25° (c=9.8, $CHCl_3$)

Analysis : Calculated for $C_{15}H_{22}$: C, 89.1; H, 10.89%

Found : C, 88.8; H, 10.84%

4-p-Tolylpentanoic acid (21) :



To a solution of alkene **20** (1 gm, 4.9 mmol) dissolved in 10 ml of acetone was added OsO_4 solution in toluene and 6.5 ml Jones reagent. After the mixture was stirred for 5 hrs at

room temperature, 1 ml of isopropanol was added followed by 0.5 gm of sodium metabisulphite. The mixture was diluted with 10 ml of water and stirred until dark green homogeneous solution was produced. This solution was extracted with ethyl acetate, dried and concentrated in vacuo furnished the residue, which was purified by column chromatography gave acid **21** as a colourless liquid.

Yield : 800 mg, 84%

IR (Neat) : 2900, 1710, 1460, 1420 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.25 (d, 3H, J = 6.5 Hz), 2.00 (m, 2H), 2.25 (t, 2H), 2.4 (s, 3H), 2.7 (m, 1H), 7.2 (s, 4H), 11.00 (bs. s, 1H).

^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 180.33 (s), 143.09 (s), 135.64 (s), 129.28 (d), 126.93 (d), 38.96 (d), 35.85 (t), 33.09 (t), 22.26 (q), 20.98 (q).

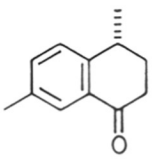
Mass (m/z) : 192 (M^+, 20%), 174 (2), 161 (2), 145 (2), 132 (66), 119 (100), 105 (8), 91 (32), 77 (12), 65 (10), 69 (4), 55 (4).

Optical rotation : $[\alpha]_D$ = -14° (c = 4.4 , $CHCl_3$)

Analysis : Calculated for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33%

Found : C, 74.60; H, 8.65%

4,7-dimethyl tetra-1-one (22) :



p-Tolyl pentanoic acid **21** (402 mg, 2 mmol) was dissolved in minimum amount of freshly distilled trifluoroacetic acid (0.2 ml) under nitrogen atmosphere. To this solution, freshly distilled trifluoroacetic anhydride (0.5 g, 2.38 mmol) was added dropwise at 0°C. The reaction mixture was stirred for 3 h at 0°C to room temperature and was neutralised with ice cold sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, dried (anhydrous sodium sulphate) and solvent evaporated under reduced pressure to furnish a crude product. Crude product when passed through column (5% EtOAc/pet·ether) furnished the tetralone **22** as a viscous liquid.

Yield : 280 mg, 80%

IR (Neat) : 1680, 1610, 1490, 1450, 1410, 1290, 1200 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.4 (d, 3H, J = 5.26 Hz), 1.8-2.00 (m, 1H), 2.15 - 2.3 (m,

1H), 2.4 (s, 3H), 2.45 - 2.9 (m, 2H), 3.1 (m, 1H), 7.2 (d, 1H), 7.3 (d, 1H), 7.9 (s, 1H).

^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 197.80 (s), 145.72 (s), 135.64 (s), 134.19 (s), 131.33 (d), 127.02 (d), 126.97 (d), 36.18 (t), 32.17 (q), 30.49 (t), 20.52 (d), 20.38 (q).

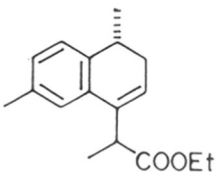
Mass (m/z) : 174 (M^+, 77%), 159 (100), 146 (44), 141 (4), 131 (75), 117 (70), 103 (14), 91 (58), 77 (26), 65 (4), 58 (8).

Optical rotation : $[\alpha]_D$ = + 9° (c = 7.0, $CHCl_3$)

Analysis : Calculated for $C_{12}H_{14}O$: C, 82.75; H, 8.04%

Found : C, 82.30; H, 7.50%

Ethyl-2-(4,7-dimethyl-3,4-dihydronaphthalene) propionate (23) :



To a stirred solution of tetralone **22** (200 mg, 1.14 mmol), ethyl bromopropionate (0.3 g, 1.16 mmol) and activated zinc (0.222 g, 3.4 mmol) in dry ether (10 ml), iodine crystals (0.210 g, 1.6 mmol) were added at such a rate as to effect the ether to reflux gently. After 3 h the reaction mixture was decomposed with 50% HCl-crushed ice organic layer was separated and aqueous layer extracted with ether. Combined organic layers were washed with aqueous $NaHCO_3$ followed by sodium thiosulphate solution. It was then dried (anhydrous sodium sulphate) and rotary evaporated to furnish a residue. Chromatographic purification (SiO_2) of residue (5% EtOAc/pet-ether) afforded ß,γ-unsaturated ester **20** as viscous yellowish oil.

Yield : 230 mg, 78%

IR (Neat) : 1740, 1620, 1460, 1380, 1350, 1220, 1180 cm^{-1}

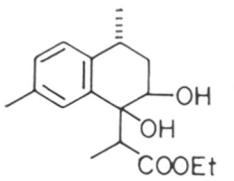
^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.17 (d, 3H, J = 7Hz), 118 (t, 3H, J = 7Hz), 1.4 (d, 3H, J = 8 Hz), 2.15 (m, 2H), 2.4 (s, 3H), 2.5 (m, 1H), 3.6 (q, J = 7 Hz, 1H), 4.2 (q, 2H, J = 7 Hz), 5.9 (t, 1H, J = 5Hz), 6.8-7.2 (m, 3H).

Mass (m/z) : 258 (M^+, 30), 243 (2), 228 (3), 197 (4), 184 (26), 169 (84), 157 (100), 142 (46), 128 (40), 115 (30), 102 (58), 91 (10), 83 (4), 74 (13), 55 (8).

Analysis : Calculated for $C_{17}H_{22}O_2$: C, 79.06; H, 8.52%

Found : C, 78.92; H, 8.46%

Ethyl-2-(1,2-dihydroxy-4,7-dimethyl-1,2,3,4-tetrahydro-naphthalene)propionate (24) :



A 20 ml test tube was charged with ß, γ-unsaturated ester (0.120 g, 0.465 mmol), N-methylmorpholine N-oxide (0.108 g, 0.930 mmol) and acetonitrile: water mixture (9:1, 0.5 ml). Catalytic amount of OsO_4 solution in toluene was injected. The reaction was monitored by TLC. After being stirred for 12 h at room temperature, the resulting solution was treated with sodium metabisulphite (0.5g) for 0.5 h. Then the reaction mixture was filtered and solid was washed repeatedly with dichloromethane. The combined washings were dried over anhydrous sodium sulfate and evaporated to afford the diol as viscous liquid which on purification by column chromatography (SiO_2) furnished the diol as a viscous liquid.

Yield : 108 mg, 80%

IR (Neat) : 3450, 2950, 1740, 1620, 1510, 1480, 1380, 1340, 1200 cm^{-1}.

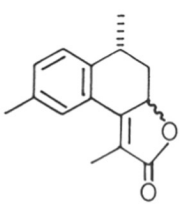
^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (d, 3H, J = 8Hz), 1.2 (t, J = 7 Hz, 3H), 1.5 (d, 3H, J = 6Hz), 2.2 (s, 3H), 1.6-3.3 (m, 4H), 4.1 (m, 3H), 6.8 - 7.4 (m, 3H).

Mass (m/z) : 292 (M^+), 274 (2), 213 (2), 200 (6), 191 (27), 173 (96), 157 (16), 145 (100), 129 (26), 115 (31), 105 (25), 91 (36), 77 (20), 69 (6), 65 (14), 55 (26).

Analysis : Calculated for $C_{17}H_{24}O_4$: C, 69.86; H, 8.21%

Found : C, 69.32; H, 8.16%

3,7,10-trimethyl 6,7-dihydronaphto (1,2b)-furan-2-(5H)-One-(25) :



A mixture of diol **24** (0.108 g, 0.36 mmol) and p-toluene sulfonic acid (catalytic) in 20 ml of dry benzene was refluxed with azeotropic removal of water. After 30 min reaction mixture was cooled, washed with aqueous $NaHCO_3$, dried and concentrated in vacuo to afford butenolide **25** as a semisolid, which was purified on SiO_2 (9:1 pet-ether:ethyl acetate) to

furnish the butenolide as white solid.

Yield : 60 mg, 71%

M.P. : 125°C

IR (Neat) : 1760, 1660, 1500, 1440, 1400, 1330, 1240, 1140 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.4 (d, 3H, J = 4Hz), 1.8 (m, 1H), 2.1 (s, 3H), 2.4 (s, 3H), 2.6 (m, 1H), 3.2 (m, 1H), 4.9 (ddq, 1H, J = 2,6, 12 Hz), 5.1 (ddq, 1H, J = 2,6,12 Hz), 7.1 (d, 1H, J = 8 Hz), 7.2 (d, 1H, J = 2Hz), 7.5 (dd, 1H, J = 2, 8 Hz).

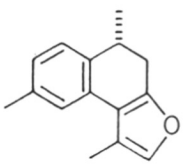
^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 174.57 (s), 156.10 (s), 155.78 (s), 142.57 (s), 141.97 (s), 129.60 (s), 127.61 (s), 127.22 (s), 127.13 (s), 125.12 (s), 124.0 (d), 117.57 (d), 116.92 (d), 77.61 (d), 75.03 (d), 38.34 (d), 35.84 (d), 32.34 (t), 31.16 (t), 23.40 (q), 21.12 (q), 9.14 (q).

Mass (m/z) : 228 (M^+, 100), 213 (52), 200 (70), 185 (72), 171 (46), 157 (69), 141 (99), 128 (71), 115 (75), 102 (13), 91 (30), 77 (71), 63 (50).

Analysis : Calculated for $C_{15}H_{16}O_2$: C, 78.9; H, 7.0%

Found : C, 78.5; H, 6.9%

(+)-Laevigatin (1) :



To a solution of butenolide **25** (50 mg, 0.21 mmol) in dry THF (5 ml) was added a 1.16 N DIBAL-H THF solution (0.5 ml) with stirring at -40°C. The mixture was stirred at this temperature for 1 hour, 10% HCl (0.5 ml) was added with stirring and the mixture was stirred under nitrogen atmosphere at same temperature for 15 min. The mixture was then added to ice/water and extracted with ether. The extracts were washed with aqueous $NaHCO_3$ solution, dried with sodium sulfate and evaporated to leave an oil. The residue was chromatographed on silica gel to furnish (+)-laevigatin **1** as a white solid.

Yield : 35 mg, 76%

M.P. : 66°C

IR (Neat) : 1620, 1604, 1553, 1550 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.3 (d, 3H, J = 7.5 Hz), 2.3 (s, 3H), 2.33 (s, 3H), 2.7 (dd, 1H), 3.1 (m, 2H), 7.00-7.5 (m, 3H).

Mass (m/z) : 212 (M^+, 100%), 197, 182, 169, 154.

Optical rotation $[\alpha]_D$ = + 89° (c=2.3, $CHCl_3$). lit.[1b] $[\alpha]_D$= +88°.

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CHAPTER-2

Synthetic Approaches Towards (+)-Artemisinin

2.1 : History, Isolation and Structure :

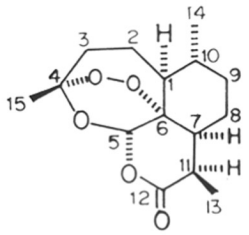
Malaria is one of the most widespread parasitic diseases caused by invasion on human body by the protozoan parasites of the class of Plasmodium. It is estimated that there are still 6.5 million people who are chronically affected and there are 3.0 million new cases are reported and of which 2 million are killed each year.[1,2]

As early as the 16th century natural products gained wide acceptance in treatment of malaria, when the therapeutic action of the bark of cinchona tree was observed by Europeans. Cinchona bark must be one of the most successful of all herbal remedies and illustrates the value of folk medicine. The active principle quinine isolated in 1820 was mainly used for malaria until other synthetic antimalarials were developed. During the 1920s a synthetic quinoline derivative pamaquin was found to be more effective than quinine in killing malaria parasites lodged in the liver. Also mepacrine was developed as a synthetic alternative to quinine. Further more research led to the production of chloroquine which has fewer side effects. Primaquin is another quinoline derivative with antimalarial properties particularly effective against Plasmodium viva. A biquanidine compound proqanil also has powerful antimalarial properties but is more generally used as a prophylactic. Pyrimidine derivative, pyrimethamine by itself is used for suppression only. Most of the drugs for the treatment of malaria are derivatives of quinoline and acridine and until recently, there was no alternative chemotherapy. Unfortunately none of the drugs mentioned above is particularly effective against Plasmodium falciparum.

In 1967, the government of the Peoples Republic of China embarked on a systematic examination of indigenous plants used in traditional remedies as sources of drugs. One such plant, a pervasive weed with a long history of use is known as Qinghao (Artemisia Annua L.). Its earlier mention dates back to 200 years in the "Recipes for 52 kinds of Diseases" found in the Mawangdui Han dynasty, tomb.[3] In that work the herb was recommended for use in haemorrhoids. This plant is mentioned further in the Zhou Hou Bei Ji Fang (Hand Book of Prescriptions for Emergency Treatment) written in 340 AD. In the 15th century Li Shizhen[4] in his Ben Cao Gang Mu (compendium of materia medica) wrote that chills and fever of malaria can be treated with qinghao. A decoction of Artemisia Annua and Carapax trionycis was suggested in the Wenbing Tiaobian in 1798 as a treatment of malaria.[5]

The crystalline active principle quinghaosu 1 was then isolated in 1972 and named qinghaosu or arteannuin and the more western sounding name "Artemisinin". Extraction of dried leaves of qinghaosu with petroleum ether at low temperature and chromatography on silica gel with subsequent recrystallization gave fine colourless crystals with m.p. 156-157°C and $[\alpha]_D$ = + 66.3° (c=1.64, $CHCl_3$).[6] The yield was variable ranging from negligible quantities to almost 1% depending on the area from which the plant was collected.[7]

Artemisia Annua was found to have other terpenes and related compounds like 1,8-cineole, borneol acetate, 1-ß-pinene, cuminal ß-caryophyllene, coumarin, stigmasterol, camphene, cadinene, arteannuin-B, camphor, ß-fernesene, arteannuin A, hydroarteannuin, scopolin, scopoletin, artemisia ketone, artemisinic acid and benzylisovalerate.[5,8]



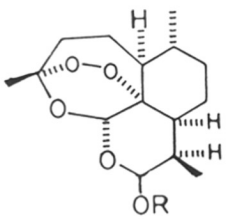
Artemisinin **1**

High resolution mass spectrum[9] (m/e. 282.1742 M^+) combined with elemental analysis led Chinese workers to assign an emperical formula of $C_{15}H_{22}O_5$ which indicated a possible sesquiterpenoid structure. The compound showed no absorption in the uv range while in the IR region there were absorption peaks at 1745 cm^{-1} (lactone) and at 722, 831, 881, 1115 cm^{-1} (peroxide). The ^{1}H-NMR and ^{13}C-NMR spectra led to the assignment of three methyl groups, an acetal function and several other carbon atoms. The structure of artemisinin together with its absolute configuration was finally resolved by x-ray diffraction studies.[10] Absolute configuration of the lactone ring has been reached by a comparison of its ORD spectrum with a structurally related known sesquiterpene arteannuin-B **7**. The most unusual feature of the chemical structure is the 1,2,4-trioxane ring which may also be viewed as a bridging peroxide group. Artemisinin is the only known 1,2,4-trioxane occurring in nature, although compounds with peroxide bridges are common, particularly in marine organisms. This unusual compound has a peroxide grouping but lacks a nitrogen containing heterocyclic ring system which is found in most antimalarial compounds.

2.2 : Biological Activity :

In extensive clinical trials in China[11] artemisinin **1** showed promise in the treatment of otherwise drug resistant malaria, notably Plasmodium falciparum. It is almost certain that the crucial structure in artemisinin which gives it's antimalarial activity is the peroxide bridge. Other parts of the molecule may be modified without loss of antimalarial activity. Removal of one or two of the methyl groups at 13 and 14, leaves a molecule which is still active against Plasmodium falciparum[12]. The lactol **2a** obtained by reduction of artemisinin is a better

antimalarial agent than artemisinin **1** itself, indicating clearly that the carbonyl function is not essential for activity. [13]



2

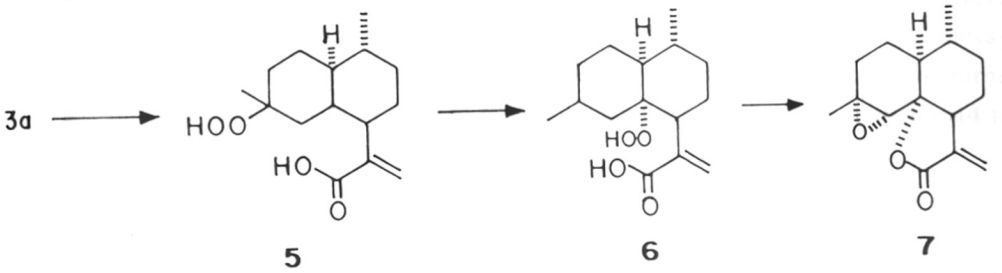
a : R = H
b : R = alkyl
c : R = COR'
d : R = COOR'
e : R = $OCOCH_2CH_2-COOH$
f : R = $OCH_2C_6H_4COONa$
g : R = NHR

Although the peroxide bridge may be the crucial structure in artemisinin, the rest of the molecule has a profound effect on the in vitro and in vivo antimalarial activity of artemisinin and related compounds. The ether derivative **2b** is a better antimalarial agent than artemisinin itself.[14] Esters **2c** are generally as effective as artemisinin but corresponding acid **2d** are much less so. Carbonates **2e** are least effective of this group of compounds. Sodium artelinate **2f** is only slightly less effective than artemisinin in vivo. A number of highly effective antimalarial agents have been obtained by replacing the carbonyl group of artemisinin by amino group **2g**.[15]

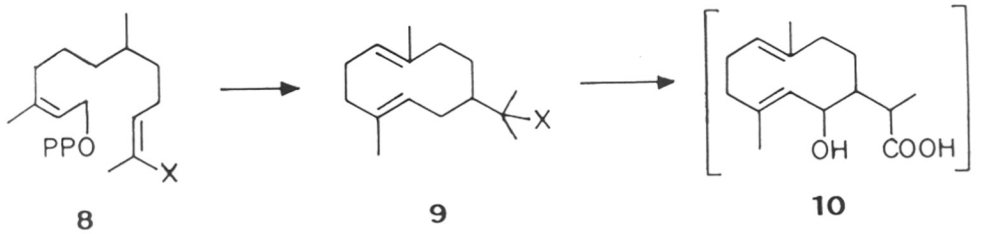
2.3 : Biosynthesis :

Artemisinin appears to be unique to Artemisia Annua and is at a maximum in the upper leaves at the beginning of budding. Labelling experiments have identified two intermediates enroute to artemisinin **1**, artemisinic acid **3a** and mevanolactone **4**[16]. El-feraly et. al.[17] reported that (Scheme - 1) artemisinic acid **3a** gets converted to hydroperoxide **5** which rearranges to **6** and epoxidation, deoxygenation followed by lactonization of which yields artennuin-B **7**. From this it was inferred that artemisinic acid **3a** can serve as a biogenetic precursor for artemisinin. In 1987 Akhila et. al.[18] reported (Scheme - 2) arteannuin B **7** to be a late precursor in the biosynthetic sequence of artemisinin **1**. Their suggested pathway is that cis-isomer of farnesyl pyrophosphate (FPP) **8** may cyclize to **9** which then enters the pathway **9** to **10** to dihydro-costunolide **11**, cadinanolide **12**, arteannuin B and finally to artemisinin **1**. In 1988, Yu et. al.[19] reported incorporation of [15-3H] isomer of artemisinic acid **3a** into biosynthesis of artemisinin **1** and arteannuin-B **7** in qinghao plant homogenate system and inferred that artemisinic acid **3a** to be a key intermediate in the biosynthesis of artemisinin and

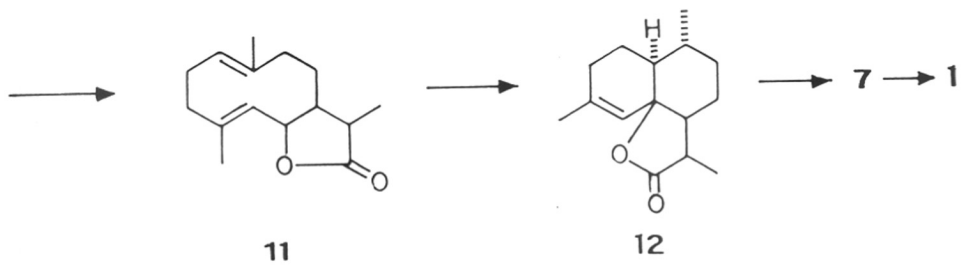
Scheme-1



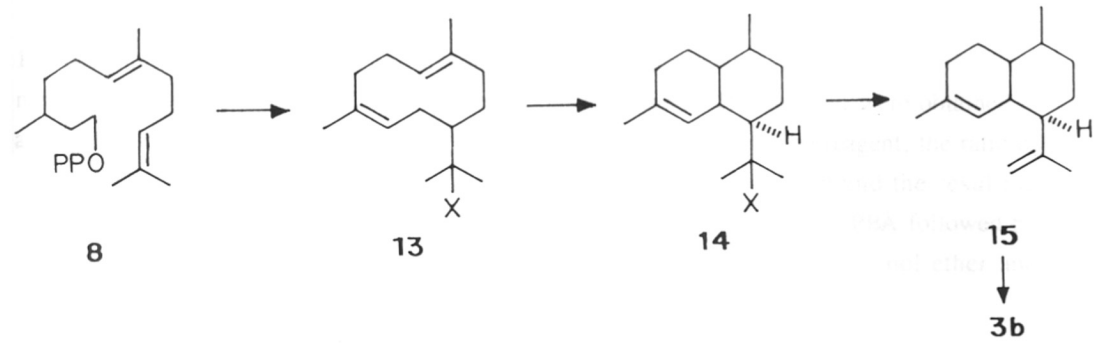
Scheme-2



X = FPP



Scheme-3

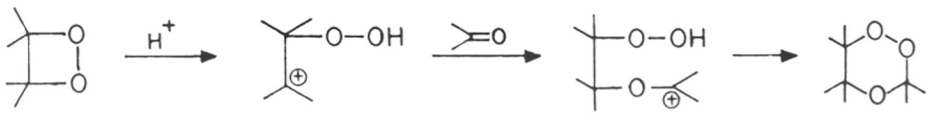


arteannuin-B. In 1990, Akhila et. al.[20] reported complete biosynthesis of artemisinic acid **3a** in Artemisia Annua which has been found to play pivotal role in the biogenetic pathway of artemisinin **1**. According to suggested biosynthetic pathway the cis isomer of farnesyl pyrophosphate **8** (Scheme - 3) cyclises to **13** which then forms the cadinane skeleton **14** from which artemisinic acid **3a** is formed via intermediate **15**.

2.4 :Synthesis of (+)-Artemisinin : A literature Survey :

The rather unusual structure of artemisinin has meant that the molecule constitutes a stimulating synthetic challenge and a number of successful total synthesis have been reported.

Scheme-4 : Jefford et.al. Helv.Chim.Acta , 1986, 69, 1778



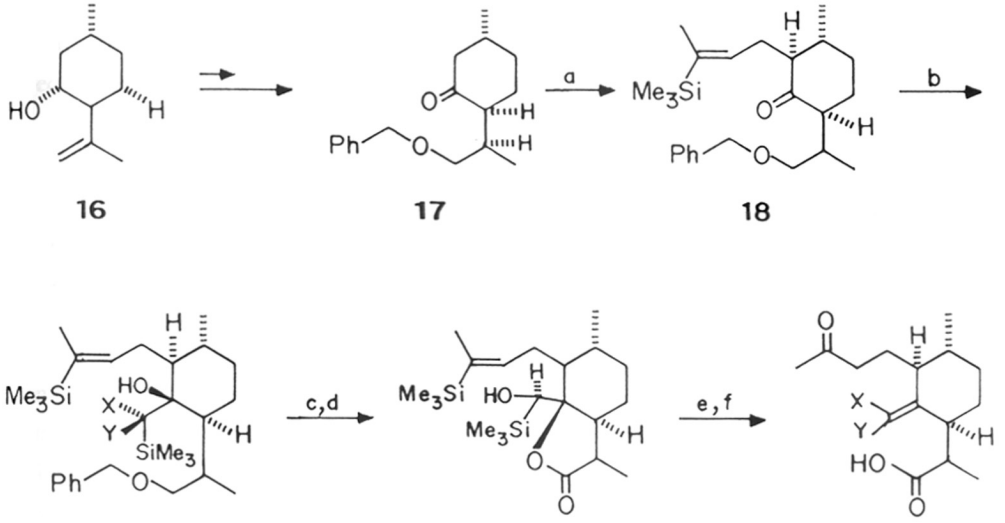
In most cases the trioxane ring has been formed by addition of singlet oxygen to an olefin in the presence of a photosensitizer followed by protonation and reaction with a carbonyl compound (Scheme - 4). This approach to the synthesis of trioxane has been fully explored by Jefford and his co-workers.[21]

Schmid's Approach[22] (Scheme-5, 1983) :

Schmid et. al. reported first total synthesis of artemisinin **1** in 1983 starting with (-)-isopulegol **16**. Isopulegol **16** was converted to the benzyloxymenthone **17** in three steps. Kinetic deprotonation of **17** and treatment of resulting enolate with E-(3-iodo-1-methyl-1-propenyl)trimethylsilane provided a 6:1 mixture of epimeric alkylation products from which major isomer **18** was isolated in 62% yield.

The key intermediate enol ether **21** was directly prepared from the reaction of ketone **18** with the silyl reagent. When ketone **18** was treated with 1-equivalent of lithium methoxy(trimethylsilyl)methylide two diastereoisomeric alcohols **19a** and **19b** were obtained in a 1:1 ratio and almost quantitative yield. By use of a 10 fold excess of the reagent, the ratio of **19a** and **19b** was shifted to 8:1. The compound **19a** was debenzylated and the resulting alcohol oxidised to lactone **20** in 75% yield. When **20** was treated with m-CPBA followed by fluoride ion, smooth desilylation occurred with simultaneous generation of enol ether and carboxylic acid function **21**.

Scheme-5 : Schmid et.al. JACS, 1983, 105, 624.



a: LDA, THF, TMS(Me)C=CH-CH_2-I

b: TMS(Li)C(OMe)H, THF, -78°C c: Li-Liq. NH_3

d: PCC e: m-CPBA, THF, TFA f: n-Bu_4NF, THF

g: O_2, MB, MeOH, hν, -78°C

h: HCOOH, CH_2Cl_2

The final key step involves the irradiation of the methanolic solution of **21** in the presence of singlet oxygen with methylene blue as sensitizer at -78°C to give hydroperoxide intermediate **22**. On treatment of the crude mixture of **22** with formic acid crystalline artemisinin **1** was obtained in 30% yield. This synthesis is noteworthy not only because of this is first synthesis of artemisinin but it provided a key sub-target viz. the enol ether **21** which can become the basis of synthetic design for other workers.

Zhou's Approach[23] (Scheme-6, 1986) :

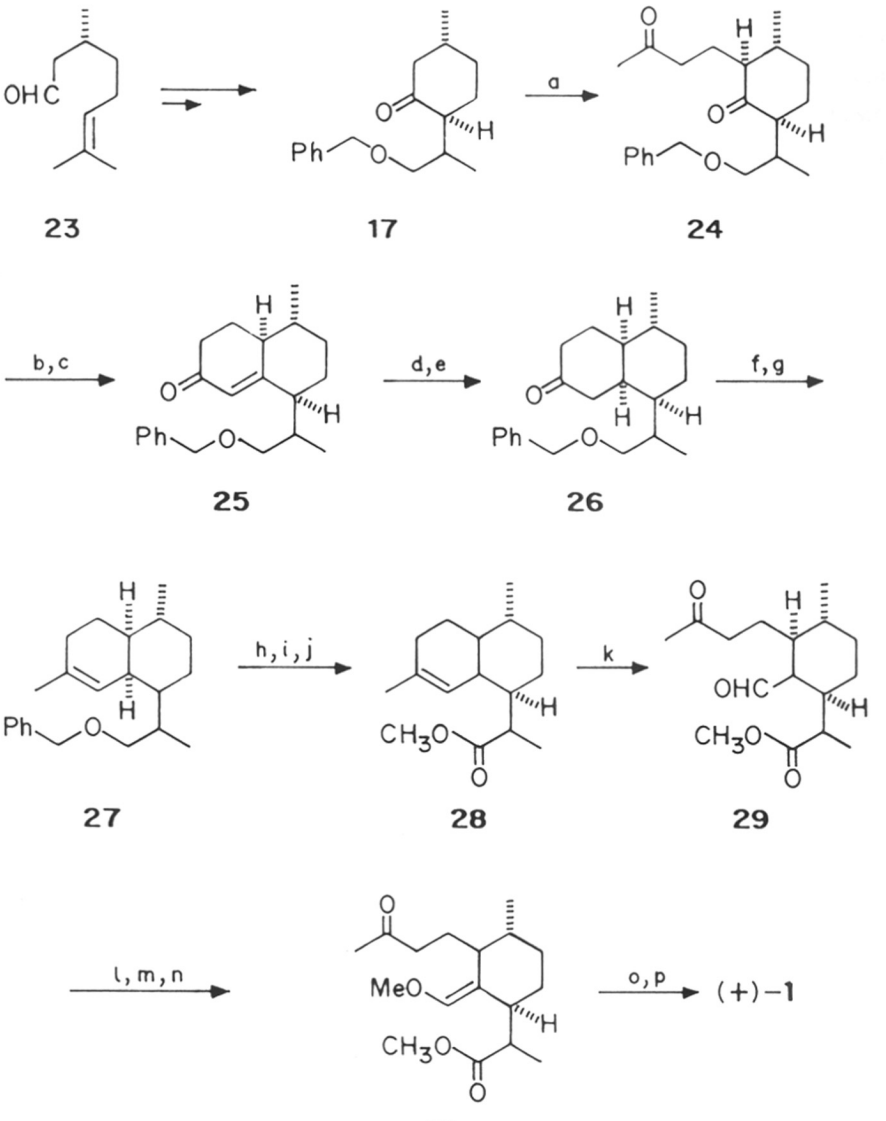
Zhou et. al. reported second synthesis of artemisinin in 1986 starting from R(+)-citronellal. Citronellal **23** was converted to benzyloxymenthone **17** in three steps. Kinetic deprotonation of **17** and the reaction of resulting enolate with silylated vinylketone gave the 1,5-diketone **24** with simultaneous cleavage of trimethylsilyl group. The 1,5-diketone **24** was cyclised with $Ba(OH)_2$ and on dehydration with 2.5% oxalic acid gave the enone **25**. This enone **25** was converted to a saturated ketone **26** by reduction with sodium borohydridepyridine followed by oxidation with Jones reagent. Ketone **27** on treatment with MeMgI and subsequent dehydration furnished the mixture of **27** it's A^3-isomer in 1:1 ratio which was separated by flash chromatography. The **27** was debenzylated with sodium and liquid NH_3 oxidised with Jones reagent and esterified with diazomethane to afford **28** in 72% overall yield in three steps. Ozonolysis of **28** afforded the ketoaldehyde **29** which was selectively protected at the ketonic carbonyl, aldehyde was converted to its acetal by treatment with trimethylorthoformate and the thioketal was deprotected using mercuric chloride to give intermediate enol ether **21**. Photooxidation of the methanolic solution of **21** in the presence of oxygen and Rose Bengal at -78°C followed by acid treatment gave artemisinin in 28% yield. The synthesis involves a long sequence (22 steps) to obtain the artemisinin starting from citronellal. The design of synthesis is mainly the application of general methodologies available for ring formation, usual functional group transformations, selective protection, deprotection etc. The chirality transfer from the starting Chiron is at best only satisfactory.

Avery's Approach[24] (Scheme-7, 1992) :

Chiral sulphoxide **30** was used as starting material and transformed into the optically active ketone **32** alongwith small amount of unwanted isomer through two steps. Reaction of ketone **32** with tosylhydrazine followed by treatment with 4-equivalents of n-BuLi and trapping of the resultant vinyl anion with DMF afforded α,ß-unsaturated aldehyde **34**.

1,2 addition of tris(trimethylsilyl)aluminium etherate to aldehyde **34** and subsequent quenching with acetic anhydride yielded a single silyl acetate **35**. Upon treatment of **35** with lithiumdiethylamide (LDEA) an Ireland-Claisen rearrangement took place, forming regioselectively the vinylsilane moiety and connecting stereoselectively the acetic acid function

Scheme-6 : Zhou et. al. Tetra, 1986, 42, 819



23 17 24 25 26 27 28 29 21

a: LDA, $CH_2=C(Me_3Si)COCH_3$ b: $Ba(OH)_2.8H_2O$ c: $(COOH)_2$

d: $NaBH_4$-Py e: Jones Oxidation f: MeMgI g: p-TsOH

h: Na-Liquid NH_3 i: Jones Oxidation j: CH_2N_2 k: O_3, Me_2S

l: $HS(CH_2)_3SH$, $BF_3.Et_2O$, CH_2Cl_2 m: $HC(OMe_3)$, p-TsOH

n: $HgCl_2$-$CaCO_3$ o: O_2, MeOH, Rose Bengal, hν, -78°C

p: 70% $HClO_4$

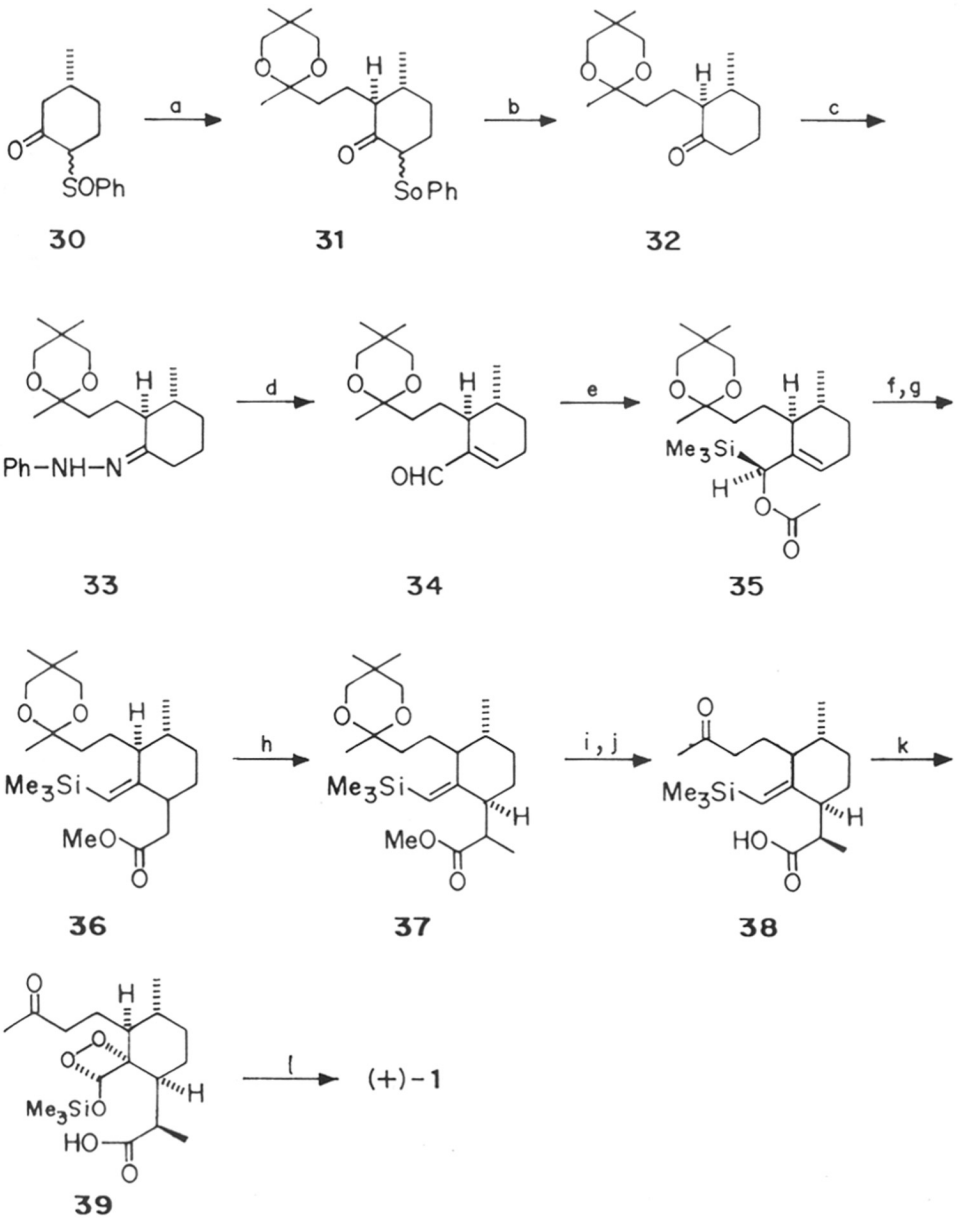
to give the desired product **36**. Methylation of **36** with 2 equivalent of LDA led to a single diastereoisomerically pure homogenous acid **37** in nearly quantitative yield. Finally acid **38** was converted in a one pot procedure involving sequential treatment with ozone followed by wet acidic silica gel to effect a complex process of dioxetane formation **39**, ketal deprotection and cyclization to the natural product artemisinin **1** in 33-39% yield. This synthesis is more elegant, and more promising from practical point of view, although lacking to some extent in terms of stereospecificity .

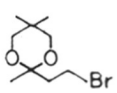
Ravindranathan's Approach[25] (Scheme-8, 1990) :

Ravindranathan et. al. reported stereoselective synthesis of artemisinin **1** from (+)-isolimonene **41** (Scheme - 8) which in turn can be easily obtained from (+)-car-3-ene a cheap abundantly available monoterpene. The epimeric mixture of alcohol **42**, which was obtained from (+)-isolimonene was converted to enol ether **43** by transetherification with 1-ethoxy-2-methyl-1,3-butadiene. The triene **43** underwent an intramolecular Diels-Alder reaction to furnish an epimeric mixture of ethers **44a** and **44b** in 25-30% yield. The mixture of **44** was epoxidised with m-CPBA, reduced with LAH and oxidised with $RuCl_3$-$NaIO_4$ to furnish the epimeric mixture (7:3) of lactones **46** which could be separated and characterized by ^{1}H-NMR and X-ray analysis. Pure **46a** could be equilibrated with NaOMe/MeOH to obtain equilibrium mixture of **46a** and **46b** in a ratio 6:4 and this help one to the both the epimers for conversion to artemisinin via **21**. The lactone **46b** was converted to known ketoaldehyde compound **21** by cleavage with $NaIO_4$. Since the conversion of the **21** to artemisinin **1** can be performed by the procedure reported by Zhou et. al.,[23] this constitutes a formal total synthesis of artemisinin.

This synthesis proceeded, overall, without any stereoselectivity problems to generate intermediate ketoaldehyde **21** in 8 steps compared to 15 steps involved in the earlier reported synthesis of Zhou et. al. In contrast to other reported methods also this method is found to be favourably not only in terms of number of steps but also in terms of stereospecificity, simplicity and practicality.

Scheme-7 : Avery et. al. JACS, 1992, 114, 974



a : LDA, HMPA, -78°C,  b : Al(Hg), THF

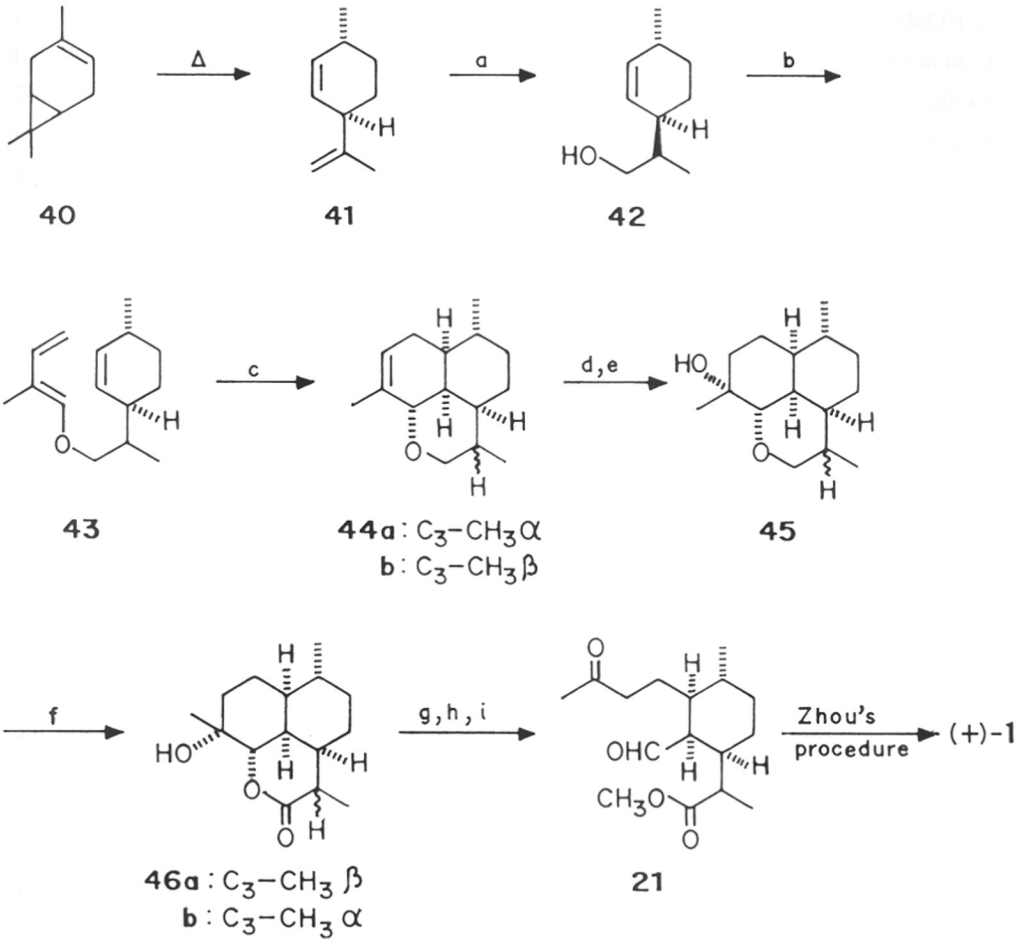
c: $TsNHNH_2$, Pyridine, THF d: n-BuLi, TMEDA, DMF

e: $(Me_3Si)_3Al.OEt_2$, -78°C, Ac_2O, DMAP, -78°C to 23°C

f: LICA, -78°C, g: K_2CO_3, Me_2SO_4 h: LICA, MeI

i: KOH, MeOH j: aq. $H_2Cr_2O_4$ k: O_3, MeOH l: CF_3COOH

Scheme-8: Ravindranathan et.al. Tet.Lett. 1990, 31, 755



a: 9-BBN, H_2O_2, NaOH b: 1-ethoxy-2-methyl-1,3-butadiene, $Hg(OAc)_2$, NaOAc

c: Toluene, 210°C, Sealed Tube d: m-CPBA, CH_2Cl_2

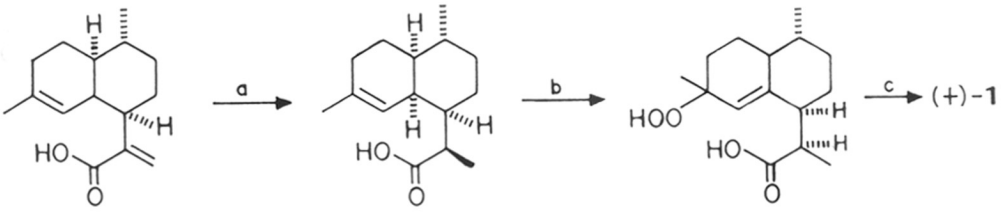
e: LAH, Et_2O f: $RuCl_3.H_2O$, $NaIO_4$ g: 1 equ^n of NaOH

i: CH_2N_2, Ether

Roth and Acton's Approach[26] (Scheme-9, 1991) partial synthesis :

Roth and Acton converted artemisinic acid **3a** into artemisinin **1** in two steps via reduction of the exocyclic methylene group and photooxidation of resulting dihydro-artemisinic acid **3b**. Thus, artemisinic acid **3a** on treatment with $NaBH_4$ and $NiCl_2.H_2O$ in MeOH gives dihydroartemisinic acid **3b** in high yields. Photooxidation of dihydroartemisinic acid **3b** at -78°C in dichloromethane with methylene blue as sensitizer followed by change of solvent to pet ether and leaving the reaction mixture at R.T. for 4 days yielded artemisinin **1** in 30% yield.

Scheme-9 : Roth et. al. J. Chem. Edu, 1991, 68, 612

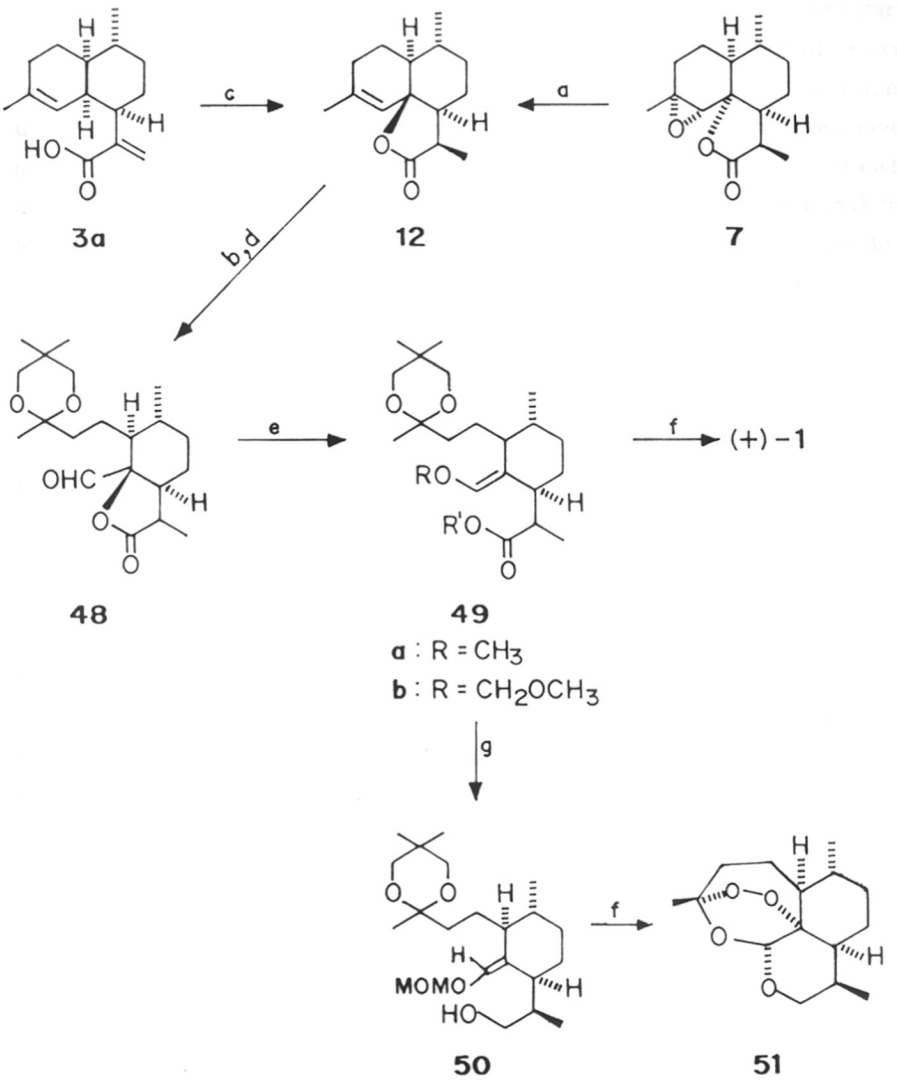


a : $NaBH_4$, $NiCl_2$ b : hν , O_2 , MB c : Air, TFA , Pet-ether

Lansbury's Approach [27] (Scheme-10, 1992) Partial synthesis :

Lansbury et. al. reported an efficient partial synthesis of artemisinin **1** through enol ether **49** in which artemisinic acid **3b** and arteannuin-B **7** were used as the starting material and separately converted into **12**. Ozonization of **12** and selective protection of the resulting ketone carbonyl afforded **48**. Reductive cleavage of **48** with sodium naphthalenide followed by in situ reaction with alkylating agents (CH_3I and CH_3OCH_2Cl) produced enol ethers-esters **49a** and **49b**, $^1O_2$ reaction of **49a** and **49b** was performed with Rose Bengal as a sensitizer to give 30-35% isolated yields of artemisinin **1**. O_2 reaction of alcohol **50** produced deoxoartemisinin **51** which has been known to possess in vitro and in vivo antimalarial activity, superior to that of artemisinin **1**.

Scheme-10: Lansbury et.al. Tet.Lett. 1992, 33, 1029.



a: n-BuLi, Tungten hexachloride, THF, b: O_3

c: CrO_3- 3,5-dimethyl Pyrazole, CH_2Cl_2

d: 1,2-bis(trimethylsilyl)oxy ethane, TMSOTf, CH_2Cl_2

e: Sodium naphthanelide, THF, then MeI, CH_3OCH_2Cl

f: O_2, Rose Bengal, Camphor Sulphonic acid g: LAH

Liu's Approach[28] (Scheme-11, 1993) :

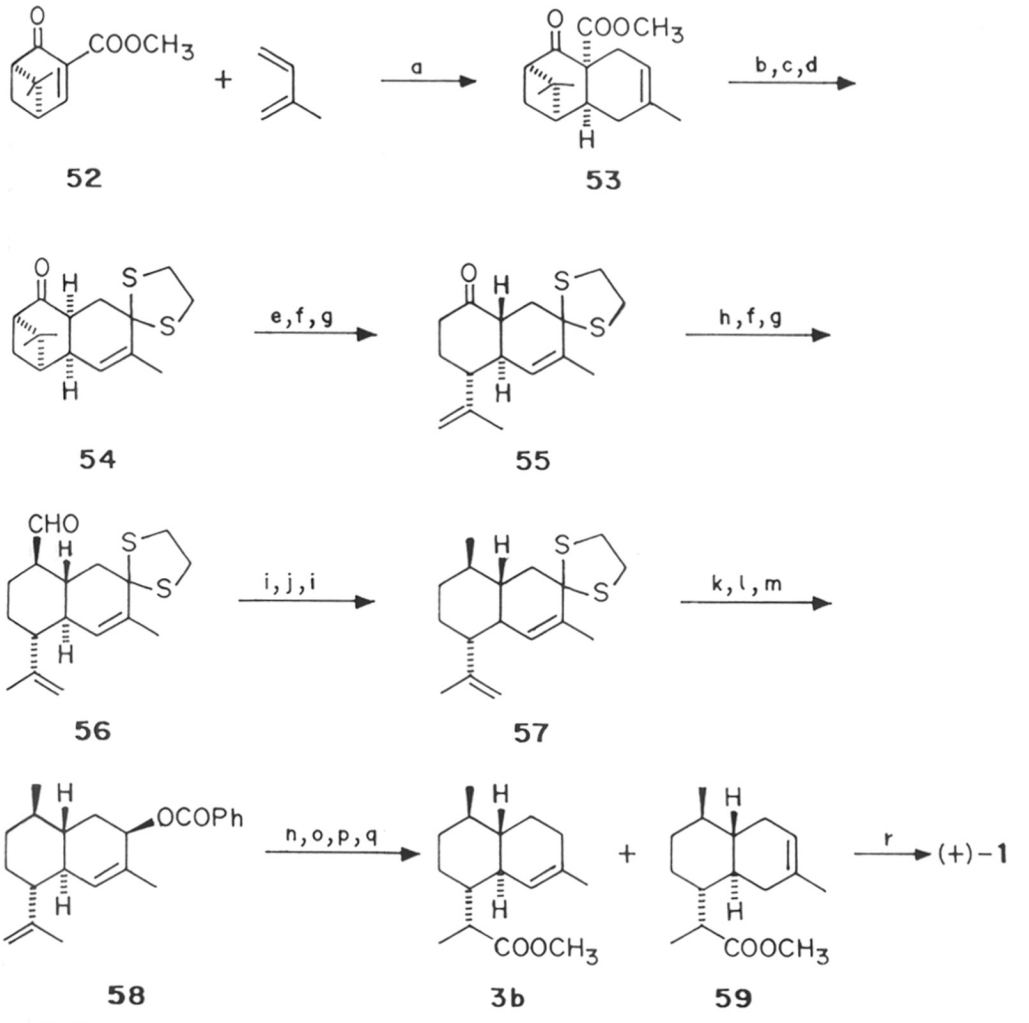
Liu et. al. reported stereoselective synthesis of artemisinin **1** in 1993 starting from (-)-ß-pinene (Scheme-11). The zinc chloride catalysed Diels-Alder addition of (+)-enone ester **52** prepared from ß-pinene proceeded with regioselective and facial selective manner to give adduct **53** which then underwent a series of functional group transformations involving the fragmentation of the cyclobutane ring in compound **54**. The installation of the methyl group with stereochemical control in compound **57** and the conversion of the isopropenyl group into a propionate unit with 9-BBN to furnish a mixture of two inseparable regioisomers **3b** and **59** in ratio of 9:5. Experiment has proved that the desired isomer **3b** with a trans fused ring system was equally easily converted to artemisinin via a photooxygenation process. This synthesis is quite lengthy (22 steps) to obtain the intermediate dihydroartemisinic acid starting from ß-pinene.

Ravindranathan's Approach[29] (Scheme-12, 1994):

Ravindranathan et al. reported second stereoselective synthesis of (+)- artemisinin in 1994 starting from menthol (Scheme-12). Menthol **60** was converted to solid ketone **61** in four steps. Epoxidation of **61** gave mainly the α-epoxide which on reduction with LAH to give ß-secondary alcohol **62** chemoselective acetylation of secondary alcohol of **62** with Ac_2O & pyridine gave **63**. For the C-2 functionalisation of C-H of primary methyl in isopropyl group in **63** a lead tetra-acetate + I_2 combination along with photolysis was carried out. Saponification followed by PCC oxidation gave **65** a mixture of stereoisomers (3:1) where both isomers separated by column chromatography. Sodium hydride treatment of **65** in DMF at -10°C subsequent addition of benzyl bromide gave kinetic benzylation product **66** since synthesis of (+)-artemisin from **66** is reported by Zhou et. al.

Alternatively, treatment of **65** with acidic alumina gave **67** in 68% isolated yield. Catalytic reduction of **67** with 10% Pd on charcoal was stereoselective and only the cis-junctured non-steriodal ketoalcohol was obtained. Treatment of ketoalcohol with 2.5 eq. MeMgI gave quantity yield of the Grignard product **68**. Subsequently, the primary alcohol of **68** was acylated which on treatment with $POCl_3$ and pyridine gave 50:50 mixture of regioisomers. The separation of the desired isomer was possible after saponification to give **69**. The conversion of artemisiol to (+)-artemisinin is reported[56,57].

Scheme-11: Liu et. al. Tet. Lett. 1993 , 34 , 4435



a: $ZnCl_2$ b: TPP, O_2, CH_2Cl_2, hν, Ac_2O, Py, DMAP

c: $BF_3.Et_2O$, $(CH_2SH)_2$, CH_2Cl_2, -10°C d: $LiI.H_2O$, 2,4,6-Collidine

e: p-TsOH, $(CH_2OH)_2$, PhH, Δ f: p-TsOH, Acetone, g: NaOH, MeOH,

h: $Ph_3P^+CH_2OCH_3Cl^-$, KH, DMSO, C_6H_6, THF i: LAH, THF,

j: Et_3N, MsCl, CH_2Cl_2 k: $HgCl_2$, CH_3CN

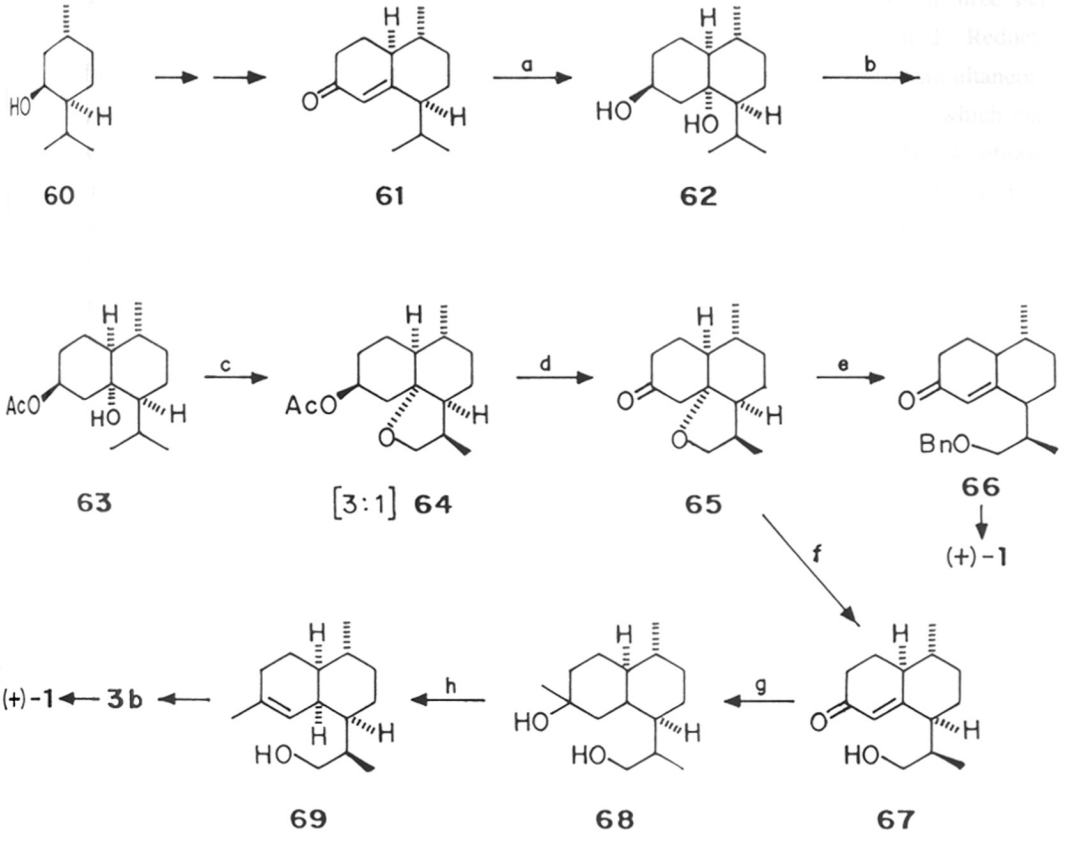
l: $NaBH_4$, $CeCl_3$, MeOH, -78°C

m: Ph_3P, DEAD, PhCOOH, THF n: 9-BBN, THF o: $H_2Cr_2O_4$, ether

p: K_2CO_3, CH_3I g: $NaBH_4$, $NiCl_2$, MeOH

r: O_2, MB, hν, CH_2Cl_2, then CF_3COOH, Pet.ether

Scheme-12 (Ravindranathan et.al. Tet.Lett, 1994, 35, 5489)



a: 30% H_2O_2, NaOH, MeOH, -10°C ii) LAH, ether, reflux b: Ac_2O, Py, RT

c: LTA, I_2, C_6H_{12}, hν, (500W, Tungsten lamp), reflux, then Zn-dust, AcOH

d: i) KOH, EtOH, H_2O, RT ii) PCC

f: NaH, DMF, -10°C, 45 min, then Ph_2CH_2Br, in DMF, -10°C, f: Acidic Alumina

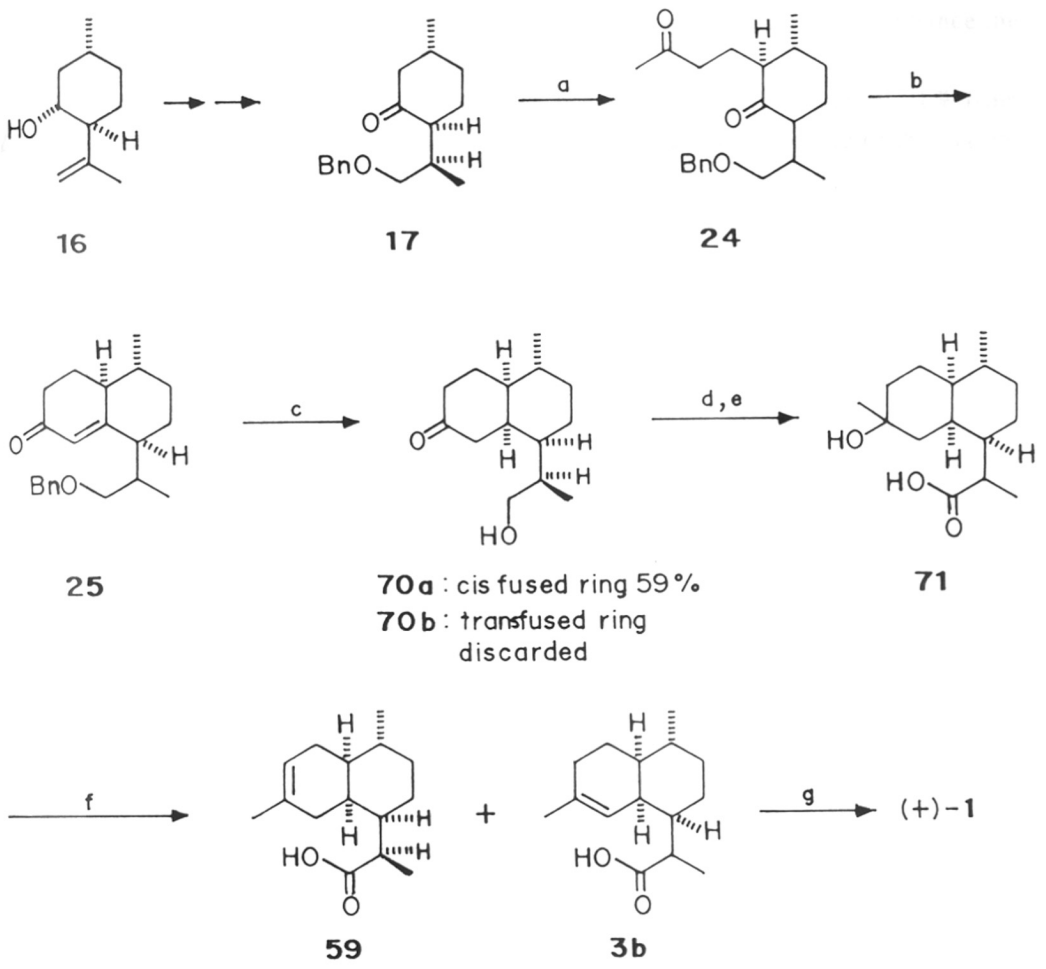
g: i) H_2(20Psi), 10% Pd/C, MeOH, RT ii) MeMgI, ether

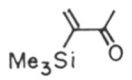
h: i) Ac_2O, Py, RT ii) $POCl_3$, Py, RT iii) KOH, EtOH, RT

Constantino's Approach[30] (Scheme-13, 1996) :

Constantino et. al. reported total synthesis of (+)-artemisinin **1** in 1996 starting from (-)-isopulegol, **16**. Isopulegol **16** was converted to the benzyloxymenthone **17** in three steps. A three step Robinson annulation starting with **17** furnished enone **25** in 51% yield. Reduction of the double bond of **25** and hydrogenolysis of benzyloxy group were effected simultaneously by treatment with hydrogen and catalyst, a mixture of two isomers produced from which major isomer was isolated by column chromatography in 59% yield. The ketanol **71** was obtained through oxidation of **70a** with PDC in 91% yield. The addition of methyl lithium to the carbonyl group of **71** produced a mixture of epimeric tertiary alcohols. Treatment of mixture of isomers **71** with pTSA in benzene gave intermediate dihydroartemisinic acid **3b** together with its regio-isomer **59**. The intermediate 3b to artemisinin **1** by Roth's procedure.[26]

Scheme-13 (Constantino's al. Synth. Commun. 1996, 26, 31)



a : LDA,  **b** : i) $Ba(OH)_2$ ii) Oxalic acid **c** : H_2, Pd/C

d : PDC **e** : 2 MeLi **f** : pTSA **g** : i) O_2, hν ii) TFA, air.

2.5 : Present work :

The present chapter primarily concerns with approaches for stereoselective synthesis of (+)-artemisinin, a naturally occurring sesquiterpene having unusual skeleton was isolated from Artemisia annua in 1972. Among different species, artemisinin occurs mainly in Artemisia annua. Although the claims of artemisinin contents are 0.01% and upwards and special horticultural methods and plant tissue cultural methods were employed to enhance the artemisinin content, success is not very high.

In India, artemisinin is reported to have been isolated to the extent 0.01% from Artemisia annua occurring around Lucknow. The comparative non-abundance of this species and low content of artemisinin would probably require a good synthetic method for its production and also analogues which may finally be found useful in therapy.

The intriguing molecular architecture and unprecedented antimalarial activity have prompted a number of organic chemists to develop synthetic routes towards these natural product.[22-28] These complex syntheses do not provide feasible methods for large scale production. Currently, this molecule appears as one of the hottest molecule in the antimalarial area where WHO is investing lot of money for its development and use in antimalarial therapy.

The combination of an outstanding biological activity, a novel chemical structure and low yield from natural sources were key factor to embark on developing a synthetic route towards this novel natural product. The present work describes attempted practical synthesis of artemisinin.

2.6 : Results and Discussions :

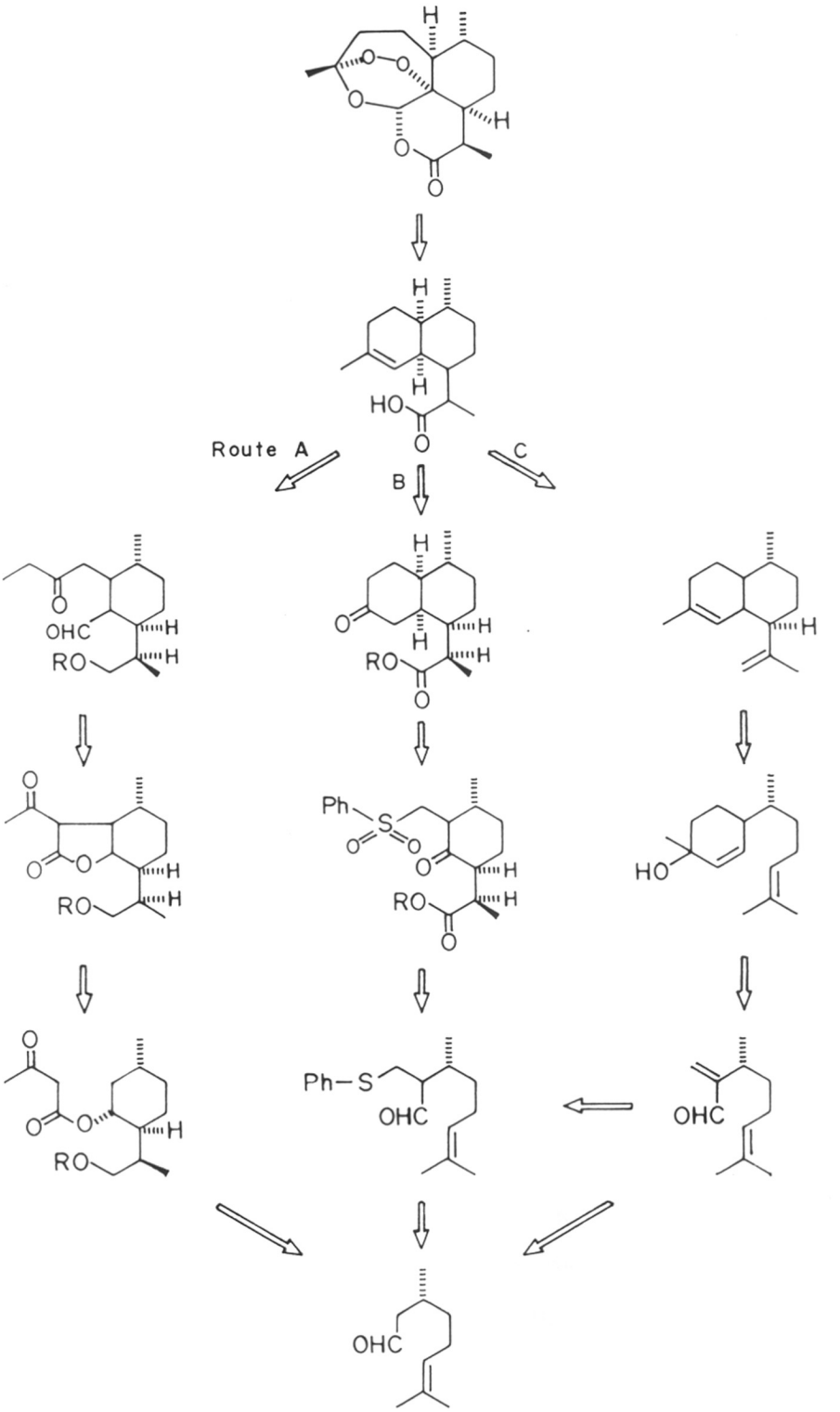
In order to have still better and practical process for (+)-artemisinin, attention was focussed on (+)-citronellal which is cheap and abundantly available in India.

From retrosynthetic analysis (Scheme - 14), it is revealed that (+)-artemisinin could be synthesized by an intramolecular carbenoid C-H insertion approach (Route A) or an intramolecular `ene' reaction approach (Route B and Route C).

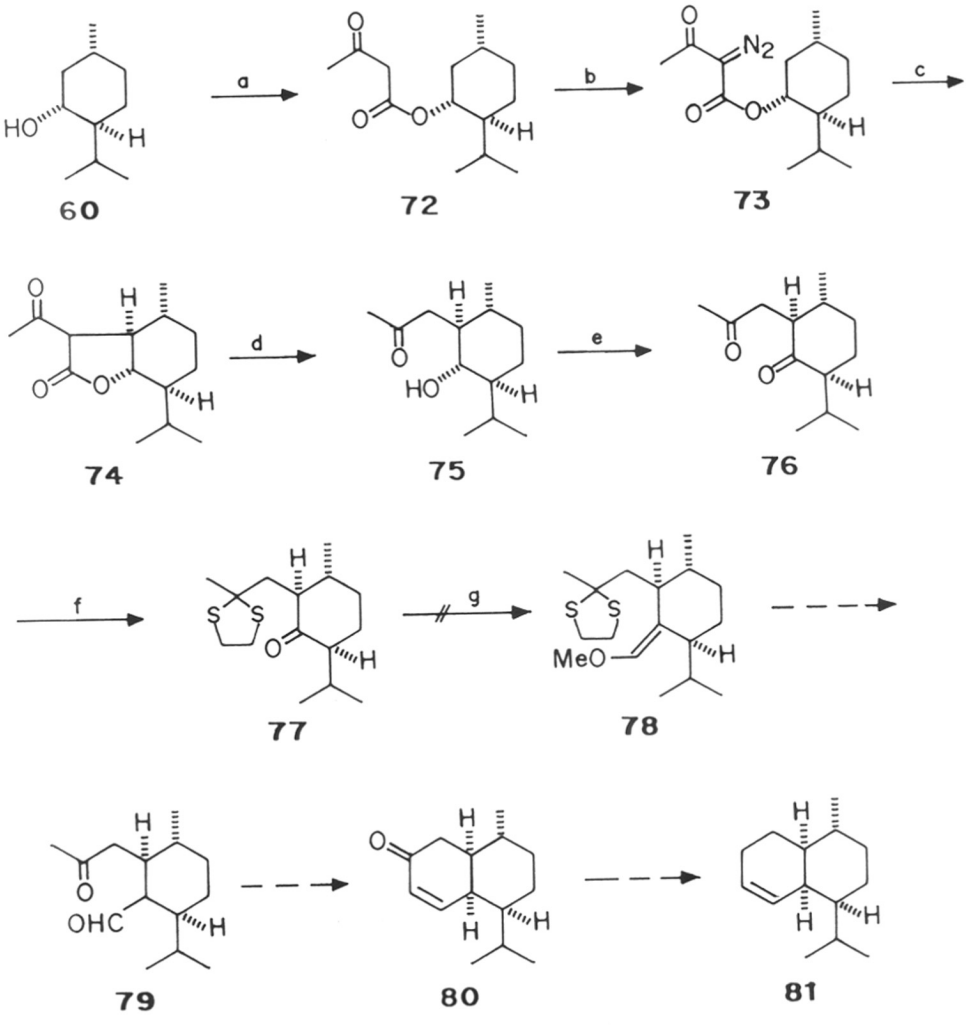
Route A : Intramolecular carbenoid C-H insertion Approach :

According to retrosynthetic plan (Scheme - 14), the key reaction involves rhodium acetate catalysed decomposition of diazoesters to forms bicyclic-γ-lactones. It was realised that bicyclicγγ-lactone **74** would be an ideal starting material for dihydroartemisinic acid **3b**. It incorporates methyl as well as isopropyl side chain in trans-stereochemical disposition and trans ring fusion was well suited for conversion to dihydroartemisinic acid **3b**. In order to study the feasibility of this route, studies were carried out on model substrate as shown in Scheme - 15.

Scheme-14 : Retrosynthetic plan



Scheme-15 (Model Scheme)

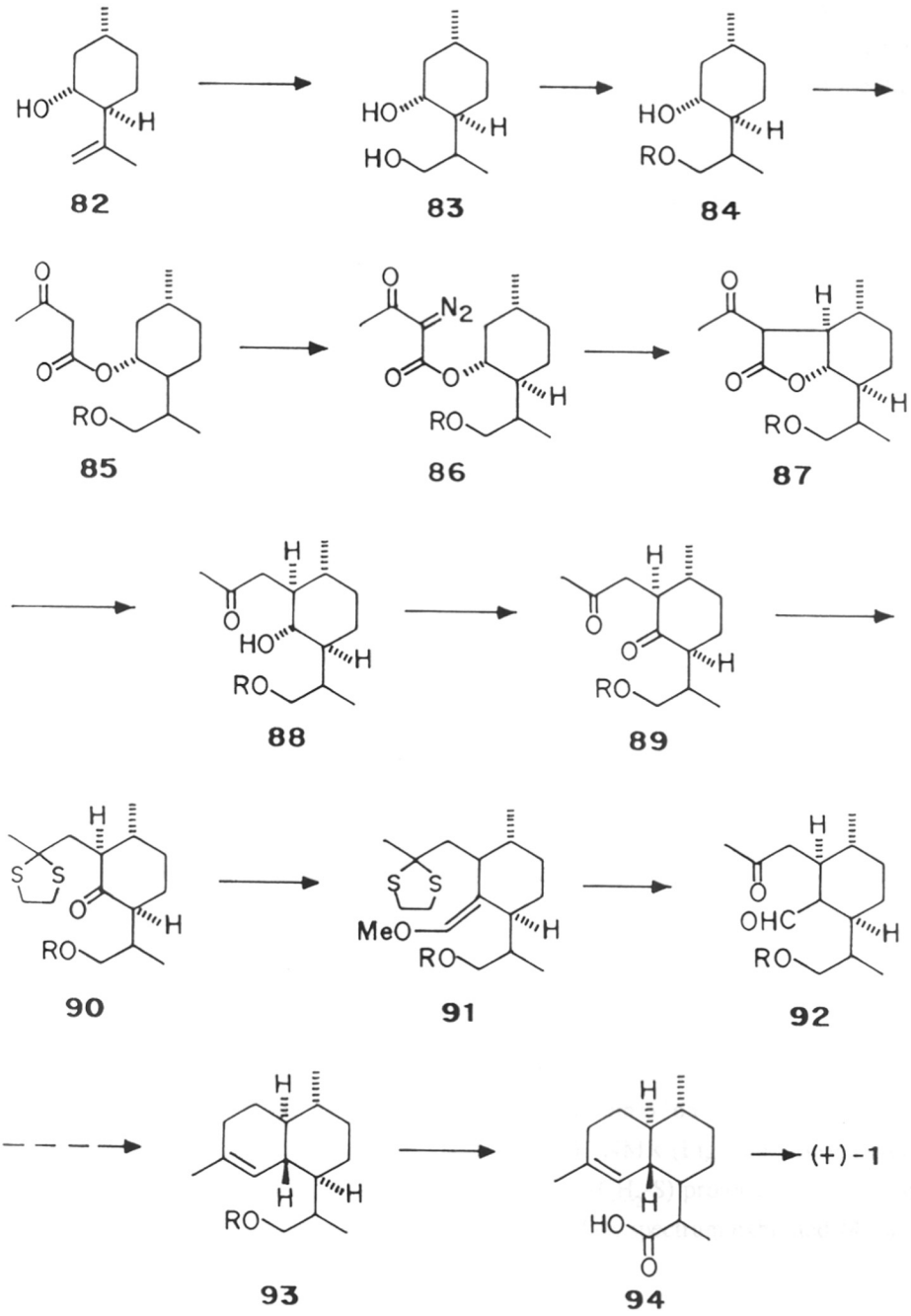


a: CH_3COCH_2COOMe, S-SnO_2, Tol,Δ b: $MeSO_2N_2$, K_2CO_3, CH_3CN

c: $Rh_2(OAc)_4$, C_6H_6, d: NaOH, MeOH, e: Jones Oxidation

f: $HSCH_2CH_2SH$, $BF_3.Et_2O$, THF, -40°C g: $MeOCH_2P^+Ph_3I^-$, BuLi, THF

Scheme-16 (Proposed Scheme)



In connection a programme on solid superacids and zeolite mediated organic transformations it has been shown from these laboratories that solid superacids (sulphated SnO_2) can serve as efficient catalyst for transesterification of ketoesters.[31] This protocol was used for preparation of starting material **72**. Methyl acetoacetate was treated with menthol **60** in the presence of catalytic sulphated tin oxide in refluxing toluene to furnish the transesterified ester **72** in 90% yield. The spectroscopic data (**Fig.1**) of **72** was found to be identical in all respects with those reported in literature.[31] Diazo compound **73** was prepared by diazotransfer reaction using methane sulfonyl azide.[32] The IR spectrum of **73** showed strong absorption at 2150 cm^{-1} which was characteristic of diazo group. The ^{1}H-NMR spectrum (**Fig.2**) **73** displayed disappearance of signal at δ 3.5 (s, 2H) of active methylene group. The mass spectrum exhibited peak at 266 (M^+, 28%) confirming the structure of diazo compound **73**.

Rhodium acetate catalysed decomposition of diazo compound **73** resulted in the formation of bicyclic-γ-lactone in 80% yield.[33] The spectroscopic data (**Fig.3**) and physical properties of the bicyclic-γ-lactone **74** was found to be identical in all respects with those reported in literature.

The hydrolysis of bicyclic-γ-lactone **74** with aqueous NaOH/MeOH[34] underwent the desired decarboxylation furnished the ketoalcohol **75** in 75% yield as a colourless oil. $[\alpha]_D$ = -49.6° (c=2.5, $CHCl_3$). IR spectrum of ketoalcohol **75** showed absorption at 1710 cm^{-1} and 3450 cm^{-1} indicating the presence of ketone and hydroxy groups. The ^{1}H-NMR (**Fig.4**) of **75** displayed signal at δ 3.2 (dd, 1H), for <u>CH</u>-OH proton. The ^{13}C-NMR showed 13 signals corresponding to 13 carbons, among them 210.6 (s) and 76.03 (d) were responsible for carbonyl carbon and secondary alcohol bearing carbon (<u>CH</u>-OH). Further confirmation of structure **75** was obtained from mass spectral data which revealed that molecular ion M^+ at 212 (10%).

The ketoalcohol **75** was further oxidised with Jones reagent to give dione **76** $[\alpha]_D$ = -35.18° (c = 5.4, $CHCl_3$) which was characterized by IR, ^{1}H-NMR and mass spectra (**Fig.5**). IR spectrum showed peaks at 1705 cm^{-1} and 1710 cm^{-1} indicating the presence of ketone groups. ^{1}H-NMR spectrum showed signals at δ 0.9 (d, J = 6.6 Hz), 1.1 (d, J = 6.6 Hz), 2.2 (s, 3H) and 2.9 (d, 1H). Mass spectrum exhibited M^+ at 210 (10%).

Selective protection of the side chain carbonyl group of dione **76** with ethanethiol in the presence of $BF_3.Et_2O$ at -40°C furnished the protected compound **77** in excellent yield (85%) as a colourless oil $[\alpha]_D$ = -40° (c=1.2 $CHCl_3$). IR spectrum of **68** showed absorption at 1700 cm^{-1} indicating the presence of carbonyl group. The ^{1}H-NMR (**Fig.6**) analysis revealed that singlet at δ 1.7 and 3.4 for methyl and methylene (S-<u>CH_2</u>-<u>CH_2</u>-S) protons. ^{13}C-NMR spectrum of **77** showed 15 signals corresponding to 15 carbons. Mass spectrum exhibited M^+ at 286.

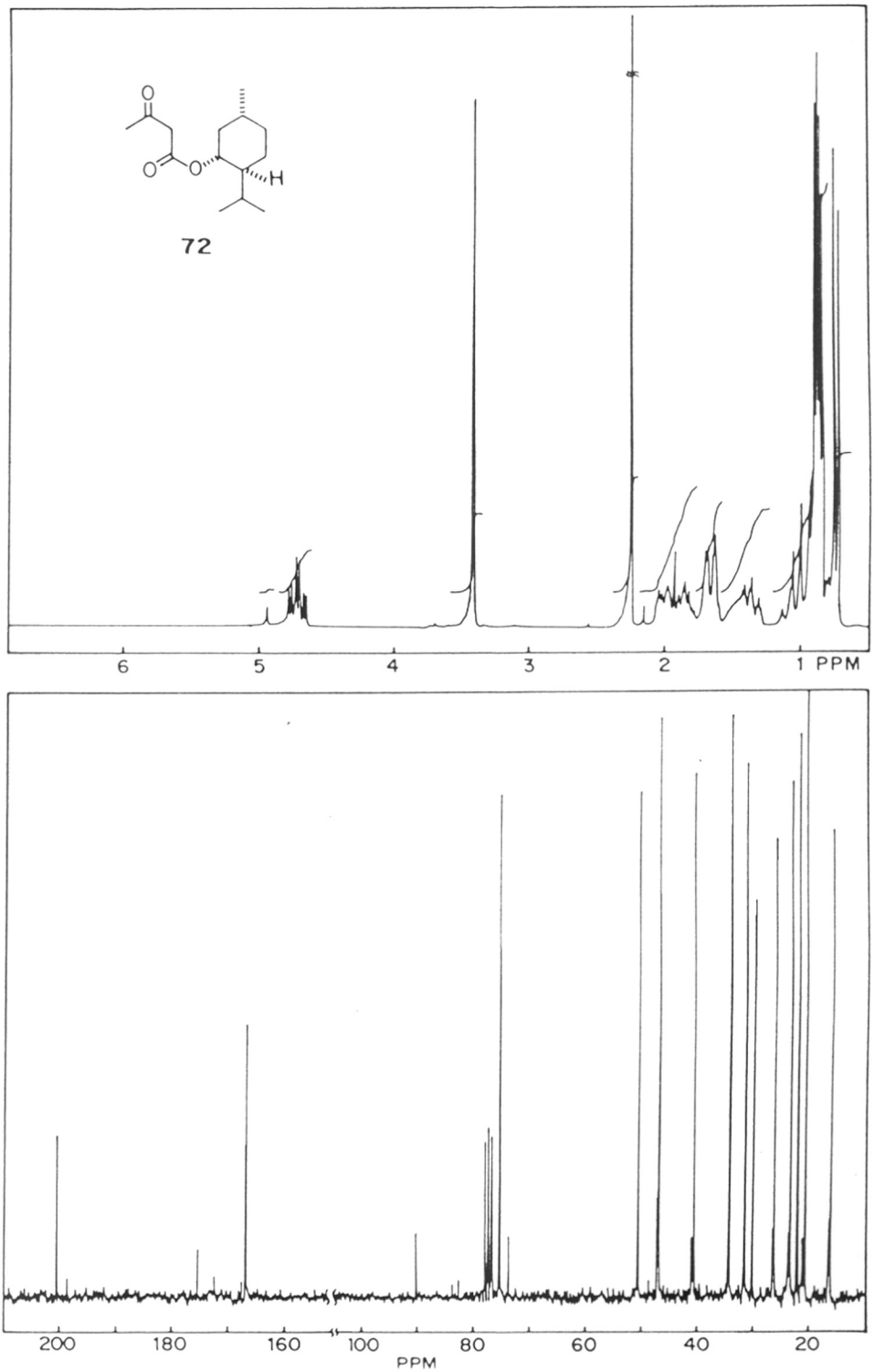


FIG.1

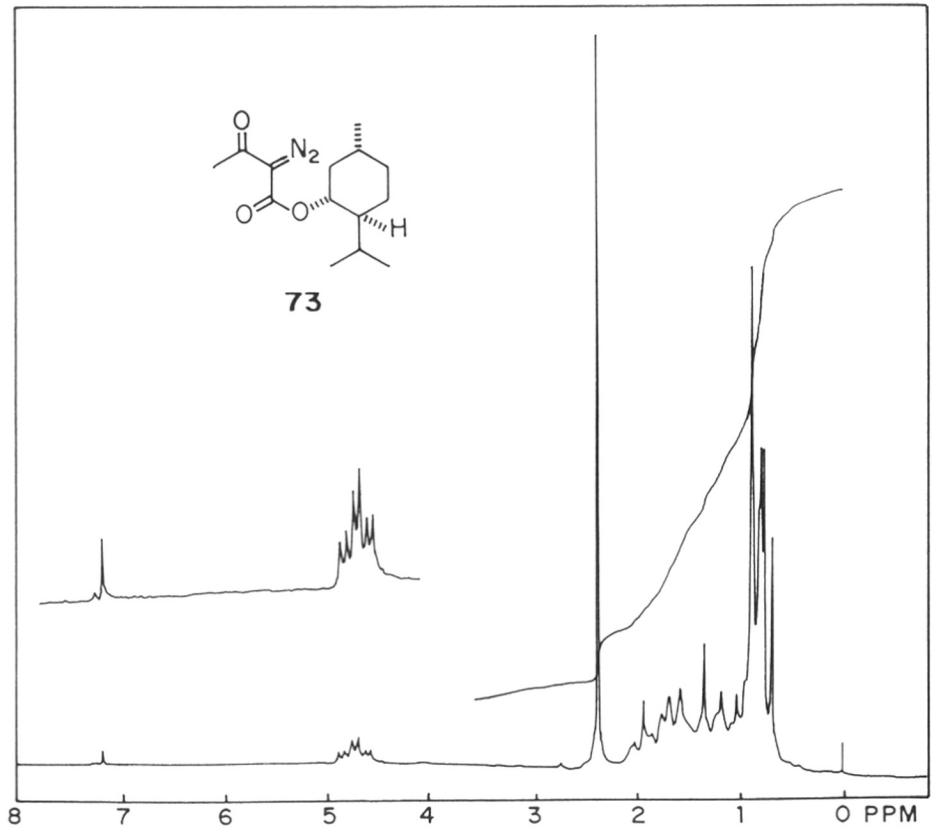


FIG. 2

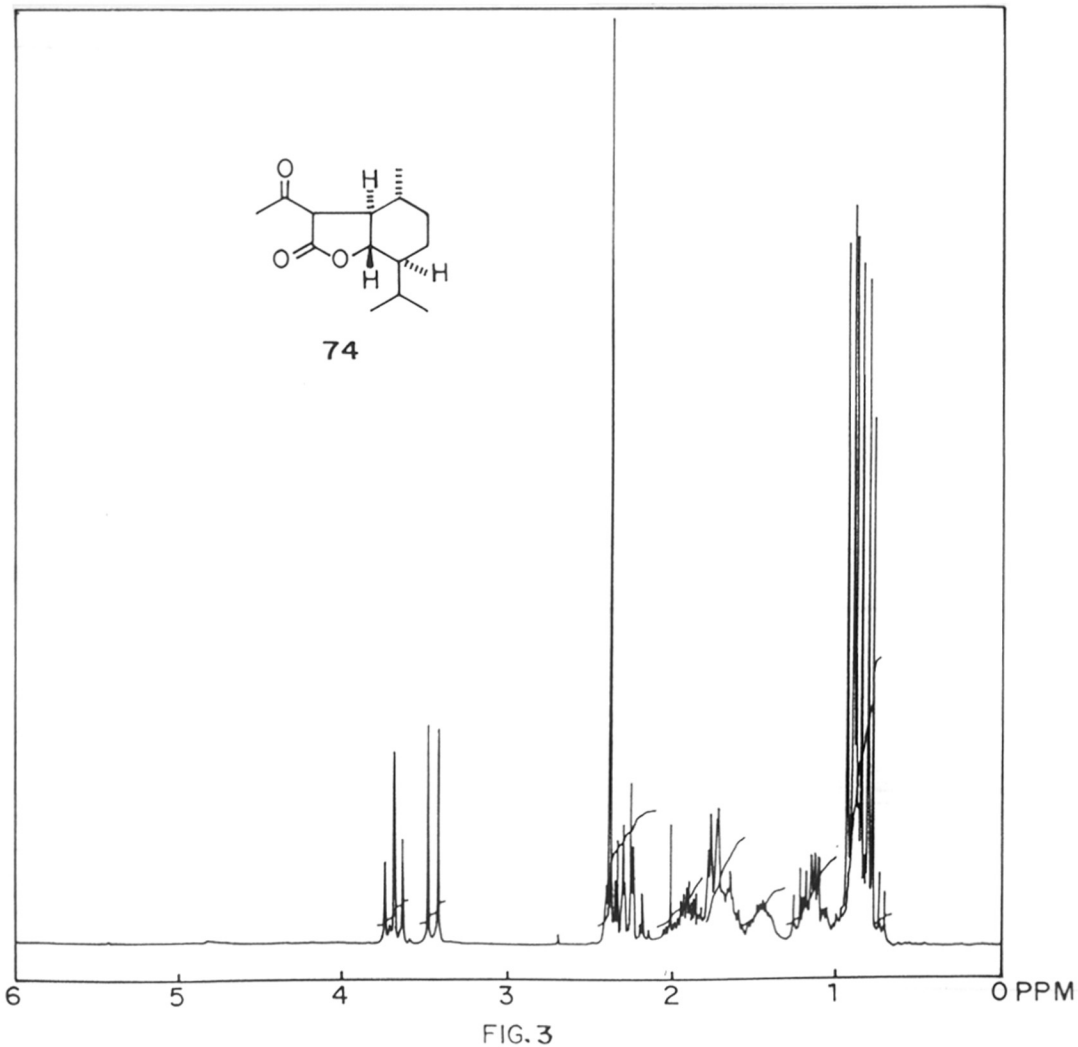


FIG. 3

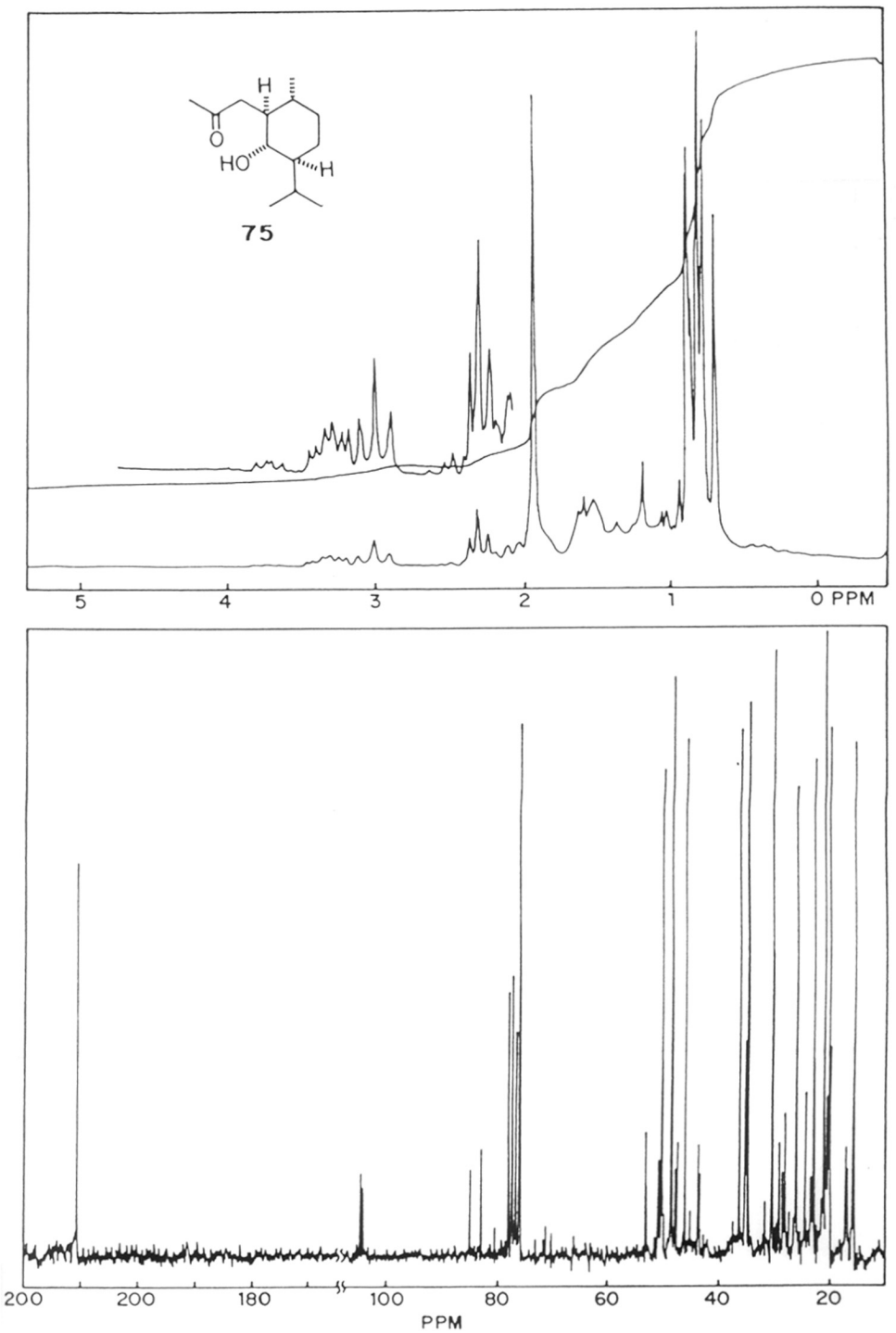


FIG. 4

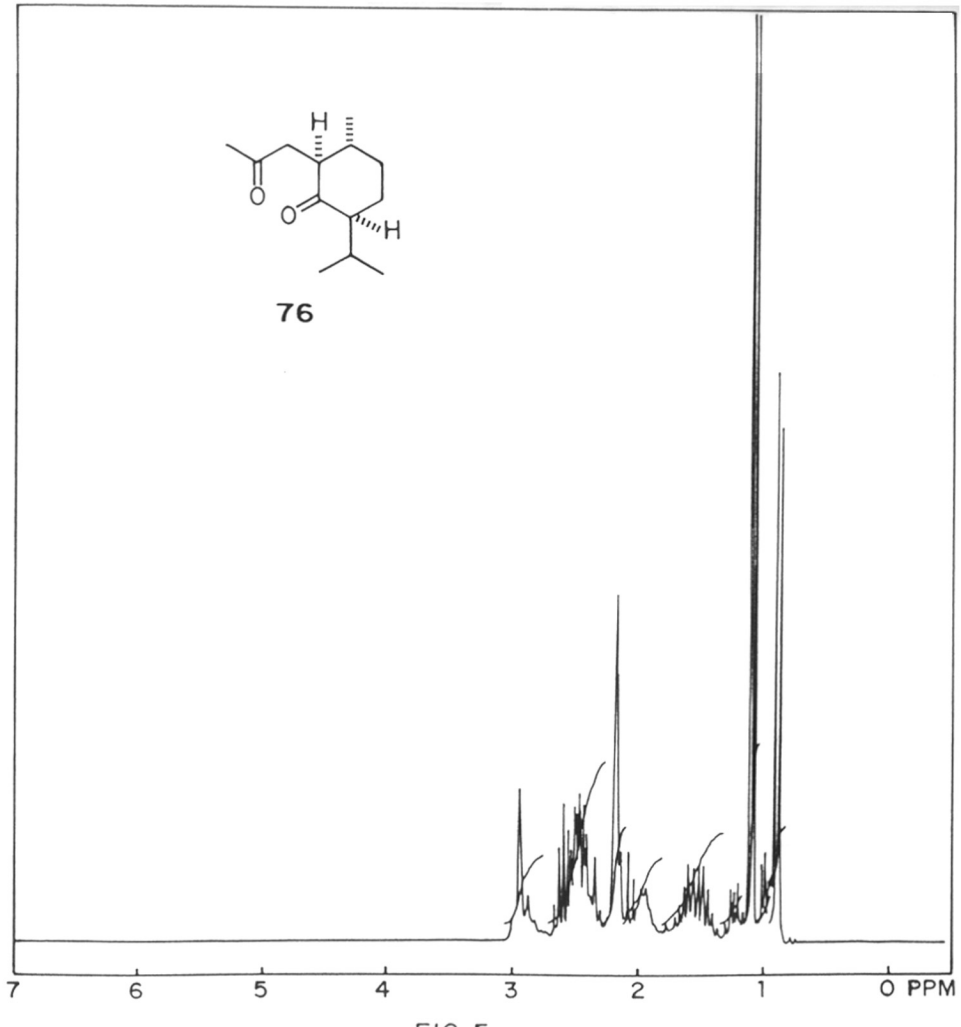


FIG. 5

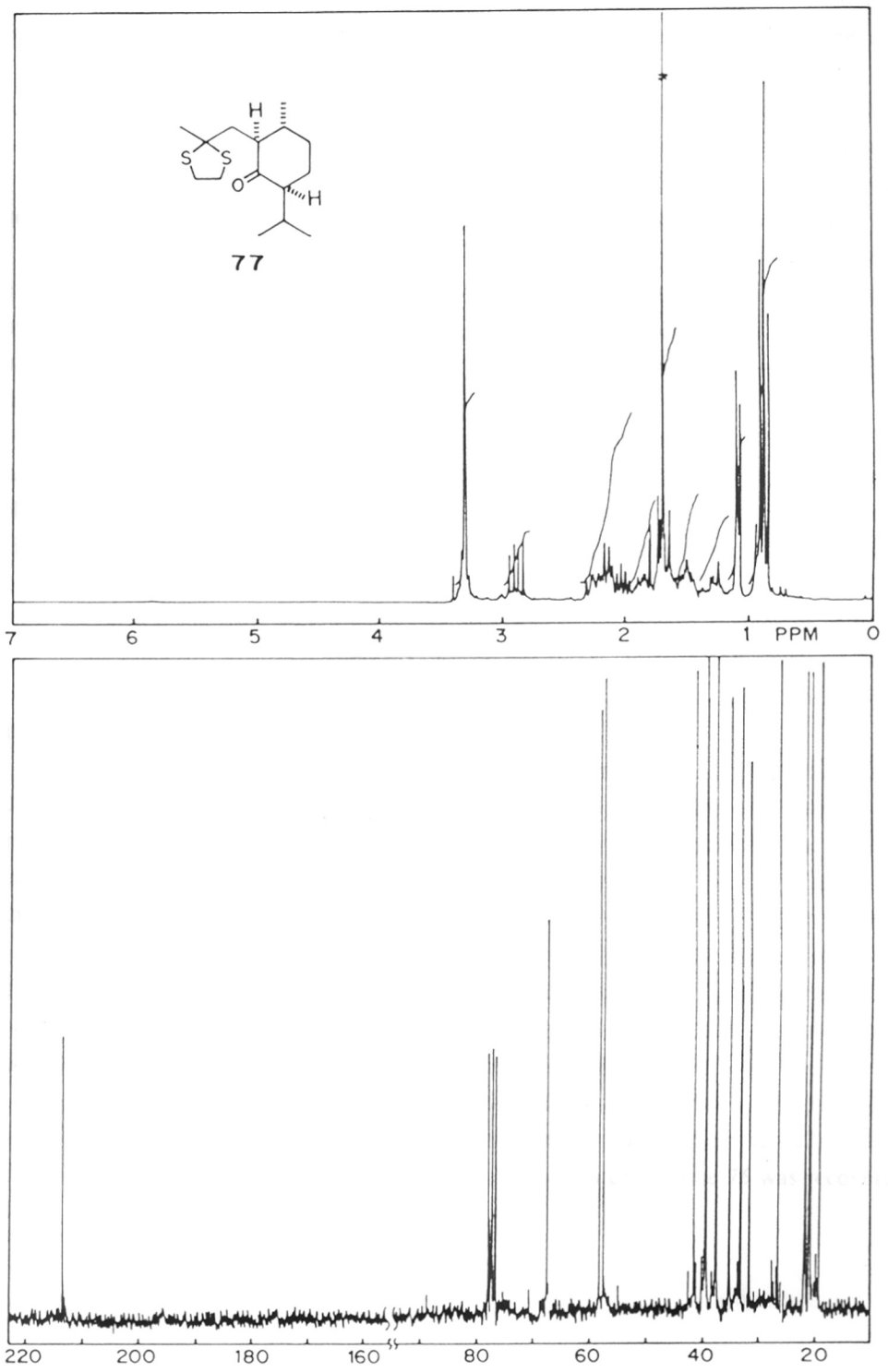


FIG. 6

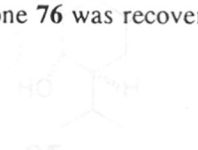
The next task was just one carbon homologation reaction, deprotection and cyclisation to get **80** and further transform it to the model skeleton **81** resembling dihydroartemisinic acid **3b**. For one carbon homologation following reactions were attempted (Scheme-17). The Wittig methoxymethylenation[35], Wittig methylenation reaction,[36] cyanohydrin formation[37], Grignard reaction (MeMgI) and oxirane forming reaction.[38] All these reactions resulted in recovery of starting material. The simple Grignard reaction (MeMgI) also failed to react with ketone. The above study indicates that the carbonyl group is highly sterically hindered.

To avoid the problem of side chain steric hindrance (Scheme - 18) was attempted. Here the strategy was conversion of ketoalcohol **75** to bromo or iodo compounds followed by formylation (Scheme - 18) reaction to get the one carbon homologated compound **78**. Accordingly, ketoalcohol **75** was treated with CBr_4/PPh_3[39] in ether and PBr_3/pyridine[40]. Both reactions resulted in complex mixture of products.

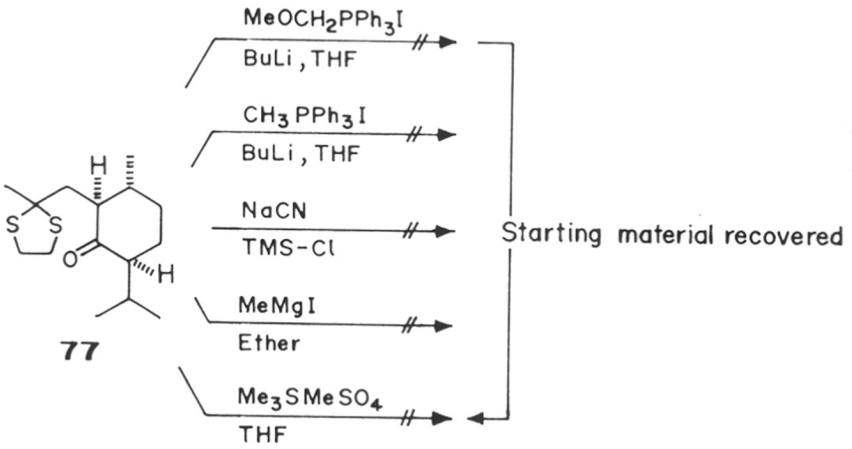
Ravindranathan et. al.[41] have recently reported a simple and rapid method for the preparation of alkyl iodides in a single step upon reaction of alcohols with iodine in refluxing petroleum ether. Ketoalcohol **75** and side chain carbonyl protected compound **95** were treated with iodine in refluxing petroleum ether. Both reactions furnished the undesired dihydrofuran compound **96** in 85% yield (Scheme - 19). The structure of **96** was fully confirmed by its IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. IR spectrum of **96** showed absence of carbonyl groups and presence of 1390 cm^{-1}, 1460 cm^{-1} for double bond. In ^{1}H-NMR spectrum of **96** displayed signals at δ 2.3 (s, 3H) and δ 5.9 (d, 1H) for methyl and olefinic protons. M^+ at confirmed the assigned structure **96**.

It was then decided to temporarily block the side chain carbonyl as less hindered olefin and then do the one carbon homologation reaction (Scheme - 20). With this idea in mind, the attempted Wittig methylenation reaction on ketoalcohol **75** was unsuccessful and starting material was recovered back. This might be due to the hydroxy group. It was then decided that to protect the hydroxy group first and then attempt Wittig methylenation reaction (Scheme - 21). When ketoalcohol **75** was treated with NaH followed by methyl iodide dihydrofuran compound **96** was obtained in excellent yield (95%) as a colourless oil. The structure of the compound **96** was confirmed by IR, ^{1}H-NMR and mass spectroscopy which was found to be identical in all respects with those obtained by above method (Scheme - 19).

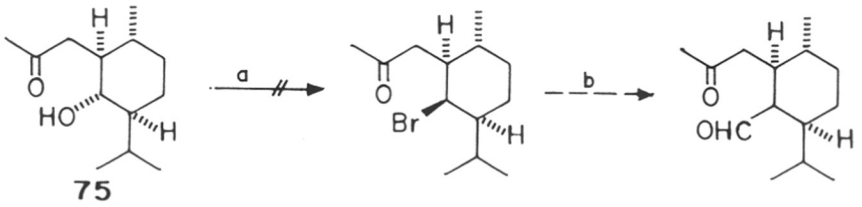
Another attempted strategy was in situ protection of side chain carbonyl group of dione **76** as silyl enol ether followed by Wittig olefination of the ring carbonyl (Scheme - 22). When dione **76** was subjected to reaction conditions only starting material dione **76** was recovered back.



Scheme-17

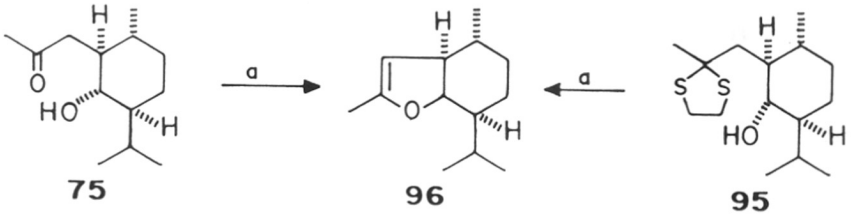


Scheme-18



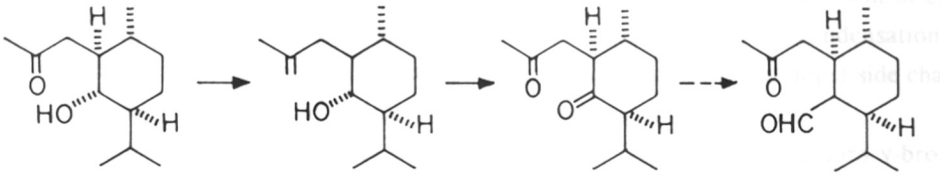
a: CBr_4 , PPh_3 or PBr_3 , Pyridine **b**: i) Protection
ii) Mg or Li, ether iii) Me_2N-CHO iv) Deprotection

Scheme-19



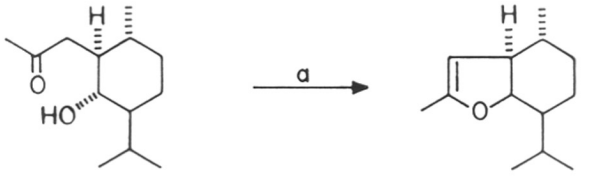
a: I_2 , Pet ether, Δ

Scheme-20



97

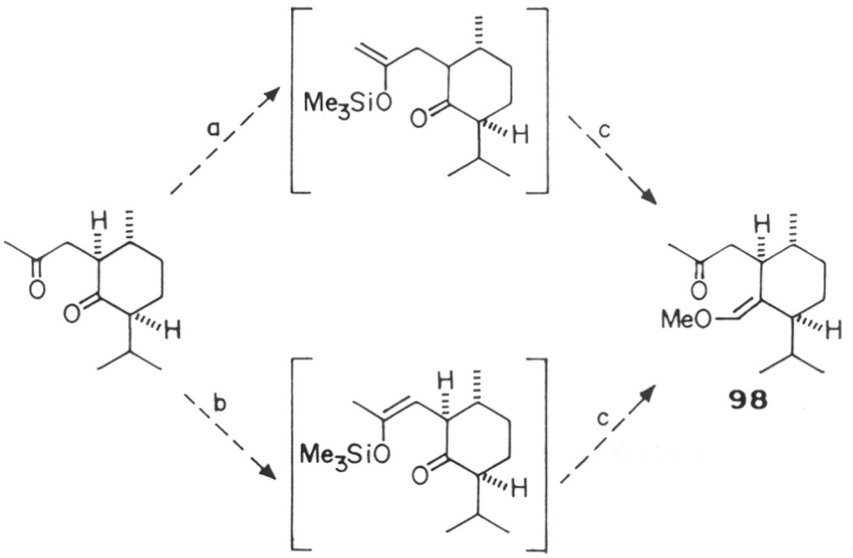
Scheme-21



75 **96**

a : NaH, CH_3I, THF

Scheme-22



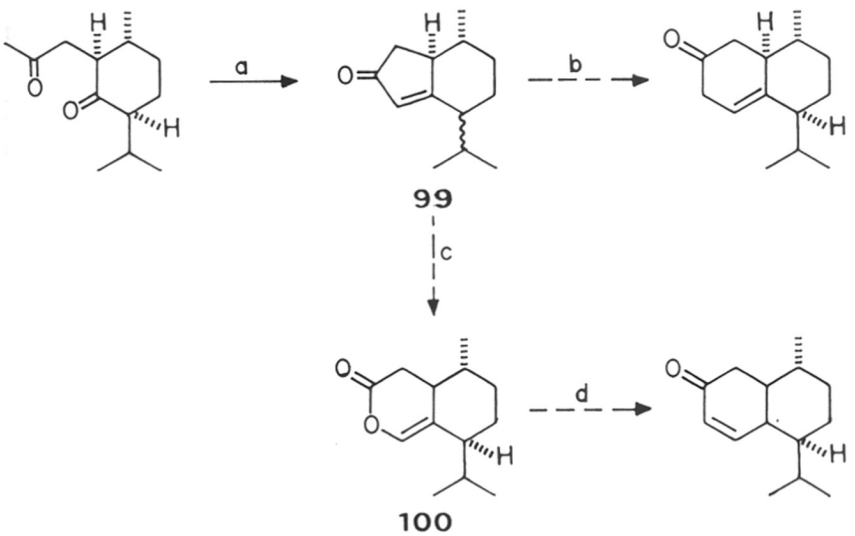
98

a : $Et_3\ddot{N}$, TMS-Cl, 0°C **b** : LDA, TBDMS-Cl, -78°C
c : $MeOCH_2PPh_3I$, BuLi, THF

The next attempt was the conversion of dione **76** to enol lactone **100** by aldol cyclisation[42] and Baeyer Villiger oxidation[43] reaction (Scheme - 23). The treatment of enol lactone with Grignard reagent to enones is well reported reaction.[44] Aldol condensation of dione to generate bicyclic enone **99** was accompanied by epimerization of isopropyl side chain. Since the stereochemical integrity was lost this Scheme was not pursued further.

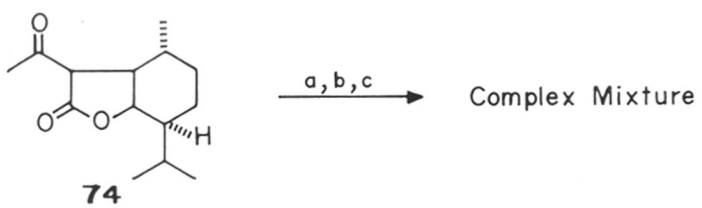
The treatment of butyrolactones with ethanolic HCl, HBr to obtain γ-chloro-γ-bromo butyrates are well reported in literature.[45] Thus, bicyclic-γ-lactone **74** was treated with HCl, HBr, NBS and NaCN[46] separately. All reactions resulted in complex mixture of products (Scheme - 24).

Scheme-23



a: NaOH **b**: CH_2N_2, ether **c**: m-CPBA, CH_2Cl_2 **d**: MeMgI, ether

Scheme-24



74

a: HCl (dry), MeOH, 0°C **b**: HBr (dry), MeOH, 0°C
c: NBS, K_2CO_3, MeOH, 0°C

Route B : Intramolecular Ene Reaction Approach :

According to retrosynthetic plan (Scheme - 14) the key reaction involves stereoselective intramolecular ene reaction of **102** to **103** based on fact that an arylsulphonyl group is sufficiently good nucleofuge that an elimination reaction is possible under basic conditions as shown in Scheme - 25.

Thus, (+)-citronellal was converted to exomethylene compound **101** by reported procedure as described in the chapter-1, section-B. Michael addition of thiophenol to exomethylene compound **101** in the presence of catalytic amount of triethylamine furnished adduct **102** in excellent yield. IR spectrum of **102** showed absorption at 1705 and 1600 cm^{-1} indicating the presence of unsaturated aldehyde and double bonds. The ^{1}H-NMR spectrum of **102** displayed disappearance of signals at δ 6.1 (s, 1H) and δ 6.2 (s, 1H) for exomethylene protons while appearance of signal at δ 7.1-7.5 (m, 5H) for the aromatic protons. The mass spectrum analysis confirmed the assigned structure **102** (M^+, 276, 4%).

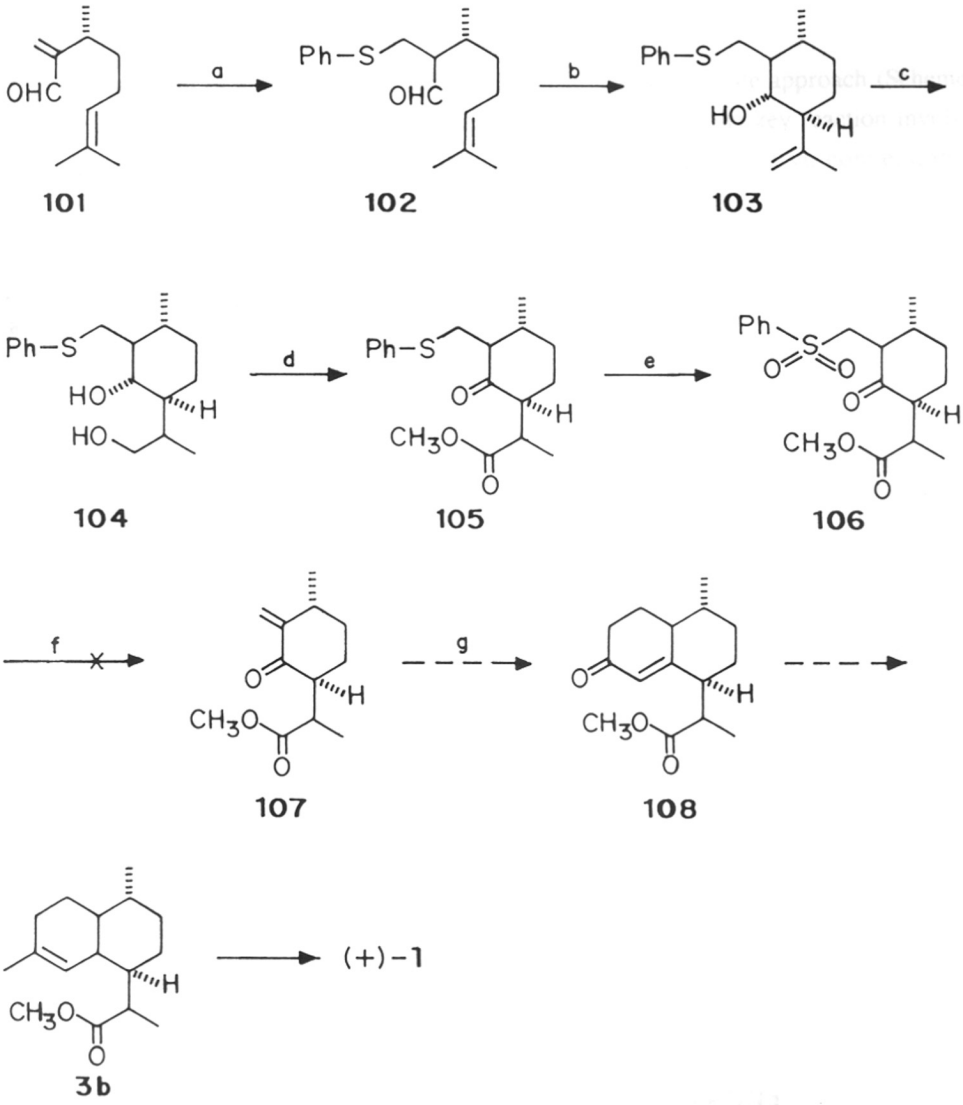
Intramolecular ene reaction was achieved by $ZnCl_2$ as the Lewis acid in benzene at 10°C to furnish the adduct **103** in 75% yield and in 95% purity of isopulegol derivative with other possible diastereisomers being present only in small amounts.[47] IR spectrum of **103** showed absorption at 3450 cm^{-1} and 1600 cm^{-1} indicating the presence of hydroxy and olefin groups. The ^{1}H-NMR spectrum of **103** displayed signals at δ 4.9 (d, 2H) and 3.5 (m, 1H) for exomethylene and -CH-OH protons. Presence of M^+ at 276 (2%) and fragmentation pattern confirmed the assigned structure **103**.

Hydroboration[48] of **103** afforded the diol **104** in good yield (80%) as a viscous liquid. IR spectrum of **104** showed strong absorption at 3450 cm^{-1} indicating the presence of hydroxy groups. ^{1}H-NMR spectrum of **104** showed disappearance of signals at δ 4.9 (d, 2H) of exomethylene protons while appearance of multiplet at δ 3.8 for CH_2-OH protons. Mass spectrum of **104** showed (M^+-18) at 276 as parent peak.

The diol **104** was further oxidised with Jones reagent[49] to give ketoacid which was esterified with diazomethane[50] to give its methyl ester **105** which was characterized by its IR, ^{1}H-NMR and mass spectra. IR spectrum of **105** showed strong absorption at 1740 cm^{-1} and 1720 cm^{-1} indicating that the presence of ester carbonyl and ketone groups. ^{1}H-NMR analysis of **105**, disappearance of multiplet at δ 3.8 of CH_2-OH protons while appearance of singlet at δ 3.5 for methyl group. Mass spectrum exhibited M^+ at 320 (2%).

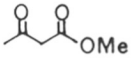
The oxidation of sulphide **105** using H_2O_2/AcOH[49] furnished sulphone **106** in good yield (80%). IR spectrum of **106** showed strong absorption at 1150 cm^{-1} and 1310 cm^{-1} characteristic of sulphone group. ^{1}H-NMR spectrum of **106** displayed signals at δ 7.5 (m, 3H) and δ 7.9 (m, 2H) for aromatic protons. The separation of aromatic protons indicated that oxidation of sulfide group. The mass spectrum of **106** exhibited M^+ at 352 confirming the assigned structure.

Scheme-25



a : $PhSH$, $Et_3\ddot{N}$, C_6H_6, RT **b**: $ZnCl_2$, C_6H_6, 0°C

c : i) BMS ii) H_2O_2, $\bar{O}H$ **d**: i) Jones oxidation ii) CH_2N_2, ether

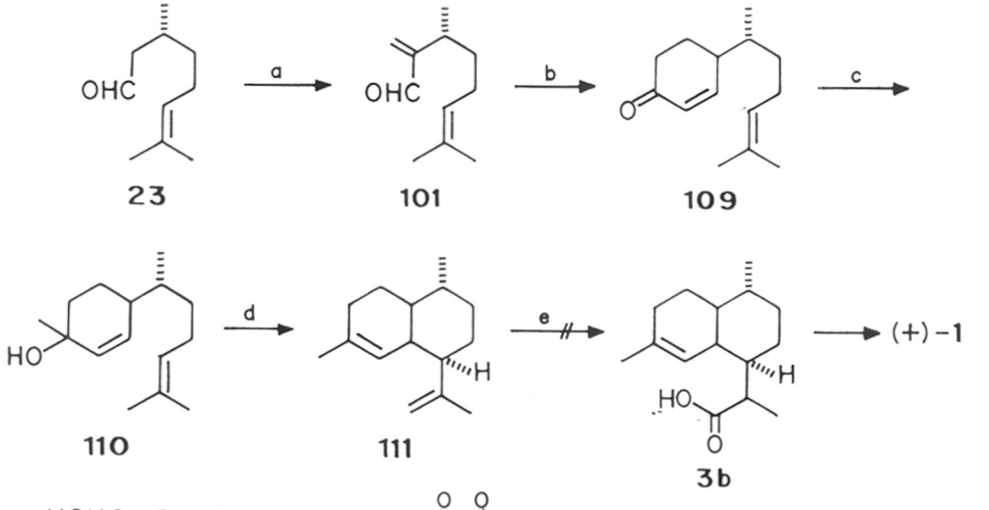
e: H_2O_2, AcOH, Δ **f** : Base **g**:  , MeOH, MeONa.

Attempts to convert the sulphone **106** to the α,ß-unsaturated ketone **107** did not meet with success. Various bases and reaction conditions were attempted such as a) $NaNH_2$, RT to b) NaH, RT to 0°C c) DBU, Δ d) MeONa/MeOH,Δ e) $(CH_3O)_3P$. THF, but all resulted in the recovery of starting material sulphone **106**. Hence this scheme was abandoned.

Route C : Intramolecular Ene Reaction Approach :

From the point of a practical synthesis of artemisinin **1** an alternate approach (Scheme - 26) was attempted. According to retrosynthetic plan (Scheme - 14), the key reaction involves an intramolecular ene reaction of carbinol **110** to **111** and regioselective conversion of isopropenyl unit into propionate. The stereochemistry problem was not unexpected in this route but aim was synthesis of diastereoisomeric mixture of containing predominantly **3b** (dihydroartemisinic acid) and separation to develop a very short and practical synthesis of (+)-artemisinin.

Scheme-26



Thus, (+)-citronellal was converted to enone **109** according to reported procedure as described in the chapter-I section-B. Grignard reaction on the enone **109** with methyl-magnesiumiodide[52] furnished the carbinol **110** which was identified by its IR, ^{1}H-NMR and mass spectra (**Fig.7**). IR spectrum of **110** showed bands at 3400 cm^{-1} for hydroxy group and at 1670 cm^{-1} for double bond stretching while disappearance of carbonyl stretch bands of the α,ß-unsaturated ketone at 1680 cm^{-1}. The ^{1}H-NMR spectrum of **110** displayed signals at δ 5.6 (br, 2H) for CH = CH protons and disappearance of signals at δ 6.3 (dd, 1H) and δ 6.9 (dd, 1H) of CH=CH-C protons. Mass spectrum showed molecular ion peak M^+ at 222.

Intramolecular ene reaction[53] of carbinol **110** was achieved by employing a wide variety of acidic reagents (see table 1). Almost all reagents gave complex mixture of products; only 10% H_2SO_4 gave diene in poor yield 50% whereas $HClO_4$ better to give 78% yield in this intramolecular ene reaction (see Table 1I. The structure of diene was confirmed by IR, ^{1}H-NMR and mass spectroscopy (**Fig.8**). IR spectrum of diene **111** showed disappearance of absorption at 3400 cm^{-1} of hydroxy group. The ^{1}H-NMR spectrum of diene **111** displayed signals at δ 4.7 (d, 2H) of exomethylene protons and δ 5.4 (δ, 1H) of olefinic proton and disappearance of signal at δ 5.6 (bs, 2H) of -CH=CH- and signal at δ 5.1 (t, 1H) of -CH= of olefinic protons. M^+ at 204 (100%) and fragmentations observed in the mass spectrum confirmed the assigned structure as **111**.

Table I

No.	Reagents	Reaction conditions	Product
1	TsOH	a: C_6H_6/ Δ	Complex mixture
		b: C_6H_6/RT	Complex mixture
2	$BF_3.Et_2O$	a: -78°C - 0°C	Complex mixture
		b: 0°C	Complex mixture
3	CF_3COOH	0°C	Complex mixture
4	$SnCl_4$	-78°C - 0°C	Complex mixture
5	$TiCl_4$	-78°C - 0°C	Complex mixture
6	H_2SO_4 (10%)	R.T	50%
7	$HClO_4$	R.T.	78%

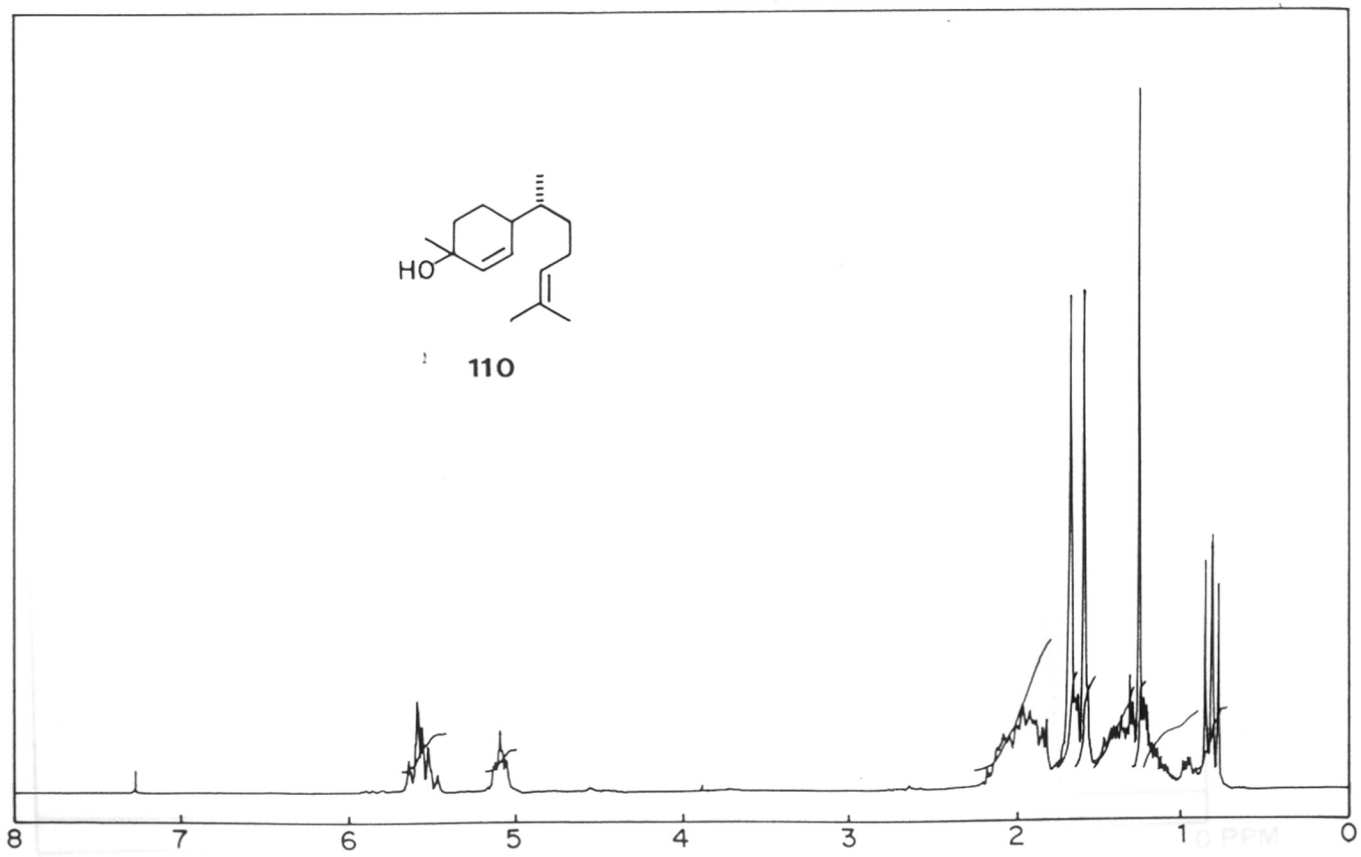


FIG.7

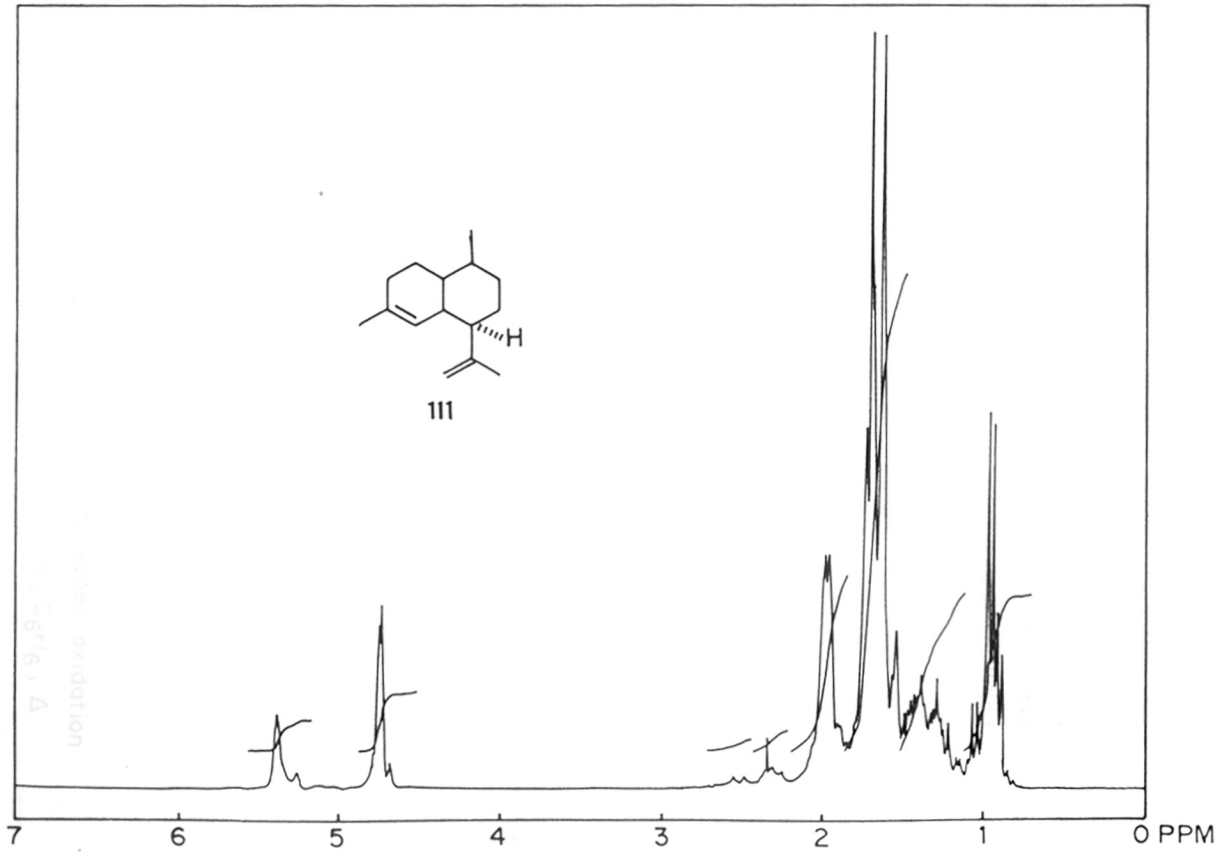
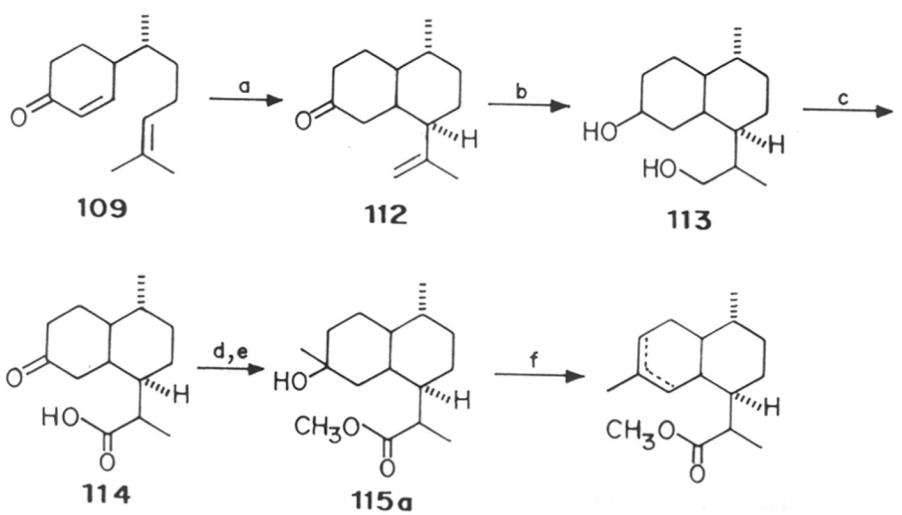


FIG. 8

The next task was the conversion of isopropenyl unit of **111** into a propionate. The attempted regioselective hydroboration of diene **111** with 9-BBN[54] resulted in recovery of starting diene. This reaction was tried without success under various reaction conditions such as a) 9-BBN addition at room temperature and stirring for 12 hours to 3 days b) refluxing for 10 hours c) 9-BBN addition at 0°C stirring for 10 hours. d) 9-BBN addition at 50°C and stirring for 10 hours.

In order to circumvent this problem slight modification (Scheme - 27) was attempted. Here strategy was the intramolecular ene reaction[55] of **109** to enone **112** and the conversion of isopropenyl unit into propionate by borane methyl sulfide complex. Thus, ene reaction of **109** was smoothly achieved by refluxing in benzene in presence of catalytic amount of p-TsOH to furnish the enone **112** in good yield (80%) as a colourless oil. IR spectrum of the enone **112** showed absorption at 1710 cm^{-1} indicating the presence of saturated ketone. The ^{1}H-NMR spectrum (**Fig.9**) of **112** displayed signals at δ 4.7 (s, 1H) and δ 4.8 (s, 1H) for olefinic protons while disappearance of signals at δ 5.1 (t, 1H), δ 6.3 (dd, 1H) and δ 6.9 (dd, 1H) of olefinic protons. Mass spectrum (M^+, 206, 18%) confirmed the assigned structure.

Scheme - 27



a: p-TsOH, C_6H_6, Δ **b**: BMS, H_2O_2, $\bar{O}H$ **c**: Jones oxidation
d: MeMgI, ether **e**: CH_2N_2, ether **f**: p-TsOH, C_6H_6, Δ

Hydroboration[48] of enone **112** furnished the desired diol **113** in excellent yield (88%) as a viscous liquid. IR spectrum of diol **113** showed absorption 3450 cm^{-1} indicating the presence of hydroxy groups. ^{1}H-NMR analysis of diol **113** showed appearance of signals at δ 3.5 (m, 2H) for $\underline{CH_2}$-OH protons while disappearance of signals at δ 4.7 (s, 1H), δ 4.8 (s, 1H) and δ 1.6 (s, 3H) of olefinic protons and methyl protons. Mass spectrum of **113** exhibited (M^+-18) at 208 as parent peak.

The diol **113** was further oxidised with Jones reagent[49] to afford ketoacid **114** in 72% yield as a viscous liquid which was characterized by its IR, ^{1}H-NMR and mass spectra. IR spectrum showed absorption at 3500 cm^{-1} and 1710 cm^{-1} revealing the presence of -COOH and ketone functionality. In the ^{1}H-NMR analysis of **114** doublet at δ 1.2 (J = 5.4 Hz) was assigned to OOC - CH_3 and disappearance of multiplet at δ 3.5 of $\underline{CH_2}$-OH protons. Mass spectrum of **114** exhibited (M^+-18) at 220 as a parent peak.

Grignard reaction on ketoacid **114** with methyl magnesium iodide to give carbinol which was esterified with diazomethane[49] in ether to give its methyl ester **115a** which was characterized by its IR, ^{1}H-NMR and mass spectral analysis. The IR spectrum of showed absorption at 3300 cm^{-1} and 1740 cm^{-1} for hydroxy and ester carbonyl groups respectively. ^{1}H-NMR analysis displayed two doublets at δ 0.9(J = 5.00 Hz)and 1.2(J= 5.00 Hz) for two methyl protons and two singlet at 1.3 and 3.6 for two methyl protons. M^+ at 268 (35%) confirmed the assigned structure **115a**.

Finally dehydration of carbinol **115a** was achieved by refluxing in benzene in the presence of p-TsOH to furnished the methyl dihydroartemisinate **3b** skeleton in 72% yield as a mixture of diastereoisomers. IR spectrum of **3b** skeleton showed absorption at 1740 cm^{-1} indicating the presence of ester carbonyl group. ^{1}H-NMR displayed singlet at δ 5.3 and multiplet at δ 5.7 for olefinic protons and singlet at δ 1.6 for methyl group. Mass spectrum exhibited M^+ at 250. All these above steps could be performed smoothy and efficiently implying mild reaction conditions and in very good yields. But ^{1}H-NMR spectrum of methyl dihydroartemisinate **3b** showed two olefinic peaks. It was very difficult to establish whether they are regioisomers or diastereoisomers.

It was then decided to focus the attention towards the resolution of enone[56] **112**. Several approaches to this problem have been reported among which are optically carbonyl reagents such as hydrazines, semicarbazides, diols and second order method such as reduction to alcohols which introduces another optical centre followed by resolution and reoxidation.

The attempted resolution of enone **112** by reduction to alcohol with $NaBH_4$ proved unsuccessful. It was not possible to separate diastereoisomers by chromatography (Scheme -28). Attempted resolution of enone by tosyl hydrazone preparation was also unsuccessful. Tosylhydrazone **117** of the enone **112** was semisolid and hence resolution could not be achieved.

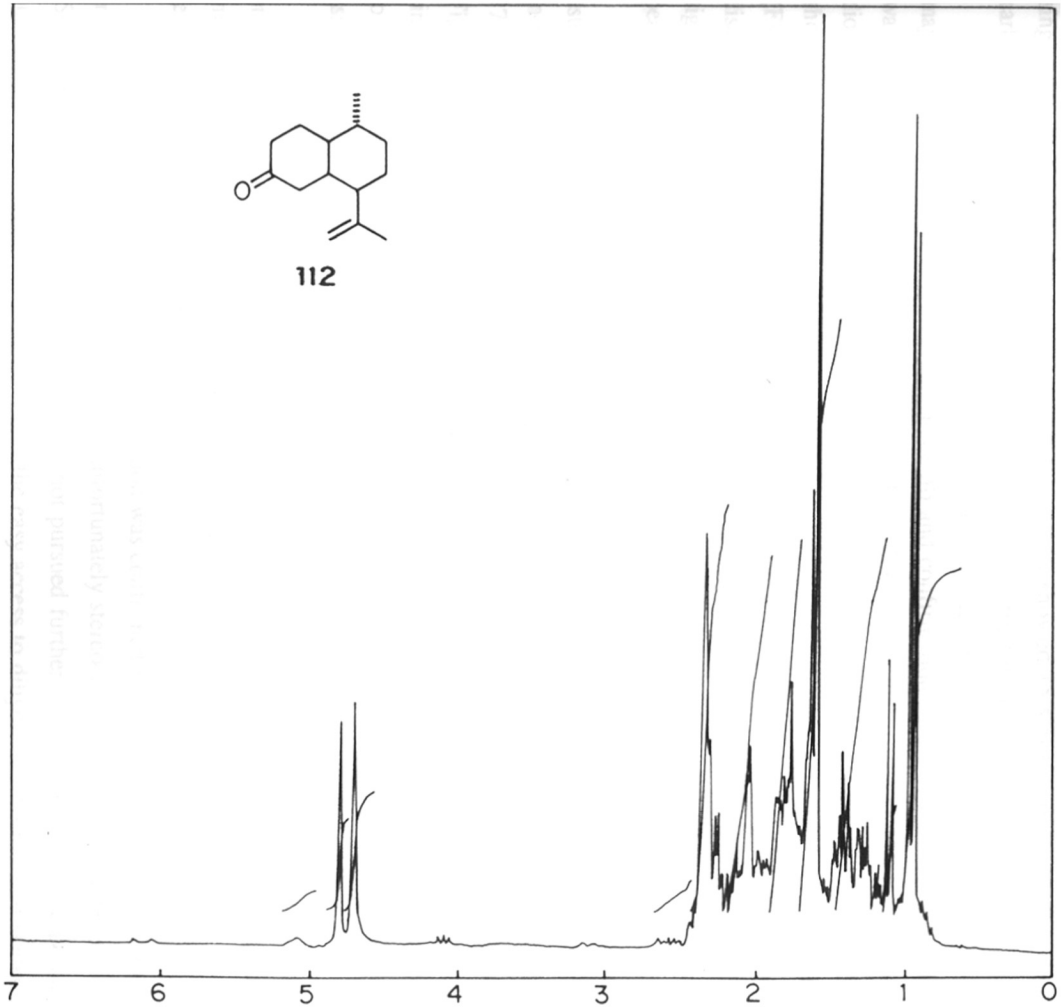


FIG. 9

Resolution of enone **112** was attempted by nucleophilic addition reaction. Grignard reaction on enone **112** with methylmagnesiumoidide furnished three isomers of carbinol **118**. These three isomers were easily separated by column chromatography, the ratio of three isomers was 70:20:10. The structure of major isomer was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy (**Fig.10**). IR spectrum showed absorption at 3400 cm^{-1} and 1650 cm^{-1} indicating the presence of -OH and double bond groups. ^{1}H-NMR analysis displayed doublet at δ 0.95(J = 5.0 Hz)singlet at δ 1.2 and δ 1.7 for three methyl groups and δ 4.8 singlet for terminal double bond protons. ^{13}C-NMR showed 15 signals corresponding to 15 carbon atoms. M^+ at 222 (2%) confirmed the assigned structure **118**.

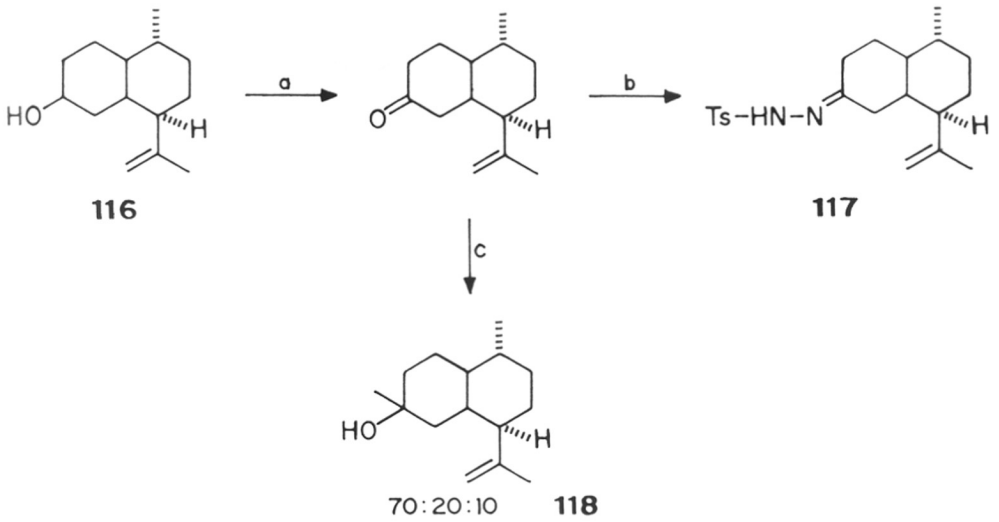
Having obtained single isomer of carbinol **118**, the next task was the conversion of the major isomer to methyl dihydroartemisinate **3b** and confirmation of the stereochemistry. This was accomplished as follows (Scheme - 29). Hydroboration of major isomer **118** furnished the diol **119** as a single diastereoisomer in 80% yield. m.p. = 77-78°C. IR spectrum of diol **119** showed absorption at 3400 cm^{-1} indicating presence of hydroxy groups. The ^{1}H-NMR (**Fig.11**) analysis revealed presence of multiplets at δ 3.4 and δ 3.7 for $\underline{CH_2}OH$ protons and disappearance of singlet at δ 4.8 of terminal double bond protons. The ^{13}C-NMR displayed 15 signals corresponding to 15 carbons. Mass spectrum exhibited (M^+-18) at 222 as the parent peak.

The diol **119** was further oxidised with Jones reagent to furnish acid **120** which was esterified with diazomethane in ether to the corresponding ester carbinol **115b** as a white solid in 80% yield. M.P. = 126°C. IR spectrum of the **115b** showed absorption at 3400 cm^{-1} and 1740 cm^{-1} indicating presence of hydroxy and ester carbonyl groups. ^{1}H-NMR of (**Fig.12** and **Fig.13**) **115b** displayed signals at δ 0.9 as doublet and 1.2 (J = 5.0 Hz, J = 5.0 Hz) and singlet at δ 1.3 and δ 3.7 for two methyl groups. ^{13}C-NMR displayed 15 signals corresponding to 15 carbons. Mass spectrum exhibited (M^+-18) at 250 as a parent peak confirmed the assigned structure **115b**.

Finally dehydration of carbinol **115b** was achieved by refluxing in benzene in the presence of p-TsOH to furnished the methyl dihydroartemisinate **3b** skeleton in 75% yield as a mixture of regioisomers. The spectroscopic data (**Fig.14**) was found to be identical in all respects with those reported in literature.[26]

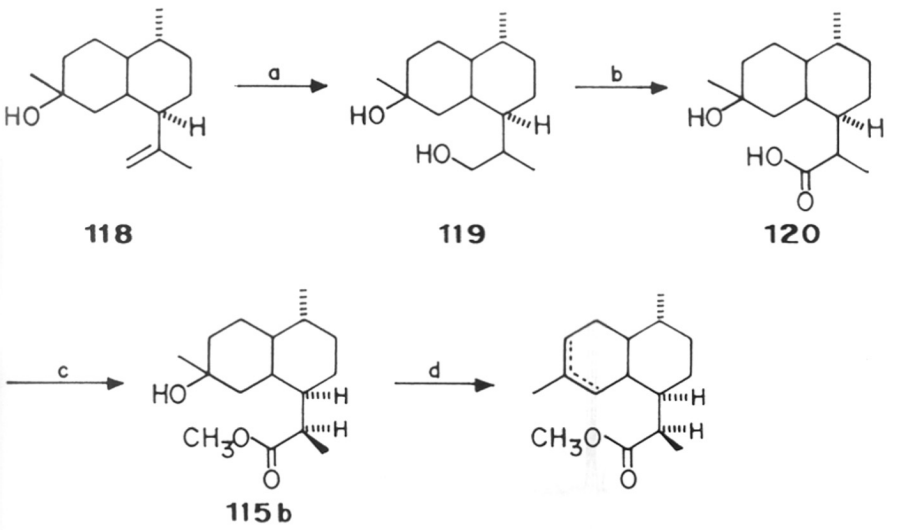
The stereochemistry of the ring junction was confirmed to be cis by single crystal X-ray analysis (**Fig.15**, **Fig.16** and Table-II), but unfortunately stereochemistry was the undesire one. (See Scheme - 29). Hence this scheme was not pursued further. However, it may be pointed out that the present synthetic scheme allows the easy access to dihydroartemisinic acid skeleton in short, simple and practical way. This becomes important for the synthesis of artemisinin analogues.

Scheme-28



a: $NaBH_4$, MeOH , RT **b**: Ts-NH-NH_2 , Py
c: MeMqI , ether , 0°C

Scheme-29



a: BMS, H_2O_2 , $\bar{O}H$, ether **b**: Jones oxidation **c**: CH_2N_2 , ether
d: p-TsOH , C_6H_6 , Δ

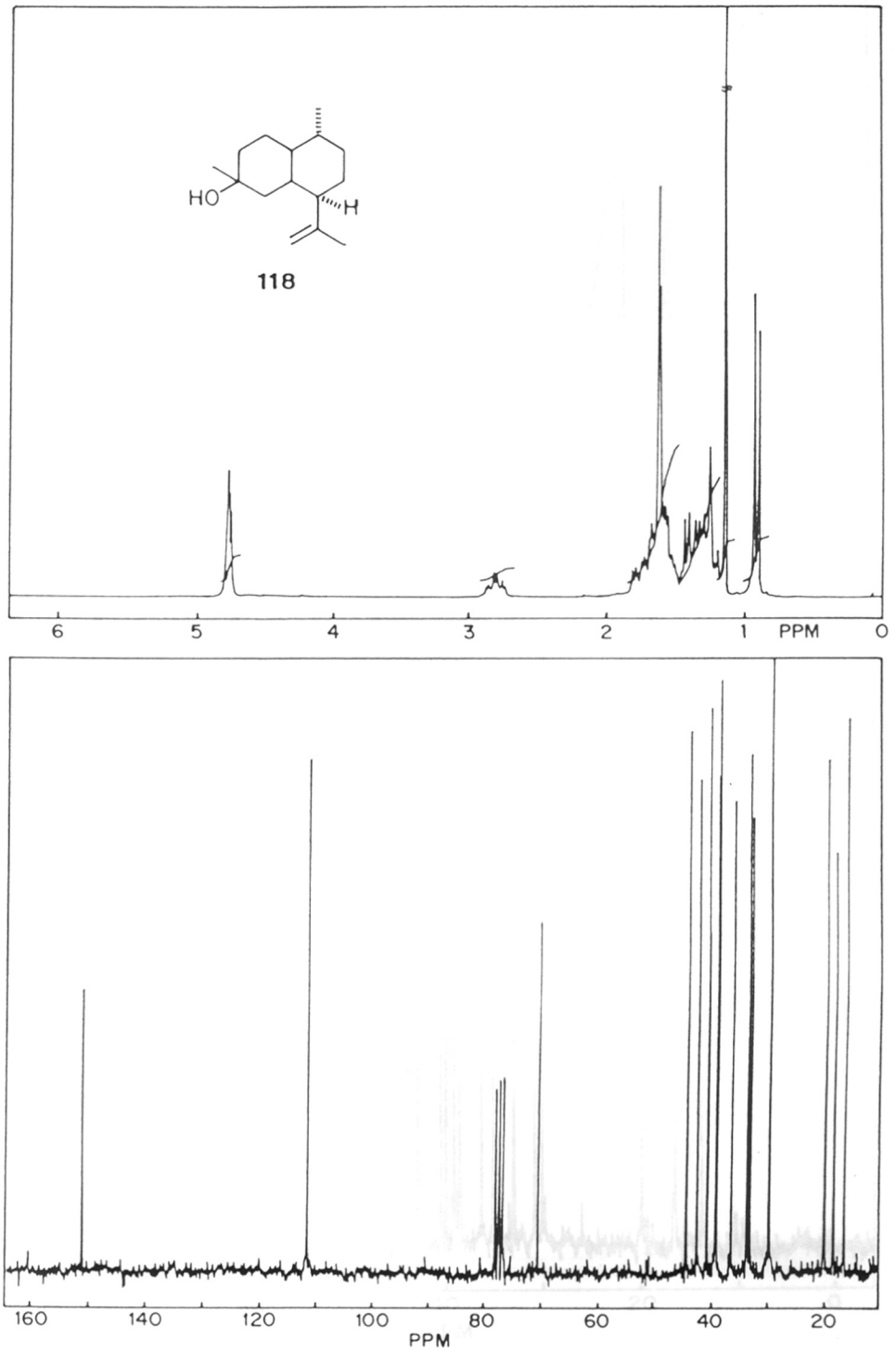


FIG. 10

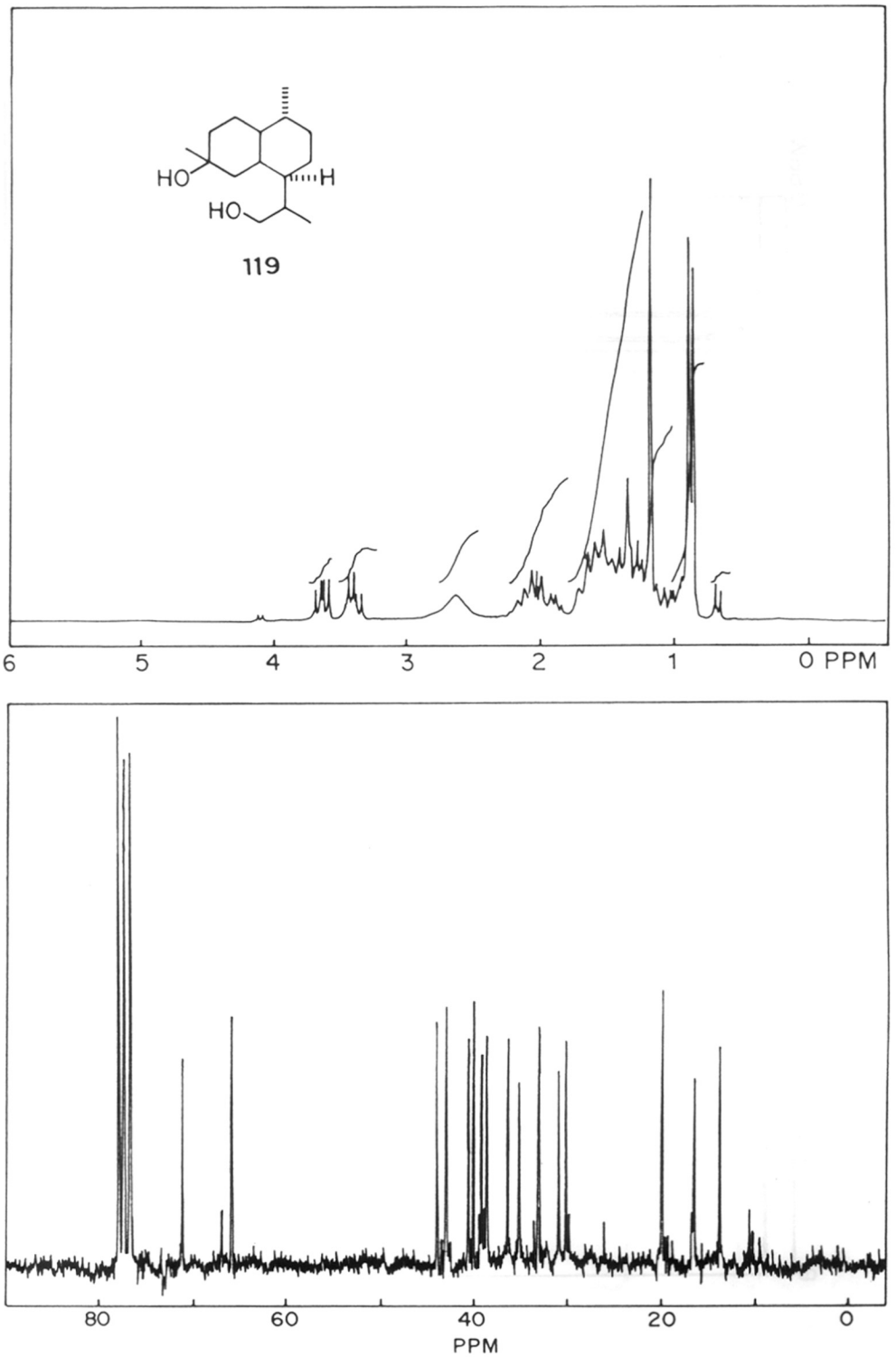


FIG.**11**

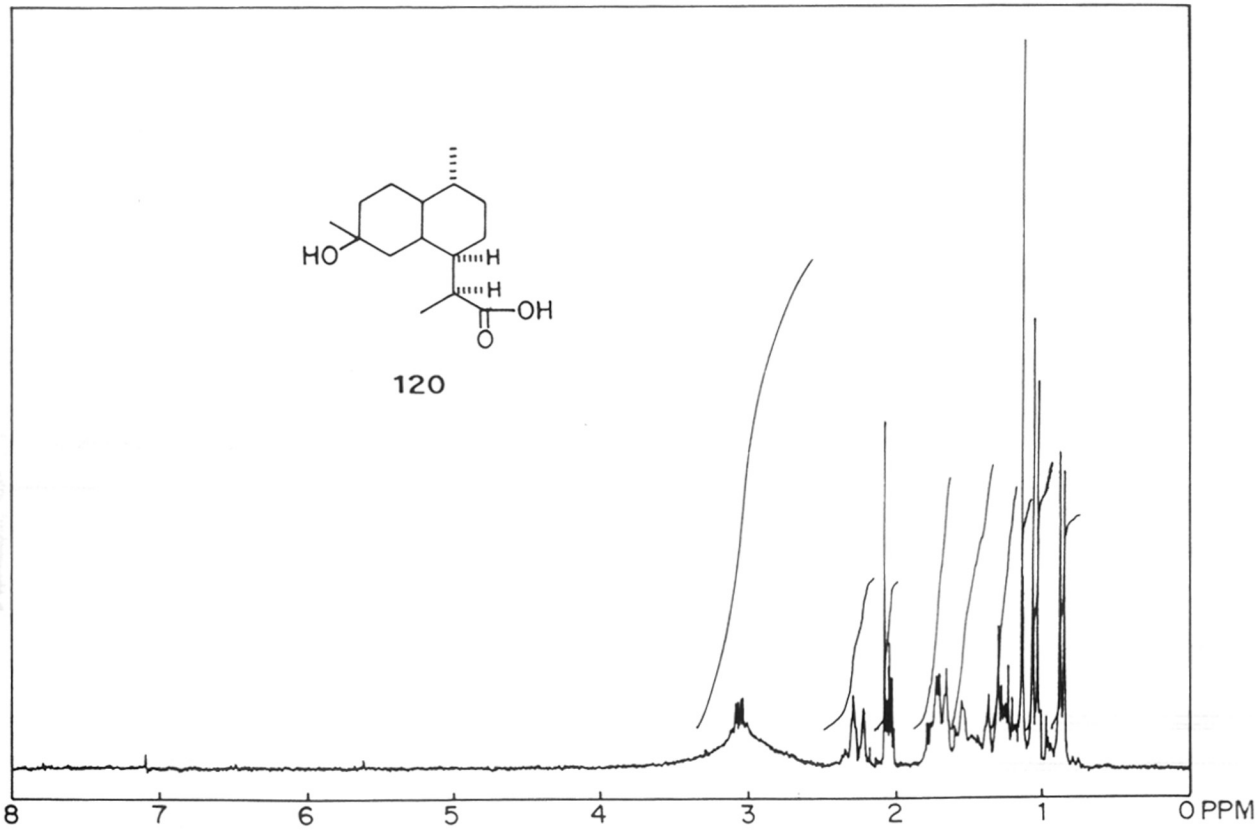


FIG.12

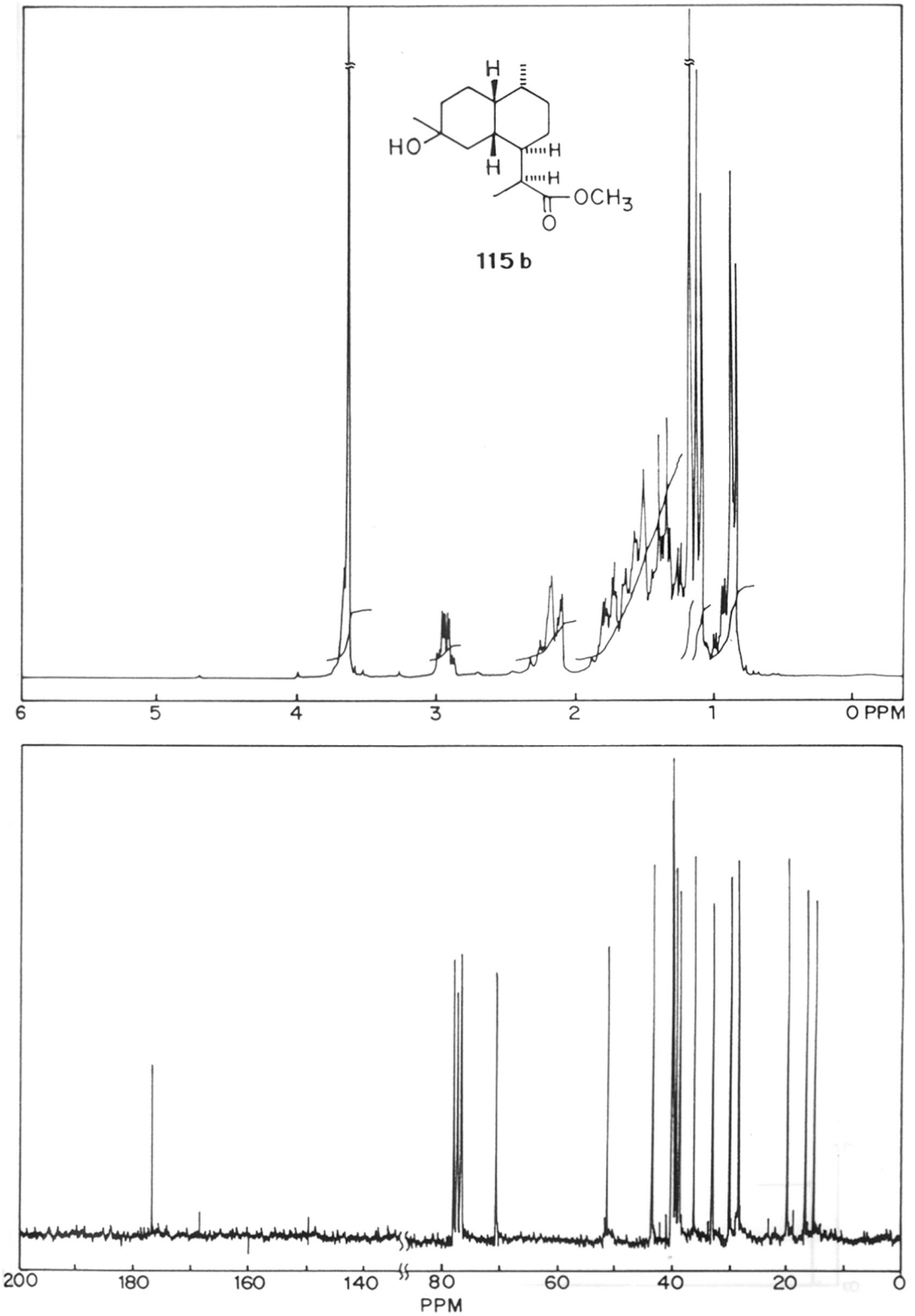


FIG.13

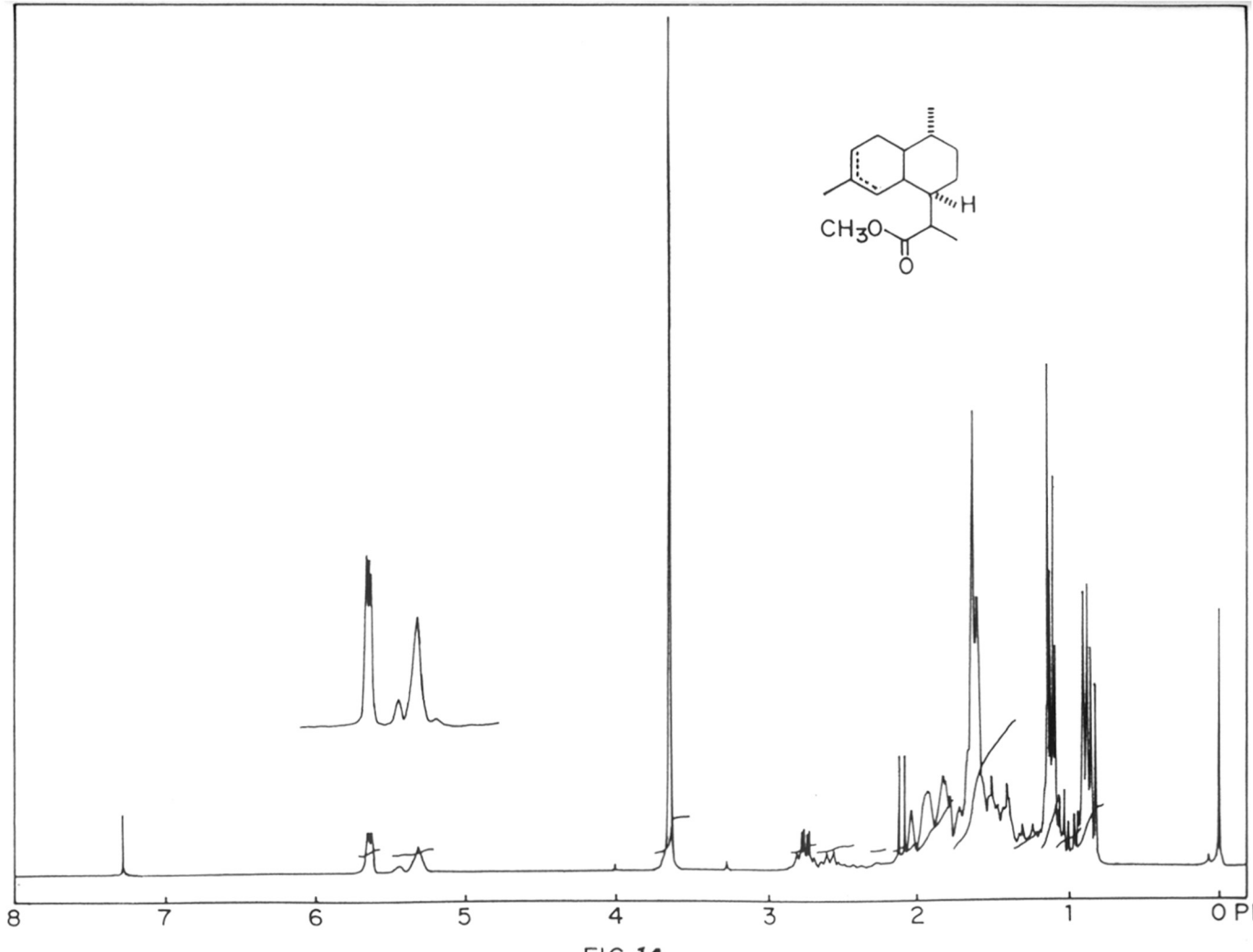


FIG. 14

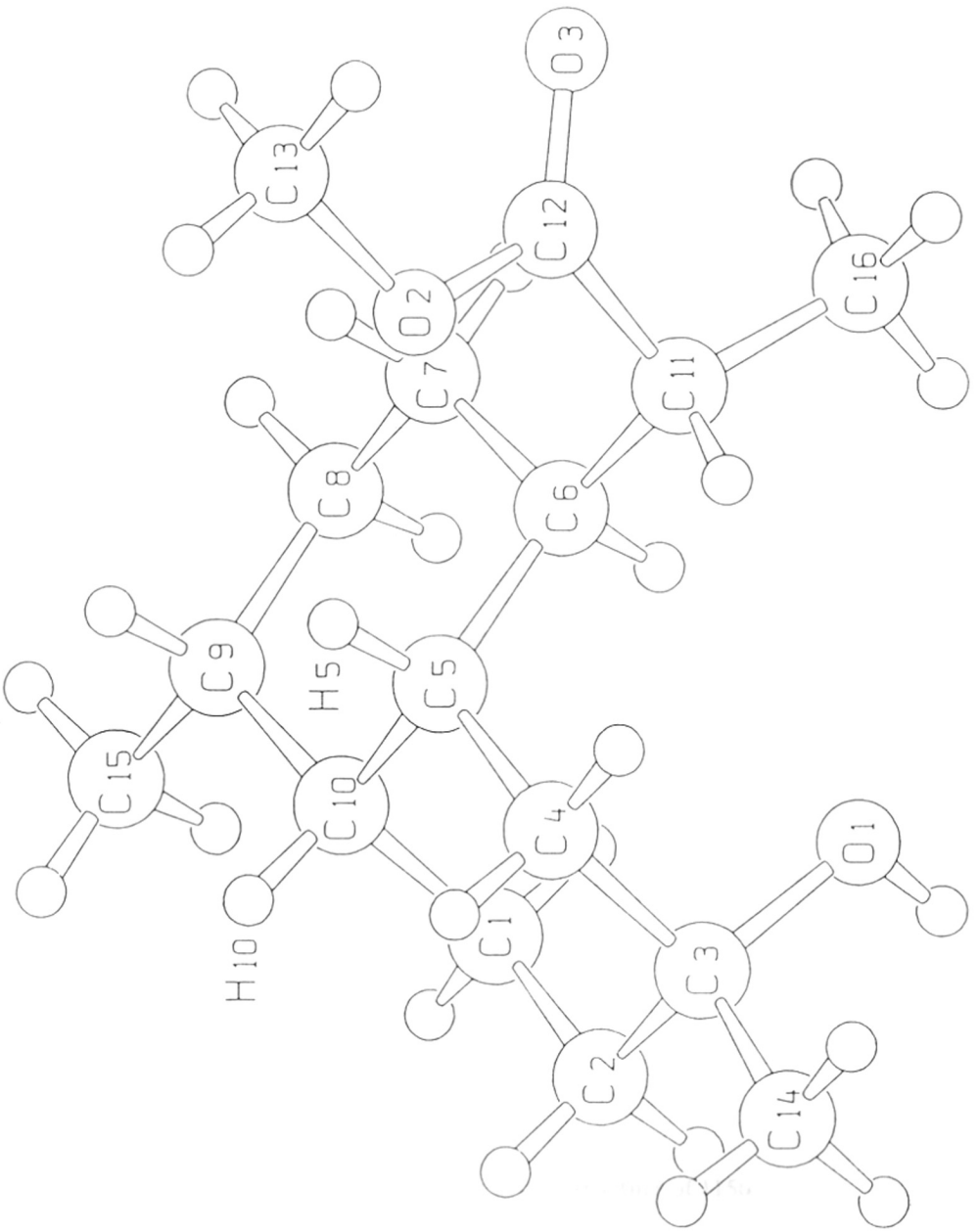


Fig. 16 : X-ray Structure of 115b

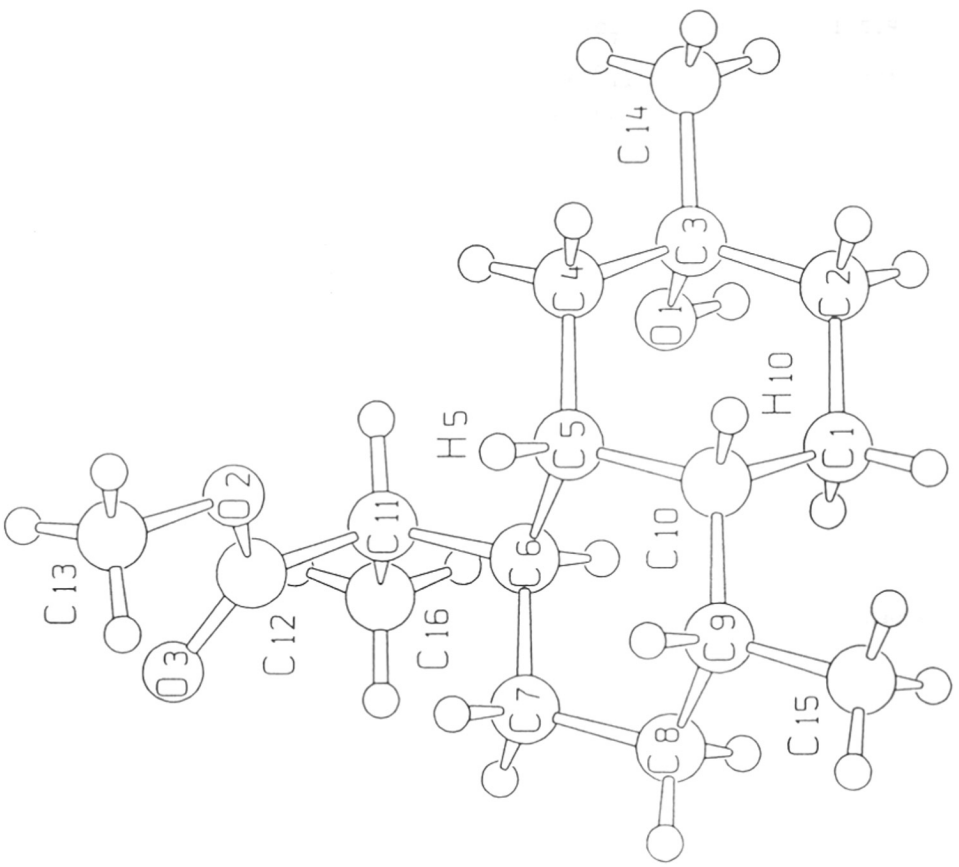


Fig. 15 : X-ray Structure of 115b

Table -II

Cell parameter: 0.7093, 9.0080, 16.8460, 10.8800, 90.0000, 105.9800, 90.000

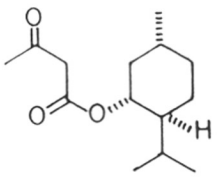
Bond lengths	(in angstroms)	Bond lengths	(in angstroms)
01 - C_3	1.425	C_6-C_7	1.519
02 C_{12}	1.312	C_6-C_{11}	1.551
C_{13}-O_2	1.452	C_7-C_8	1.521
O_3-C_{12}	1.199	C_8-C_9	1.541
C_1-C_2	1.518	C_9-C_{15}	1.514
C_1-C_{10}	1.544	C_9-C_{10}	1.532
C_2-C_3	1.517	C_{10}-C_5	1.539
C_3-C_4	1.523	C_{10}-C_1	1.544
C_3-C_4	1.543	C_{11}-C_{12}	1.517
C_4-C_5	1.532	C_{11}-C_{16}	1.520
C_5-C_6	1.536	C_{12}-C_{11}	1.517
C_5-C_{10}	1.539	C_{13}-O_2	1.452

Bond angles	(in degree)	Bond angles	(in degree)
C_2-C_1-C_{10}	111.16	C_7-C_6-C_{11}	111.94
C_1-C_2-C_3	113.73	C_6-C_7-C_8	112.12
01-C_3-C_2	110.41	C_9-C_8-C_7	111.54
01-C_3-C_{14}	109.08	C_{15}-C_9-C_8	110.85
01-C_3-C_4	106.67	C_{15}-C_9-C_{10}	113.91
C_2-C_3-O_{14}	111.41	C_9-C_{10}-C_1	111.79
C_2-C_3-C_{14}	109.08	C_9-C_{10}-C_1	114.45
C_2-C_3-C_4	106.67	C_{12}-C_{11}-C_{16}	110.23
C_3-C_4-C_5	115.15	C_{12}-C_{11}-C_6	111.89
C_4-C_5-C_6	115.78	O_3-C_{12}-O_2	122.95
C_4-C_5-C_{10}	109.68	O_3-C_{12}-C_{11}	124.29
C_7-C_6-C_5	110.00		

Torsion angles	(in degrees)	Torsion angles	(in degrees)
$C_{10}-C_1-C_3-C_3$	- 56.65	$C_8-C_9-C_{10}-C_5$	52.98
$C_1-C_2-C_3-O$	- 64.47	$C_{15}-C_9-C_{10}-C_1$	53.18
$C_1-C_2-C_3-C_{14}$	-174.14	$C_8-C_9-C_{10}-C_1$	- 73.48
$C_1-C_2-C_3-C_4$	52.39	$C_4-C_5-C_{10}-C_9$	176.40
$O_1-C_3-C_4-C_5$	67.11	$C_6-C_5-C_{10}-C_9$	- 54.43
$C_2-C_3-C_4-C_5$	- 52.11	$C_4-C_5-C_{10}-C_1$	- 54.96
$C_{14}-C_3-C_4-C_5$	-174.64	$C_6-C_5-C_{10}-C_1$	74.21
$C_3-C_4-C_5-C_6$	- 72.04	$C_2-C_1-C_{10}-C_9$	-175.97
$C_3-C_4-C_5-C_{10}$	54.44	$C_2-C_1-C_{10}-C_5$	56.85
$C_4-C_5-C_6-C_7$	-178.15	$C_7-C_6-C_{11}-C_{12}$	44.97
$C_{10}-C_5-C_6-C_7$	56.01	$C_5-C_6-C_{11}-C_{12}$	- 81.91
$C_4-C_5-C_6-C_{11}$	- 50.30	$C_7-C_6-C_{11}-C_{16}$	- 79.13
$C_{10}-C_5-C_6-C_{11}$	-176.14	$C_5-C_6-C_{11}-C_{16}$	153.99
$C_5-C_6-C_7-C_8$	- 57.11	$C_{13}-O_2-C_{12}-O_3$	- 0.24
$C_{11}-C_6-C_7-C_8$	173.21	$C_{13}-O_2-C_{12}-C_{11}$	-178.61
$C_6-C_7-C_8-C_9$	56.02	$C_{16}-C_{11}-C_{12}-O_3$	13.52
$C_7-C_8-C_9-C_{15}$	178.45	$C_6-C_{11}-C_{12}-O_3$	-111.40
$C_7-C_8-C_9-C_{10}$	- 53.24	$C_{16}-C_{11}-C_{12}-O_2$	-168.13
$C_{15}-C_9-C_{10}-C_5$	179.64	$C_6-C_{11}-C_{12}-O_2$	66.94

2.7 : Experimental:

Menthyl acetoacetate (72) :



Procedure :

A mixture of methyl acetoacetate (3.72 g, 32 mmol), menthol **60** (5 g, 32 mmol) and catalyst (10% by weight) in toluene (50 ml) was heated to 110°C in a two-necked round bottom flask provided with a distillation condenser to remove methanol. The reaction was monitored by T.L.C. After completion of the reaction (5 hours), the catalyst was filtered and the filtrate was concentrated and chromatographed on SiO_2 (95:5 pet. ether: ethylacetate) to afford the ester as a viscous colourless liquid.

Yield : 6.9 gm, 90%

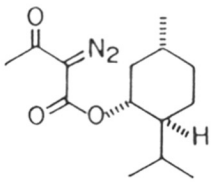
IR (Neat) : 1740, 1700, 1650, 1450, 1400, 1350, 1300, 1240, 1120, 1080, 1020, 980 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.8 (d, 3H, J = 5.5 Hz), 1.1 (d, 6H, J = 5.5 Hz), 1.2 (m, 4H), 1.35 (m, 2H), 1.55-1.85 (m, 3H), 2.3 (s, 3H), 3.5 (s, 2H), 4.7 (dt, J = 4.4 & 10.9 Hz, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 16.16 (q), 16.44 (q), 20.69 (q), 21.94 (q), 23.35 (t), 23.60 (t), 26.12 (t), 29.91 (q), 31.38 (q), 34.18 (t), 40.11 (t), 41.0 (t), 46.87 (d), 50.41 (t), 73.60 (d), 75.31 (d), 89.98 (d), 166.66 (s), 200.4 (s).

Mass (m/e) : 240 (M^+), 138, 123, 103, 95, 85, 43.

Menthyl diazoacetoacetate (73) :



A flame dried, one necked flask equipped with nitrogen inlet and septum was charged with ester **72** (10 g, 41.66 mmol) and K_2CO_3 (11.5 g, 83.33 mmol) and acetonitrile (50 ml). To this solution was added mesyl azide (4.23 g, 45.83 mmol). The reaction was followed by TLC. Typically, it was complete in 5 hours. The mixture was diluted with 10% aqueous NaOH and extracted with ether (3 x 30 ml). The combined organic extracts were washed with brine, water and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure to give residue as oil, which was chromatographed on silica gel with 5% ethyl acetate in pet-ether to furnish the α-diazo-ß-keto ester **73**.

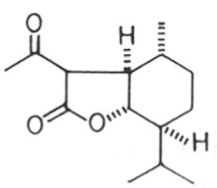
Yield : 10 g, 90%

IR (Neat) : 2150, 1710, 1610 cm^{-1}

^{1}H-NMR (80 MHz, $CDCl_3$) : δ 0.9 (3H, d, J = 5.5 Hz), 1.00 (d, J = 5.5 Hz, 6H), 1.00-2.00 (m, 8H), 2.2 (s, 3H), 4.9 (dt, 1H, J = 4.4 and 10.5 Hz).

Mass (m/e) : 266 (M^+, 28%), 238 (1), 147 (7), 182 (1), 176 (3), 171 (1), 155 (50), 150 (2), 138 (6), 129 (1), 123 (5), 105 (55), 95 (14), 91 (100), 81 (19), 77 (12), 71 (19), 65 (26), 55 (14).

Bicyclic-γ-lactone (74) :



A solution of α-diazo-ß-keto ester **73** (0.45 g, 1.68 mmol) and Rhodium acetate (catalytic) in 10 ml of dry benzene was refluxed under nitrogen atmosphere. After 5 hours reaction mixture was cooled, filtered, washed with brine, dried (anhydrous Na_2SO_4) and

concentrated in vacuo to afford the bicyclic-γ-lactone as a semisolid. Chromatographic purification of lactone (10% EtOAc in pet-ether) afforded bicyclic-γ-lactone **74** as a white solid.

Yield : 295 mg, 83%

M.P. : 98-99°C (Lit. 99°C)

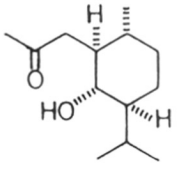
IR (Neat) : 1770, 1720 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.82 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 7.0 Hz), 0.95 (d, 3H, J = 7.0 Hz), 1.00 - 1.23 (m, 2H), 1.3-1.6 (m, 1H), 1.62-1.8 (m, H), 1.8 - 2.00 (m, 1H), 2.31 (dt, 1H, J = 12.4, 10.7, 10.7 Hz), 2.40 (s, 3H), 3.44 (d, J = 12.4 Hz), 3.7 (t, 1H, J = 10.7 Hz).

Mass (m/e) : 238 (M^+, 8%), 220 (2), 210 (9), 205 (1), 196 (44), 178 (16), 167 (4), 151 (31), 136 (59), 121 (29), 109 (30), 95 (80), 85 (75), 69 (47).

Optical rotation $[\alpha]_D$: - 37.35° (c = 2.1, $CHCl_3$), lit. $[\alpha]_D$=-38° (c = 2.1, $CHCl_3$).

2-[(ß)-2-oxo-propane]-3(α)-methyl-6(ß)-isopropyl cyclohexa- 1-ol (75) :



A stirred solution of lactone **74** (2.870 g, 12 mmol) in MeOH (15 ml) was treated with a solution of KOH (1.6 gm) in water (8 ml) and refluxed for 5 hours. The mixture was concentrated in vacuo, treated with saturated sodium chloride solution, extracted with ether (3 x 20 ml). The organic layer was dried (anhydrous Na_2SO_4) and concentrated in vacuo. The residue thus obtained was chromatographed to furnish ketoalcohol (10% ethyl acetate in pet ether) **75** as colourless oil.

Yield : 1.93 g, 75.8%

IR (Neat) : 3450, 1710 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.8 (d, 3H, J = 6 Hz), 0.9 (d, 6H, J = 6Hz), 1.1-1.8 (m, 7H), 2.00 (s, 3H), 2.2 (t, 1H, J = 4Hz), 3.00 (t, 2H, J = 6Hz), 3.4 (dt, 1H, J = 4.4, 10.9 Hz).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 210.6 (s), 76.031 (d), 50.19 (d), 48.38 (t), 47.25 (d), 36.21 (d), 34.83 (t), 30.23 (d), 25.87 (q), 23.9 (t), 20.96 (q), 20.40 (q), 15.86 (q).

Mass (m/e) : 212 (M^+, 10%), 194 (20), 183 (3), 179 (7), 165 (1), 161 (4), 154 (87), 139

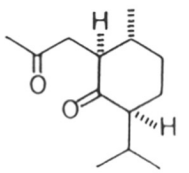
(71), 127 (80), 121 (56), 99 (20), 95 (84), 81 (100), 71 (74), 55 (61).

Optical rotation $[\alpha]_D$: -49.6° (c = 2.5, $CHCl_3$).

Analysis : Calculated for $C_{13}H_{24}O_2$: C, 73.58, H, 15.09%

Found : C, 73.10; H, 14.66%

2[(ß)-2-oxo-propane]-3(α)-Methyl-6(ß)-isopropyl cyclohexa-1-one (76) :



A solution of ketoalcohol **75** (1.1 g, 5.1 mmol) in acetone (10 ml) was cooled to 0°C. The Jones reagent was added over a period of 20 min until an organge tint colour persisted in the reaction mixture. The reaction mixture was stirred at 0°C to room temperature for 3 hours. The acetone was removed in vacuo & water was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate and combined organic extracts were washed with brine, water, dried over anhydrous sodium sulphate and concentrated to give a residue. The residue on purification by column chromatography (5% ethylacetate in pet-ether) afforded dione **76** as a colourless liquid.

Yield : 850 mg, 80%

IR (Neat) : 1710, 1410, 1380, 1220, 1050 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 6.6 Hz), 1.1 (d, 6H, J = 6.6 Hz), 1.15-1.4 (m, 1H), 1.45-1.9 (m, 3H), 1.95-2.15 (m, 2H), 2.2 (s, 3H), 2.3-2.7 (m, 3H), 2.9-3.1 (m, 2H).

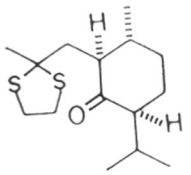
Mass (m/e) : 210 (M^+, 6%), 195 (5), 177 (1), 168 (12), 153 (60), 137 (12), 125 (16), 110 (33), 95 (34), 81 (34), 69 (80), 55 (100).

Optical rotation $[\alpha]_D$: -35.18° (c = 5.4, $CHCl_3$).

Analysis : Calculated for $C_{13}H_{22}O_2$: C, 74.28; H, 15.23%

Found : C, 73.90; H, 14.95%

2[ß-2-oxo-propane dithioacetal] 3(α)-methyl-6(ß)-isopropyl cyclohexa-1-one (77) :



To a stirred solution of dione **76** (0.9 g, 4.2 mmol) and 1,2-ethanethiol (0.402 g, 4.2 mmol) in dry dichloromethane (10 ml) was added at -40°C a solution of boron trifluoride etherate (0.604 g, 4.2 mmol) in dry dichloromethane (2 ml). The reaction mixture was stirred at same temperature for 3 hours and was neutralised with sodium bicarbonate solution (5%, 5 ml). The aqueous layer was extracted with ether (3 x 10 ml) and washed with aqueous KOH solution, brine, water and dried (anhydrous Na_2SO_4). The solvent ether was evaporated under reduced pressure to furnish a crude product, which was purified by column chromatography (SiO_2) to afford desired monoprotected compound **77** as a colourless liquid.

Yield : 1.05 g, 85.7%

IR (Neat) : 1700, 1450, 1370, 1300, 1310, 1270, 1100 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5.4 Hz), 1.00 (d, 6H, J = 5.4 Hz), 1.1 (d, 2H, J = 3 Hz), 1.2-1.4 (m, 2H), 1.45 -1.6 (m, 2H), 1.7 (s, 3H), 1.8 - 1.9 (m, 2H), 2.00-2.4 (m, 1H), 3.9 (m, 1H), 3.4 (s, 4H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 213.23 (s), 67.41 (d), 58.17 (d), 57.47 (q), 41.49 (t), 39.52 (d), 39.41 (d), 37.67 (t), 35.28 (t), 31.68 (t), 26.48 (d), 21.78 (q), 20.96 (q), 19.32 (q).

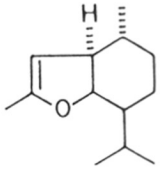
Mass (m/e) : 226 (M^+, 60), 206 (2), 208 (2), 198 (6), 193 (1), 180 (5), 165 (5), 155 (28), 137 (22), 126 (50), 109 (30), 99 (58), 95 (30), 86 (38), 71 (100), 61 (85), 55 (65).

Optical rotation $[\alpha]_D$: -40°C (c=1.2, $CHCl_3$)

Analysis Calculated for $C_{15}H_{26}O\ S_2$: C, 62.93; H, 9.09%

Found : C, 62.40; H, 8.8%

Dihydrofuran (96) :



Yield : 95%

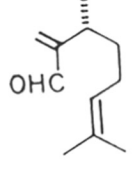
IR (Neat) : 1600, 1460, 1380, 1210, 1140 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.8 (d, 3H, J = 3.0 Hz), 1.1 (d, 3H, J = 5.0 Hz), 1.2 (d, 3H, J = 5.0 Hz), 1.5 (m, 3H), 1.6-2.2 (m, 4H), 2.25 (s, 3H), 2.6 (m, 2H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 150 (s), 105.20 (d), 40.75 (d), 40.77 (d), 32.67 (d), 30.77 (d), 30.09 (d), 30.03 (d), 28.72 (t), 27.95 (t), 24.54 (d), 22.81 (d), 21.53 (t), 20.60 (t), 19.86 (q), 19.69 (q), 18.78 (q), 13.77 (q).

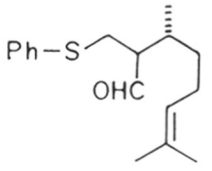
Mass (m/e) : 194 (M^+), 190 (10), 185 (30), 170 (75), 81 (100), 60 (10), 55 (60).

α-Methylene-3,7-dimethyl-6-octanol (101) :



This compound was prepared from (+)-citronellal by reported procedure as described in the chapter-I, Section-C.

Michael Adduct (102) :



To a stirred solution of exomethylene compound **101** (10.750 g, 64.75 mmol) and thiophenol (7.123 g, 64.75 mmol) in dry benzene (50 ml), triethyl amine (catalytic) was added and reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was then poured into aqueous potassium hydroxide solution and was extracted with ether. The ether extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to a residue which was chromatographed on SiO_2 to afford the Michael adduct **102** as a colourless liquid.

Yield : 15 g, 84%

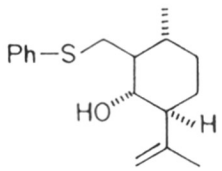
IR (Neat) : 1705, 1640, 1600, 1460, 1390, 1260 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.00 (d, 3H, J = 5.4 Hz), 1.3-1.5 (m, 4H), 1.6 (s, 3H), 1.7 (s, 3H), 2.00 (m, 2H), 2.5 (m, 1H), 3.00 (m, 1H), 3.3 (m, 1H), 5.1 (t, 1H, J =3.5 Hz), 7.1-7.5 (m, 5H), 9.7 (d, 1H, J = 1.5 Hz).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 203.81 (s), 202.90 (s), 202.60 (s), 135.74 (s), 135.64 (s), 131.60 (d), 129.75 (d), 129.64 (d), 129.09 (d), 128.83 (d), 126.26 (d), 125.81 (d), 123.60 (d), 55.44 (d), 55.34 (d), 33.94 (t), 33.16 (t), 32.32 (t), 30.44 (t), 30.00 (t), 29.10 (t), 25.51 (t), 22.91 (t), 22.15 (q), 17.51 (q), 16.25 (q), 15.94 (q).

Mass (m/e) : 276 (M^+, 4%), 258 (2), 207 (1), 177 (1), 165 (2), 148 (6), 135 (100), 123 (40), 110 (94), 95 (31), 81 (34), 77 (20), 69 (75), 55 (38).

Ene Adduct (103) :



To an ice cooled, stirred solution of Michael adduct **102** (15 g, 54.34 mmol) in anhydrous benzene (60 ml), powdered zinc chloride (76.4 g, 56.17 mmol) was added carefully (in portions), while the reaction temperature kept at 5-10°C. After complete addition (~10 min) stirring was continued for 10 min at 5-10°C. The precipitate of $ZnCl_2$ was filtered off and water was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (3 x 50 ml), combined ethyl acetate extracts were washed with brine, water and concentrated gave residue. The residue on purification by column chromatography (SiO_2) afforded ene product **103** as colourless viscous liquid.

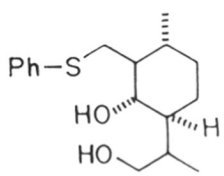
Yield : 13.645 g, 91%

IR (Neat) : 3450, 1600, 1480, 1440, 1380, 1090, 1040 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.00 (d, 3H, J = 5.0 Hz), 1.2-1.6 (m, 4H), 1.7 (s, 3H), 1.9-2.2 (m, 2H), 2.25-2.5 (m, 1H), 2.75 (m, 1H), 3.2 (m, 1H), 3.5 (m, 1H), 4.9 (d, 2H), 7.00-7.5 (m, 5H).

Mass (m/e) : 276 (M^+, 2%), 166 (2), 149 (8), 135 (56), 123 (50), 110 (100), 93 (31), 81 (26), 77 (20), 69 (30), 61 (4), 55 (35).

Diol (104) :



To a stirred solution of borane dimethyl sulfide complex (1.1 g, 14.47 mmol) in ether at 0°C was added the ene adduct **103** (2 g, 7.2 mmol) dropwise and the reaction mixture was stirred for 24 hours. To this solution was added 30% NaOH (1.8 ml) dropwise under ice cooling followed by 30% H_2O_2 (1.5 ml) dropwise. After stirring the above reaction mixture for 0.5 h,

it was extracted with dichloromethane, dried and the solvent was removed under vacuum to afford a viscous oil, which was chromatographed over SiO_2 (20% ethyl acetate : pet-ether) to furnish the diol **104**.

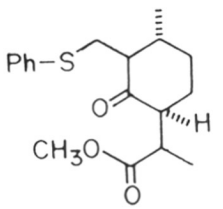
Yield : 1.7 g, 80%

IR (Neat) : 3450, 1600, 1500, 1400, 1350, 1330, 1300, 1260, 1100 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 6H, J = 5.0 Hz), 1.15-2.00 (m, 6H), 2.00-2.2 (m, 2H), 2.4 (m, 1H), 2.8 (m, 1H), 3.3 (m, 1H), 3.5 (m, 1H), 3.8 (m, 2H), 7.4 (m, 5H).

Mass (m/e) : 294 (M^+), 252 (1), 235 (1), 217 (1), 207 (1), 194 (8), 179 (16), 165 (4), 149 (8), 135 (18), 123 (37), 109 (46), 95 (60), 91 (30), 87 (27), 81 (79), 77 (42), 67 (66), 61 (38), 55 (100).

Ketoester (105) :



The diol **104** (0.5 g, 1.70 mmol) was dissolved in acetone (2 ml) and was cooled to 0°C. To this solution Jones reagent was added dropwise until the colour of the reagent persists. The reaction mixture was stirred at room temperature for another two hours. The acetone was removed in vacuum and water was added to the reaction mixture and extracted with ethyl acetate (3 x 10 ml). The combined ethyl acetate extracts were washed with water, brine, dried (anhydrous sodium sulphate) and solvent was removed in vacuo to furnish the crude keto acid (500 mg).

To a solution of above acid (500 mg) in ether cooled to 0°C was added portionwise the ethereal solution of CH_2N_2. After standing for 0.5 hr excess CH_2N_2 was removed. The ethereal solution was washed, dried and concentrated to give a crude product, which was purified by chromatography to afford the ketoester **105** as colourless viscous liquid.

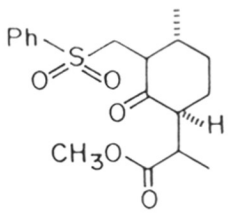
Yield : 350 mg, 70%

IR (Neat) : 1740, 1720, 1600, 1450, 1420, 1390, 1220, 1100, 1040 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.00 (d, 3H, J = 3.00 Hz), 1.2 (d, 3H, J = 5.00 Hz), 1.6-2.1 (m, 5H), 2.25-2.6 (m, 2H), 2.55 (m, 1H), 3.7 (s, 3H), 7.8 (m, 3H), 8.1 (m, 2H).

Mass (m/e) : 320 (M^+, 10%), 290 (5), 258 (10), 218 (5), 198 (2), 192 (1), 166 (20), 151 (40), 126 (35), 123 (80), 109 (90), 95 (60), 88 (60), 77 (7), 67 (10), 55 (100).

Sulphone (106) :



To a stirred solution of ketoester **105** (1.2 gm, 3.75 mmol) in glacial acetic acid (5 ml) was added 3 ml of 30% H_2O_2 solution. The reaction mixture was left at room temperature for 12 hours and then evaporated under reduced pressure to a small volume. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 20 ml), washed with bicarbonate solution, dried (anhydrous sodium sulphate) and concentrated in vacuo to furnish the residue which was purified by column chromatography to afford sulphone **106** as colourless viscous liquid.

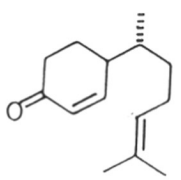
Yield : 1.05 g, 80%

IR (Neat) : 1740, 1720, 1600, 1450, 1380, 1310, 1150, 1020 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.05 (d, 3H, J = 5.00 Hz), 1.2 (d, 3H, J = 5.0 Hz), 1.5-2.1 (m, 5H), 2.25-2.5 (m, 2H), 2.55 - 2.8 (m, 1H), 3.00-3.5 (m, 2H), 3.7 (s, 3H), 7.5 (m, 3H), 8.00 (m, 2H).

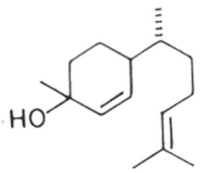
Mass (m/e) : 352 (M^+), 320 (2), 290 (2), 276 (4), 258 (1), 234 (2), 218 (4), 210 (4), 198 (2), 192 (4), 178 (30), 166 (15), 156 (25), 151 (30), 141 (15), 135 (126), 123 (70), 109 (92), 100 (65), 95 (95), 88 (60), 85 (80), 77 (70), 67 (75), 58 (60), 55 (100).

Enone (109) :



This compound was prepared from exomethylene compound **101** by reported procedure as described in the chapter-I, Section -C.

Carbinol (110) :



Grignard reagent was prepared from Mg turnings (174 mg, 7.25 mmol) and methyl iodide (1.026g, 7.25 mmol) in anhydrous ether (10 ml). To this Grignard reagent enone **109** (1 g, 4.854 mmol) was added dropwise in anhydrous ether under ice cold conditions and stirred at same temperature for 3 hours. Excess Grignard reagent was destroyed by careful addition of aqueous ammonium chloride solution at 0°C and extracted with ether (3 x 10 ml). The ether extract was washed with brine, water, dried over anhydrous sodium sulphate and concentrated in vacuo to furnish the residue which was purified by column chromatography (SiO_2) to afford carbinol **110** as a colourless oil.

Yield : 800 mg, 75%.

IR (Neat) : 3400, 1670, 1450, 1390, 1110, 980, 910 cm^{-1}.

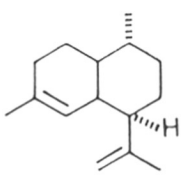
^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.8 (d, 3H, J = 5.0 Hz), 1.00-1.2 (m, 3H), 1.3 (s, 3H), 1.35-1.5 (m, 2H), 1.6 (s, 3H), 1.7 (s, 3H), 1.8-2.2 (m, 6H), 5.1 (t, 1H), 5.5 (m, 2H).

Mass (m/e) : 222 (M^+, 10%), 204 (100), 81 (8), 70 (50), 55 (10).

Analysis: Calculated for $C_{15}H_{26}O$: C, 81.08; H, 11.71%

Found : C, 80.80; H, 11.20%

7(s)-Isopropene 10(R), 4-dimethyl bicyclo [4:4:0]-dec-4-ene (111) :



To a stirred solution of carbinol **110** (50 mg, 0.22 mmol) in aqueous THF (3 ml), was added $HClO_4$ solution (catalytic) at room temperature and reaction mixture was stirred at same temperature for 5 hours. The THF was removed under reduced pressure and diluted with

water (30 ml). It was extracted with ethyl acetate (3 x 10 ml), washed with brine, water and concentrated in vacuo to give residue which was purified by column chromatography (SiO_2) to furnish diene **111** as a colourless oil.

Yield : 35 mg, 78%

IR (Neat) : 1440, 1380, 1200, 1030 cm^{-1}

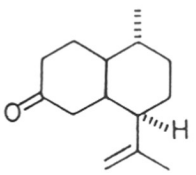
^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5.00 Hz), 1.1-1.5 (m, 6H), 1.6 (s, 3H), 1.7 (s, 3H), 1.8-2.1 (m, 5H), 2.3 (m, 1H), 4.7 (d, 2H, J = 3.0 Hz), 5.4 (s, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 148.70 (s), 148.53 (s), 144.67 (t), 133.35 (s), 133.18 (s), 131.24 (s), 110.44 (t), 110.02 (t), 48.26 (t), 48.13 (t), 40.73 (t), 40.31 (t), 39.98 (t), 39.64 (t), 39.18 (t), 38.64 (t), 34.42 (d), 33.18 (d), 37.36 (d), 30.63 (d), 27.97 (q), 26.75 (q), 26.32 (q), 25.80 (q), 19.84 (q), 19.72 (q).

Mass (m/e) : 204 (M^+, 100%), 189 (22), 75 (4), 161 (33), 147 (15), 133 (30), 119 (76), 115 (10), 105 (9), 77 (4), 55 (2).

Analysis : Calculated for $C_{15}H_{24}$: C, 88.23; H, 12.74%
Found : C, 87.80; H, 12.40%

7(ß)-Isopropene-10(α)-methyl-4-oxo-bicyclo [4:4:0] decalone (112) :



A mixture of enone **109** (1.4 g, 6.796 mmol) and p-toluene sulfonic acid (catalytic) in 30 ml of dry benzene was refluxed under nitrogen atmosphere. After 5 hours reaction mixture was cooled, washed with aqueous $NaHCO_3$, dried (anhydrous Na_2SO_4) and concentrated in vacuo to afford a residue. Purification of residue on SiO_2 (5% ethyl acetate in pet.ether) furnished the ene product **112** as a colourless viscous liquid.

Yield : 1.120 gm, 80%

IR (Neat) : 1700, 1580, 1430, 1200 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, 3H, J = 5.4 Hz), 1.1-4.5 (m, 7H), 1.6 (s, 3H), 1.75-1.95 (m, 3H), 2.00-2.15 (m, 2H), 2.3-2.5 (m, 2H), 4.7 (s, 1H), 4.8 (s, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 216.08 (s), 211.27 (s), 146.77 (s), 146.66 (s), 111.97 (t), 111.72 (t), 44.30 (t), 44.15 (t), 43.78 (t), 43.42 (t), 41.40 (t), 41.04 (t), 40.49 (d), 36.69 (d), 36.44 (d), 36.02 (d), 32.47 (d), 32.02 (d), 31.66 (q), 30.42 (q), 20.75 (q), 20.41 (q).

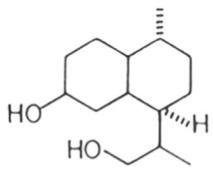
Mass (m/e) : 206 (M^+, 18%), 191 (4), 173 (1), 163 (6), 148 (8), 136 (8), 123 (30), 107 (34),

95 (18), 91 (22), 82 (20), 77 (50), 67 (34), 55 (100).

Analysis :Calculated for $C_{14}H_{22}O$: C, 81.50; H, 10.60%

Found : C, 81.00; H, 10.10%

7(ß)-(hydroxy methyl ethyl)-10(α)-methyl 4-hydroxy bicyclo [4:4:0]-decalin (113) :



To a stirred solution of borane dimethyl sulfide complex (0.413 g, 2 mmol) in ether at 0°C was added the ene product **112** (0.228 mg, 3.00 mmol) dropwise and reaction mixture was stirred for 12 h at room temperature. To this solution was added 30% NaOH (0.8 ml) dropwise under ice cooling followed dropwise addition of 30% H_2O_2 (0.7 ml). After stirring the above reaction mixture for 0.5 hr, it was extracted with dichloromethane (3 x 10 ml), dried (anhydrous sodium sulphate) and concentrated in vacuo to give residue. The residue was purified on column chromatography (SiO_2) to furnish the diol **113** as a viscous liquid.

Yield : 402 mg, 88%

IR (Neat) : 3450, 1440, 1350, 1300, 1200, 1150, 1050 cm^{-1}.

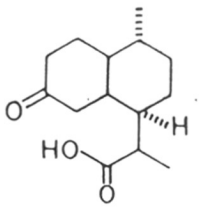
^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5.0 Hz), 1.00 (d, 3H, J = 5.0 Hz), 1.05 - 1.3 (m, 7H), 1.35-1.6 (m, 7H), 1.75 - 2.25 (m, 3H), 3.15-3.5 (m, 2H), 3.55 - 3.7 (m, 1H).

Mass (m/e) : 208 (M^+-18, 7%), 190 (M^+-36, 4), 177 (10), 166 (11), 161 (2), 149 (100), 141 (1), 135 (20), 121 (17), 107 (33), 93 (40), 88 (10), 81 (43), 70 (35), 67 (44), 61 (25), 55 (44).

Analysis : Calculated for $C_{14}H_{26}O_2$: C, 74.33; H, 11.50%

Found : C, 73.90; H, 11.00%

7(ß) (2-propionic acid)-10(α)-methyl-4-oxo-bicyclo [4:4:0] decalone (114) :



A solution of diol **113** (0.402 g, 1.77 mmol) in acetone (10 ml) was cooled to 0°C. To this solution Jones reagent was added dropwise until the colour of reagent persists. The reaction mixture was stirred at room temperature for another two hours. The acetone was removed in vacuo, water was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (3 x 10 ml), washed with brine, water, dried and concentrated to give residue which was purified by column chromatography (SiO_2) to furnish the ketoacid **114** as a colourless viscous liquid.

Yield : 302 mg, 72%

IR (Neat) : 1710, 1300, 1200, 1150, 1000 cm^{-1}

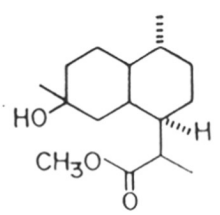
^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 6.6 Hz), 1.2 (d, 3H, J = 6.00 Hz), 1.4-1.95 (m, 6H), 2.00-2.5 (m, 5H), 2.55-3.1 (m, 4H), 11.00 (bs, 1H).

Mass (m/e) : 221 (M^+-17, 26%), 209 (45), 195 (59), 181 (56), 167 (56), 149 (36), 135 (24), 121 (36), 107 (76), 93 (80), 81 (54), 74, (34), 67 (68), 55 (100).

Analysis : Calculated for $C_{14}H_{22}O_3$: C, 70.58; H, 9.24%.

Found : C, 70.05; H, 8.70%

7(ß) (2-methyl propionate) 10(α),4-dimethyl 4-hydroxy bicyclo [4:4:0]-decalin (115a)



Grignard reagent was prepared from Mg turnings (45 mg, 1.8 mmol) and methyl iodide (267 mg, 1.8 mmol) in anhydrous ether (10 ml). To this reagent ketoacid **114** (302 mg, 1.2 mmol) was added dropwise in anhydrous ether under ice cold conditions and stirred at same temperature for 5 hours. Excess reagent was destroyed by careful addition of aqueous

ammonium chloride solution at 0°C and the aqueous solution was extracted with dichloromethane (3 x 10 ml). The dichloromethane extract was washed with brine, water dried (anhydrous sodium sulphate) and concentrated in vacuo to furnish the crude carbinol acid (324 gm) as a colourless viscous liquid.

To a solution of above crude carbinol acid (324 mgm) in ether cooled to 0°C was added portionwise the ethereal solution of CH_2N_2. After standing for 1 hour excess CH_2N_2 was removed to give a crude product which was purified by chromatography to afford carbinol ester **115a** as a viscous liquid.

Yield : 160 mg, 47%

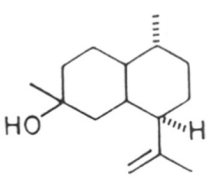
IR (Neat) : 3500, 1740, 1450, 1380, 1220 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5.4 Hz), 1.2 (d, 3H, J = 6.00 Hz), 1.3 (s, 3H), 1.4-2.00 (m, 13H), 2.1-2.3 (m, 2H), 2.7 (m, 1H), 3.7 (s, 3H).

Mass (m/e) : 253 (M^+-15, 4%), 237 (1), 221 (4), 206 (28), 194 (10), 177 (11), 173 (4), 163 (94), 147 (18), 135 (19), 121 (35), 107 (53), 93 (61), 88 (55), 84 (30), 81 (72), 71 (56), 60 (34), 55 (100).

Analysis : Calculated for $C_{16}H_{28}O_3$: C, 71.64; H, 10.44%
Found : C, 71.00; H, 10.80%

7(ß)-Isopropene 10 (α)-4(α)-dimethyl- 4(ß)-hydroxy bicyclo (cis) [4:4:0]-decalin (118) :



Grignard reagent was prepared from Mg turnings (400 mg, 16.91 mmol) and methyl iodide (2.391 g, 16.91 mmol) in anhydrous ether (20 ml). To this Grignard reagent, Ketone **112** (2.330 g, 11.31 mmol) was added dropwise in anhydrous ether under ice cold conditions. The reaction mixture was stirred at 0°C to room temperature for 3 hours. Excess Grignard reagent was destroyed by careful addition of aqueous ammonium chloride solution at 0°C and extracted with ether (3 x 20 ml). The combined ether extracted were washed with brine, water, dried over anhydrous sodium sulphate and concentrated to give a residue. The residue was purified on column chromatography (SiO_2) with 5% ethyl acetate:pet-ether to furnish the faster moving carbinol (first isomer, 1.220g, 70%) while the second isomer eluted with 7%

ethyl acetate in pet-ether and the third was the last to be eluted with 10% ethyl acetate in pet-ether.

First isomer (major isomer)

Yield : 1.75 g, 70%

IR (Neat) : 3500, 1650, 1450, 1380, 1230, 1200, 1120, 1050 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, 3H, J = 5.0 Hz), 1.2 (s, 3H), 1.25-1.5 (m, 8H), 1.65 (s, 3H), 1.55-1.9 (m, 6H), 2.8 (dt, 1H, J = 2.5, 5.00, 10 Hz), 4.8 (s, 2H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 151.05 (s), 111.59 (s), 70.54 (t), 44.31 (d), 42.51 (t), 40.76 (d), 39.27 (t), 39.03 (t), 36.45 (d), 33.63 (t), 33.17 (d), 29.85 (t), 19.88 (q), 18.33 (q), 16.54 (q).

Mass (m/e) : 222 (M^+, 1%), 213 (1), 204 (16), 189 (10), 175 (3), 161 (13), 146 (100), 133 (16), 127 (4), 119 (36), 105 (21), 93 (34), 81 (30), 67 (33), 55 (49).

Analysis : Calculated for $C_{15}H_{26}O$: C, 81.08; H, 11.71%

Found : C, 80.74; H, 11.59%

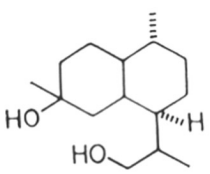
Second isomer

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5 Hz), 1.2 (s, 3H), 1.3-1.6 (m, 8H), 1.7 (s, 3H), 1.75-2.00 (m, 4H), 2.3 (broad s, 1H), 2.5 (s, 1H), 2.6 (s, 1H), 3.1 (t, 1H), 2.7 (m, 2H), 4.65 (s, 2H).

Third isomer

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, 3H, J = 5.0 Hz), 1.3 (s, 3H), 1.3-1.5 (m, 8H), 1.6 (s, 3H), 1.65-2.00 (m, 4H), 2.7 (m, 2H), 4.65 (s, 2H).

7(ß)-(2-hydroxy methyl ethyl) 10(α)-methyl 4-hydroxy 4-methyl bicyclo [4:4:0]-decalin (119) :



The major isomer **118** (0.141 g, 0.63 mmol) in dry ether (5 ml) was placed in 50 ml of two necked round bottomed flask and cooled to 0°C with ice salt mixture. The BMS complex

(0.072 g, 0.949 mmol) was added dropwise under nitrogen atmosphere with stirring and reaction mixture was stirred for 12 hours. To this solution was added 30% NaOH (1 ml) dropwise under ice cooling followed by 30% H_2O_2 (1 ml) and stirred for 0.5 hour. The reaction mixture was extracted with dichloromethane (3 x 10 ml), washed with brine, water, dried over anhydrous sodium sulphate and concentrated in vacuo to furnish a residue. Chromatographic (SiO_2) purification of the residue (20% ethyl acetate in pet-ether) afforded diol **119** as a white solid.

Yield : 120 mg, 80%

M.P. : 77-78°C

IR ($CHCl_3$) : 3400, 1460, 1390, 1120, 1220, 1130, 1030, 990 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 6H, J = 5.4 Hz), 1.2 (s, 3H), 1.25-2.8 (m, 12H), 2.35-2.25 (m, 3H), 2.5 (bs, 2H), 3.4 (m, 1H), 3.7 (m, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 71.063 (s), 65.80 (t), 43.90 (d), 42.84 (d), 40.52 (t), 39.96 (t), 39.15 (d), 38.97 (d), 38.57 (d), 36.36 (d), 32.98 (q), 30.91 (t), 30.16 (t), 19.83 (q), 16.46 (t), 13.76 (q).

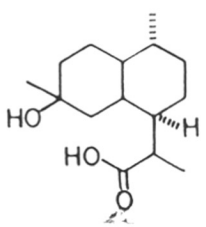
Mass (m/e) : 222 (M^+-18, 6%), 204 (4), 191 (8), 177 (4), 163 (84), 149 (25), 135 (64), 121 (42), 115 (4), 107 (72), 95 (76), 81 (100), 88 (2), 67 (71), 67 (70), 61 (10), 55 (97).

Optical rotation $[\alpha]_D$: + 9.75° (c = 1.6 $CHCl_3$).

Analysis : Calculated for $C_{15}H_{28}O_2$: C, 75.00; H, 11.66%

Found : C, 74.50; H, 11.00%

7(ß)-[2-propionic acid]-10(α)-4,dimethyl-4-hydroxy bicyclo [4:4:0]-decalin (120) :



Procedure :

A solution of diol **119** (1 g, 4.16 mmol) in acetone (10 ml) was cooled to 0°C. To this solution Jones reagent was added dropwise until the colour of reagent persists. The reaction mixture was stirred at room temperature for another two hours. The acetone was removed in vacuo, water was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (3 x 20 ml), washer with brine, water dried and concentrated to give residue which was purified by column chromatography SiO_2 to furnish the acid **120** a colourless solid.

Yield : 500 mg, 60%

M.P. *: 186-188°C*

IR ($CHCl_3$) : 3500, 3450, 1700, 1450, 1380, 1310, 1220, 1120 cm^{-1}.

^{1}H-NMR (200 MHz, Acetone-d_6) : δ 0.9 (d, 3H, J = 5.4 Hz), 1.1 (d, 3H, J = 6.0 Hz), 1.2 (s, 3H), 1.25-1.35 (m, 4H), 1.4-1.65 (m, 4H), 1.7-1.85 (m, 4H), 2.00 -2.1 (m, 2H), 2.25 (m, 2H), 3.00 (bs, 1H).

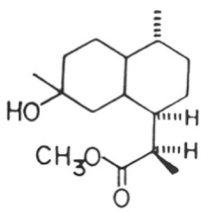
Mass (m/e) : 236 (M^+-H_2O), 221 (1), 206 (5), 191 (4), 180 (6), 175 (2), 163 (25), 155 (2), 149 (8), 141 (4), 135 (5), 129 (4), 121 (11), 115 (4), 107 (20), 91 (25), 85 (30), 81 (24), 74 (11), 71 (50), 55 (100).

Optical rotation $[\alpha]_D$: + 10.5° (c= 0.9, MeOH).

Analysis : Calculated for $C_{15}H_{26}O_3$: C, 70.86; H, 10.23%

Found : C, 70.30; H, 10.45%

7(ß)-[2-methyl propionate]-10(α)-4(α)-dimethyl-4(ß)-hydroxy bicyclo cis [4:4:0] decalin (115b):



To a solution of the acid **120** (0.5 g, 1.86 mmol) in MeOH (5 ml) cooled to 0°C was added protionwise the etheral solution of CH_2N_2. After allowing the mixture to stand for 0.5 hour, the excess CH_2N_2 was removed. The reaction mixture was diluted with water (10 ml), extracted with ethyl acetate (3 x 10 ml), washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo gave a residue. The residue was purified by column chromatography (SiO_2) afforded ester **115b** as a colourless solid.

Yield : 0.425 g, 80%

M.P. : 126°C

IR ($CHCl_3$) : 3500, 1740, 1450, 1380, 1220 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5.00 Hz), 1.2 (d, 3H, J = 5.00 Hz), 1.3 (s, 3H), 1.3- 1.9 (m, 4H), 2.1-2.4 (m, 2H), 3.9 (m, 1H), 3.6 (s, 3H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 176.70 (s), 70.57 (s), 51.138 (d), 43.42 (t), 40.18 (s), 40.07 (t), 39.42 (d), 38.82 (d), 36.22 (d), 33.02 (d), 29.93 (t), 28.50 (q), 19.78 (t), 16.52 (q), 15.05 (q).

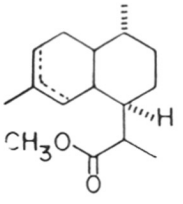
Mass (m/e) : 253 (M^+-15, 4%), 237 (1), 221 (4), 206 (28), 194 (10), 177 (11), 173 (4), 163 (94), 147 (18), 135 (19), 121 (35), 107 (53), 93 (61), 88 (55), 84 (30), 81 (72), 71 (56), 60 (34), 55 (100).

Optical rotation $[\alpha]_D$: -29.1° (c = 2.2, $CHCl_3$).

Analysis : Calculated for $C_{16}H_{28}O_3$: C, 71.64; H, 10.44%

Found : C, 71.10; H, 11.04%.

Dihydro artemisinate skeleton :



A mixture of the carbinol **115b** (170 mg, 0.63 mmol) and p-toluene sulfonic acid (catalytic) in 20 ml dry benzene was refluxed for 30 min. The reaction mixture was cooled, washed with aqueous $NaHCO_3$, dried (anhydroys Na_2SO_4) and concentrated in vacuo to afford residue which was purified on SiO_2 (9:1 pet.ether:ethylacetate) to afford methyl dihydroartemisinate as a mixture of regioisomers.

Yield : 120 mg, 72%

IR (Neat) : 1740, 1610, 1450, 1390, 1220 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (d, 3H, J = 5.0 Hz), 1.15 (d, 3H, J = 6 Hz), 1.4-1.55 (m, 6H), 1.6 (s, 3H), 1.65-2.1 (m, 6H), 2.6 (m, 1H), 2.8 (m, 1H), 3.65 (s, 3H), 5.4 (s, 1H), 5.7 (m, 1H).

Mass (m/e) : 250 (M^+), 206 (12), 191 (4), 184 (1), 177 (1), 173 (4), 162 (80), 147 (21), 138 (3), 132 (16), 128 (2), 121 (32), 115 (6), 105 (46), 93 (64), 88 (14), 79 (48), 71 (44), 67 (46), 55 (100).

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CHAPTER-3

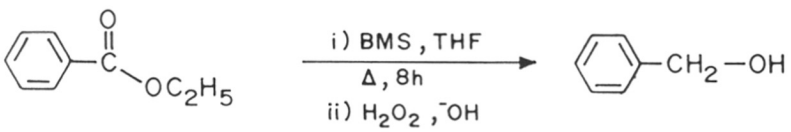
Assisted Reduction of ß, γ-unsaturated Esters by Borane Dimethyl Sulfide Complex

3.1 : Introduction :

Traditionally, carboxylic esters are considered to undergo very slow[1,2] hydroboration even under reflux conditions[3], infact they are considered non-reducible by borane. The reduction of such esters by diborane[4] or by borane tetrahydrofuran[5] is at best only relatively slow.

Brown et. al.[5] reported that the borane dimethyl sulphide complex (BMS) is stable in refluxing tetrahydrofuran for long periods of time. Under these conditions, the BMS-complex reduces carboxylic esters (scheme-1). The reaction was 67% complete in 0.25 h but then required more than 8 to 9 hours for essential completion.

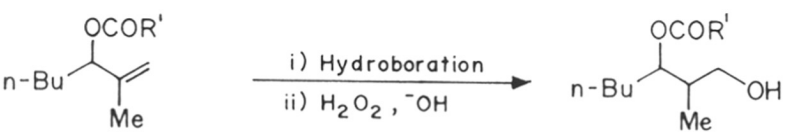
Scheme-1



1 2

Even as recently as 1992[6] rhodium catalysed hydroboration of allylic alcohols was carried out by acetyl protection of the hydroxy group. Ester group remained intact during this hydroboration process (scheme-2).

Scheme-2



3 4

R = Me , CF_3 , t-Bu

3.2 : Present work :

In connection with our interest in the synthesis of Heritol[7], Heritonin and related compounds, it was observed that hydroboration of ß γ-unsaturated ester (Entry 8a , Table-II) furnished the unexpected diol as the major compound along with minor amount of the desired hydroxy ester. The noteworthy point in the above transformation is the hydroboration of double bond followed by reduction of carboxylic ester at normal hydroboration conditions (BMS). This reaction although unexpected and unusual was not investigated further.

This unexpected greater reactivity of the ß,γ-unsaturated esters was investigated further this phenomenon in details. The generality and efficacy of this methodology has been demonstrated by reduction of eight different ß,γ-unsaturated esters.

3.3: Results and Discussions

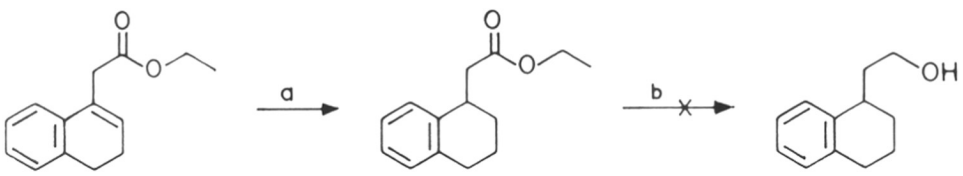
Synthesis of ß,γ-unsaturated esters (8a-8f, Scheme - 3) :

A variety of substituted ß,γ-unsaturated esters were prepared by the literature procedures.[8] Reformatsky reaction on different ketones with ethyl 2-bromopropionate or ethylbromoacetate in ether at room temperature followed by dehydration furnished the ß,γ-esters (Scheme - 3, Table-I). In case of cyclohexanone the Reformatsky reaction with ethyl 2-bromopropionate or ethylbromoacetate after usual work up afforded the alcohols **5a** and **5b** which were dehydrated in a separate step using thionyl chloride/pyridine.[9] All ß,γ-unsaturated esters were characterised by IR, ^{1}H-NMR and mass spectroscopic data and they were in agreement with the reported values.

Hydroboration of ß,γ-unsaturated esters : (Scheme - 5)

In order to confirm the role of double bond in "assisted" reduction of ß,γ-unsaturated esters, saturated ester **9** was prepared by hydrogenation of ß,γ-unsaturated ester **8c** using 10% Pd/C in methanol (Scheme - 4).

Scheme - 4



8c **9** **10**

a : H_2 , 10% Pd/C , MeOH **b** : i) BMS , Et_2O ii) H_2O_2 , $\bar{O}H$

Scheme-3

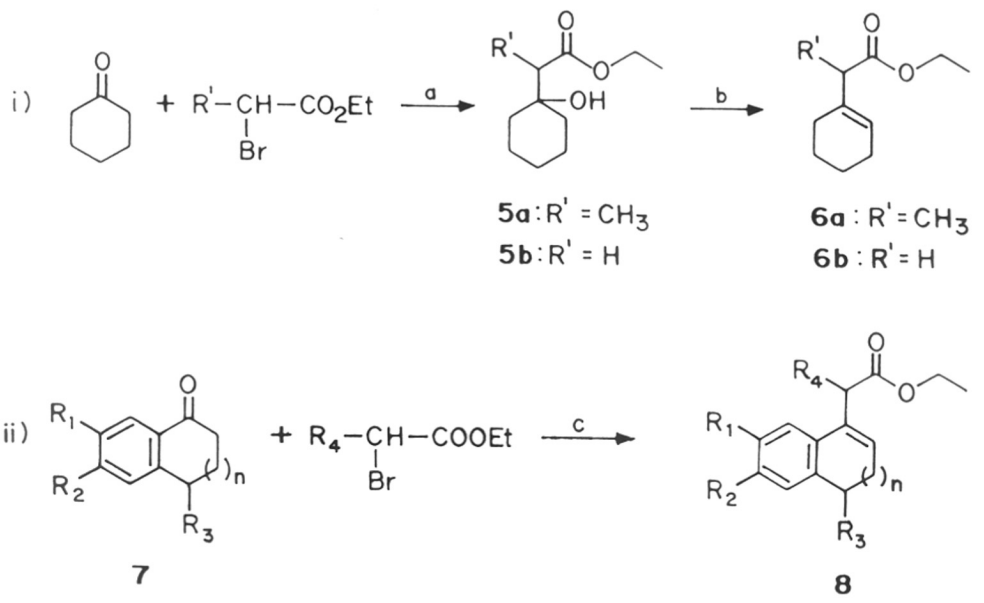


Table-I

Starting	R_1	R_2	R_3	R_4	n	t(h)	% Yield
8a	CH_3	OMe	CH_3	CH_3	1	2	81
8b	H	H	H	CH_3	1	2	80
8c	H	H	H	H	1	1·5	88
8d	H	H	H	CH_3-CH_2-	1	3	82
8e	H	OMe	H	CH_3	1	2	80

The structural assignment of saturated ester **9** was based on its IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. IR spectrum of **9** showed absorption at 1730 cm^{-1} indicating the presence of ester carbonyl group. The ^{1}H-NMR spectrum of **9** showed disappearance of signal at δ 5.9 (t, 1H) of olefinic proton. The ^{13}C-NMR showed 14 signals correponding to the 14 carbons. The structure was further confirmed by its mass spectrum which exhibited M^+ at 218 (13%). The saturated ester **9** was subjected to reduction under identical conditions and as anticipated ester was not reduced to the corresponding alcohol but was recovered unchanged (80%).

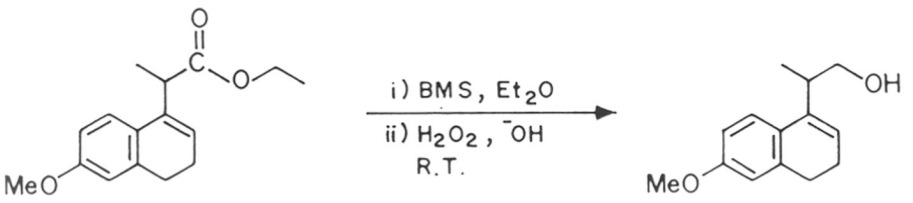
All ß,^{Y}-unsaturated esters **6a-6b** and **8a-8d** (except **8e**) were smoothly hydroborated (Scheme - 5, Table-II) with BMS complex followed by 30% NaOH and 30% H_2O_2 treatment to furnish the hydroxy esters **13a-13d** as the minor products and diols **14a-14d** as the major products. In a typical experiment ß,^{Y}-unsaturated ester **8b** (7 mmol) was added to the solution of BMS complex (10M solution in DMS, 7 mmol) in ether at 0°C and reaction mixture was stirred at room temperature for 24 h. The reaction mixture was treated with 30% NaOH followed by 30% H_2O_2 at 0°C. After usual workup followed by chromatography on SiO_2 the hydroxy ester **13b** was obtained in 9.3% yield as a minor product while diol **14b** was obtained in 56% yield as a major product.

The hydroxy ester was characterised by its IR, ^{1}H-NMR and mass spectroscopy. The IR spectrum revealed an absorption at 3460 and 1730 cm^{-1} for the hydroxyl and ester carbonyl respectively. ^{1}H-NMR spectrum of **13b** showed disappearance of the signal at δ 5.8 (t, 1H) of olefinic proton and appearance of new signal at δ 4.00 (m, 1H) for the methine proton on the carbon bearing hydroxyl group. The M^+ at 248 confirmed the assigned structure of hydroxy ester **13b**.

The structure of diol **14b** was also established by its IR, ^{1}H-NMR and mass spectroscopy. The IR spectrum showed absorption at 3450 cm^{-1} for hydroxy groups and no absorption at 1730 cm^{-1} of ester functionality. The ^{1}H-NMR spectrum of diol **14b** displayed the disappearance of signals at δ 1.3 (t, 3H) of methyl group and quartet at δ 4.3 of -$\underline{CH_2}$- group while appearance of signals at δ 3.8 (m, 1H) and δ 4.00 (q, 2H) for $\underline{CH}$-O and $\underline{CH_2}$-O protons. The mass spectrum showed M^+ at 188 (M^+-18, 29%) confirmed the structure of diol **14b**. The result may be contrasted with **8a** where there is presence of extra methyl.

In case of **8e**, hydroboration of **8e** under identical conditions furnished the unexpected γ-δ-unsaturated alcohol **15** as a product (Scheme - 6).

Scheme-6



8e **15**

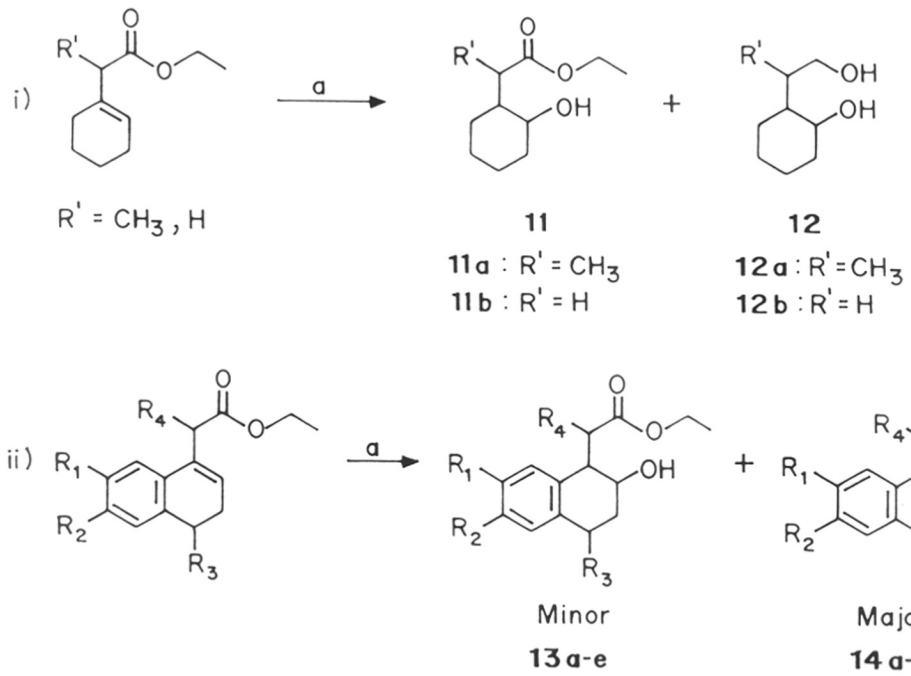
The structure of **15** was fully characterised by its IR, ^{1}H-NMR and mass spectroscopy. IR spectrum of **15** showed absorption at 3350 cm^{-1} for hydroxy group. The ^{1}H-NMR spectrum of **15** displayed signals at δ 3.75 (t, 2H) and δ 5.85 (t, 1H) for -$\underline{CH_2}$-OH and olefinic protons while disappearance of signals δ 1.2 (t, 3H) and 4.15 (q, 2H) of methyl and $\underline{CH_2}$-CH_3 protons. The mass spectrum of **15** showed M^+ at 218 (40%) confirmed the assigned structure 15. Although formation of this is completely unexpected It could be postulated that probably BMS forms a loose complex with the double bond and further reduces the ester selectively. Other possibility of formation of borane and alcohol and further elimination also cannot be ruled out.

Conclusion :

This probably is the first example of assisted reduction of esters aided by double bond.

1. This methodology demonstrates the utility of BMS-complex as mild reducing agent for ß,γ-unsaturated esters at room temperature in high yields.
2. Increasing steric bulk at α-position does not inhibit the ease of ester reduction.
3. Normal esters are not reduced with BMS-Complex in ether confirming the assistance of double bond.
4. No complex reagent for external catalyst or high temperature are required for hydroboration.

Scheme-5



a: i) BMS , Et_2O ii) H_2O_2 , ^-OH

Table-II

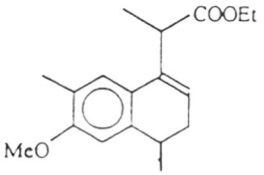
Starting	R_1	R_2	R_3	R_4	t(h)	Product	
						13+14 % Yield	Ratio 13:14
8a	CH_3	OMe	CH_3	CH_3	24	90	1:2
8b	H	H	H	CH_3	24	65·3	3:2
8d	H	H	H	CH_3-CH_2-	24	73	1:7
8e	H	OMe	H	CH_3	24	90	Product No.15
8c	H	H	H	H	24	80	1:7

3.4: Experimental

Synthesis of ß,γ-unsaturated esters: General procedure :

Ethyl bromopropionate (15.00 mmol) was added slowly to a stirred solution of tetralone (13.6 mmol), iodine (13.6 mmol) and zinc (excess) in 20 ml dry ether and gentle reflux of ether was maintained. The reaction was monitored by tlc. After 3h the reaction mixture was treated with 50% HCl for 10 min and extracted with ether. The ether extract was dried (anhydrous Na_2SO_4) and rotary evaporated to afford viscous oil. Column purification of viscous oil over silica (pet.ether : ethyl acetate) furnished the ß, γ-ester as colourless oil.

Ethyl-2(4,7-dimethyl-6-methoxy-3,4-dihydro naphthalene) propionate (8a) :



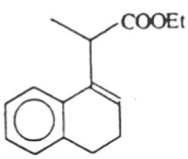
Yield : 81%

IR (Neat) : 1740, 1620, 1580, 1510, 1470, 1460, 1410, 1390, 1350, 1330, 1310, 1280, 1250, 1200, 1150, 1140, 1110, 1090, 1020, 1000 cm^{-1}.

^{1}H-NMR (90 MHz, $CDCl_3$) : δ 1.2 (t, J = 7 Hz, 3H), 1.4 (d, J = 7 Hz, 3H), 2.2 (s, 3H), 2.4 (m, 2H), 2.8 (m, 1H), 3.8 (s, 3H), 4.15 (q, J = 7 Hz, 2H), 5.8 (t, J = 5 Hz, 1H), 6.7 (s, 1H), 7.2 (s, 1H).

Mass (m/e) : 288 (M^+, 35%), 221 (5), 215 (22), 191 (61), 187 (100), 186 (50), 172 (28), 155 (9), 141 (15), 128 (11), 115 (7), 102 (3), 91 (3), 77 (2), 65 (1).

Ethyl-2(3,4-dihydronaphthalene)propionate (8b) :



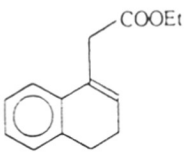
Yield : 80%

IR (Neat) : 1740, 1610, 1470, 1350, 1300, 1220, 1240, 1180, 1140, 1110, 970 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.17 (t, J = 7 Hz, 3H), 1.42 (d, 3H, J = 8 Hz), 2.31 (m, 2H), 2.75 (t, 2H, J = 7 Hz), 3.75 (q, 2H, J = 8 Hz), 4.13 (q, J = 7 Hz, 2H), 6.06 (t, J = 4 Hz, 1H), 7.2 (m, 4H).

Mass (m/e) : 230 (M^+, 33%), 215 (4), 198 (1), 187 (4), 169 (4), 155 (53), 141 (46), 129 (100), 115 (34), 102 (47), 91 (6), 74 (6), 63 (2).

Ethyl-2(3,4-dihydronaphthalene)acetate (8c) :



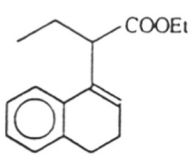
Yield : 88%

IR (Neat) : 1740, 1630, 1610, 1500, 1460, 1440, 1400, 1360, 1340, 1320, 1250, 1180, 1040, 760, 740 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (t, 3H, J = 7 Hz), 2.3 (m, 2H), 2.8 (t, 2H, J = 7 Hz), 3.4 (d, J = 2 Hz, 2H), 4.1 (q, 2H, J = 7 Hz), 5.9 (t, 1H, J = 4 Hz), 7.1 (m, 4H).

Mass (m/e) : 216 (M^+), 141 (80), 128 (100), 115 (75), 88 (10).

Ethyl-2(3,4-dihydronaphthalene) butyrate (8d) :



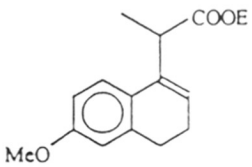
Yield : 90%

IR (Neat) : 2900, 1740, 1640, 1490, 1450, 1390, 1340, 1200, 1120, 1040, 750 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.9 (t, J = 8 Hz, 3H), 1.2 (t, 3H, J = 8 Hz), 1.5 - 2.4 (m, 4H), 2.7 (t, 2H, J = 8 Hz), 3.5 (t, 3H, J = 8 Hz), 6.06 (t, 1H, J = 4 Hz), 7.2 (m, 4H).

Mass (m/e) : 244 (M^+, 32%), 232 (3), 215 (36), 197 (1), 186 (20), 169 (76), 153 (28), 141 (75), 129 (100), 115 (50), 101 (20), 91 (6), 77 (8), 73 (1), 63 (2), 51 (4).

Ethyl-2(6-methoxy-3,4-dihydronaphthalene)propionate (8e) :



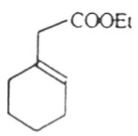
Yield : 80%

IR (Neat) : 1730, 1610, 1580, 1500, 1460, 1440, 1380, 1310, 1260, 1160, 1100, 1050 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (t, 3H, J = 5.00 Hz), 1.5 (d, 3H, J = 5.00 Hz), 2.3 (m, 2H), 2.75 (t, 2H, J = 2.5 Hz), 3.7 (q, 1H), 3.8 (s, 3H), 4.15 (q, 2H), 5.9 (t, 1H), 6.8 (m, 2H), 7.2 (m, 1H).

Mass (m/e) : 228 (M^+-OMe, 14%), 183 (10), 157 (30), 144 (2), 135 (6), 129 (37), 115 (10), 101 (100), 91 (5), 87 (17), 83 (20), 73 (68), 69 (10), 55 (84).

Ethyl-2(cyclohexalene)acetate (6b) :



To a stirred solution of alcohol **5b** (7.5 g, 40.32 mmol) and pyridine (6.3 g, 80.00 mmol) in dry CH_2Cl_2 at 0°C, thionyl chloride (4.80 g, 40.32 mmol) was added dropwise and stirred for 3h at room temperature. It was then poured in to aqueous $NaHCO_3$ and extracted with ether, dried (anhydrous Na_2SO_4) and concentrated to afford viscous oil. Vacuum distillation of oil furnished the ester **6b** as a colourless liquid.

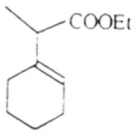
Yield : 3.482 g, 51%.

IR (Neat) : 1740, 1650, 1450, 1380, 1340, 1260, 1220, 1170, 1040, 930, 860 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.5 (t, 3H, J = 5 Hz), 1.9 (m, 4H), 2.3 (bs, 3H), 3.2 (bs, 2H), 4.4 (q, 2H), 5.8 (bs, 1H).

Mass (m/e) : 168 (M^+, 16%), 152 (8), 130 (44), 95 (50), 67 (100), 41 (12), 55 (40).

Ethyl-2(cyclohexalene)propionate (6a) :



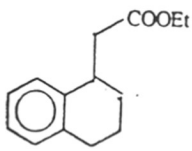
Yield : 68%

IR (Neat) : 1740, 1450, 1380, 1330, 1250, 1190, 1050 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (d, 3H, J = 5 Hz), 1.2 (t, 3H, J = 7 Hz), 1.5 (m, 4H), 2.00 (m, 4H), 3.00 (q, 1H), 4.1 (q, 2H), 5.6 (bs, 1H).

Mass (m/e) : 182 (M^+, 15%), 167 (4), 152 (4), 136 (15), 129 (4), 121 (2), 109 (76), 102 (54), 97 (10), 93 (26), 87 (4), 79 (77), 74 (36), 67 (100), 55 (68).

Ethyl-2-[1,2,3,4-tetrahydronaphthalene] acetate (9) :



A mixture of ß,γ-unsaturated ester **8c** (1.545 g, 7.1 mmol) and 10% palladium on charcoal (154 mgm) in methanol (10 ml) was hydrogenated (35psi) at room temperature for 5 hour. Catalyst was removed by filtration through celite, methanol was rotary evaporated and residue was purified by column chromatography to afford ester **9** as a viscous liquid.

Yield : 1.425 g, 91.38%

IR (Neat) : 1730, 1450, 1375, 1350, 1295, 1250, 1170, 1040 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.3 (t, 3H, J = 5.4 Hz), 1.65-2.05 (m, 4H), 2.55 (m, 1H), 2.7 (d, 1H, J = 2.75 Hz), 2.85 (t, 2H), 2.4 (m, 1H), 4.2 (q, 2H), 7.1 (m, 4H).

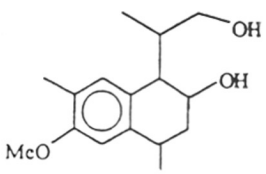
^{13}C-NMR (50 MHz, $CDCl_3$) : δ 170 (s), 139.45 (s), 137.21 (s), 129.42 (d), 128.40 (d), 126.18 (d), 126.00 (d), 60.44 (t), 42.21 (t), 34.78 (d), 29.74 (t), 28.44 (t), 19.84 (t), 14.46(q).

Mass (m/e) : 218 (M^+, 13%), 176 (6), 155 (1), 144 (91), 131 (100), 115 (36), 103 (10), 91 (36), 77 (9), 71 (2), 65 (8).

Hydroboration of ß,γ-unsaturated esters : General procedure :

To a stirred solution of borane dimethyl sulfide complex (7 mmol), in ether at 0°C, was added the ß, γ-unsaturated ester (7 mmol) dropwise and the reaction mixture was stirred for 24 h. To this solution was added 30% NaOH (13 mmol) dropwise under ice cooling followed by 30% H_2O_2 (13 mmol) dropwise. After stirring the above reaction mixture for 2 h, it was extracted with dichloromethane, dried over anhydrous sodium sulphate and solvent was removed under vacuum to afford a viscous oil, which was chromatographed over SiO_2 (10-20% ethylacetate:pet·ether) to furnish the hydroxy esters (6-30%) as a viscous oils. Further elution with 1:1 ethyl acetate:pet. ether, resulted in the diols **66** (80%) as a viscous oils.

2-(2-hydroxy-4,7-dimethyl-6-methoxy-1,2,3,4-tetrahydronaphthalene)propanol (14a) :

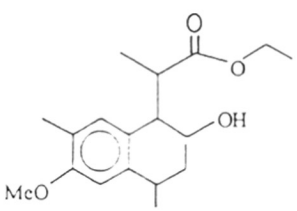


Yield : 60%

IR (Neat) : 3450, 1610, 1560, 1500, 1460, 1450, 1400, 1380, 1310, 1250, 1200, 1050 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 0.88 (d, 3H, J = 6.5 Hz), 1.36 (d, 3H, J = 7 Hz), 1.76 (m, 2H), 2.16 (s, 3H), 2.8 (m, 2H), 3.68 (d, 2H, J = 6.6 Hz), 3.84 (s, 3H), 4.15 (m, 2H), 6.84 (s, 1H), 6.96 (s, 1H).

Ethyl-2(2-hydroxy-4,7-dimethyl-6-methoxy-1,2,3,4-tetrahydronaphthalene)propionate (13a) :

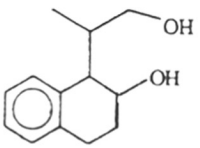


Yield : 30%

IR (Neat) : 3420, 1730, 1610, 1580, 1500, 1460, 1430, 1380, 1310, 1240 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (t, 3H, J = 7 Hz), 1.3 (d, 3H, J = 8 Hz), 1.4 (d, 3H, J = 8 Hz), 1.9 (m, 1H), 2.2 (s, 3H), 2.3 (m, 1H), 2.7 (m, 1H), 3.1 (m, 2H), 3.8 (s, 3H), 4.2 (q, 2H), 4.38 (m, 1H), 5.1 (bs, D_2O exchangeable, 1H), 6.62 (s, 1H), 7.21 (s, 1H).

2(2-hydroxy-1,2,3,4-tetrahydronaphthalene)propanol (14b) :



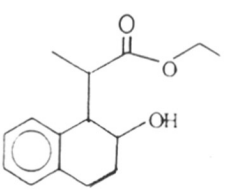
Yield : 56%

IR (Neat) : 3400, 2940, 1500, 1460, 1060, 780 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.1 (d, 3H, J = 7 Hz), 1.6-2.6 (m, 6H), 2.7 (bs, 2H, D_2O exchangeable), 3.8 (m, 3H), 7.2 (m, 4H).

Mass (m/e) : 188 (M^+ 18, 29%), 171 (8), 157 (28), 141 (42), 129 (100), 115 (38), 102 (5), 91 (11), 84 (8), 77 (7), 65 (2), 57 (1).

Ethyl-2(2-hydroxy-1,2,3,4-tetrahydronaphthalene) propionate (13b) :



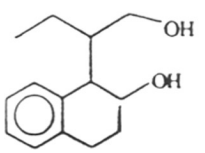
Yield : 9.3%

IR (Neat) : 3460, 2940, 1730, 1500, 1460, 1340, 1300, 1240, 1200, 1040, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (t, 3H, J = 6.4 Hz), 1.6 (d, 3H, J = 6.5 Hz), 1.7-2.2 (m, 4H), 2.5 (t, 2H, J = 3.2 Hz), 3.00 (t, 1H, J = 3.2 Hz), 3.8 (m, 1H), 4.00 (q, 2H), 7.5 (m, 4H).

Mass (m/e) : 248 (M^+), 200 (1), 180 (1), 165 (2), 154 (2), 146 (42), 131 (14), 118 (76), 103 (6), 90 (100), 77 (16), 63 (32), 57 (2).

2(2-hydroxy 1,2,3,4-tetrahydronaphthalene)butanol (14d) :



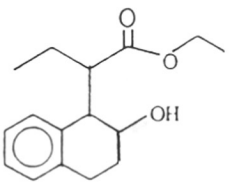
Yield : 66%

IR (Neat) : 3400, 1490, 1450, 1390, 1340, 1270, 1230, 1190 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 80 MHz) : δ 1.00 (t, 3H, J = 6.5 Hz), 1.3-1.6 (m, 4H), 1.7-2.4 (m, 3H), 2.7 (m, 2H), 3.7 (m, 1H), 3.8 (m, 2H), 7.2 (m, 4H).

Mass (m/e) : 202 (M^+-18, 26%), 184 (3), 169 (20), 155 (26), 141 (39), 129 (100), 115 (33), 107 (8), 102 (5), 91 (12), 83 (2), 77 (8), 65 (2), 55 (5).

Ethyl-2(2-hydroxy-1,2,3,4-tetrahydronaphthalene)butyrate (13d) :



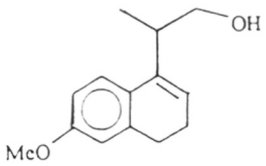
Yield : 7%

IR (Neat) : 3400, 1730, 1500, 1400, 1390, 1350, 1200, 1100 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 80 MHz) : δ 0.9 (t, 3H, J = 8 Hz), 1.2 (t, 3H, J = 8 Hz), 1.5-2.4 (m, 4H), 2.8 (m, 2H), 3.2 (m, 2H), 3.8 (m, 1H), 4.1 (q, 2H), 7.2 (m, 4H).

Mass (m/e) : 244 (M^+-18, 2%), 230 (2), 213 (2), 202 (12), 186 (9), 169 (29), 157 (11), 141 (35), 131 (100), 120 (16), 115 (36), 107 (8), 91 (29), 83 (4), 77 (14), 69 (6), 63 (8), 55 (14).

2(6-Methoxy-3,4-dihydronaphthalene)propanol (15) :



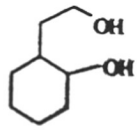
Yield : 90%

IR ($CHCl_3$) : 3350, 1600, 1560, 1490, 1450, 1420, 1300, 1350, 1150, 1040, 800 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.25 (d, 3H, J = 5.0 Hz), 1.9 (bs, 1H), 2.3 (m, 2H), 2.7 (t, 2H, J = 5.0 Hz), 3.1 (m, 1H), 3.6 (m, 1H), 3.75 (t, 2H), J = 2.5 Hz), 3.8 (s, 3H), 5.85 (t, 1H), 6.85 (m, 2H), 7.25 (m, 1H).

Mass (m/e) : 218 (M^+, 40%), 200 (M^+-18, 14%), 187 (25), 172 (25), 159 (100), 144 (44), 128 (44), 115 (48), 102 (8), 91 (28), 77 (20), 69 (5), 63 (14), 55 (8).

2(Cyclohexa-1-ol)ethanol (12b) :



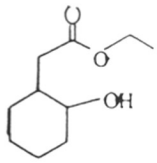
Yield : 57%

IR (Neat) : 3300, 1450, 1070, 980, 860 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) :δ 1.00-2.00 (m, 11H), 3.00 (m, 1H), 3.6 (m, 2H).

Mass (m/e) : 144 (M^+, 16%), 125 (61), 109 (20), 98 (100), 93 (40), 88 (4), 83 (79), 70 (38), 67 (77), 55 (40), 41 (22).

Ethyl-2(cyclohexanol)acetate (11b) :



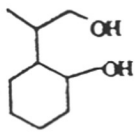
Yield : 7.3%

IR (Neat) : 3400, 1730, 1500, 1420, 1350, 1220, 1170, 770 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (t, 3H, J = 8 Hz), 1.3-1.8 (m, 8H), 2.00 (m, 2H), 3.6 (bs, 1H), 4.1 (q, 2H).

Mass (m/e) : 186 (M^+), 168 (M^+ - 18), 126 (70), 98 (100), 85 (60), 67 (44), 55 (30).

2(cyclohexa-1-ol)propanol (12a) :



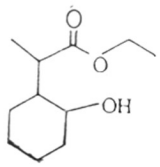
Yield : 60%

IR (Neat) : 3400, 1450, 1380, 1320, 1250, 1170, 1040 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.00 (d, 3H, J = 5.0 Hz), 1.1-1.4 (m, 5H), 1.5-1.9 (m, 5H), 2.00 (m, 2H), 3.4 (m, 1H), 3.65 (m, 2H).

Mass (m/e) : 158 (M^+, 2%), 149 (1), 140 (4), 127 (10), 122 (6), 110 (24), 98 (20), 81 (43), 67 (67), 55 (100).

Ethyl-2(cyclohexa-1-ol) propionate (11a) :



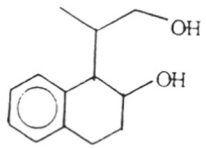
Yield : 10%

IR (Neat) : 3400, 1740, 1430, 1345, 1220, 1100 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (d, 3H, J = 5.00 Hz), 1.2 (t, 3H, J = 7 Hz), 1.5 (m, 4H), 1.9 (m, 4H), 3.00 (m, 1H), 3.9 (m, 1H), 4.1 (q, 2H).

Mass (m/e) : 200 (M^+, 10%), 182 (8), 169 (17), 155 (10), 139 (100), 123 (12), 110 (13), 81 (19), 67 (21), 55 (21).

2(2-hydroxy-1,2,3,4-tetrahydronaphthalene) ethanol (14c) :



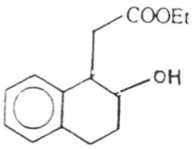
Yield : 70%

IR (Neat) : 3450, 1490, 1450, 1300, 1150, 1120 cm^{-1}

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 2.00 -1.5 (m, 4H), 2.5 (m, 3H), 3.65 (m, 1H), 3.8 (t, 2H), 7.2 (m, 4H).

Mass (m/e) : 192 (M^+), 170 (1), 156 (1), 147 (28), 130 (88), 119 (75), 105 (50), 91 (100), 77 (32), 65 (36).

Ethyl-2(2-hydroxy-1,2,3,4-tetrahydronaphthalene)acetate (13c) :



Yield : 10%

IR (Neat) : 3450, 1740, 1450, 1400, 1350, 1150, 1110 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz) : δ 1.2 (t, 3H, J = 8 Hz), 1.4-1.8 (m, 5H), 2.00 (1, 2H), 3.8 (m, 1H), 4.1 (q, 2H), 7.2 (m, 4H).

Mass (m/e) : 234 (M^+), 218 (1), 208 (1), 188 (4), 170 (4), 156 (10), 146 (36), 141 (29), 130 (68), 118 (100), 104 (26), 97 (2), 90 (49), 85 (4), 77 (18), 63 (11).

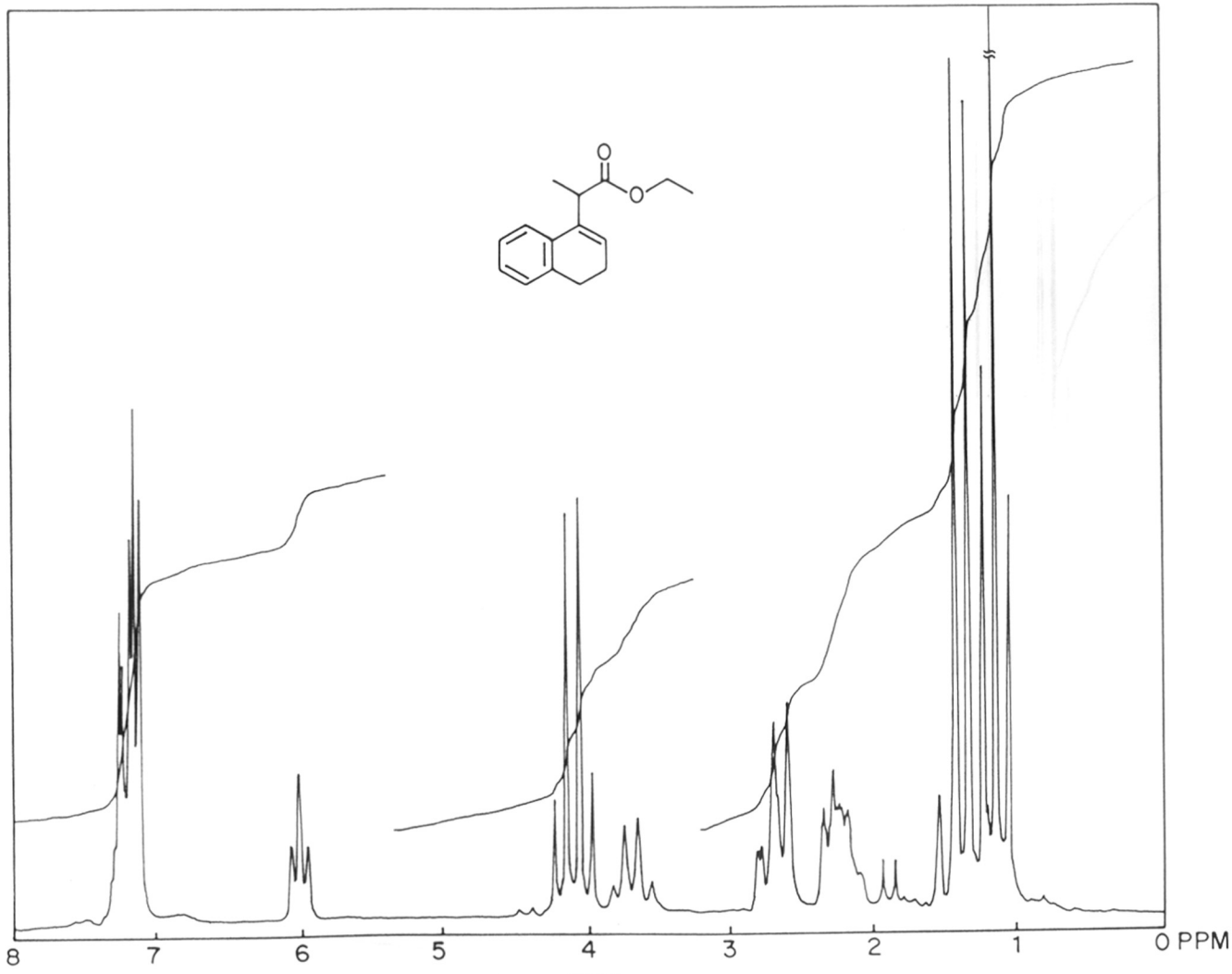


FIG.1

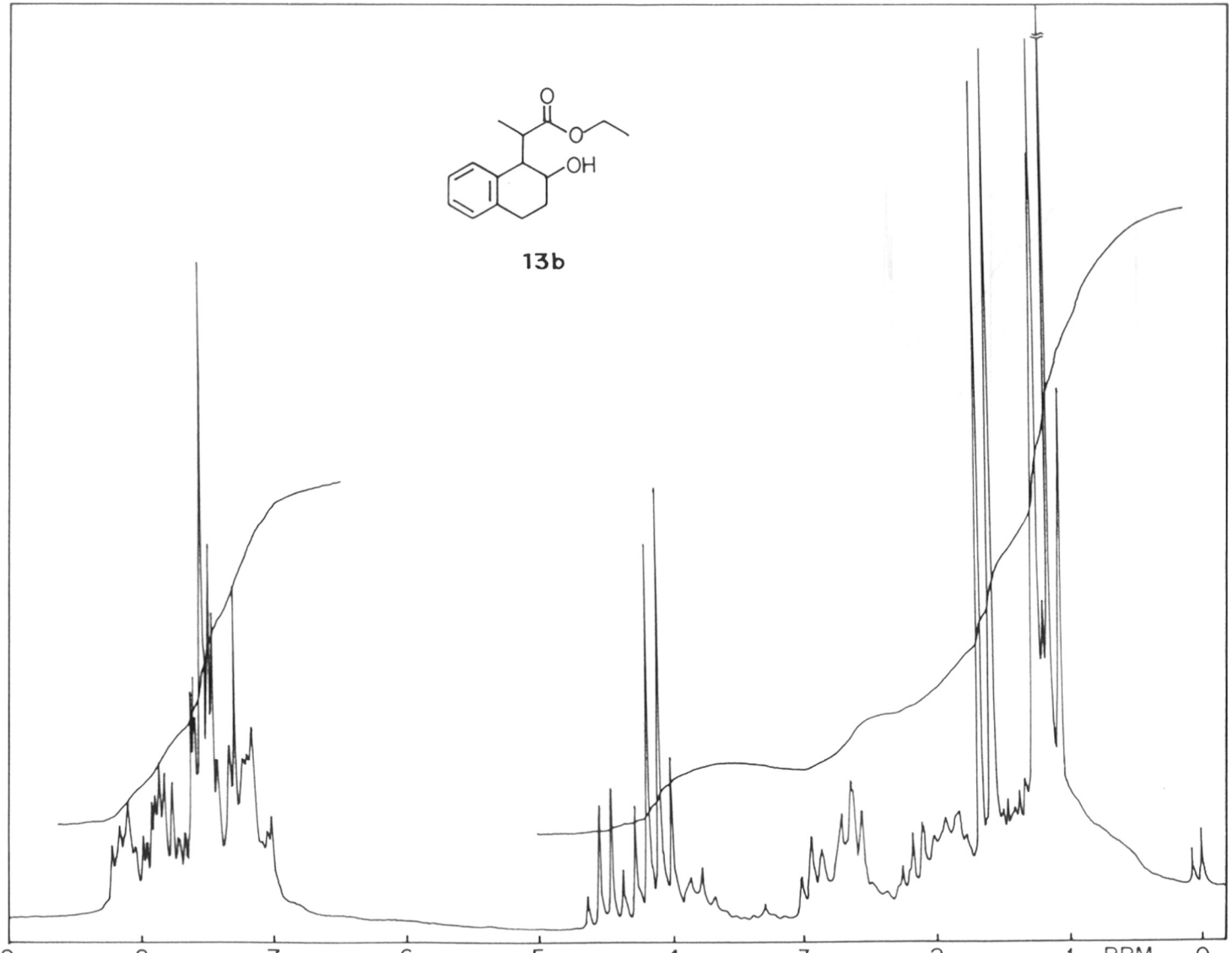


FIG. 2

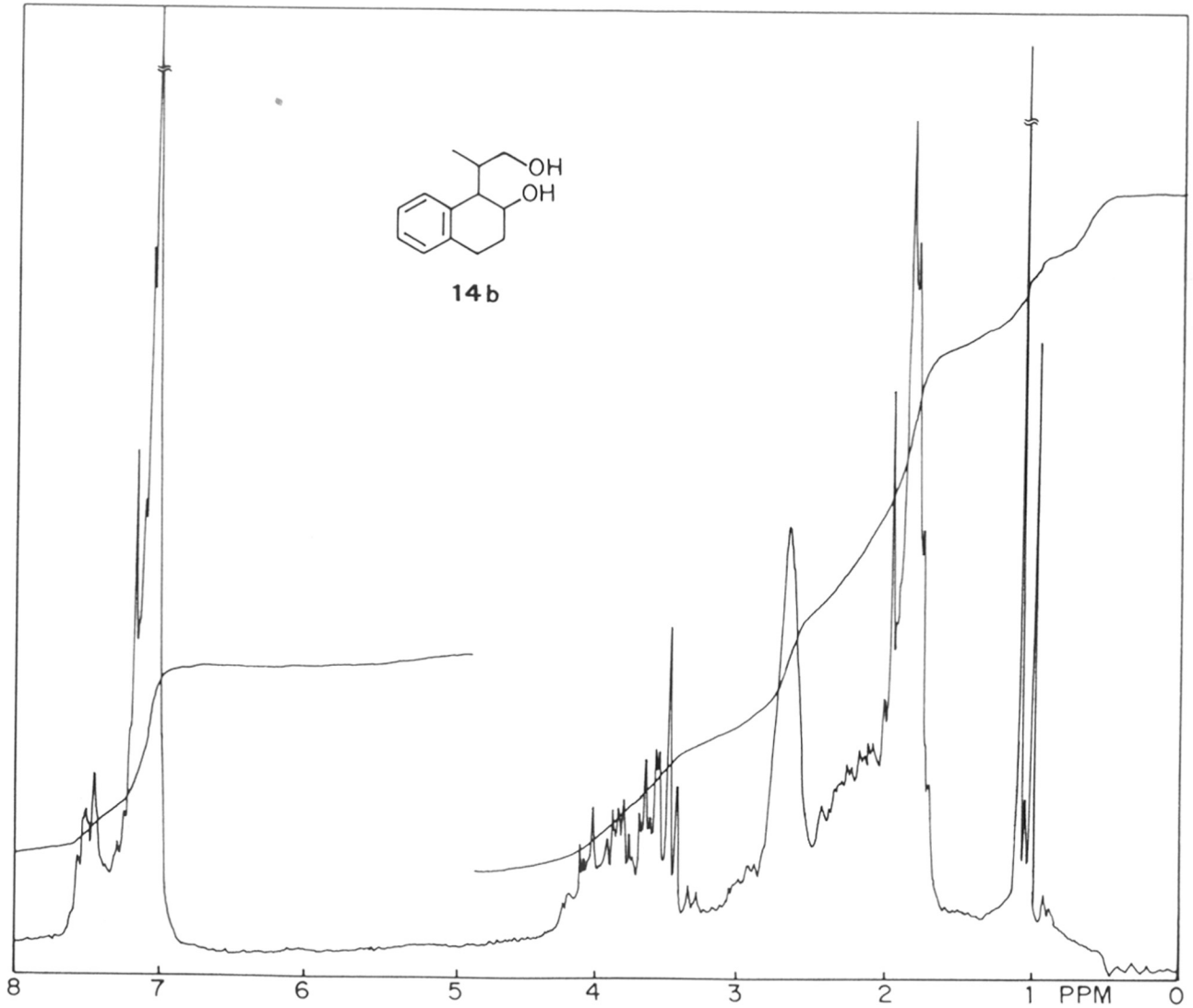


FIG.3

3.5 : References

1. Braun, L.M., Braun, R.A., Crissman, H.R., Opperman, M and Admas R. *J. Org. Chem.* 1971, **36**, 2388.
2. Lane, C.F. *Aldrichimica Acta* 1975, **8**, 20.
3. Brown, H.C. and Choi, Y.M. *Synthesis* 1981, 439.
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9. Smith, A.B., Toder, B.H., Brance, S.J. and Dieter, R.K. *J. Am. Chem. Soc.* 1981 **103(8)**, 2004.

List of Publications

1. A Short and Efficient Synthesis of (-)-Mintlactone and (+)-iso-Mintlactone.
   Subhash P. Chavan, P.K. Zubaidha and **Vijay D. Dhondge**.
   Tetrahedron, 1993, 49, 6429-6436.

2. An Efficient Synthesis of α-Cuparenone.
   Suhbash P. Chavan, T. Ravindranathan, Sachindra S. Patil, **Vijay D. Dhondge** and Shubhada W. Dantale.
   Tetrahedron Lett. 1996, 37(15), 2629-2630.

3. Total Synthesis of (+)-Laevigatin.
   Subhash P. Chavan, T. Ravindranathan, **Vijay D. Dhondge**, Sachnidra S. Patil and Shubhada W. Dantale.
   Tetrahedron Lett. (To be communicated)

4. Synthesis of (+)-Menthofuran.
   Subhash P. Chavan and **Vijay D. Dhondge**.
   Syn. Lett. (To be communicated)

5. Assisted Reduction of ß,γ-unsaturated Esters by Methyl Sulfide Complex.
   Subhash P. Chavan, P.K. Zubaidha and **Vijay D. Dhondge**.
   (To be Communicated)

6. A Non Catalytic Oxidative Deprotection of Oxathioacetals.
   T. Ravindranathan, Subhash P. Chavan, Shubhada W. Dantale, Sachin S. Patil and **Vijay D. Dhondge**.
   Tetrahedron (Communicated)

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