SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

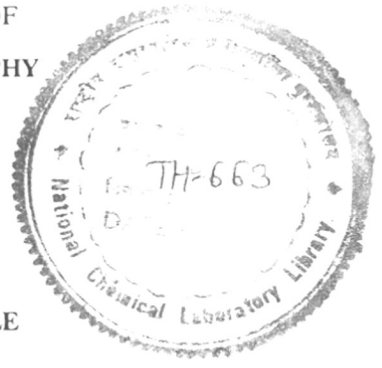
SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)



BY

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OCTOBER 1992

DEDICATED TO MY

PARENTS AND TEACHERS

CERTIFICATE

COMPUTERISED

This is to certify that the work included in the thesis entitled " SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS " submitted by Mr. Jayendra B. Bhonsle was carried out by the candidate under my supervision in the National Chemical Laboratory, Pune - 411008. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

S. N. Kulkarni

(S. N. KULKARNI)

Supervisor

ACKNOWLEDGEMENT

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I am also grateful to Drs. T. Ravindranathan and V.H. Deshpande for helpful suggestions, keen intrest and constant encouragement.

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I am also thankful to Mr. D. Narayan and Mrs. J.A. Phatak for their assistance.

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(J.B. BHONSLE)

National Chemical Laboratory

Pune 411008

October 1992.

CONTENTS

GENERAL REMARK

1. The figure numbers, scheme numbers and reference numbers, etc. given in each chapter refer to that particular chapter only. The refernces and figures are given at the end of each chapter.

2. All melting points and boiling points are uncorrected. Temperatures are recorded on centigrade scale.

3. All solvents were distilled before use. petroleum ether refers to the fraction boiling in the range of 60-80^{o}C.

4. Column chromatography was carried out using silica gel (60-120 mesh) which was activated at 125-130^{o}C for 5 hours. Unless otherwise mentioned, alumina refers to neutral alumina made in this laboratory.

5. The TLC plates were prepared by spreading an aqueous suspension of silica gel (200-300 mesh, containing 13% $CaSO_4$ as binder) uniformly over glass plates using an applicator. After initial drying at room temperature, the plates were activated at 100^{o}C for use. Various solvent systems used for TLC are:

Solvent A : Benzene

Solvent B : Pet. Ether

Solvent C : Benzene +20% Ethyl acetate

6. The spots on TLC were visualised by exposing them to iodine vapours or by spraying with conc. H_2SO_4 followed by charring in an oven.

7. All extracts were finally dried over anhydrous Na_2SO_4.

CHAPTER 1

PART A

REVIEW OF ARTEMISININ

History :

Data released by the World Health Organisation in 1985 showed that in 1982 about 6.5 million cases of malaria were recorded[1]. Of the total world population (1983) of about 4.7 billion only 2.2 billion live in places where malaria has been almost eliminated, but almost 400 million people of the rural tropical areas are exposed to its full brunt. Schecter[2] reported that malaria infects upto 300 million people and kills upto 2 million each year.

As early as the 16th century natural products gained wide acceptance in treatment of malaria, when the therapeutic action of bark of cinchona tree was learnt by the Europeans. Quinine, isolated in 1834, was mainly used for malaria until other synthetic antimalarials were developed. However the real problem was that the resistance of P.falciparum to chloroquine seemed to stimulate resistance to other compounds and appeared to confer to the resistant strains a greater capacity for transmission[3]. In the view of the increasing number of chloroquine-resistant strains of Plasmodium falciparum emerging in Asia, South and Central America and Africa the need for new antimalarials could not be overemphasised.

In China, a pervasive weed known as qinghao was used for treatment of fever. A brief history of artemisinin (1) or qinghao in China is as follows. In 168 BC, qinghao was recommended for hemorrhoids in the "Recipes for 52 kinds of diseases". In 340 AD, Ge Hong in his book "Zhou Hou Bei Ji Fang"

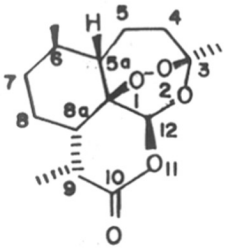
recommended it for reducing fevers. In the 15th century, Li Shizhen in his "Ben Cao Gang Mu" wrote that chills and fever of malaria can be treated with qing hao. In 1798, a decoction of A.annua and Corapax trionycis was suggested in "Wenbing Tiaobian" for treating malaria. In 1967, the Chinese government undertook a systematic examination of this drug "qing hao su" (meaning "active principle of qing hao") which was identified in 1971 and isolated in pure form in 1972[4]. In 1977, the enantiomer (2) of artemisinin (1) was isolated from Artemisia annua and its structure was determined by X-ray crystallography, mass, IR, NMR spectra and chemical reactions[5]. Other peroxidic antimalarial reported in 1984 from Chinese medicinal herb is yingzhaosu from Artabotrys uncinatus[6].

Nomenclature :

The chemical abstract nomenclature is 3,12-Epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10(3H)-one,octahydro-3,6,9-trimethyl-[3R-(3α,5aß,6ß,8aß,9α,12ß,12aR*)] and the chemical abstract registry number being 63968-64-9. Another numbering system is also prevalent for artemisinin (1A)[7]. It is commonly known as artemisinin[8], arteannuin[9] or qinghaosu[10].

Extraction :

Artemisinin (1) was first extracted by the Chinese from the aerial portions of A.annua[4]. Klayman et al[11] reported



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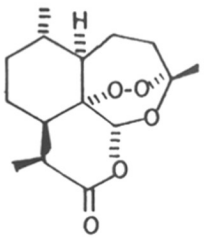

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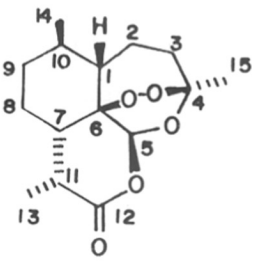

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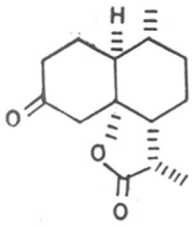

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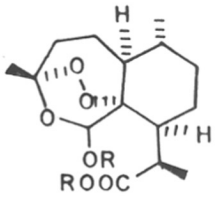

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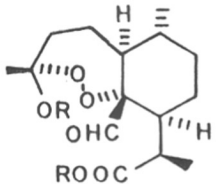
a : R = CH_3

b : R = CH_2CH_3



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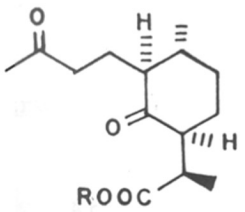

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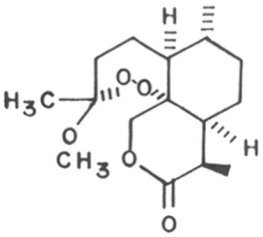

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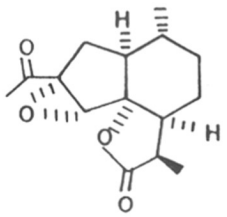

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satisfactory yields of artemisinin (1) by extracting various air-dried components of the plant A.annua in petroleum ether (30°-60°C). Liersch et al[12] reported 0.1% yield of artemisinin (1) from A.annua when the plant material of two weeks before flowering was extracted. They also established presence of artemisinin (1) in A.apiaceae. Except these varieties artemisinin is not known to be isolated from any other variety. The artemisinin (1) content in the leaves of A.annua is reported to be affected by cultivation temperature and illumination, and a maximum accumulation of 32 mgs of artemisinin (1) in 10.0 gms of leaves was achieved by manipulation of these factors[13]. Several workers have tried improved techniques including tissue culture for enhancing artemisinin (1) quantity in A.annua[14-18]. In India, artemisinin (1) was isolated in 0.06% yield from A.annua species growing in Lucknow and several other artemisia species were shown to be devoid of artemisinin[15].

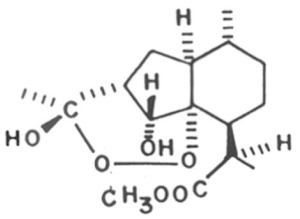
Structure determination and spectral characterisation :

Artemisinin (1) belongs to the amorphane subgroup of cadinenes[19]. The emperical formula of artemisinin (1) $C_{15}H_{22}O_5$ was found by elemental analysis and high resolution mass spectrum[4]. Artemisinin (1) was shown to have a unique endo-peroxide ketal-acetal lactone[20] moiety, and presence of the peroxide group was proved by quantitative reaction with triphenyl phosphine and occurence of fragment ion peak of M^+-32 in mass spectrum[21]. The IR spectrum of artemisinin (1) shows an intense

peak at 1745 cm^{-1} (δ-lactone)[21,22] and peaks at 831, 881, 1115 cm^{-1} (peroxide)[22-25]. The ^{1}H-NMR[25,26] and C^{13} NMR spectra[25-28] indicated the presence of three methyl (one tertiary and two secondary), an acetal and several kinds of aliphatic carbon atoms. The structure and relative configuration was unambiguously determined by X-ray diffraction[29,30]. The absolute configuration of artemisinin (1) was also ascertained by study of the spectral characteristics of its degradation[31-34] products and analogues[35]. Mass spectral studies of artemisinin (1), its analogues and its degradation products were reported by several workers[36,37]. The ORD-CD of artemisinin (1) and its degradation products was reported by several workers[38-41]. Special experiments for structure elucidation like 2D NMR[42], NOESY[43], $^{3}J_{HH}$ and C^{13}-NMR of artemisinin (1) and its analogues were reported by several workers[44,45].

Chemical Transformations :

Artemisinin (1) is poorly soluble in water and decomposes in other protic solvents. It is soluble in most aprotic solvents and is unaffected[46] by them upto 150°C. Artemisinin (1) degrades on treatment with 10% sulphuric acid in glacial acetic acid to yield keto lactone (3)[21,47]. Treatment of artemisinin (1) with p-toulene sulphonic acid monohydrate or 14% hydrogen chloride in anhydrous methanol gave three products (4a), (5a), and (6a) and in anhydrous ethanol gave (4b), (5b) and (6b)[48]. Ying et al[49] reported (5a) and (7) as acid degradation product of



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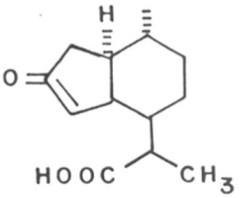

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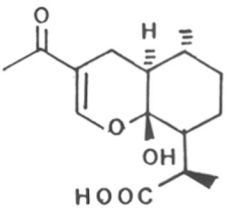

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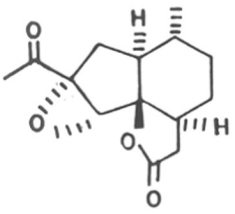

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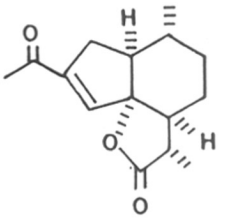

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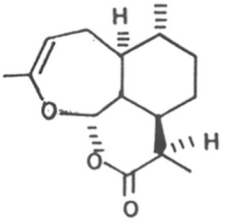

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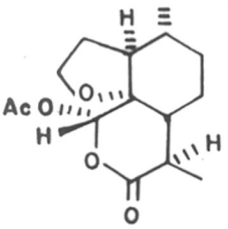

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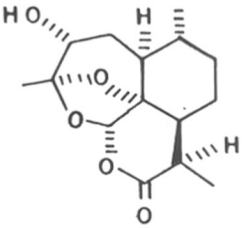

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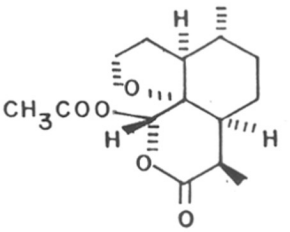

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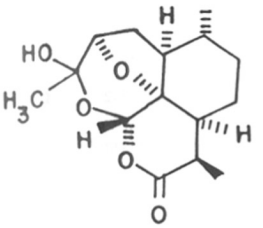
artemisinin (1).

Zhou et al[21,50] reported that artemisinin (1) on treatment with potassium carbonate in methanol at room temperature gave an intramolecular epoxidation product α-epoxide (8) and a new peroxidic product (9). Under same conditions Zeng et al[46] reported obtaining in low yields compound (10). Shang et al[51] reported that artemisinin (1) degraded to form (9), (11), (12) and (13) in alkaline media of potassium carbonate or sodium hydroxide. Isomerisation of artemisinin (1) can be affected with a base to yield 9-epi-artemisinin (25).

Artemisinin (1) shows remarkable thermal stability and does not explode at its melting point as expected but exists unchanged for about 3 minutes at 50°C above its melting point (156°-157°C) and can be purified by sublimation[4], Lin et al[52] reported formation of pyrolysis product (14), (15) and (16) by heating artemisinin (1) at 190°C for 10 minutes. Artemisinin (1) on heating in xylene for 22 hours afforded decomposition products (17) and (18), whereas refluxing in toulene effected no change in artemisinin (1)[53].

Hydrogenation of artemisinin (1) over 5% palladium on calcium carbonate (Pd-$CaCO_3$) gave deoxyartemisinin (19)[20,54] whereas refluxing of artemisinin (1) with lithium aluminium hydride in tetrahydrofuran for 3 hours gave (20) and (21)[55]. The lactonic carbonyl of artemisinin (1) can be reduced by sodium borohydride to yield dihydroartemisinin (22), without affecting the peroxy group[20,54].

Bromination of artemisinin (1) with N-bromo succinimide



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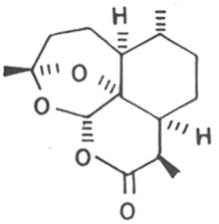

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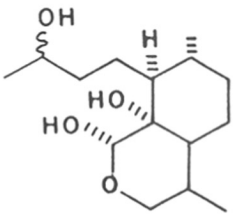
deoxyartemisinin



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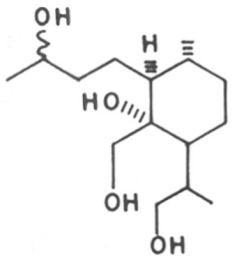

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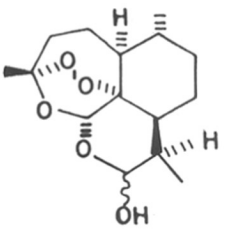

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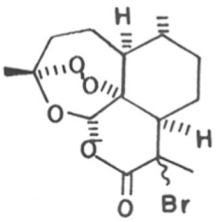

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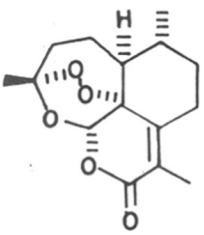
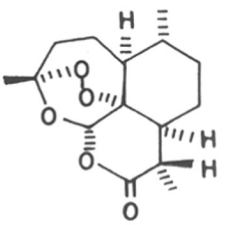
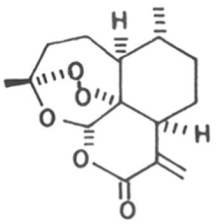


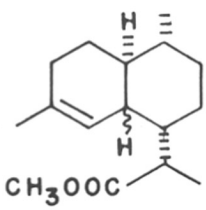
Iso-artemisitene 24



9-epi-artemisinin 25



artemisitene 26



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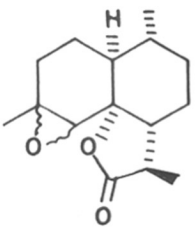

isohydro-arteannuin B-28

furnished a mixture of two isomeric bromides (23), which on treatment with DBU gave (24)[7]. Several workers have tried microbial transformations[56-58] techniques for isolating useful metabolites of artemisinin (1).

Artemisinin (1) has been converted to several analogues and derivatives. Acton et al[59] reported conversion of artemisinin (1) to isoartemisitene (24) and 9-epi-artemisinin (25). Artemisinin (1) has been converted to artemisitene or dehydroartemisinin or desdihydroartemisinin (26) by several routes[60-62]. Isodihydroartemisic acid methyl ester (27) was prepared via acid degradation of artemisinin (1) followed by hydrolysis, esterification, Wittig methylenation and hydrogenation by Gai et al[63]. Li et al[64] reported transformation of artemisinin (1) to isodihydroarteannunin B (28). Desdihydroartemisinin or artemisitene (26) was obtained from artemisinin (1) by treatment with phenyl selenium bromide followed by oxidation with 30% hydrogen peroxide by Lian et al[61].

Synthesis :

In the last seven years several publications reviewing the reported total and partial/formal synthesis of artemisinin (1) have appeared[4,21,65-67]. The first total synthesis of artemisinin (1) was reported in 1983 by Schmid and Hofheinz[68] starting with (-)-isopulegol (29) (scheme-1). (-)-Isopulegol (29) was converted to the benzyl-oxymenthone (30), which was elaborated to (31) in several steps. The final key step involved

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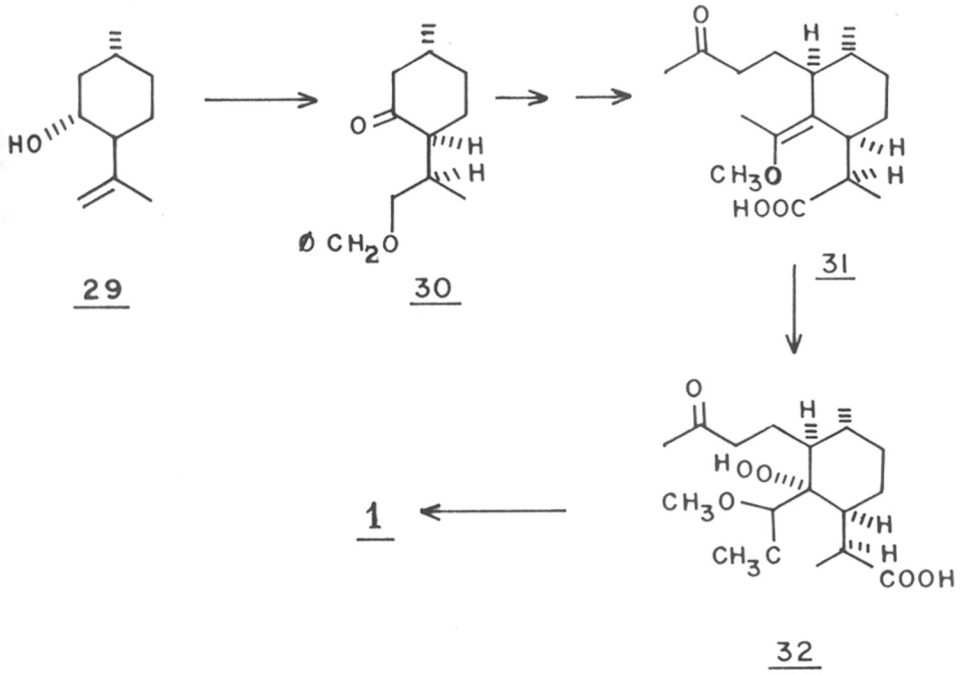

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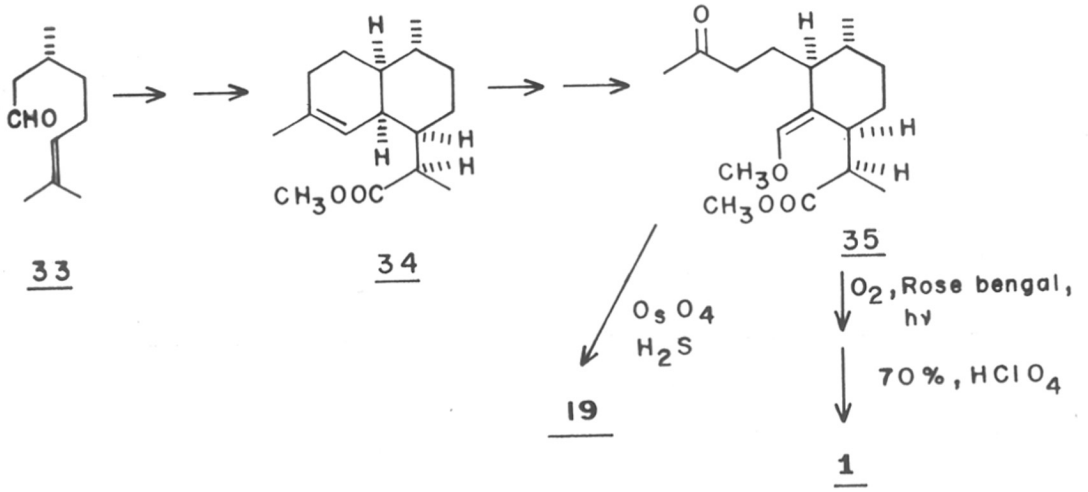
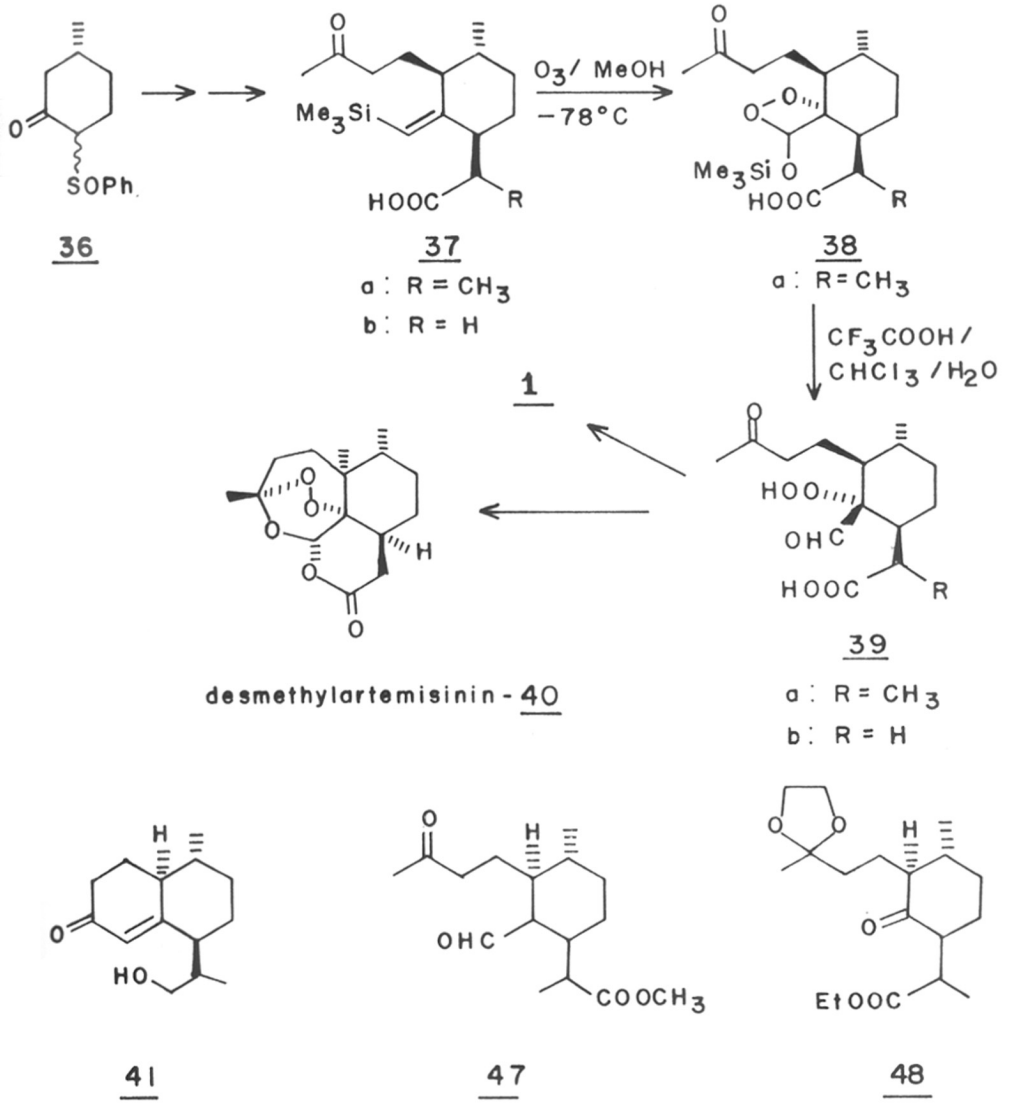
SCHEME – 2



33 34 35 19 1

the irradiation of the methanol solution of (31) in the presence of singlet oxygen with methylene blue as sensitizer at -78°C to give the hydroperoxide intermediate (32). The hydroperoxide (32) on treatment with formic acid in methylene chloride for 24 hours at 0°C gave 30% yield of artemisinin (1). In 1986, Zhou et al[69] synthesised artemisinin (1) starting from R-(+)-citronellal (33) (scheme-2). R(+)-citronellal (33) was converted to 12R-(-)-methyl dihydroartemisinate (34) in 14 steps. The key intermediate (35) was then obtained in 4 steps in 33% yield. Compound (35) on photo-oxidation and further treatment with 70% perchloric acid gave artemisinin (1). Hydroxylation of (35) with OsO_4 in ether at room temperature followed by treatment with hydrogen sulphide yielded deoxyartemisinin (19). In 1987 Avery et al[70] used the chiral sulfoxide derivative (36) (obtained from 3R-methyl cyclohexanone) as the starting material for synthesis of artemisinin (1) and 9-desmethyl-artemisinin (40) (scheme-3). Compound (36) was converted to (37a) by using abnormal course of reaction of vinyl silanes with ozone, discovered by Buchi et al[71]. The key step involved the ozonolysis of (37a) and the ring opening of the transient siloxydioxetane (38a) to labile α-hydroperoxyaldehyde (39a) with trifluoroacetic acid, which undergoes further selective cyclisation to give artemisinin (1) in 37% yield. They also reported synthesis of 9-desmethyl-artemisinin (40) from the same starting material via the intermediates (37b) and (39b). In 1988 Kulkarni et al[72] reported the synthesis of keto alcohol (41) which can be converted to artemisinin (1). In 1990 Ravindranathan et al[73] reported a

SCHEME – 3



36

37

a : R = CH_3

b : R = H

38

a : R = CH_3

1

39

a : R = CH_3

b : R = H

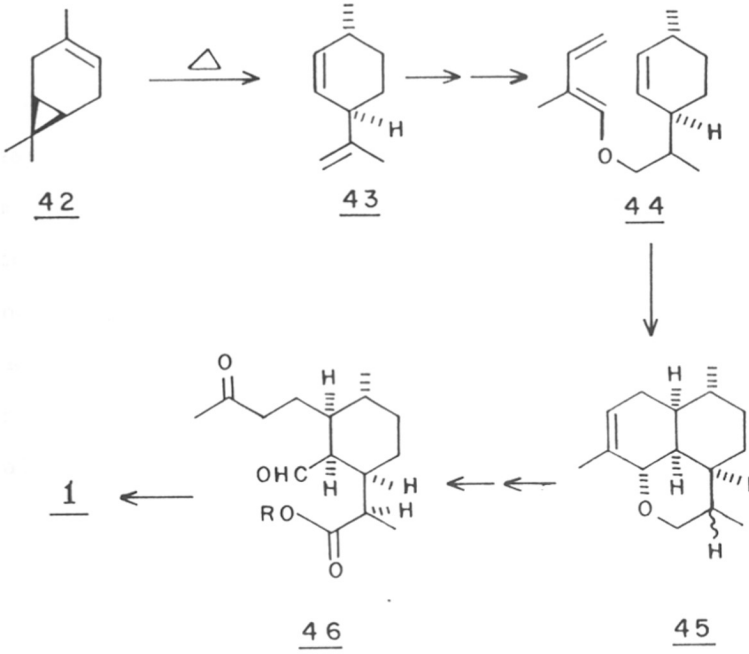
desmethylartemisinin - 40

41

47

48

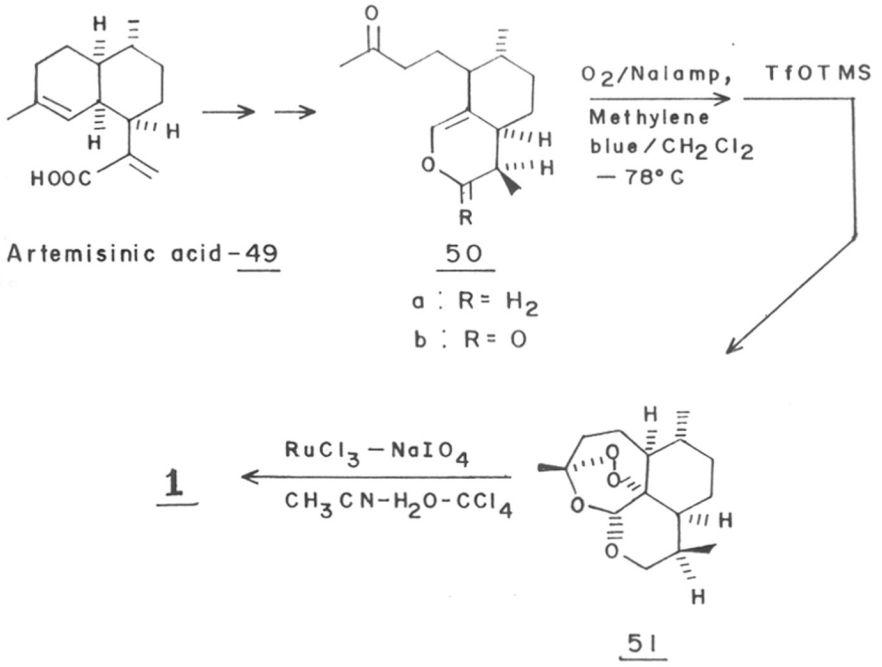
SCHEME – 4



a : R = CH_3

b : R = H

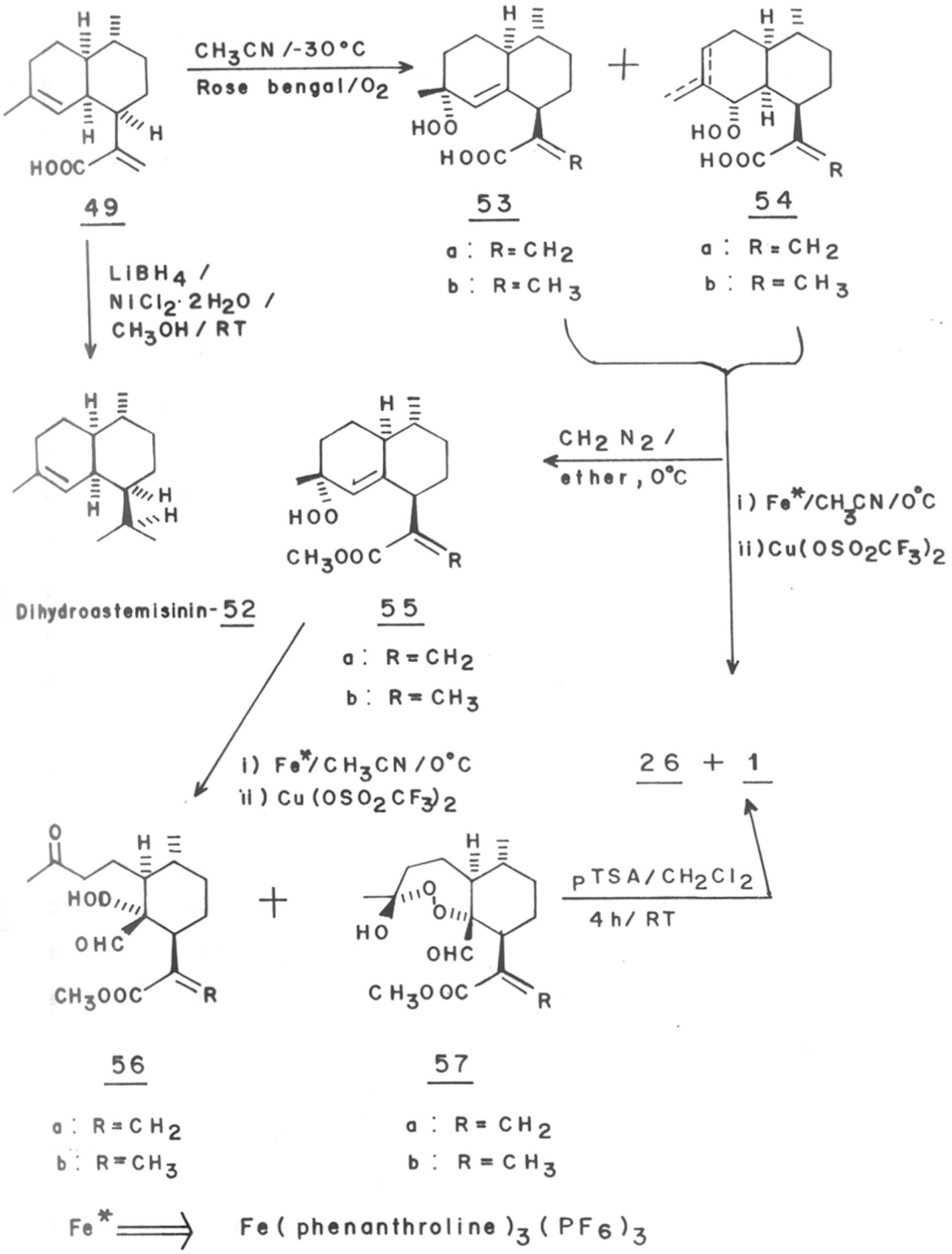
SCHEME – 5



stereoselective synthesis of artemisinin (1) from (+)-isolimonene (43) (scheme-4) which can be easily obtained from (+)-car-3-ene (42) a cheap and abundantly available monoterpene. They prepared the intermediate (44), which underwent intramolecular Diels-Alder reaction to furnish the ether (45). The ether (45) was converted to compound (46a) in seven steps which in turn can be converted to artemisinin (1) by the procedure reported by Zhou et al[69]. Partial or formal synthesis of artemisinin (1) were also reported by Wu et al[74], Xu et al[75] and Jie et al[76]. Wu et al[74] reported the synthesis of the important intermediate (47) for the synthesis of artemisinin (1). Xu et al[75] reported the synthesis of another intermediate (48) for the synthesis of artemisinin (1) starting from (+)-citronellal (33). Jie et al[76] reported the synthesis of key intermediate (35), which was also reported by Zhou et al[69].

Artemisinic acid or qinghao acid (49) has been reported to be converted to artemisinin (1) by several workers[77-79]. Artemisinic acid (49) is abundantly available in the A.annua[80] extract and hence methodologies were developed for preparation of artemisinin (1) from artemisinic acid (49). Ye et al[77] converted artemisinic acid (49) (scheme-5) to an intermediate (50a) in 6 steps, which when subjected to O_2, sodium lamp light with methylene blue in dichloromethane at -78°C and subsequent treatment with trimethylsilyltrifluoromethane sulphonate (TfOTMS) afforded, among others, compound (51). Oxidation of (51) with RuO_4, generated in situ by $RuCl_3$-$NaIO_4$, gives artemisinin (1). Haynes et al[78] reported the conversion of artemisinic acid (49)

SCHEME — 6

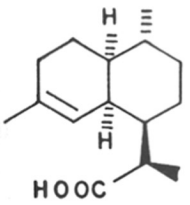

CH3CN /-30°C
Rose bengal/O2
49
53
a : R=CH2
b : R=CH3
54
a : R=CH2
b : R=CH3
LiBH4 /
NiCl2·2H2O /
CH3OH / RT
CH2 N2 /
ether , 0°C
i) Fe*/CH3CN/0°C
ii)Cu(OSO2CF3)2
Dihydroartemisinin-52
55
a : R=CH2
b : R=CH3
i) Fe*/CH3CN/0°C
ii) Cu(OSO2CF3)2
26 + 1
pTSA/CH2Cl2
4h/ RT
56
a : R=CH2
b : R=CH3
57
a : R=CH2
b : R=CH3
Fe* ⟹ Fe(phenanthroline)3(PF6)3

to a mixture of regio isomers (53a) and (54a) by photo-oxygenation in acetonitrile at -30°C (Rose Bengal, tungsten lamp 500 W) in the ratio of 4.5:1 respectively (scheme-6). The mixture was esterified (CH_2N_2, ether, 0°C) and the major isomer (55a) isolated. The hydroperoxide (55a) in acetonitrile under oxygen at 0°C on treatment with Fe (Phenanthroline)$_3$ $(PF_6)_3$, followed immediately thereafter by Cu $(OSO_2CF_3)_2$, and after 30 minutes at room temperature gave hydroperoxide (56a) and peroxy hemiacetal (57a). The crude mixture when treated with p-toulene sulphonic acid monohydrate in dichloromethane for 4 hours at room temperature gave dehydroartemisinin (26) in 30% overall yield. Dehydroartemisinin (26) was obtained directly from the mixture of regioisomers (53a) and (54a) by treatment with Fe (phenanthroline)$_3$ $(PF_6)_3$ at 0°C in acetonitrile under oxygen and thereafter with $Cu(OSO_2CF_3)_2$ followed by warming the reaction mixture to room temperature and stirring for 12 hours in 38% overall yield. The same reaction sequence on dihydro artemisinic acid (52) yielded artemisinin (1).

Roth et al[79] reported that photo-oxygenation of dihydro artemisinic acid (52) at -78°C in dichloromethane with methylene blue followed by change in solvent to petroleum ether and leaving the reaction mixture at room temperature for 4 days yielded on trituration artemisinin (1) (scheme-7).

Jung et al[81] attempted to synthesize artemisinin (1) from artemisinic acid (49) via reduction to dihydro artemisinic acid (52) (scheme-6) followed by ozonolysis in dichloromethane and methanol at -78°C to yield keto aldehyde (46b) which on treatment

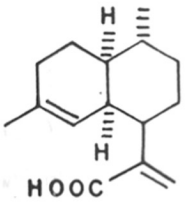
SCHEME – 7



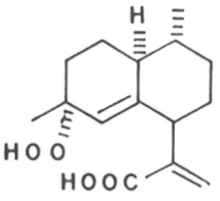
52

Methylene blue / O_2 / –78°C / CH_2Cl_2 → Pet. Ether / RT / 4 days → 1

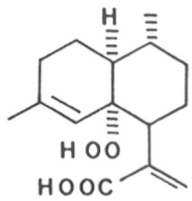
SCHEME – 8



49



53a



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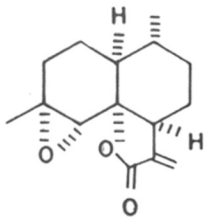


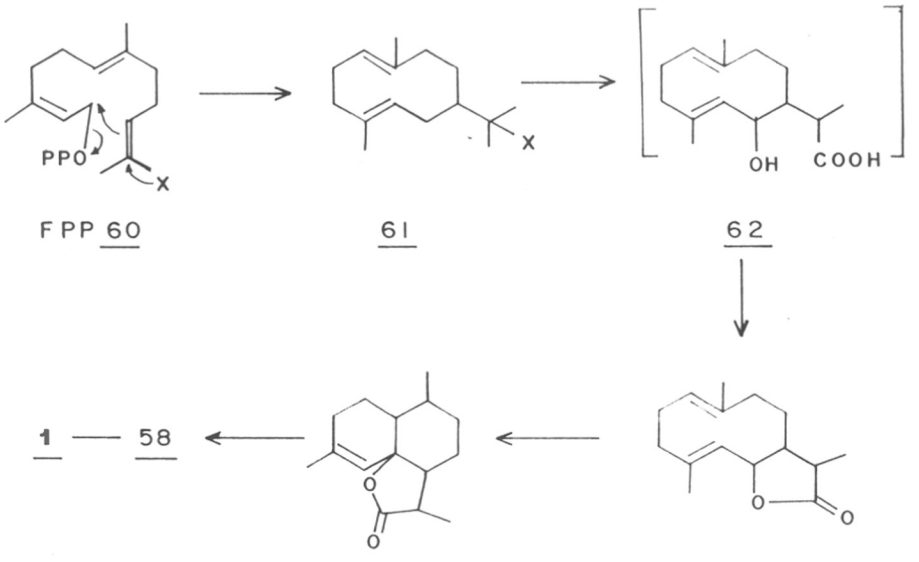
Arteannuin B – 58

with 70% perchloric acid at room temperature gave enol lactone (50b). However Jung et al failed to convert the enol lactone (50b) to artemisinin (1).

Biosynthesis :

The first report on biosynthesis of artemisinin appeared in 1986, where EL-Feraly et al[82] reported conversion of artemisinic acid (49) to arteannuin B (58) by singlet oxygen generated by dye-sensitized photo-oxygenation. They reported that artemisinic acid (49) gets converted to hydroperoxide (53a) which rearranges to (59) and epoxidation, deoxygenation followed by lactonization of which yields arteannuin B (58). From this it was infered that artemisinic acid (49) can serve as a biogenetic precursor for artemisinin (1). In 1987, Akhila et al[18] reported arteannuin B (58) to be a late precursor in the biosynthetic sequence of artemisinin (1). The suggested pathway is that cis-isomer of farnesyl pyrophosphate (FPP) (60) (which is an established precursor in the biosynthesis of sesquiterpenes[83]) may cyclise to (61) (scheme-9) which then enters the pathway (61) to (62) to dihydro-costunolide (63) to cadinanolide (64) to arteannuin B (58) and finally to artemisinin (1). In 1988, Yu et al[84], reported incorporation of [15-^{3}H] isomer of artemisinic acid (49) into the biosynthesis of artemisinin (1) and arteannuin B (58) in a qing hao plant (Artemisia annua) homogenate system and infered that artemisinic acid (49) to be a key intermediate in the biosynthesis of artemisinin (1) and arteannuin B (58). Recently

SCHEME – 9

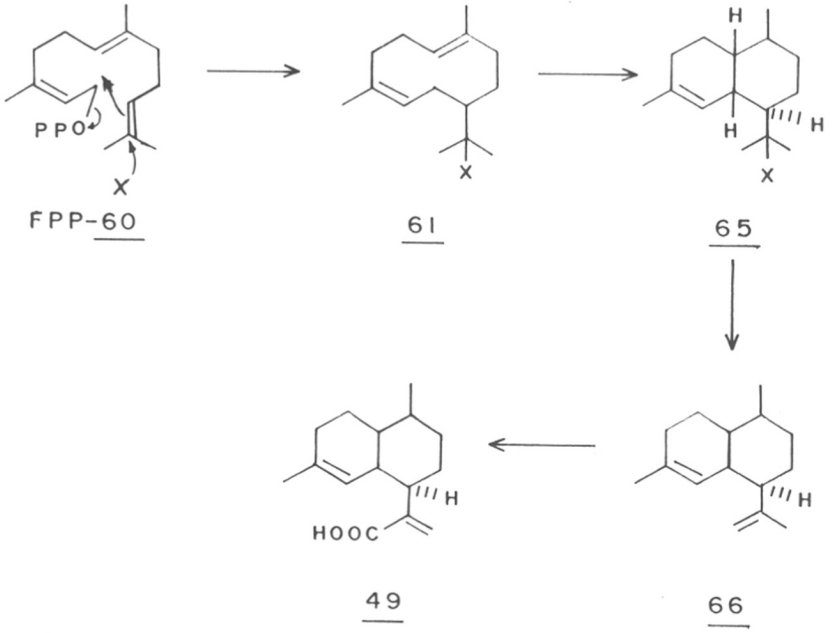


FPP 60 61 62

1 — 58 Cadinanolide 64 dihydrocostunolide 63

(X) = Enzyme

SCHEME – 10



FPP-60 61 65

49 66

in 1990, Akhila et al[85] reported, the complete biosynthesis of artemisinic acid (49) in Artemisia annua, which has been found to play a pivotal role in the biogenetic pathway of artemisinin (1). According to the suggested biosynthetic pathway the cis-isomer of farneysl pyrophosphate (FPP) (60) (scheme-10) cyclises to (61) which then forms the cadinane skeleton (65) from which artemisinic acid (49) is formed via intermediate (66).

Biological Activity :

The literature survey and review of biological activity of artemisinin (1) its analogues and derivatives will be dealt in detail in Chapter 2 Part A.

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CHAPTER 1

PART B

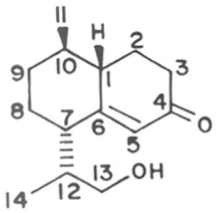
SYNTHESIS OF 7(S)-(BENZYLOXYMETHYLETHYL) -10(R)-METHYL-1(S)-4-OXOBICYCLO[4.4.0.]DEC-5ENE AND ATEMISIOL.

Introduction :

Salunkhe[1,2] reported the synthesis of conjugated keto alcohol (1) from l-menthol (2) using scheme-1. Zhou et al[3] had reported compound (13) as a key intermediate in the total synthesis of artemisinin (14). Salunkhe[1] reported unsuccessful attempts to convert keto alcohol (1) to benzyl derivative (13) by refluxing the keto alcohol (1) with potassium carbonate and benzyl chloride in acetone, and also by treatment with sodium hydride followed by benzyl bromide in dry dimethly formamide. Thus to synthesise the benzyl derivative (13) preparation of keto alcohol (1) using scheme-1 was undertaken.

Present work :

l-Menthol (2) was oxidised to l-menthone (3) in quantitative yields. The Mannich base (4) was obtained from l-menthone (3) in quantitative yields, as against the yields of 46% reported by Belavadi[4], 48% reported by Rangaishenvi[5] and 58% reported by Salunkhe[1], by employing a modified procedure described in the experimental section. Quaternary salt (5) was obtained in 80% yield from Mannich base (4). It is pertinent to mention that the diethyl ether used as solvent for the quaternisation reaction should be absolutely dry (over sodium), otherwise moisture from the solvent not only makes the work up difficult but also decreases the yields drastically. (30%). The quaternary salt (5) was subjected to Robinson annuelation reaction by overnight



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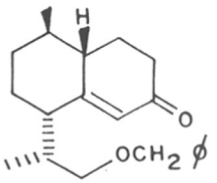
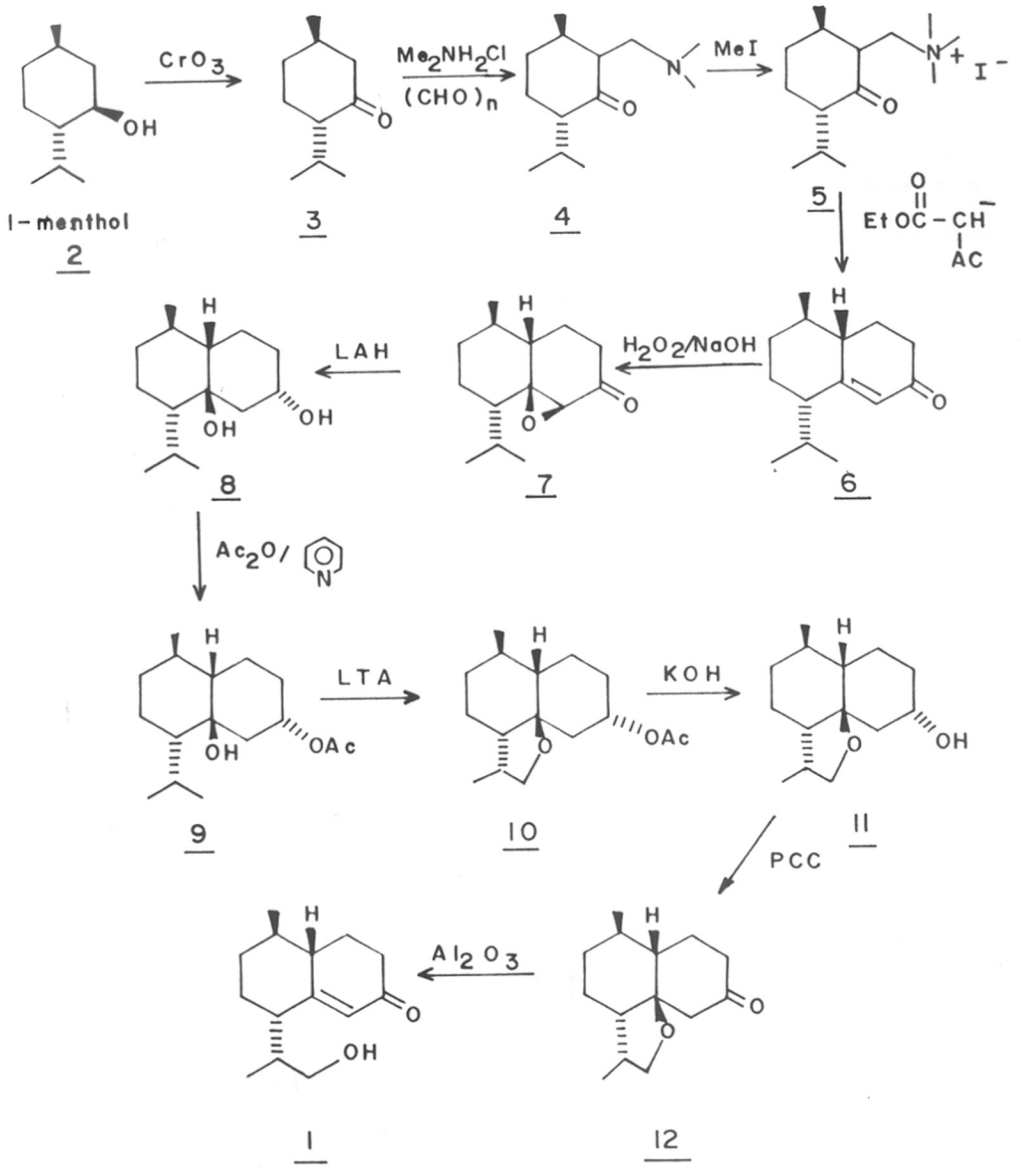


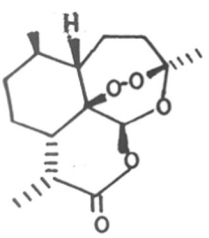
13

SCHEME – I


CrO3
Me2NH2Cl
(CHO)n
MeI
I⁻
OH
O
N
N+
H
1-menthol
2
3
4
5
Et OC – CH
AC
LAH
H2O2/NaOH
OH
OH
8
7
6
Ac2O/
LTA
OAc
OAc
9
10
KOH
OH
11
PCC
Al2O3
OH
1
12

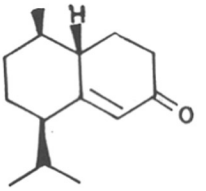
stirring at room temperature with ethylacetoacetate anion, (obtained by treatment of ethylacetoacetate with sodium ethoxide) followed by refluxing for 6 hours, to obtain solid ketone (6) in a meagre 35% yield, as against the 43% reported by Salunkhe[1] and 53% claimed by Rangaishenvi[5]. GC studies showed that the other compound formed in the Robinson annuelation reaction was α,ß-unsaturated ketone (liquid ketone) (15)[1,4,5]. Rangaishenvi[5] reported the isomerisation of solid ketone (6) to the thermodynamically more stable liquid ketone (15) by Lewis acid catalyst (BF_3Et_2O), base catalyst (2% NaOMe) and in polar solvents like chloroform. Thus it was clear that solid ketone (6) though formed in the reaction, was converted to liquid ketone (15) due to the strong basic pH of the reaction mixture. To standardise the reaction condition the reaction mixture aliquots were removed, worked up and GC recorded every hour. The percentages found, of solid ketone (6) formed, were as follows. 0hr-12%; 1hr-44%; 2hrs-47%; 3hrs-48%; 4hrs-49%; 5hrs-52% and 6hrs-48%. Thus as against the reported reflux time of 6 hours, 5 hours reflux time was found to be better. Repetition of the reaction with lesser reflux time also failed to obtain better yields. It was found that solid ketone (6) remained unaffected in benzene for 21 days and it was known that solid ketone (6) isomerises to liquid ketone (15) in polar solvents. With this knowledge, the Robinson annuelation reaction was tried in benzene and the reaction was monitored periodically by GC. The percentages found, of solid ketone (6) formed, were 0hr-12%; 1hr-14%; 2.5hrs-47%; 3.5hrs-49%; 4.5hrs-52%; and 6hrs-42%. Thus a

better yield than 53% in the reaction mixture and 35% in hand could not be obtained. As was evident from the studies described above solid ketone (6) was formed in the reaction but was isomerising to liquid ketone (15) during the workup time, and efforts to reduce workup time, maintaining neutral pH after completion of reaction (5 hour reflux) gave no improvement in the yields of solid ketone (6). Bhattacharyya[6] reported the formation of an intermediate ester (which was neither isolated nor characterised) on condensation of ethylacetoacetate anion with Mannich base methiodide (16), in the synthesis of cadalene. Belavadi[4], Rangaishenvi[5] and Salunkhe[1] reported that such intermediate ester could not be isolated from the Robinson annuelation reaction. When the quaternary salt (5) was treated with the ethylacetoacetate anion in the absolute alcohol and stirred at room temperature for 9 hours a thick gel was formed, which on usual work up yielded an orange coloured oil. Column chromatography of the oil gave a mixture of ester (17) and (18). The individual compounds could be not separated and were identified by the IR, NMR and C^{13}-NMR spectra of the mixture. IR spectrum showed bands at 1705 C=O stretch, 1665 C=C stretch and 1115 cm^{-1} C-O stretch. NMR spectrum displayed signals at δ 7.1 (s, 1H, C=C$\underline{H}$CO), 3.3-3.8 (m, 3H, $CH_3C\underline{H}_2OCO$ and C=CHCOC$\underline{H}$CO), 2.25 (s, 2H, CHOHC$\underline{H}_2$COCHCO) and 0.75-1.0 (d, 9H, J=7Hz, isopropyl methyls and methyl). C^{13} NMR spectrum assignment of characteristic carbon atoms are as shown on the formulae (17A), (17B), (18A) and (18B). Obtaining solid ketone (6) from the mixture of esters (17) and (18) by use of various mild bases,



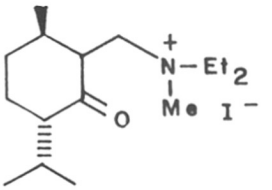
ARTEMISININ

14



LIQUID KETONE

15



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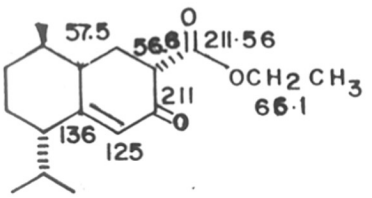
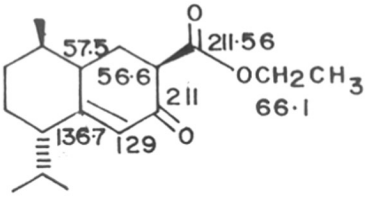
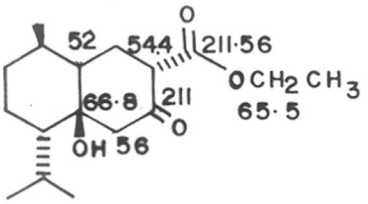


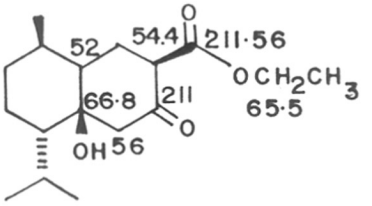
17 A



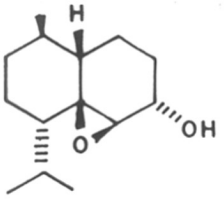
17 B



18 A



18 B



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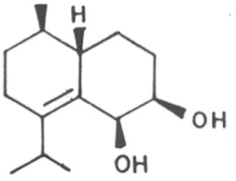

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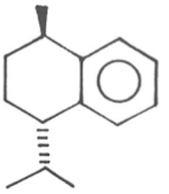


21

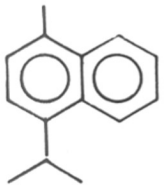
desmethyl calamenene

different reaction conditions and different solvents gave no better yields than 40%.

Solid ketone (6) was converted to epoxide (7) in quantitative yields, which on reduction with lithium aluminium hydride afforded diol (8), in quantitative yields by modified procedure as described in the experimental section. Salunkhe[1,2] had reported 66% yield for the same. During the course of the work, the lithium aluminium hydride reduction reaction was repeated several times to usually yield the diol (8), except in one experiment when enigmatically epoxide alcohol (19) and probably alkene diol (20) were formed alongwith the diol (8). The epoxide alcohol (19) was identified by its IR, NMR and mass spectra. IR spectrum showed bands at 3420, O-H stretch, 1060 cm^{-1} C-O stretch and absense of bands due to C=O stretch, NMR spectrum displayed signals at δ 4.0 (t, 1H, J=9Hz, $CH_2C\underline{H}(OH)CHOC$), 3.05 (s, 1H, $CH_2CH(OH)C\underline{H}OC$), 0.86 (d, 6H, J=7Hz isopropyl methyl and methyl), 0.76 (d, 3H, J=7Hz, isopropyl methyl) and 1.0-2.0 (13H, other methylene and methine protons). Mass spectrum showed peaks at m/e 224 (M^+), 209 (M^+-CH_3), 206(M^+-H_2O), 167 ($M^+-CH_3-CH_3CHCH_2$), 154 ($M^+-H_2O-C_4H_4$) and 139 ($M^+-H_2O-C_4H_4-CH_3$) as base peak. (see scheme-9).

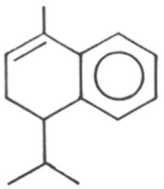
The alkene diol (20) was identified by its NMR, IR and mass spectra. IR spectrum showed bands at 3360 O-H stretch, 3340 O-H stretch, 1615 C=C stretch, 1015 C-O stretch and 1390, 1370 cm^{-1} geminal dimethyl stretch. NMR spectrum displayed signals at δ 4.68 (d, 1H, J=2Hz, $CH_2CH_{ax}(OH)C\underline{H}_{eq}(OH)C$), 3.84 (m, 1H, $CH_2C\underline{H}_{ax}(OH)CH_{eq}(OH)C$), 2.9 (m(7lines), 1H, J=7Hz, $CH_3C\underline{H}CH_3$), 1.0

(d, 6H, J=7Hz, isopropyl methyl and methyl), 0.9 (d, 3H, J=7Hz, isopropyl methyl) and 1.1-2.3 (12H, rest of the methylene and methine protons). Mass spectrum showed peaks at m/e 224 (M^+),206 (M^+-H_2O), 188 (M^+-2H_2O), 181 ($M^+-C_3H_7$), 163 ($M^+-C_3H_7-H_2O$) and 145 ($M^+-C_3H_7-2H_2O$). All attempts to repeat the reaction to obtain the above mentioned enigmatic products drew a blank, with the formation of the usual diol (8). The diol (8) was converted to alcohol acetate (9) in quantitative yields. Photochemical reaction on acetate (9) with lead tetra acetate and iodine in refluxing cyclohexane gave the cyclic ether acetate (10). While purifying the cyclic ether acetate (10) by column chromatography a very non-polar compound was eluted in the first fraction by pet-ether. The fraction was identified as a mixture of desmethyl calamemene (21), desmethyl cadalene (22), desmethyl α-calacorene (23) and desmethyl Γ-calacorene (24), by the NMR, IR, mass spectra and GC of the mixture. IR showed bands at 3030 aromatic C-H stretch, 1620 aromatic C=C stretch, and 1385, 1400 cm^{-1} geminal dimethyl stretch. NMR showed signals at δ 6.6-8.2 (m, aromatic protons), 3.1 (m, $CH_3\underline{C}HCH_3$), 2.23 (s, aromatic methyl of (22), 2.16 (s, olefinic methyl of (23)), 1.0-1.3 (d, J=7Hz, isopropyl methyls and methyl of (21), (23) and (24)). Mass spectrum showed peaks at m/e 188 (M^+), 173 (M^+-CH_3) and 145 ($M^+-C_3H_7$) for (21); 184 (M^+), 169 (M^+-CH_3), 141 ($M^+-C_3H_7$) and 126 ($M^+-CH_3-C_3H_7$) for (22); 186 (M^+), 171 (M^+-CH_3), 143 ($M^+-C_3H_7$) and 128 ($M^+-CH_3-C_3H_7$) for (23) and (24). Similar side reactions have been reported by Ellis et al[7] and Cavill et al[8]. Amorosa et al[9] reported that compound (25), when subjected to photochemical



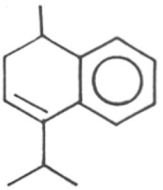
22

desmethyl cadalene



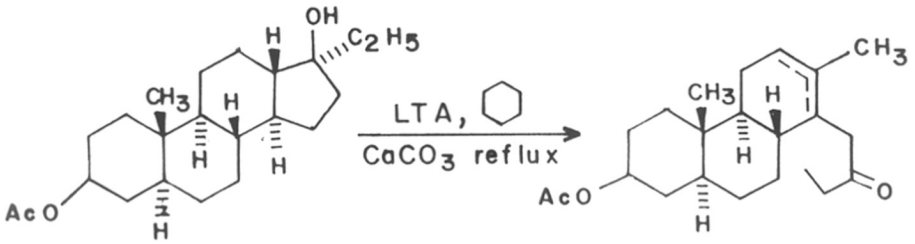
23

desmethyl α-calacorene

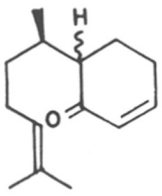


24

desmethyl γ-calacorene



25 26



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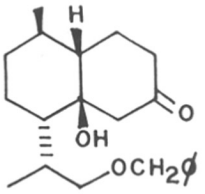

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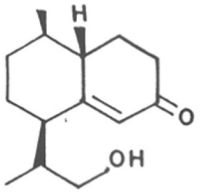


29

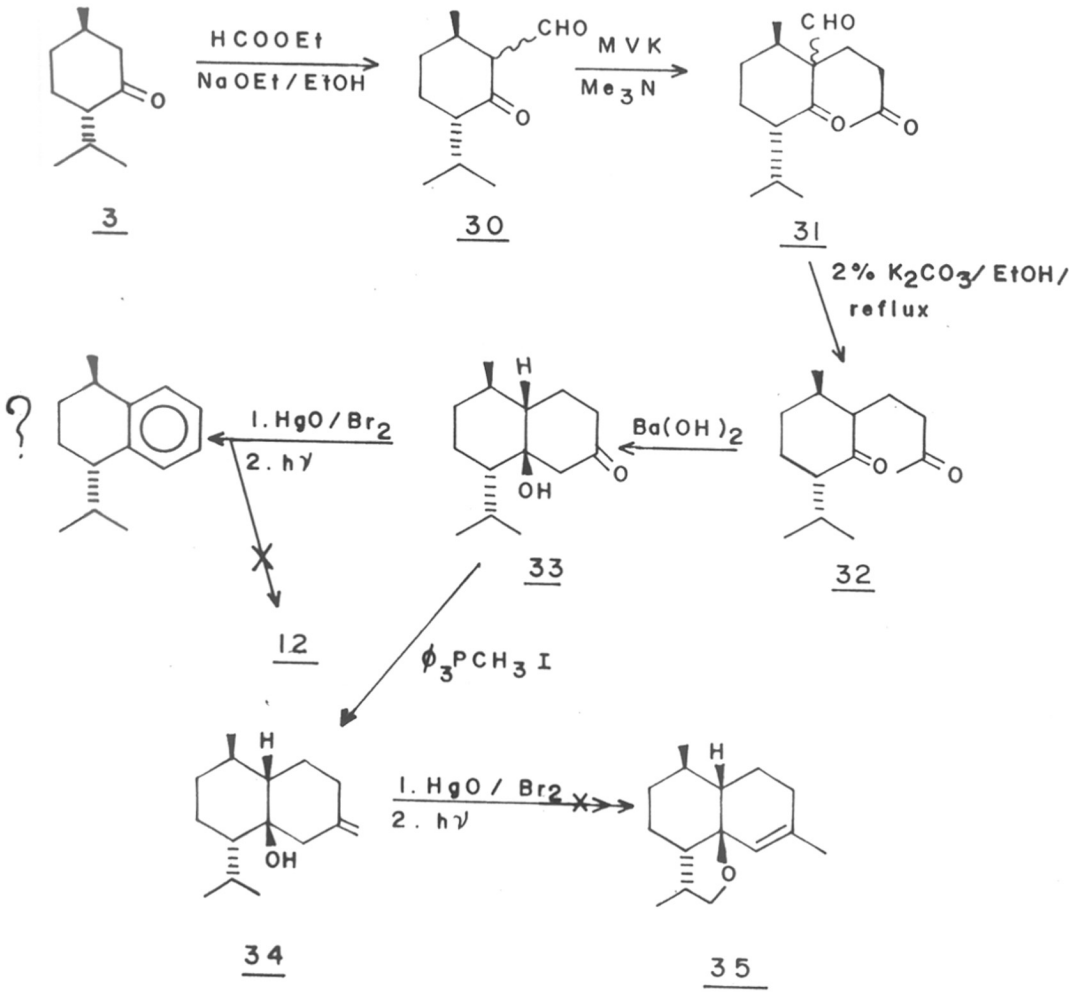
reaction with lead tetraacetate and calcium carbonate in refluxing cyclohexane gave compound (26) formed by the cleavage of the C-C bond α to the tertiary alcohol, a dehydrogenation and oxidation of the alcohol to ketone. A similar reaction was observed leading to the formation of the compound (27), which was eluted from the cyclic ether acetate (10) chromatography column in 10% ethylacetate : 90% benzene fraction. Compound (27) was characterised by its IR, NMR and mass spectra. IR showed bands at 1685 C=O stretch and 1630 cm^{-1} C=C stretch. NMR displayed signals at δ 6.86 (dd, 1H, J_{cis}=10Hz, J_{vic}=5Hz, $CH_2C\underline{H}$=CHC=O), 5.92 (dd, 1H, J_{cis}=10Hz, J_{ally}=1Hz CH_2CH=C$\underline{H}$C=O), 5.06 (t, 1H, J=8Hz, $CH_2C\underline{H}$=CMe_2), 1.6 (s, 3H, CH_2CH=C$C\underline{H}_3$Me), 1.5 (s, 3H, CH_2CH=CMe$C\underline{H}_3$), 0.88 (d, 3H, J=7Hz, $CH_{ax}CHC\underline{H}_3CH_2$), 0.78 (d, 3H, J=7Hz, $CH_{eq}CHC\underline{H}_3CH_2$) and 1.0-2.6 (10H, other methylene and methine protons). Mass spectrum showed peaks at m/e 206 (M^+), 123 ($M^+-C_6H_{11}$), 109 ($M^+-C_6H_8O$), 96 ($M^+-C_8H_{14}$) and 95 ($M^+-C_8H_{15}$). (see scheme-9).

The hydroxy cyclic ether (11) was obtained by treating the cyclic ether acetate (10) by potasium hydroxide in alcohol in almost quantitative yields. Pyridinium chlorochromate oxidation of the hydroxy cyclic ether (11) gave keto cyclic ether (12). On passing the keto cyclic ether (12) through an acidic alumina column and using pet-ether, benzene and ethylacetate as eluent, yielded the keto alcohol (1), (which was eluted in 40% ethyl acetate : 60% benzene) in 55% yield, as against the 35% yield reported by Salunkhe[1]. The unreacted keto ether (12) eluted in the benzene and 10% ethylacetate, 90% benzene fractions. The

keto alcohol (1) was identified by its IR, NMR and mass spectra which agreed in totality with those reported by Salunkhe[1]. Salunkhe[1] proposed the formation of keto alcohol (1) from keto cyclic ether (12) by an acid catalysed mechanism involving the protonation of the ether oxygen of (12). To improve the yield of keto alcohol (1) from keto cyclic ether (12), a mild acid catalysed reaction was attempted. Xu et al[3] had reported use of oxalic acid in refluxing ethanol to convert hydroxy ketone (28) to conjugated ketone (13). Thus refluxing keto ether (12) with oxalic acid in ethanol gave a conjugated ketone, which was identified as (29) by its NMR spectrum, whereas the IR, mass spectra and GC were identical to those of keto alcohol (1). NMR spectrum displayed the isopropyl methyl and methyl signals at δ 0.8 and 1.0 as against those in the keto alcohol (1) at δ 0.88 and 1.04 respectively. A similar upfield shift was observed for the isopropyl methyls in the NMR spectrum of liquid ketone (15) as compared to those in solid ketone (6). The isomerisation of the isopropyl moiety in acidic or basic condition due to the α,β-unsaturated ketone is well established[1,5] and is attributed to the driving force of release of steric strain between the olefinic proton and the hydroxyl group. Lewis acids like boron trifluoride etherate are known to catalyse the ether opening reactions. The keto ether (12) when treated with borontrifluoride etherate in various solvents and at various temperatures yielded consistently the isomerised iso-ketoalcohol (29).

The overall yield of the synthesis of keto ether (12) from

SCHEME – 2

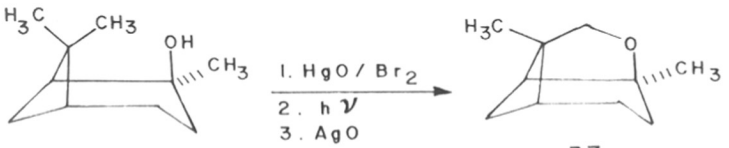

HCOOEt
NaOEt / EtOH
CHO
MVK
Me3N
CHO
3
30
31
2% K2CO3 / EtOH / reflux
?
1. HgO / Br2
2. hν
H
Ba(OH)2
OH
33
32
12
ϕ3PCH3 I
H
1. HgO / Br2
2. hν
OH
34
35

l-menthol (2) was a meagre 15% and involved 10 steps. To obtain the keto ether (12) in good yields and less number of steps, scheme-2 was devised. Ladwa[10] reported the synthesis of diketone (32) as depicted in scheme-2. The procedure reported were used and the diketone (32) obtained in 55% yield. Xu et al[3] reported cyclisation of a compound similar to diketone (32) using barium hydroxide in ethanol. Thus on treating the diketone (32) with barium hydroxide in ethanol, the keto alcohol (33) was obtained, which was identified by its IR, NMR and mass spectra. All the spectra were in complete agreement with those reported by Salunkhe[1], who had prepared it by pyridinium chlorochromate oxidation of the diol (8). Welankiwar[11] reported Barton reaction on a tertiary alcohol (36) by treatment with mercuric oxide, bromine, followed by irradiation with UV light and finally treatment with silver oxide to obtain cyclic ether (37) in 96% yield. The keto alcohol (33) was subjected to an identical photochemical reaction to yield some unidentified aromatic compounds but no keto ether (12). The probable reason for the failure of this approach was that, due to enolisation of the ketone the α-position of the ketone probably got brominated and then underwent dehydrobromination to yield the aromatic compound. Xu et al[3] reported compound (38) in the synthesis of artemisinin (14). Thus ether alkene (35) was attempted to be synthesised from keto alcohol (33) via the Wittig product (34), which could easily be converted to (38). The keto alcohol (33) was converted to the Wittig intermediate (34), but the following photochemical reaction did not yield the desired ether alkene (35). The

products of the photochemical reaction could not be characterised. Thus this scheme was abandoned.

The determination of stereochemical disposition of C_{14}-methyl (see structure (1)) was not reported earlier and hence the following work was undertaken to ascertain tht same. The 2,4-dinitrophenyl hydrazone derivative of the keto ether (12) was prepared, but a good crystal for X-ray crystallographic study could not be obtained. Attempts to obtain the 3,5-dinitrobenzoate derivative of the hydroxy cyclic ether (11) did not succeed. Zeng et al[12] reported the keto lactone (39). The iso- keto alcohol (29) was subjected to Jones oxidation to obtain the keto acid (40), but efforts to cyclise the acid to obtain the lactone (39) did not succeed. The reason was evident from the fact that the keto alcohol (1) cyclised readily (15% cyclisation in 0.5 hours) in polar solvents like chloroform to form the keto ether (12), but the iso keto alcohol (29) under identical conditions resisted cyclisation.

Meanwhile for the synthesis of some potential antimalarial compounds the cyclic ether acetate (10) was converted to lactone (41) (see chapter 2 for details) which was obtained as a crystalline solid. X-ray crystallographic studies of the lactone (41)[13] revealed that the stereochemical disposition of the methyl group is ß, as shown in structure (41). Attempts to epimerise the methyl group[14] by use of sodium methoxide in methanol, yielded the hydroxy lactone (42), but no change in the stereochemical disposition of the methyl group. Anilkumar[14] reported the oxidation of the cyclic ether moiety as in ether



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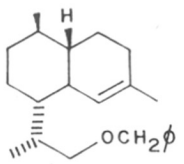

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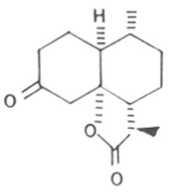

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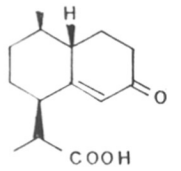

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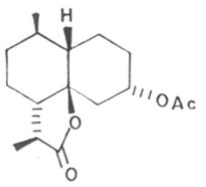

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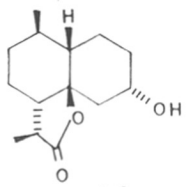

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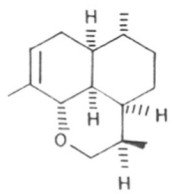

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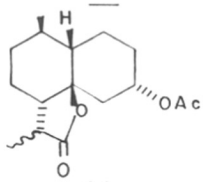

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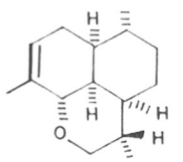

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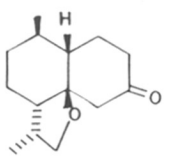
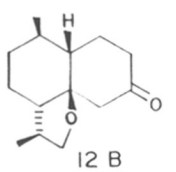
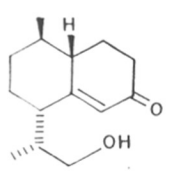


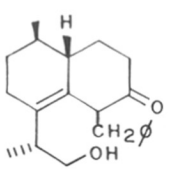
12 A



12 B



1 A



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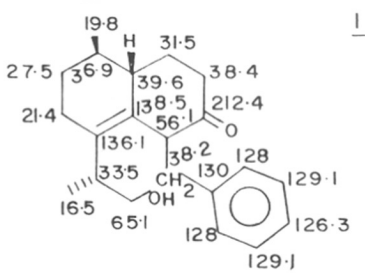


46 A

(43) to the corresponding δ-lactone by use of ruthenium trichloride and sodium meta periodate without affecting the stereochemistry of the methyl group, the same procedure was used to convert cyclic ether acetate (10) to the lactone (44), which was identified by its IR, NMR, mass spectra and GC. The IR, NMR mass spectra and GC retention times were identical to those of the lactone obtained by chromium trioxide oxidation, except the optical rotations. The chromium trioxide oxidation lactone showed $(\alpha_D)^{26} = -8.0°$ (c, 0.525), whereas the ruthenium tetraoxide oxidation lactone showed $(\alpha_D)^{26} = +3.8°$ (c, 0.266). However this could not be considered as conclusive proof for claiming the stereochemical disposition of the C_{14}-methyl as α.

In attempts to recycle the unreacted keto ether (12) eluted from the acidic alumina column, it was observed that the keto ether (12) showed two very close moving spots on TLC. Careful TLC study of the keto ether (12) obtained from hydroxy cyclic ether (11) also showed similar close moving spots. Flash chromatography using silica-gel gave two compounds with similar IR and mass spectra, but different NMR spectrum and very close but different retention time on GC. Anilkumar[14] reported that the methyls in ether (43) appeared at δ 0.76 and 0.68 and in ether (45) at δ 0.76 and 1.16. This clearly shows that when the methyls are trans to each other, they appear closer (0.08δ apart) and when they are cis they appear far apart (0.4δ apart). The keto ether (12) eluting first showed methyl signals at δ 1.06 and 0.96 (0.1δ apart) and the keto ether (12) eluting second showed methyl signals at δ 1.04 and 0.99 (0.05δ apart). Thus as the

methyl groups in the keto ether eluting first appear farther than the methyl groups in the keto ether eluting second. The first eluting keto ether was assigned structure (12A) and the second eluting keto ether structure (12B). The complete NMR signal assignments of the two isomers are as follows. NMR spectra of (12A) showed signals at δ3.98 (dd, 1H, J_{gem}=9Hz, J_{vic}=9Hz, $OC\underline{H}HCHCH_3$), 3.28 (dd, 1H, J_{gem}=9Hz, J_{vic}=9Hz, $O\text{-}CH\underline{H}CHCH_3$), 0.962 (d, 3H, J=7Hz, $OCH_2CHC\underline{H}_3$), 1.06(d, 3H, J=7Hz, $CHCHC\underline{H}_3$ CH_2) and 1.1-2.8 (14H, rest of the methylene and methine protons). NMR spectrum of (12B) showed signals at δ 4.07 (dd, 1H, J_{gem}= 9Hz, J_{vic}=8Hz, $OC\underline{H}HCHCH_3$), 3.31 (dd, 1H, J_{gem}=9Hz, J_{vic}=8Hz, $OCH\underline{H}CHCH_3$), 0.99 (d, 3H, J=7Hz, $OCH_2CHC\underline{H}_3$), 1.04 (d, 3H, J=7Hz, $CHCHC\underline{H}_3CH_2$) and 1.1-2.8 (14H, rest of the methylene and methine protons).

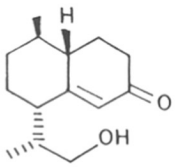
In all the further experiments only the keto ether (12A) or keto alcohol (1A) obtained from the keto ether (12A) was used. The IR, NMR and mass spectral values of the keto alcohol (1A) are as follows. IR showed bands at 3440 O-H stretch, 1675 C=O stretch, 1615 C=C stretch and 1040 cm^{-1} C-O stretch. NMR displayed signals at δ 5.88 (s, 1H, $C=C\underline{H}COCH_2$), 3.53 (d, 2H, J=7Hz, $CH_3CHC\underline{H}_2OH$), 1.04(d, 3H, J=7Hz, $CHCHC\underline{H}_3CH_2$), 0.88 (d, 3H, J=7Hz, $C\underline{H}_3CHCH_2OH$) and 1.1-2.5 (13H, rest of methylene and methine protons). Mass spectrum showed peaks at m/e 222 (M^+), 207 (M^+-CH_3) and 165 (M^+-CH_3CHCHO) as base peak. (see scheme 9).

Salunkhe[1] reported unsuccessful attempts (reaction condition 1 and 2, Table - I) for the conversion of keto alcohol (1) to its benzyl derivative (13). In both the cases the keto alcohol (1)

recyclised to yield the keto ether (12). It was observed that the keto alcohol (1A) did not recyclise in benzene solvent, hence benzene was decided to be used as solvent for all reactions involving the keto alcohol (1A). Thus keto alcohol (1A) was refluxed with potassium carbonate and benzyl iodide in benzene (reaction condition 3, Table-I) to obtain the keto ether (12A) and keto alcohol (1A), but no benzyl derivative (13). Potassium carbonate probably is not strong enough a base for the reaction, hence the same reaction was tried with potassium hydroxide (reaction condition 4, Table-I) to yield again keto ether (12A), keto alcohol (1A) and iso keto alcohol (29).

It was evident that the base employed (K_2CO_3 or KOH, could not abstact the primary alcohol proton and hence stronger base like sodium hydride (1 mole) was used and the reaction repeated (reaction condition 5, Table-I) when incomplete consumption of keto alcohol (1A) was observed on TLC, and after addition of benzyl chloride and refluxing the recyclised keto ether (12A) and unreacted benzyl chloride was obtained. The reaction was repeated with excess of sodium hydride to ensure complete consumption of keto alcohol (1A) and substituting benzyl chloride by the more reactive benzyl bromide (reaction condition 6, Table-I). The reaction yielded some unidentifiable products but no (13). The plethora of unidentifiable products were formed probably due to the vigorous reflux conditions and excess base. Hence the reaction was repeated with milder reaction conditions (reaction conditions 7, Table-I) to again obtain the recyclised product (12A) but no (13). As the anion was not condensing with

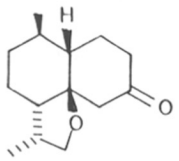
TABLE – 1



Reaction Condition → PRODUCTS

S.No	REACTION CONDITIONS	PRODUCTS
1	K_2CO_3/$PhCH_2Cl$/Acetone/reflux	no 13
2	NaH/$PhCH_2Br$/dry DMF	no 13
3	K_2CO_3/Benzene/$PhCH_2I$/reflux 2hrs	12A, 1A, no 13
4	KOH/Benzene/$PhCH_2I$/reflux 2 hrs	29, 1A, no 13
5.	a) NaH(1mole)/Benzene/R.T. 2.5 hrs	
	b) $PhCH_2Cl$/reflux 3 hrs	12A, BzCl,no 13
6	a) NaH(excess)/Benzene/R.T. 2.5hrs	Unidentified
	b) $PhCH_2I$/reflux 3 hrs	Products, no 13
7	a) NaH/Benzene/RT 2.5 hrs	
	b) $PhCH_2I$/10°C/4hrs	12A, 29, no 13
8	a) NaH(1mole)/Benzene/RT 2.5 hrs	
	b) $PhCH_2I$/RT 9hrs/reflux 3 hrs	46, 12A, no 13
9	K_2CO_3/Benzene/$PhCH_2I$/TBAI/H_2O/reflux 3 hrs	46, no 13

TABLE – 2



Reaction Condition → PRODUCTS

S.No	REACTION CONDITIONS	PRODUCTS
1	$PhCH_2Br$/K_2CO_3/Acetone/TBAI/H_2O/reflux 8hrs	12A, 29, no 13
2	$PhCH_2Br$/KOH/Acetone/TBAI/reflux 3 hrs	46, no 13
3	a) NaH/dry DMF/-10° to -15°C/ 45 minutes	
4	b) $PhCH_2Br$/dry DMF/-10° to -15°C/ 3 hrs	13

the benzyl iodide in 2.5 hours period, the reaction was repeated with the anion being stirred with benzyl iodide for 9 hours and when some benzyl iodide and sodium salt of keto alcohol (1A) (R_f value 0.01) (TLC solvent C) were found unreacted. The reaction was then refluxed for 3 hours (reaction condition 8, Table-I). Elaborate chromatography yielded a new compound alongwith small quantities of keto ether (12A) and iso keto alcohol (29). The new compound was identified as benzyl keto alcohol (46) by its IR, NMR and mass spectra. IR spectrum showed bands at 3420 O-H stretch, 1720 C=O stretch, 3020 aromatic C-H stretch, 1615 aromatic C=C stretch and 1045 cm^{-1} C-O stretch. NMR displayed signals at δ 7.1-7.4 (m, 5H, aromatic protons), 3.68 (t, 1H, J=7Hz, $=CC\underline{H}(CH_2Ph)C=OCH_2$), 3.12 (dd, 1H, J_{vic}=7Hz, J_{gem}=11Hz, $CH_3CHC\underline{H}HOH$), 2.97 (d, 2H, J=7Hz, $CCH(C\underline{H}_2Ph)C=OCH_2$), 2.91 (dd, 1H, J_{vic}=7Hz, J_{gem}=11Hz, $CH_3CHCH\underline{H}OH$), 1.1 (d, 3H, J=7Hz, $CHCHC\underline{H}_3CH_2$), 0.8 (d, 3H, J=7Hz, $C\underline{H}_3CHCH_2OH$) and 1.15-2.8 (12H, rest of the methylene and methine protons). Mass spectrum showed peaks a m/e 312 (M^+), 313 (M^++1), 294 (M^+-H_2O), 281 (M^+-CH_2OH), 253 ($M^+-CH_3CHCH_2OH$), 221 (M^+-CH_2Ph) as base peak and 91 ($C_7H_7^+$ or tropolium ion). The C^{13} NMR assignments are as shown on structure (46A).

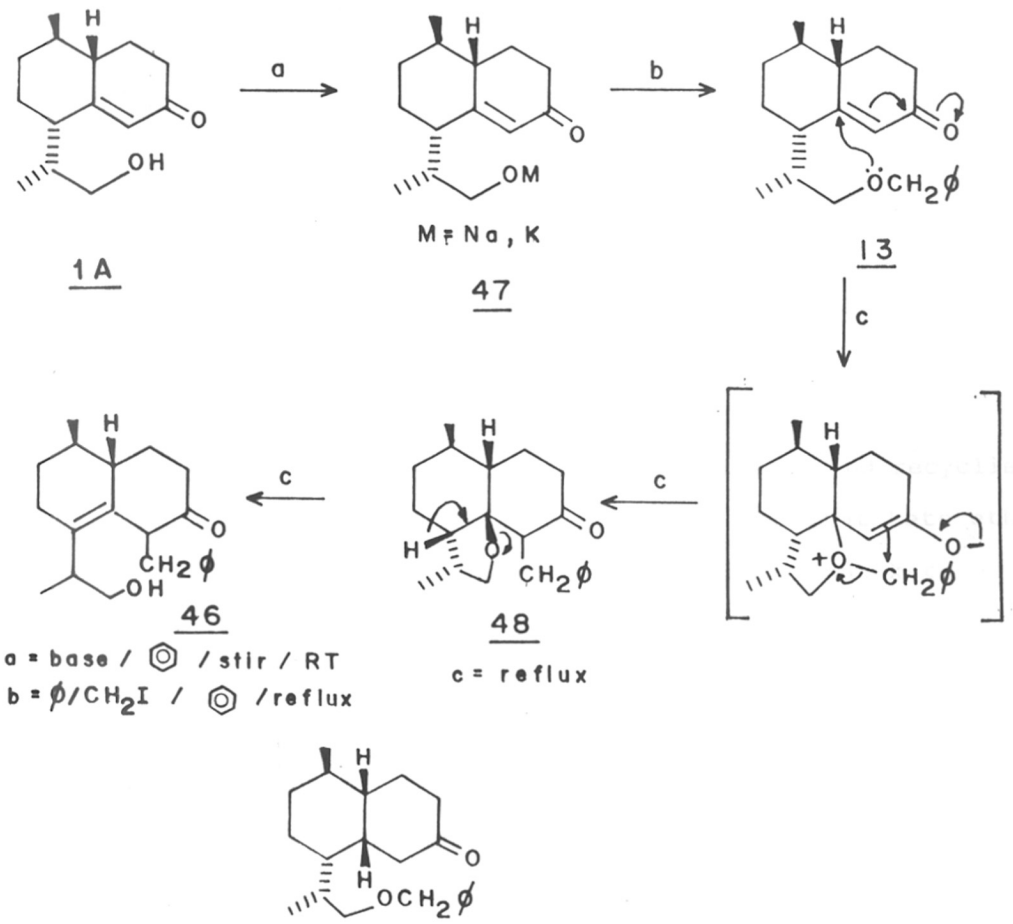
To ascertain whether the strong base sodium hydride had any specific role in the formation of the rearranged product benzyl keto alcohol (46), the reaction was done with mild base, potassium carbonate. It was learnt from previous experiments that potassium carbonate is unable to abstract the primary hydroxyl proton, in benzene, being insoluble in benzene, so a few

drops of water were added. Thus there were two heterogeneous phases viz. benzene and water. Phase transfer catalysts are known to be widely used in heterogeneous phase reactions[15]. Thus TBAI (tetrabutylammoniumiodide) a well known phase transfer catalyst was added and the reaction refluxed (reaction condition 9, Table-I). The benzyl keto alcohol (46) was obtained as the sole product with no trace of the desired benzyl derivative (13).

Meanwhile as keto alcohol (1A) failed to give the desired benzyl derivative (13) and keto alcohol (1A) either recyclised to keto ether (12A) or isomerised to the iso-keto alcohol (29), the precursor of keto alcohol (1A), the keto ether (12A) was tried for obtaining the benzyl derivative (13). The keto ether (12A) was refluxed with potassium carbonate, benzyl bromide, tetrabutylammoniumiodide (TBAI), a few drops of water, in acetone for 8 hours to obtain the starting keto ether (12A) and iso keto alcohol (29) (see reaction condition 1, Table II) but no (13). The same reaction was attempted with a stronger base potassium hydroxide (reaction condition 2, Table II) to yield the benzyl keto alcohol (46) but no (13).

Based on these observations a mechanism for the formation of benzyl keto alcohol (46) was proposed as shown in scheme-3. The keto alcohol (1A) forms the alkali metal salt (47) with the base ($NaH/KOH/K_2CO_3$) which condenses with benzyl iodide, to give the desired benzyl derivative (13), under reflux conditions. The C_6 carbon of (13) being electron deficient readily accepts the lone pair from electron rich ether oxygen to form benzyl keto ether (48). The strain in the rings and the strain due to steric

SCHEME – 3



1A

47

13

48

46

ETHER KETONE 49

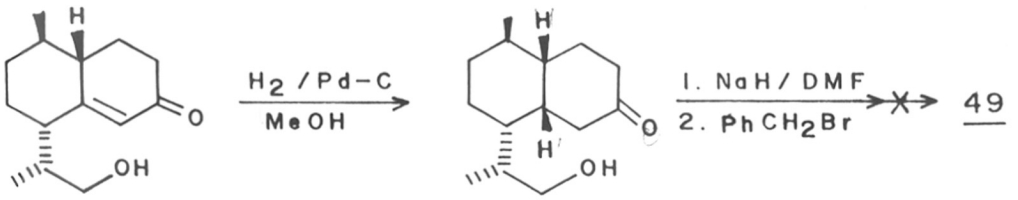
crowding is relieved by rearrangement of the benzyl keto ether (48) to benzyl keto alcohol (46).

It was evident from the above experiments that the benzyl derivative (13) cannot be obtained under refluxing solvent temperatures (65°-80°C) as it rearranges to form benzyl keto alcohol (46). It was also observed that the alkali metal salt of the keto alcohol (47) did not condense with benzyl halides at temperatures less than the reflux temperatures in non polar solvents like benzene. Another important observation was that keto alcohol (1A) was not stable in polar solvents and recyclised to the keto ether (12A) at room temperature and that keto ether (12A) was found to be stable in polar solvents. Thus keto ether (12A) was treated with sodium hydride in a highly polar solvent dimethyl formamide (purified by reported procedures[16]) at -10°C to -15°C. Benzyl bromide (purified by reported procedures[17]) was added dropwise to this cooled solution under stirring (reaction condition 3, Table II) and stirred for further 3 hours. The reaction was warmed to room temperature and worked up as usual to yield an oil, from which after elaborate chromatography the much desired benzyl derivative (13) was obtained. The benzyl derivative (13) was identified by its IR, NMR and mass spectra as follows. IR showed bands at 3030 aromatic C-H stretch, 1675 C=O stretch and 1620 cm^{-1} C=C stretch. NMR displayed signals at δ 7.25 (bs, 5H, aromatic protons), 5.8 (s, 1H, $C=C\underline{H}COCH_2$), 4.4 (s, 2H, $OC\underline{H}_2Ph$), 3.5 (d, 2H, J=7Hz, $CH_3CHC\underline{H}_2OCH_2Ph$) and 0.8-1.1 (d, 6H, J=8Hz, $C\underline{H}_3CHCH_2OCH_2Ph$ and $CHCHC\underline{H}_3CH_2$). Mass spectrum showed molecular ion peak at m/e 312.

Xu et al[3] reported ether ketone (49) as a crucial intermediate in the total synthesis of artemisinin (14). As consistent failures were faced for the conversion of the keto alcohol (1A) to the benzyl derivative (13), simultaneous efforts were directed towards synthesis of crucial intermediate ether ketone (49) by employing scheme-4 and scheme-5. The keto alcohol (1A) was subjected to catalytic hydrogenation in methanol to yield saturated ketone (50) (see scheme-4), which was identified by its IR, NMR and mass spectra. IR showed bands at 3420 O-H stretch, 1715 C=O stretch and 1015 cm^{-1} C-O stretch. NMR displayed signals at δ3.45 (d, 2H, J=9Hz, $CH_3CHC\underline{H}_2OH$), 0.8-1.1 (d, 6H, J=7Hz, $C\underline{H}_3CHCH_2OH$ and $CHCHC\underline{H}_3CH_2$). Mass spectrum showed molecular ion peak at m/e 224. Efforts to obtain the ether ketone (49) from the saturated ketone (50) by employing various bases, solvents and benzyl halides failed for unknown reasons.

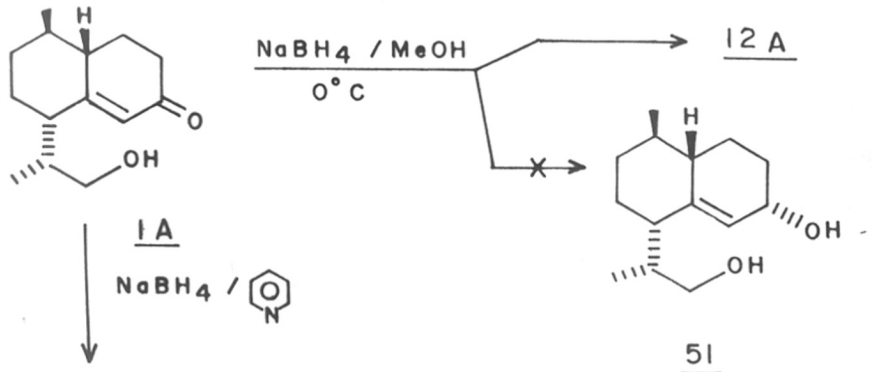
The synthesis of alkene diol (51) was attempted from keto alcohol (1A) by sodium borohydride reduction in methanol, which failed and instead the keto ether (12A) was obtained. Xu et al[3] had reduced an α,β-unsaturated ketone (which is similar to the keto alcohol (1A) to the corresponding alcohol by use of sodium borohydride in pyridine. Using an identical procedure the keto alcohol (1A) was converted to diol (52) (see scheme-5) which was characterised by its IR, NMR and mass spectra. IR showed bands at 3380 O-H stretch and 1043 cm^{-1} C-O stretch. NMR displayed signals at δ 3.3-3.7 (m, 3H, $CH_2C\underline{H}(OH)CH_2$ and $CH_3CHC\underline{H}_2OH$), 0.83 (d, 3H, J=7Hz, $C\underline{H}_3CHCH_2OH$), 0.94 (d, 3H, J=7Hz, $CHCH(C\underline{H}_3)CH_2$) and 1.0-2.3 (23H, rest of the methylene and methine protons). Mass

SCHEME – 4



1A 50

SCHEME – 5



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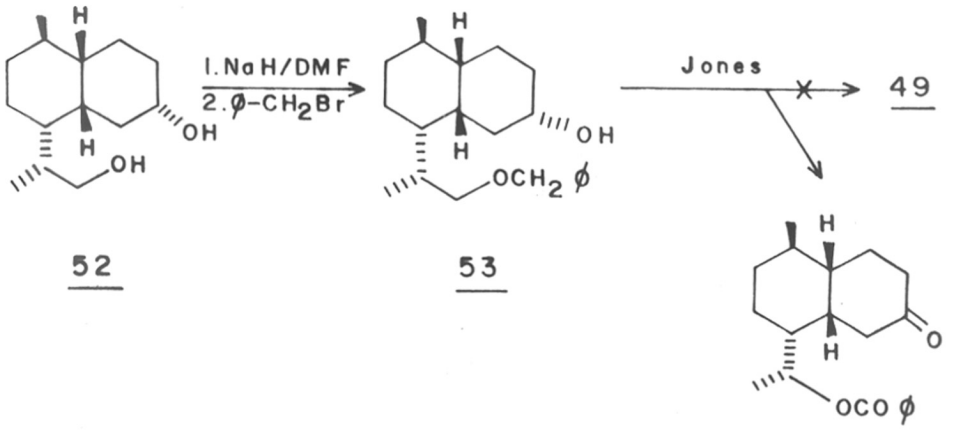
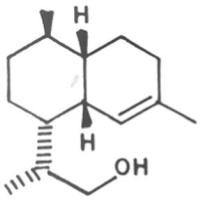


52 53 54

spectrum showed peaks at m/e 226 (M^+), 208 (M^+-H_2O), 190 (M^+-2H_2O), 177 ($M^+-H_2O-CH_2OH$) and 149 ($M^+-H_2O-CH_3CHCH_2OH$) as base peak. The diol (52) on treatment with sodium hydride followed by benzyl bromide in dimethylformamide gave the ether alcohol (53), which was characterised by IR, NMR and mass spectra IR showed bands at 3380 O-H stretch, 3040 aromatic C-H stretch, 1620 aromatic C=C stretch and 1065 cm^{-1} C-O stretch. NMR displayed signals at δ 7.3(bs, 5H, aromatic protons), 4.5(s, 2H, $CH_3CHCH_2OC\underline{H}_2Ph$), 4.0 (m, 1H, $CH_2C\underline{H}(OH)CH_2$), 3.2-3.7 (m, 2H, $CH_3CHC\underline{H}_2OCH_2Ph$), 2.0 ($D_2O$ exchangeable proton, $CH_2CH(O\underline{H})CH_2$) and 0.7-2.3 (20H, rest of the methyl, methylene and methine protons). Mass spectrum showed molecular ion peak at m/e 316. Xu et al[3] reported that the benzyl group remained intact under Jones oxidation reaction conditions. Howéver when the ether alcohol (53) was subjected to identical conditions of Jones oxidation, instead of the desired ether ketone (49), the ester ketone (54) was obtained, which was characterised by its IR, NMR and mass spectra. IR showed band at 3030 aromatic C-H stretch, 1720 C=O stretch, 1725 ester C=O stretch, 1110 C-O stretch and 1610 cm^{-1} aromatic C=C stretch. NMR displayed signals at δ 7.3(bs, 5H, aromatic protons), 3.75 (m, 1H, $CH_3CHC\underline{H}HOCOPh$), 3.35 (m, 1H, $CH_3CHC\underline{H}HOCOPh$), 0.75-1.0 (d, 6H, J=7Hz, $C\underline{H}_3CHCH_2OCOPh$ and $CHCHC\underline{H}_3CH_2$) and 1.0-2.5 (15H, rest of the methylene and methine protons). Mass spectrum showed molecular ion peak at m/e 330. Meanwhile as benzyl derivative (13) was successfully obtained any further attempts to obtain the ether ketone (49) were not made.

In 1989, Bustos et al[18] reported artemisiol (55) in the



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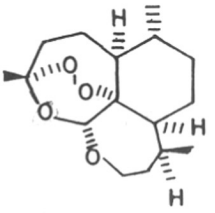
Artemisiol



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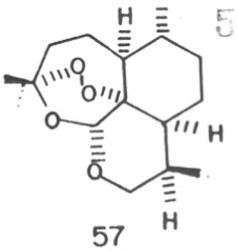
Homodeoxoartemisinin



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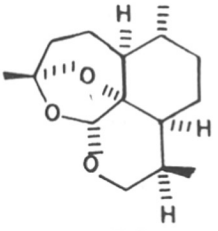
Deoxoartemisinin



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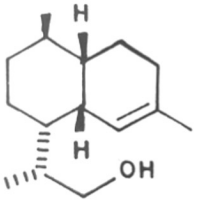
Deoxodesoxyartemisinin

RETRO SYNTHETIC SCHEME –6



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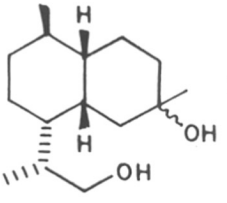

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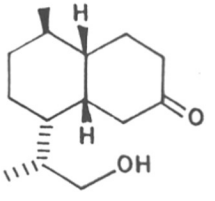

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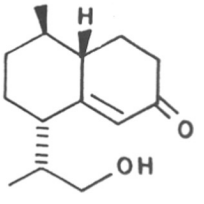


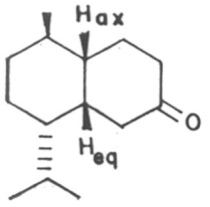
1A

synthesis of homodeoxoartemisinin (56) and Jung et al[19] reported artemisiol (55) in the synthesis of deoxoartemisinin (54) and deoxodesoxyartemisinin (58). In 1990, Jung et al[20] reported artemisiol (55) in the synthesis of deoxoartemisinin (57). In 1990, Ye et al[21] reported conversion of deoxoartemisinin (57) to artemisinin (14) by use of ruthenium trichloride and sodium meta-periodate in acetonitrite, water and carbontetrachloride mixture. Thus synthesis of artemisinin (14) from artemisiol (55) is known.

Artemisiol (55) can be synthesised from keto alcohol (1A) as per retrosynthetic scheme-6. The double bond between C_4 and C_5 in artemisiol (55) could be obtained by dehydration of the tertiary alcohol of diol (56), which in turn could be obtained from the saturated ketone (50). Saturated ketone (50) was successfully prepared as discussed earlier in scheme-4. The stereochemistry of the ring junction could not be ascertained from the IR, NMR and mass spectra of the saturated ketone (50). It is known that the ORD of cis-non steriodal decalone (59) shows a positive cotton effect, whereas the trans decalone (60) shows a negative cotton effect. The ORD curve of saturated ketone (50) showed a positive cotton effect, and thus the ring junction was proved to be cis non-steriodal as depicted in scheme-7.

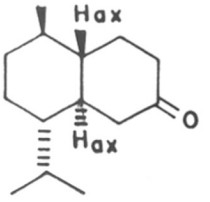
The saturated ketone (50) was treated with Grignard reagent, methyl magnesium iodide to yield the diol (56), which was identified by its IR, NMR and mass specta. IR showed band at 3350 O-H stretch, 1110 C-O stretch, and 1027 cm^{-1} C-O stretch. NMR spectrum displayed signals at δ 3.5 (d, 2H, J=7Hz, $CH_3CH\underline{H}_2OH$), 1.28 (s, 3H, $CH_2COH\underline{H}_{3(ax)}CH_2$) and 1.2 (s, 3H,

SCHEME – 7



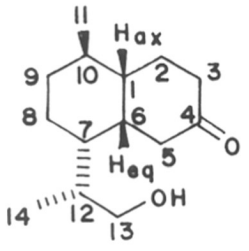
59

cis-nonsteriodal +ve cotton effect

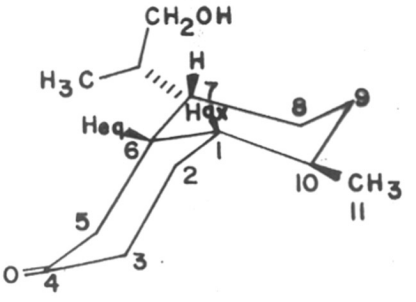


60

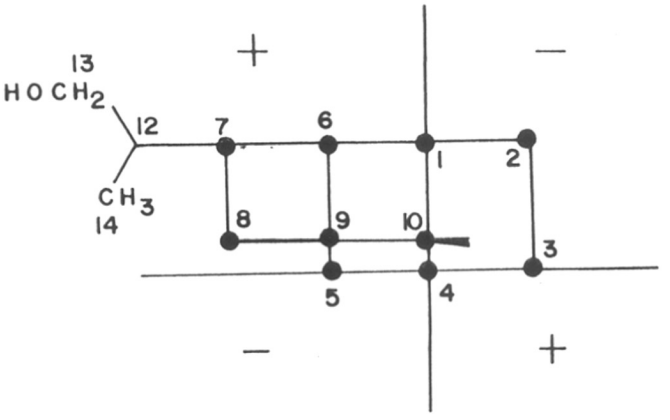
trans – ve cotton effect



50



50 A

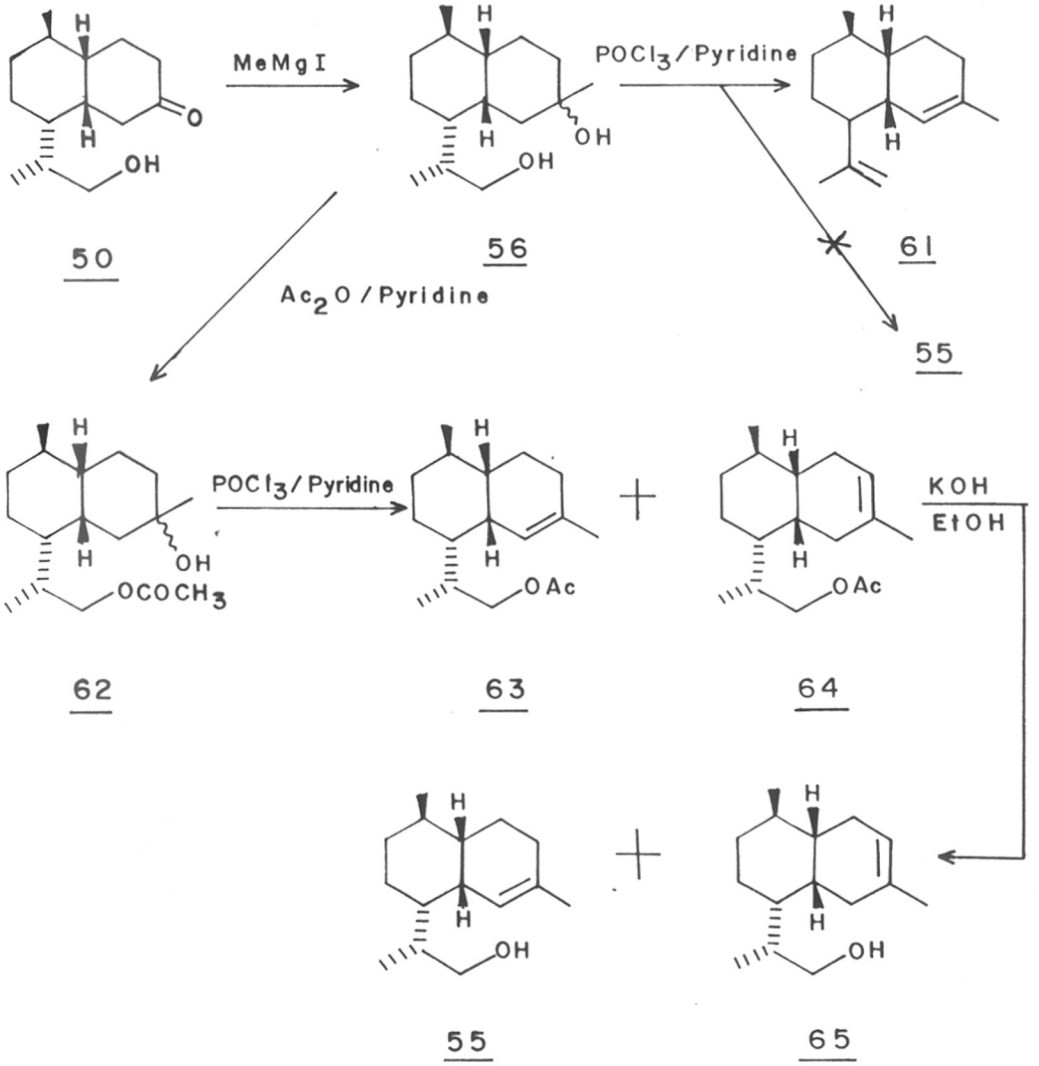


OCTANT DIAGRAM FOR CIS NONSTERIODAL DECALONE 50

$CH_2COHC\underline{H}_{3(eq)}CH_2$). Mass spectrum showed molecular ion peak at m/e 240. The diol (56) on treatment with phosphorous oxychloride[22,23] in pyridine did not yield the desired artemisiol (55) as expected but the hydrocarbon (61), which was characterised by its IR, NMR and mass spectra. IR showed bands at 2960 C-H stretch, 1446 C-H scissoring, 1378 cm^{-1} C-H deformation and absense of O-H stretch. NMR spectrum displayed signals at δ 5.3 (bs, 1H, $CHC\underline{H}=CCH_3CH_2$), 5.2(bs, 1H, $CH^3C=CH\underline{H}^{cis}$), 4.6 (bs, 1H, $CH_3C=CH\underline{H}_{trans}$), 1.65 (bs, 6H, $CHCH=CC\underline{H}_3CH_2$ and $C\underline{H}_3C=CH_2$) and 0.75-2.2 (21H, rest of the methylene and methine protons). Mass spectrum showed peaks at m/e 204 (M^+), 189 (M^+-CH_3), and 163($M^+-CH_3C=CH_2$) as base peak.

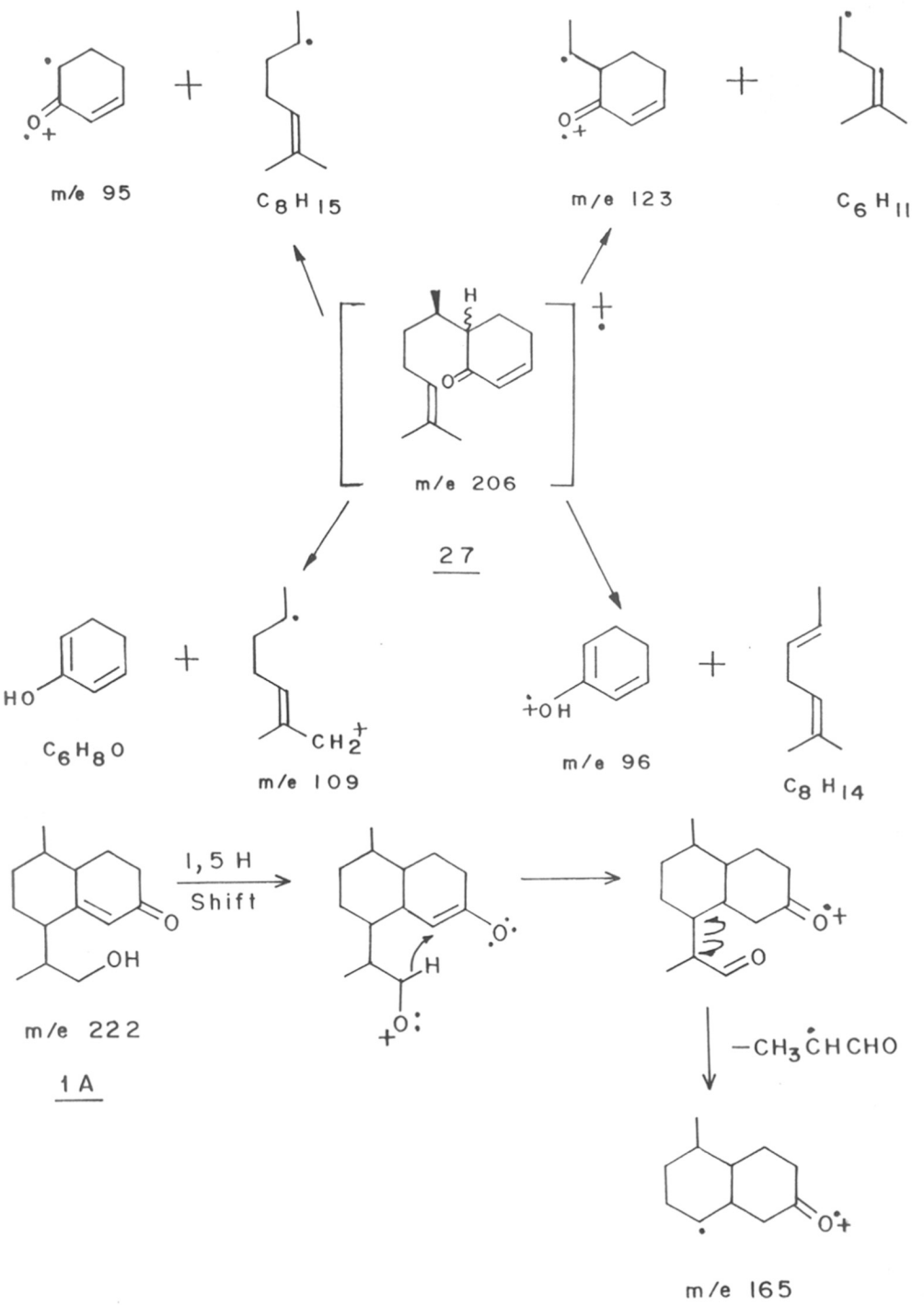
Schwartz et al[24] reported dehydration of a tertiary alcohol without affecting an acetyl group present in the molecule by use of phosphorous oxychloride and pyridine. Thus the diol (56) was converted to monoacetate alcohol (62) by acetic anhydride in pyridine. The mono acetate alcohol (62) was identified by its IR, NMR and mass spectra. IR showed bands at 3446 O-H stretch, 1740 C=O stretch, 1168 C-O stretch and 1032 cm^{-1} C-O stretch. NMR showed signals at δ 4.0(m, 1H, $CH_3CHCH\underline{H}OCOCH_3$), 3.8(m, 1H, $CH_3CHC\underline{H}HOCOCH_3$), 1.95(s, 3H, $CH_3CHCH_2OCOC\underline{H}_3$) and 1.13(s, 3H, $CH_2COHC\underline{H}_3CH_2$). Mass spectra showed molecular ion peak at m/e 282. The monoacetate alcohol (62) was subjected to dehydration by treatment with phosphorus oxychloride in pyridine to yield a mixture of alkene acetates (63) and (64). The mixture was identified by its IR, NMR and mass spectra. IR showed bands at 1742 C=O stretch, 1653 C=C stretch and 1033 cm^{-1} C-O stretch.

SCHEME-8

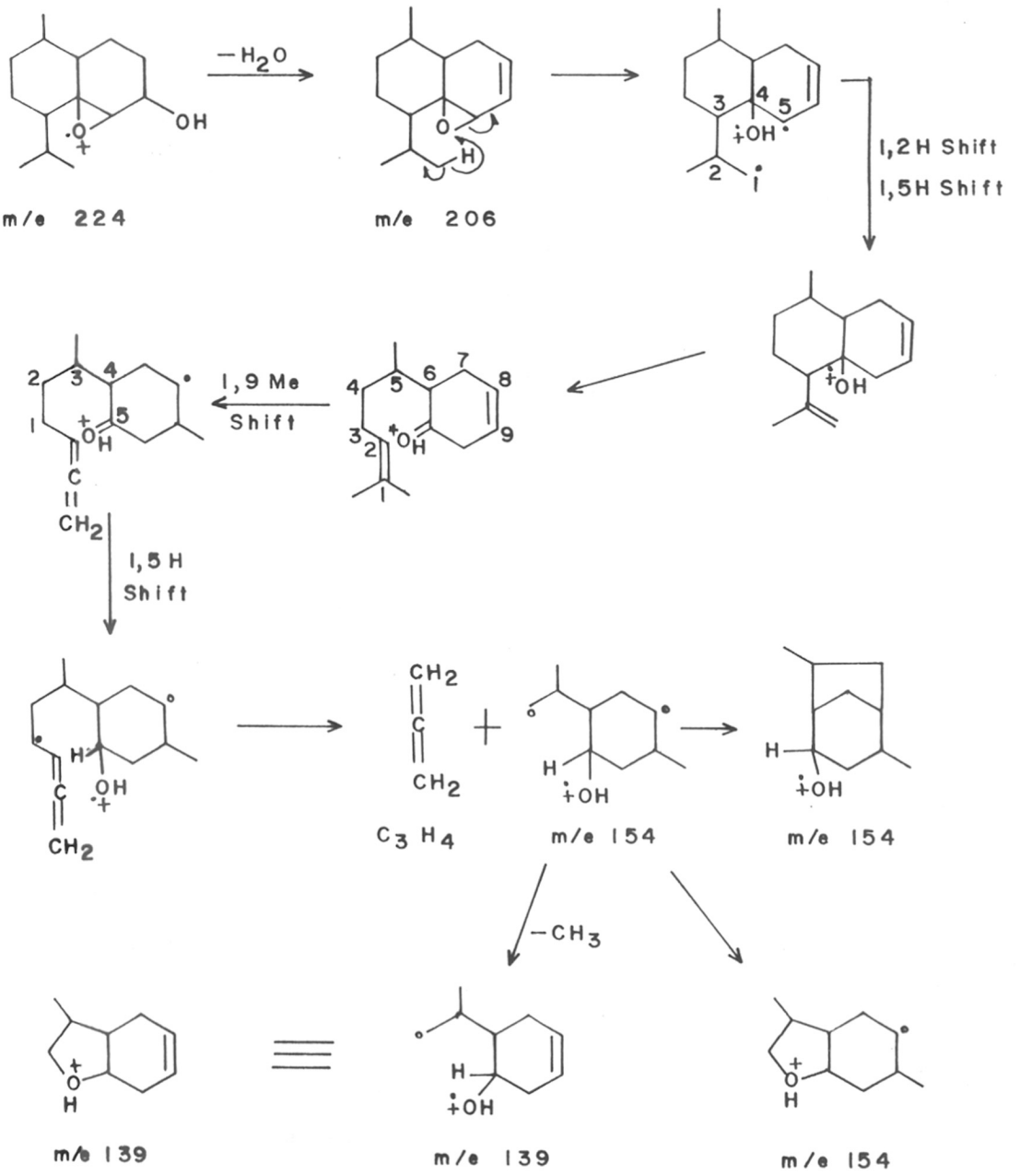

MeMgI
POCl3/Pyridine
Ac2O/Pyridine
POCl3/Pyridine
KOH
EtOH
50
56
61
55
62
63
64
55
65

NMR displayed signals at δ 5.22 (s, 1H, $CHC\underline{H}=CCH_3CH_2$), 4.15(m, 1H, $CH_3CHCH\underline{H}OCOCH_3$), 3.9(m, 1H, $CH_3CHC\underline{H}HOCOCH_3$), 2.05(s, 3H, $CH_3CHCH_2OCOC\underline{H}_3$), and 1.6(bs, 3H, $CHCH=CC\underline{H}_3CH_2$). Mass spectrum showed molecular ion peak at m/e 264. The mixture of alkene acetate (63) and (64) was used as such for further saponification reaction using potassium hydroxide in ethanol to yield a mixture of artemisiol (55) and alkene alcohol (65) in the ratio of 7:3. The mixture was separated by repeated careful argentic preparative TLC to yield pure artemisiol (55). Artemisiol (55) was characterised by its IR, NMR and mass spectra. IR spectrum showed bands at 3405 O-H stretch, 1653 C=C stretch, and 1027 cm^{-1} C-O stretch. NMR spectrum displayed signals at δ 5.2(s, 1H, $CHC\underline{H}=C(CH_3)CH_2$), 3.3-3.7(m, 2H, $CH_3CHC\underline{H}_2OH$), 1.7(D_2O exchangeable proton, $CH_3CHCH_2O\underline{H}$), 1.6(s, 3H, $CHCH=C(C\underline{H}_3)CH_2$) and 0.75-2.5(23H, all remaining methine, methylene and methyl protons). Mass spectrum showed peaks at m/e 222 (M^+), 204(M^+-H_2O), 163($M^+-CH_3CHCH_2OH$) as base peak and 121, 107. Artemisiol (55) was obtained as an oil and could not be successfully crystallised despite several attempts. All the spectra data was in good agreement with the reported[20].

SCHEME — 9


m/e 95
C8H15
m/e 123
C6H11
m/e 206
27
C6H8O
m/e 109
m/e 96
C8H14
1,5 H
Shift
OH
m/e 222
1A
-CH3ĊHCHO
m/e 165

SCHEME – 9 CONTD ---



EXPERIMENTAL

Mannich base (4) from l-menthone (3).

A mixture of l-methone (3, 192 gms, 1.25 m), dimethyl ammonium hydrochloride (130 gms, 1.59 m), paraformaldehyde (122gms) and concentrated hydrochloric acid (4 ml) in absolute alcohol (150 ml) was vigorously stirred and refluxed in an oil bath for 10 hours. The solvent was removed in vacuo, and water (250 ml) added to the reaction mixture. The reaction was extracted with dichloromethane (3x500 ml). The combined organic layer was washed with water (3x500 ml), brine (1x250 ml), dried over anhydrous sodium sulphate and solvent removed in vacuo to yield the Mannich base (4, 260 gms, 99% yield).

Diol (8) from Epoxide (7).

To a cooled, stirred suspension of lithium aluminium hydride (2.2 gms, 57.9 mmoles) in dry diethyl ether (50 ml) was added epoxide (7, 2.28 gms, 10.3 mmoles) and refluxed by aid of an infra-red lamp for 10 hours. The reaction was allowed to stand at room temperature for 7 days and then was poured into dichloromethane (1000 ml). Excess lithium aluminium hydride was destroyed by dropwise addition of water under stirring. The reaction was filtered through a buchner funnel and the residue washed thoroughly with dichloromethane (2x250 ml). The combined dichloromethane layer was washed with water (2x300 ml), brine (1x250 ml), dried over anhydrous sodium sulphate and solvent removed in vacuo in yield a white solid (2.31 gms, 99.6% yield).

Benzyl derivative (13) from keto ether (12A).

To a cooled (ice-NH_4Cl mixture) suspension of sodium hydride (15mg, 0.62 mmoles) in dry dimethyl formamide (5 ml) was added under stirring keto ether (12A, 100 mg, 0.45 mmoles). After stirring for 45 minutes, benzyl bromide (0.2 ml, 1.7 mmoles) was added to the cooled solution, under stirring, dropwise. The reaction was further stirred for 3 hours. Usual workup and chromatography yielded the benzyl derivative (40 mgms, 28 % yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 7.25 (bs, 5H, aromatic protons), 5.8 (s, 1H, C=C$\underline{H}$C(O)-CH_2), 4.4 (s, 2H, PhC$\underline{H}_2$O-), 3.5 (d, 2H, J=7Hz, $CH_3CHC\underline{H}_2OCH_2Ph$), 0.8-1.1 (d, 6H, J=8Hz, CHCH(C$\underline{H}_3$)CH_2 and C$\underline{H}_3$$CHCH_2O$-), 1.1-2.5 (12H, rest of the methylene and methine protons). IR showed bands at 3030, aromatic C-H stretch, 1675 C=O stretch and 1620 cm^{-1} C=C stretch. MS:m/e 312 (M^+), 313 (M^++1), 212 (M^+-CH_2Ph), 191 ($M^+=CH_2OCH_2Ph$), 163 ($M^+-CH_3CHCH_2OCH_2Ph$) and 91 ($C_7H_7^+$). $(\alpha_D)^{26}$= +12.1° (c, 0.231).

Benzyl keto alcohol (46) from keto alcohol (1A).

A suspension of keto alcohol (1A, 100 mg, 0.45 mmoles) two drops of water, anhydrous potassium carbonate (6.2 mg, 0.045 mmoles) and tetrabutylammoniumiodide (TBAI) (1.67 mg, 0.0045 mmoles) in thiophene free dry benzene (15 ml) was taken in two neck round bottom flask equipped with a reflux condensor, rubber septum and was flushed and maintained under iolar nitrogen gas. To the suspension, a solution of benzyl iodide (981 mg, 4.5 mmoles) in benzene (5 ml) was added by aid of a syringe through the septum. The reaction was refluxed on a water bath for three

hours. The reaction mixture was poured in ice-water and extracted with dichloromethane (3 x 50 ml). The organic extract was washed thrice with water (100 ml), followed by brine, dried over anhydrous sodium sulphate and concentrated under vacuo. The lachrymatory oil was immediately chromatographed. The benzyl keto alcohol (46) was obtained in 25% ethyl acetate -75% benzene eluate (47 mg, 66% yield). TLC (solvent C). NMR ($CDCl_3$) :δ 7.1-7.4 (m, 5H, aromatic protons), 3.68 (t, 1H, J=7Hz, $=CC\underline{H}(CH_2Ph)C=OCH_2$), 3.12 (dd, 1H, J_{vic}=7Hz, J_{gem}=11Hz, $CH_3CHC\underline{H}HOH$), 2.97 (d, 2H, J=7Hz, $CCH(C\underline{H}_2Ph)C=OCH_2$), 2.91 (dd, 1H, J_{vic}=7Hz, J_{gem}=11Hz, $CH_3CHCH\underline{H}OH$), 1.1 (d, 3H, J=7Hz, $CHCHC\underline{H}_3CH_2$), 0.8 (d, 3H, J=7Hz, $C\underline{H}_3CHCH_2OH$) and 1.15-2.8 (12H, rest of the methylene and methine protons). IR (Neat) showed bands at 3420 O-H stretch, 1720 C=O stretch, 3020 aromatic C-H stretch, 1615 aromatic C=C stretch and 1045 cm^{-1} C-O stretch. MS : m/e 312 (M^+), 313 (M^++1), 294 (M^+-H_2O), 281 (M^+-CH_2OH), 253 ($M^+-CH_3CHCH_2OH$), 221 (M^+-CH_2Ph) as base peak and 91 ($C_7H_7^+$ or tropolium ion). $(\alpha_D)^{26}$= -13.54 (c, 0.254), M.P.=85-86°C.

Saturated ketone (50) from keto alcohol (1A).

A solution of keto alcohol (1A, 500 mg, 2.25 mmoles) in methanol was placed in a Paar hydrogenation bottle with 10% palladium on charcoal (100mg) and hydrogenated at room temperature at 20 PSI hydrogen gas pressure for 6 hours. The solution was then filtered and alcohol was removed in vacuo, to yield an oil (495 mg, 98% yield). The oil was then purified by silica-gel column chromatography. The saturated ketone (50) was

obtained in 20% ethyl acetate -80% benzene (400 mg). TLC (Solvent C). NMR ($CDCl_3$) : δ 3.45 (d, 2H, J=7Hz, $CH_3CHC\underline{H}_2OH$), 0.8-1.1 (d, 6H, J=7Hz, $CHCH(C\underline{H}_3)CH_2$ and $C\underline{H}_3CHCH_2OH$) and 1.1-2.4 (16H, rest of the methylene and methine protons). IR showed bands at 3420 O-H stretch, 1715 C=O stretch and 1050 cm^{-1} C-O stretch. MS : m/e 224 (M^+), 225 (M^++1), 206 (M^+-H_2O), 191 ($M^+-H_2O-CH_3$), 123 ($M^+-H_2O-C_6H_{11}$), 95 ($M^+-H_2O-C_8H_{15}$) and 55 ($C_4H_7^+$). $(\alpha_D)^{26}$= -14.3° (c, 0.755). GC, 200°C, r.t. 4.65 min.

Diol (56) from saturated ketone (50).

The saturated ketone (50, 100 mg, 0.45 mmoles) was taken in a two neck round bottom flask equipped with magnetic needle, rubber septum and two way stop cock with ultra pure argon gas balloon. The apparatus was flushed with argon gas thrice by employing vaccum-argon gas release cycle. To this dry diethyl ether (10 ml) was added. The reaction was cooled to 0-5°C by ice, stirred and 3M Grignard reagent (0.39 ml, 1.17 mmoles) added dropwise. The reaction was further stirred for 15 minutes and then brought to room temperature. The reaction was stirred for 9 hours. Excess of unreacted Grignard reagent was destroyed by cooling of the flask by ice and dropwise careful addition of saturated aqueous ammonium chloride solution (1 ml). Usual work up furnished an oil (92 mg, 85% yield). TLC (solvent C). NMR ($CDCl_3$) : δ 3.5 (d, 2H, J=7Hz, $CH_3CHC\underline{H}_2OH$), 1.28 (s, 3H, $CH_2C(OH)(C\underline{H}_{3(ax)}CH_2)$, 1.2 (s, 3H, $CH_2C(OH)(C\underline{H}_{3(eq)}CH_2)$, 0.8-1.1 (6H, 2 x methyls), 1.1-2.2 (2OH, rest of the methylene and

methine protons). IR showed bands at 3350 O-H stretch, 1110 C-O stretch and 1027 cm^{-1} C-O stretch. MS:m/e 240 (M^+), 222 (M^+-H_2O), 207 (M^+-H_2O-CH_3), 225 (M^+-CH_3) and 163 (M^+-H_2O-CH_3CHCH_2OH) as base peak. $(\alpha_D)^{26}$= -8.2° (c, 0.22).

Artemisiol (55) from alkene acetates (63)+(64).

To a solution of alkene acetate (63+64, 88mg, 0.33 mmole) in absolute alcohol (5ml) was added potassium hydroxide (83 mg, 1.5 mmoles) in a portion and two drops of water under stirring. The reaction was stirred further for 4 hours. The alcohol was removed in vacuo and water was added to the reaction mixture. The pH was adjusted to 7 by careful and dropwise addition of dilute hydrochloric acid. The aqueous layer was extracted with dichloromethane (3x50ml), and then the combined organic layer washed with water (1x25 ml), brine and dried over anhydrous sodium sulphate. The solvent was removed in vacuo to furnish an oil (70 mg, 95% recovery), which was subjected to argentic preparative TLC and pure artemisiol (55, 30 mg, 40% yield) was obtained. TLC (Solvent C). IR (Neat) showed bands at 3405 O-H stretch, 1653 C=C stretch, and 1027 cm^{-1} C-O stretch. NMR ($CDCl_3$) : δ 5.2(s, 1H, $CHC\underline{H}=C(CH_3)CH_2$), 3.3-3.7(m, 2H, $CH_3CHC\underline{H}_2OH$), 1.7(D_2O exchangeable proton, $CH_3CHCH_2O\underline{H}$), 1.6(s, 3H, $CHCH=C(C\underline{H}_3)CH_2$) and 0.75-2.5(23H, all remaining methine, methylene and methyl protons). MS : m/e 222 (M^+), 204(M^+-H_2O), 163(M^+-CH_3CHCH_2OH) as base peak and 121, 107. $(\alpha_D)^{26}$= -8.7° (c, 0.23). GC, 200°C, r.t.= 2.61 min.

Hydrocarbon (61) from diol (56).

The diol (56, 68.0 mg, 0.28 mmoles) was taken in a two neck round bottom flask, equipped with a magnetic needle, rubber septum and two way stop cock with ultra pure argon gas balloon. The apparatus was flushed with argon gas thrice by employing vaccum argon gas release cycle. To this dry pyridine (5 ml) was added by aid of syringe. The solution was stirred and cooled to 0-5°C by ice. To this phosphorus oxychloride (0.03 ml, 0.3 mmoles) was added dropwise. The reaction was brought to room temperature after 15 minutes and stirred further for 12 hours. The reaction mixture was poured in ice water and extracted with dichloromethane (3x50 ml). The organic extract was washed with water, saturated copper sulphate (3x50 ml), water (1x50 ml), brine (1x25 ml) and dried over anhydrous sodium sulphate. The solvent was removed in vacuo to yield an oil (25 mg, 43% yield). TLC (Solvent B). IR (Neat) showed bands at 2960 C-H stretch, 1446 C-H scissoring, 1378 cm^{-1} C-H deformation . NMR ($CDCl_3$V): δ 5.3 (bs, 1H, $CHC\underline{H}=CCH_3CH_2$), 5.2(bs, 1H, $CH^3C=CH\underline{H}^{cis}$), 4.6 (bs, 1H, $CH_3C=CH\underline{H}_{trans}$), 1.65 (bs, 6H, $CHCH=CC\underline{H}_3CH_2$ and $C\underline{H}_3C=CH_2$) and 0.75-2.2 (21H, rest of the methylene and methine protons). MS : m/e 204 (M^+), 189 (M^+-CH_3), and 163($M^+-CH_3C=CH_2$) as base peak. $(\alpha_D)^{26}$= -8.5° (c, 0.47). GC, 200°C, r.t.= 2.38 min.

Monoacetate alcohol (62) from diol (56).

To a solution of diol (56, 80 mg, 0.33 mmoles) in dry pyridine (5 ml) was added freshly distilled acetic anhydride

(0.3 ml, 3.2 mmoles) under stirring. The reaction was further stirred for 12 hours and worked up as usual to yield an oil (90mg, 96 % yiled). TLC (Solvent D). NMR ($CDCl_3$) : δ 4.0 (m, 1H, $CH_3CHC\underline{H}OAc$), 3.8 (m, 1H, $CH_3CHC\underline{H}HOAc$), 1.95 (s, 3H, $CH_3CHCH_2CH_2OCOC\underline{H}_3$), 1.13 (s, 3H, $CH_2C(OH)C\underline{H}_3CH_2$), 0.7-1.0 (d, 6H, J=7Hz, $C\underline{H}_3CHCH_2OAc$ and $CHCH(C\underline{H}_3)CH_2$) and 1.0-2.3 (22H, methyls, and other methylene and methine protons). IR showed bands at 3446 O-H stretch, 1740 C=O stretch, 1168 C-O stretch and 1032 cm^{-1} C-O stretch. MS:m/e 282 (M^+), 267 (M^+-CH_3), 222 (M^+-CH_3COOH), 204 ($M^+-CH_3COOH-H_2O$), 189 ($M^+-CH_3COOH-H_2O-CH_3$) and 162 ($M^+-CH_3CHCH_2OC(OH)CH_3-H_2O$) as base peak. $(\alpha_D)^{26}$= +6.2° (C, 0.2). GC, 200°C, r.t.=4.74 min.

Alkene acetates (63)+(64) from monoacetate alcohol (62).

The monoacetate alcohol (62, 93 mg, 0.33 mmoles) was subjected to reaction with phosphorus oxychloride (0.05 ml, 0.6 mmoles) using the procedure described for conversion of the diol (56) to the hydrocarbon (61). Usual work up furnished oil (82 mg, 94% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 5.22 (bs, 1H, $CHC\underline{H}=C(CH_3)CH_2$), 4.15 (m, 1H, $CH_3CHCH\underline{H}OAc$), 3.9 (m, 1H, $CH_3CHC\underline{H}HOAc$), 2.05 (s, 3H, $CH_3CHCH_2OCOC\underline{H}_3$), 1.6 (bs, 3H, $CHCH=C(C\underline{H}_3)CH_2$), 0.75-1.05 (d, 6H, J=7Hz, $C\underline{H}_3CHCH_2OAc$ and $CHCH(C\underline{H}_3)CH_2$) and 1.05-2.3 (13H, rest of the methylene and methine protons). IR shows bands at 1742 C=O stretch, 1653 C=C stretch and 1033 cm^{-1} C-O stretch. MS:m/e 264 (M^+), 204 (M^+-CH_3COOH), 189 ($M^+-CH_3COOH-H_2O$) and 162 ($M^+-CH_3CHCH_2OC(OH)CH_3$) as base peak. $(\alpha_D)^{26}$= -13.6° (c, 0.265). GC, 200°C, r.t.= 3.4 min.

Iso-ketoalcohol (29) from keto ether (12A).

To a stirred cooled (10°C) solution of keto ether (12A, 100 mg, 0.45 mmoles) in benzene (5 ml) was added boron trifluoride etherate (0.1 ml) in one portion. The reaction was stirred at room temperature for 4 hours and worked up as usual to yield an oil (98 mg, 98 % yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 5.88 (s, 1H, C=C<u>H</u>-C=O-CH_2), 3.53 (d, 2H, J=8Hz, $CH_3CHC\underline{H}_2OH$), 1.00 (d, 3H, J=7Hz, $CHCH(C\underline{H}_3)CH_2$), 0.8 (d, 3H, J=7Hz, $C\underline{H}_3CHCH_2OH$) and 1.1-2.5 (13H, rest of the methylene and methine protons). IR showed bands at 3420 O-H stretch, 1665 C=O stretch, 1615 C=C stretch and 1050 cm^{-1} C-O stretch. MS:m/e 222 (M^+), 207 (M^+-CH_3), 165 (M^+-CH_3CHCHO) and 191 (M^+-CH_2OH). $(\alpha_D)^{26}$= -38.83° (c, 0.515), GC, 200°C, r.t.= 3.41 min.

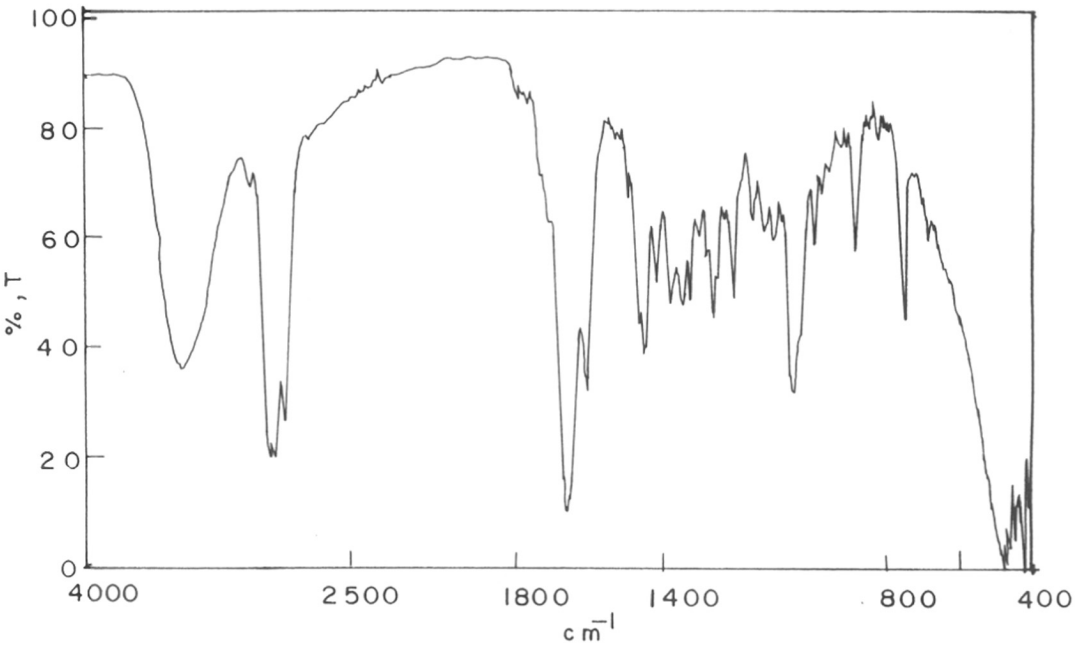


FIG. 1.1 : IR OF KETO ALCOHOL (1A)

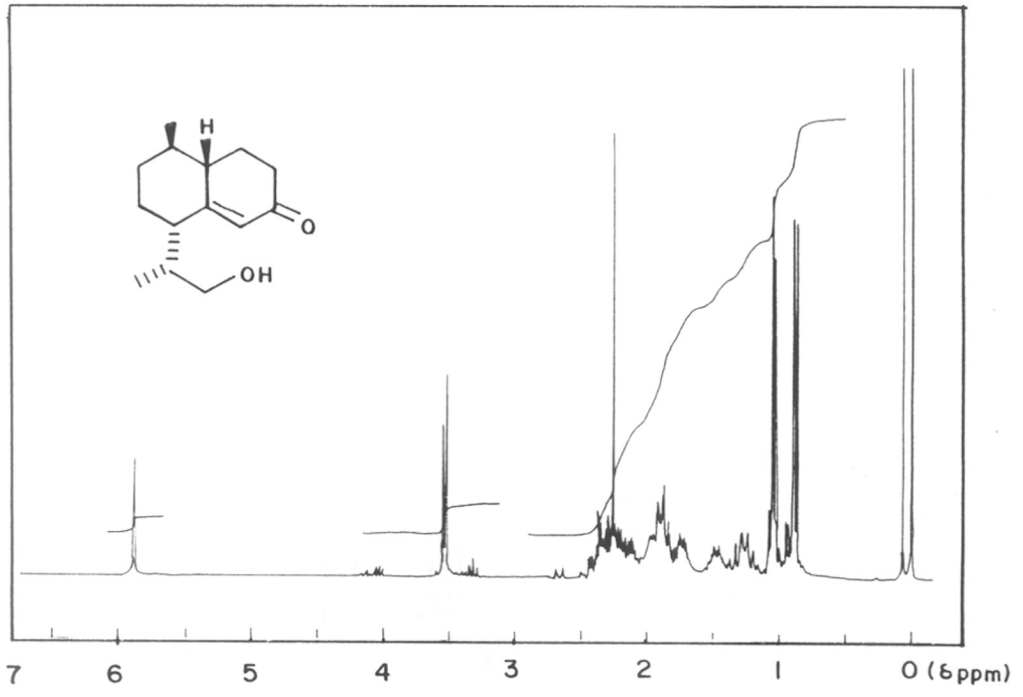


FIG. 1.2 : NMR OF KETO ALCOHOL (1A)

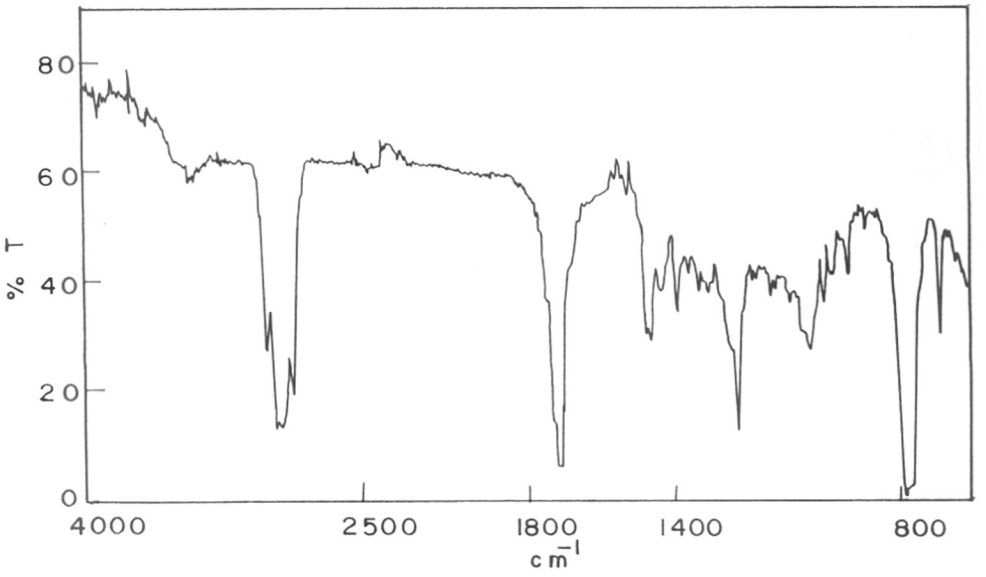


FIG. I.3 : IR OF KETO ETHER (12A)

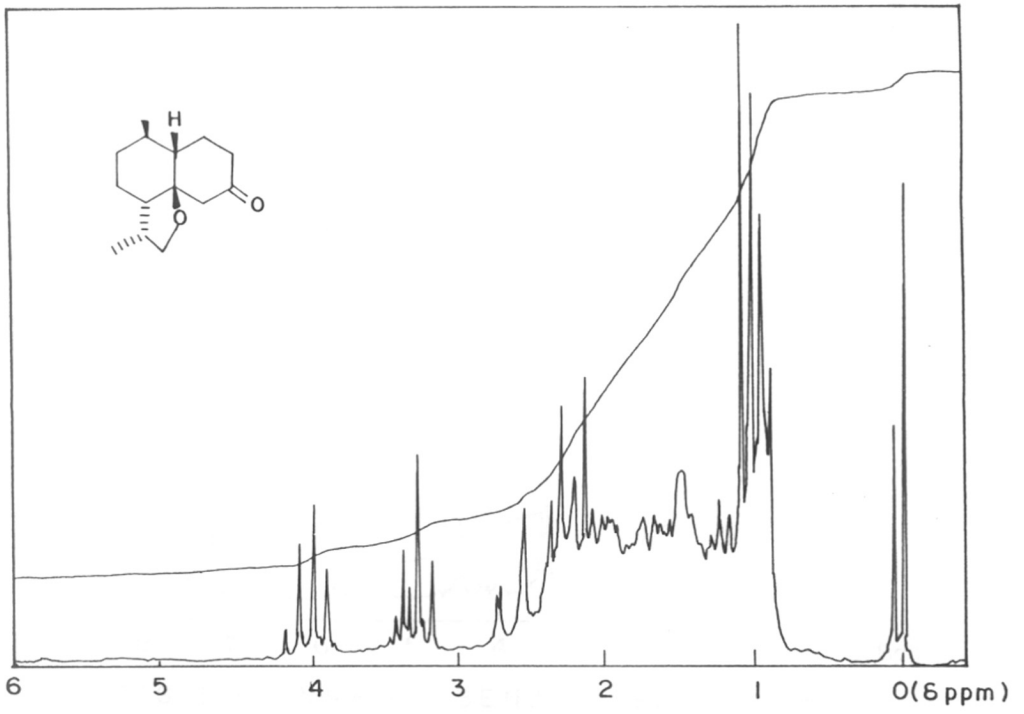


FIG. I.4 : NMR OF KETO ETHER (12A).

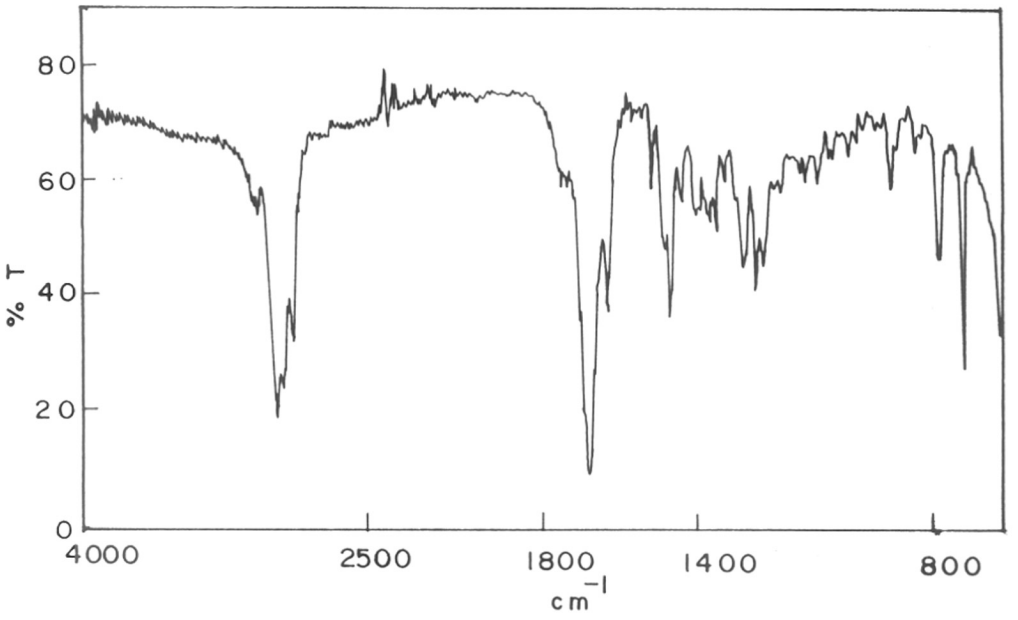


FIG. I.5 : IR OF BENZYL DERIVATIVE (13).

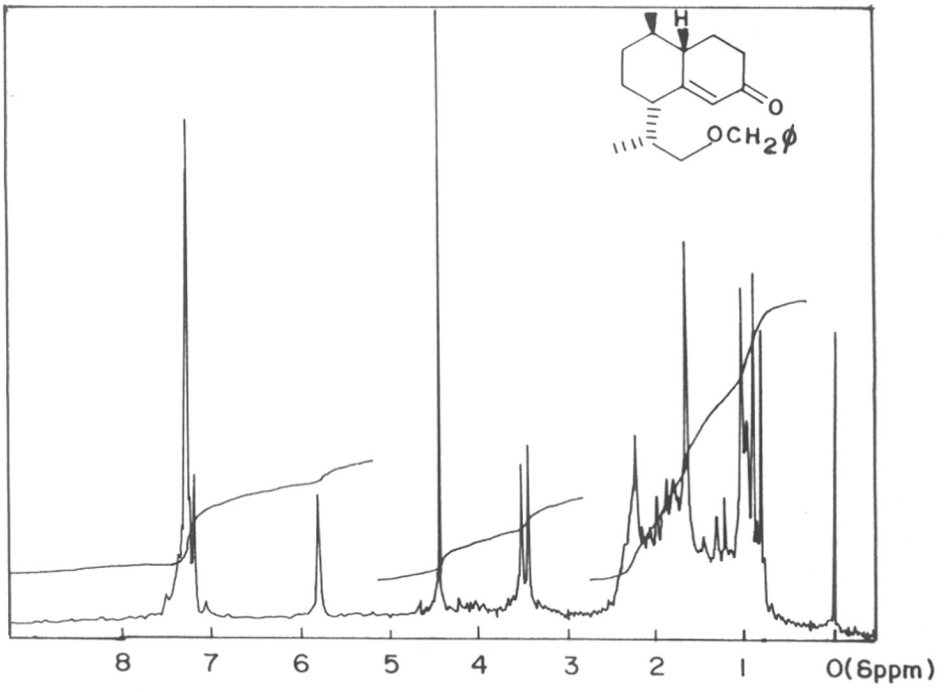


FIG. I.6 : NMR OF BENZYL DERIVATIVE (13)

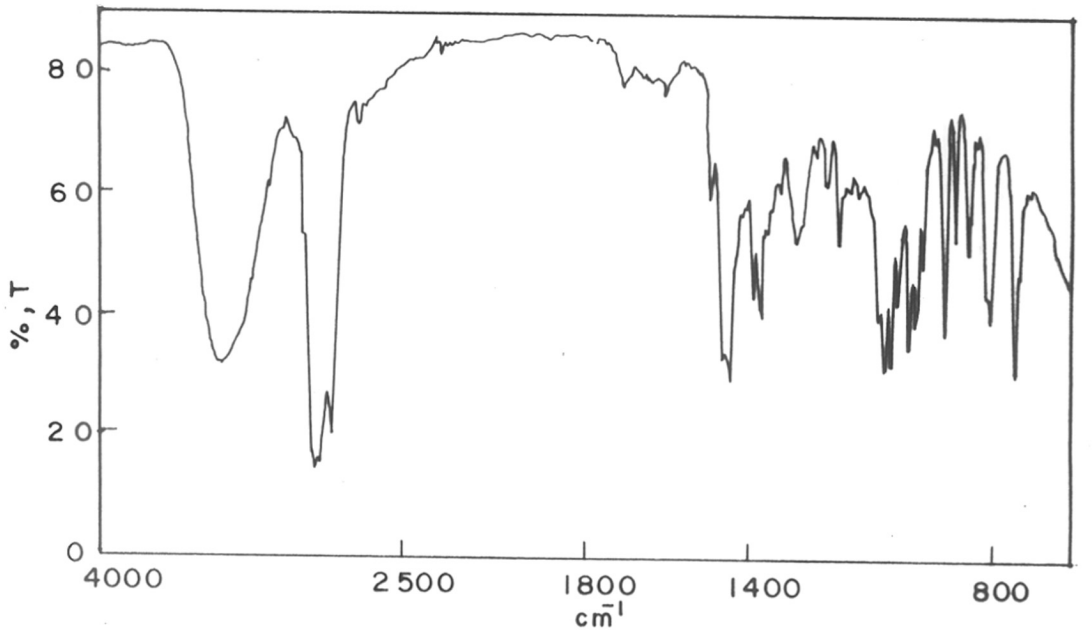


FIG. I. 7 : IR OF EPOXIDE ALCOHOL (19).

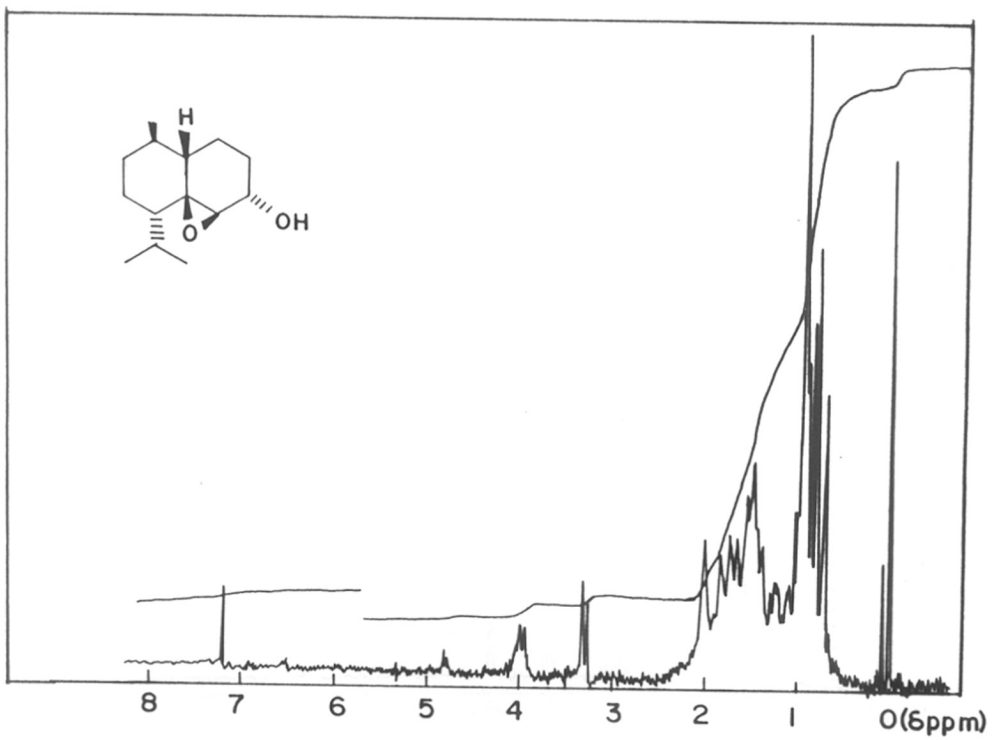


FIG. I. 8 : NMR OF EPOXIDE ALCOHOL (19)

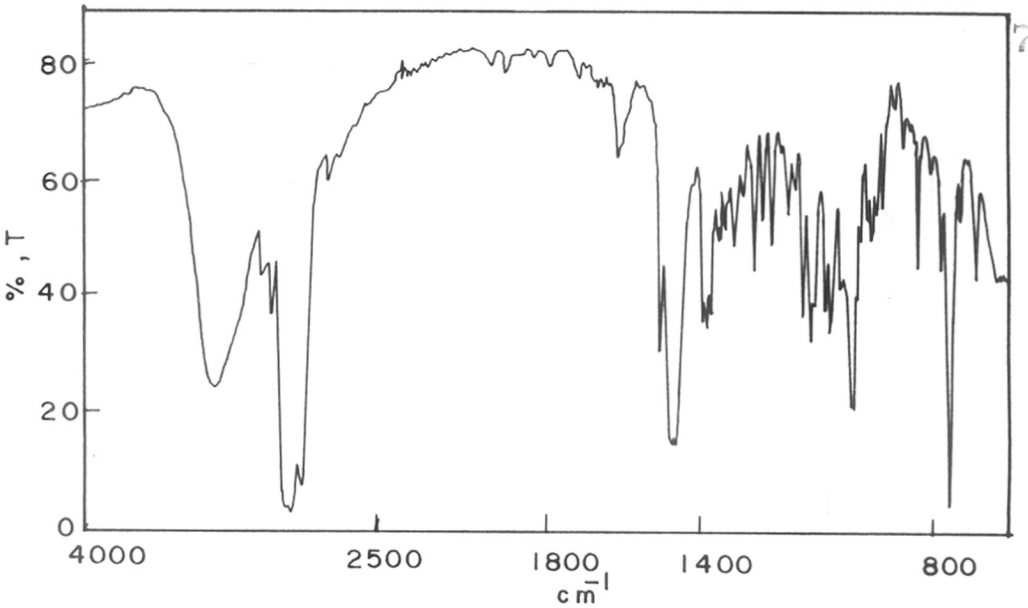


FIG. I. 9 : IR OF ALKENE DIOL (20)

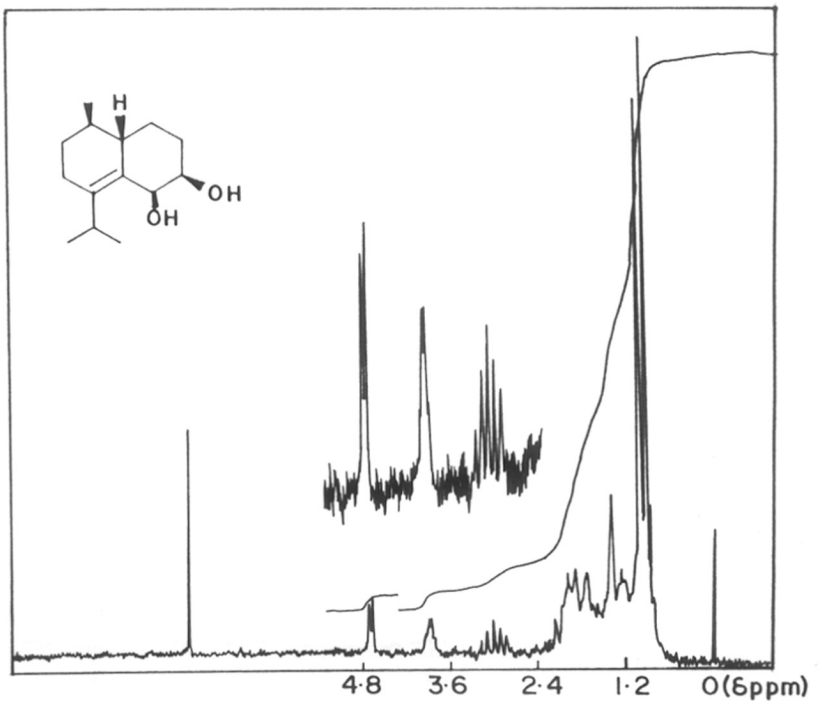


FIG. I. IO : NMR OF ALKENE DIOL (20)

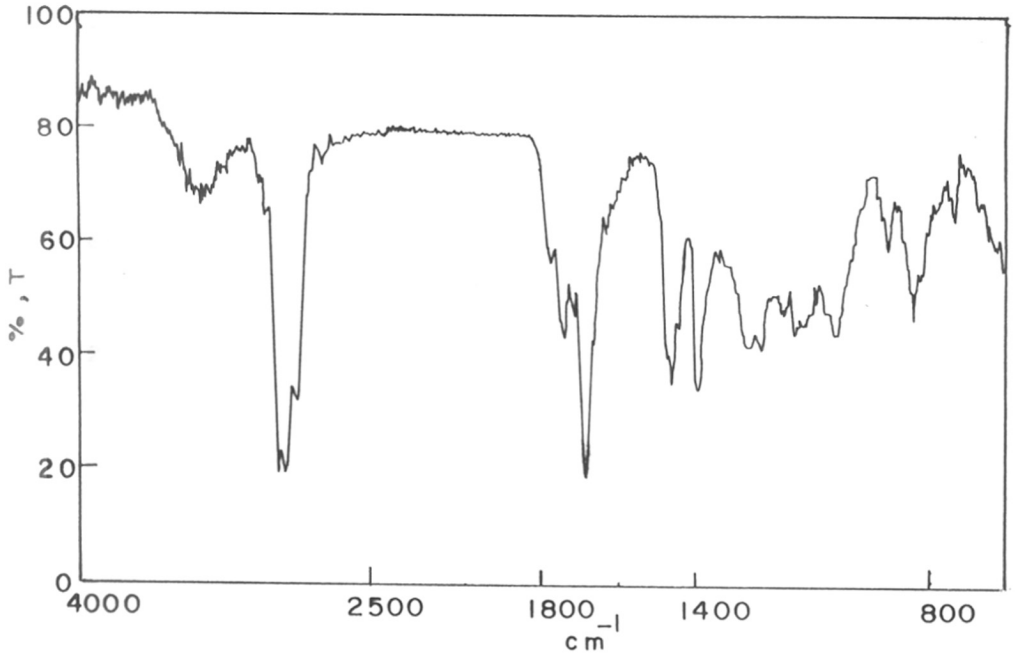


FIG. I.11 : IR OF COMPOUND (27)

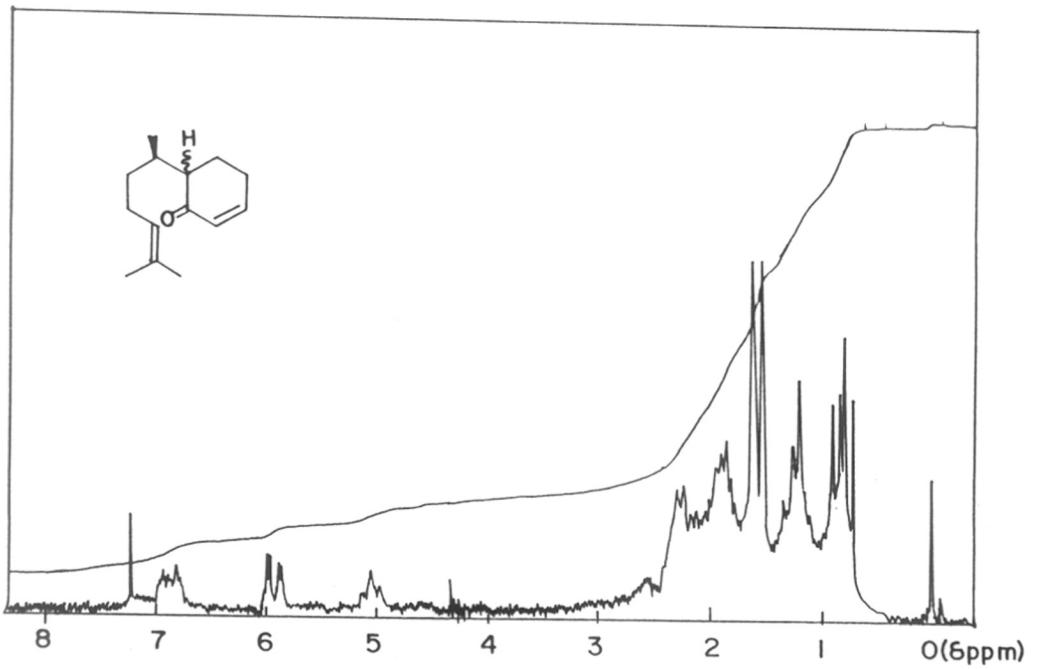


FIG. I.12 : NMR OF COMPOUND (27)

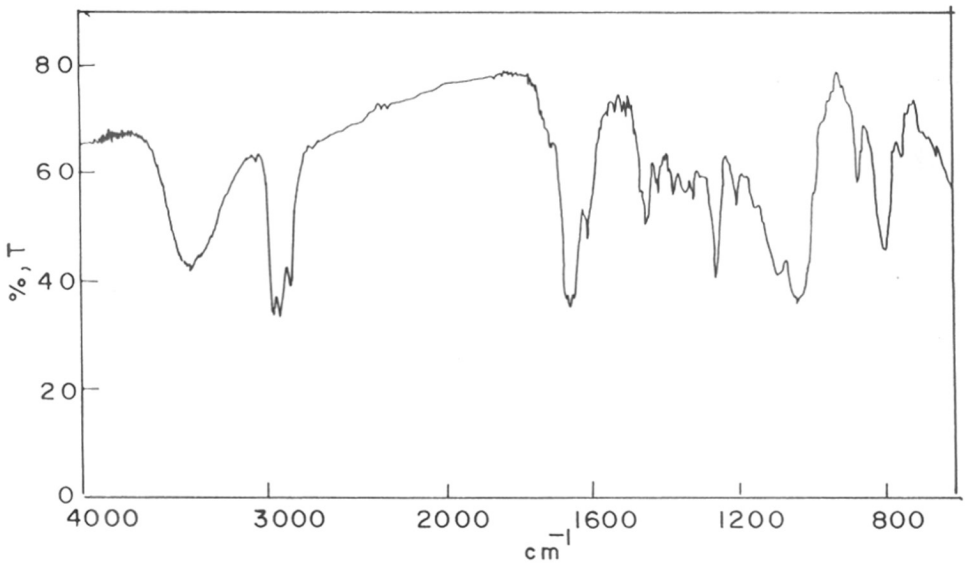


FIG. I.13 : IR OF ISO-KETO ALCOHOL (29)

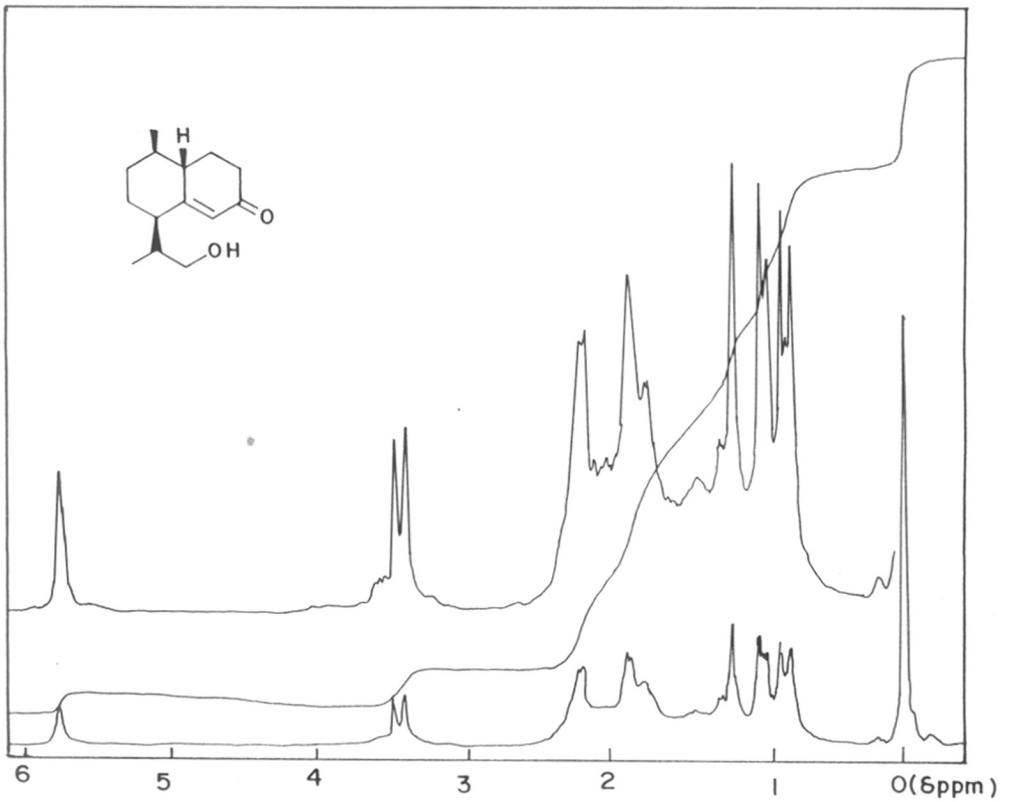


FIG. I.14 : NMR OF ISO-KETO ALCOHOL (29)

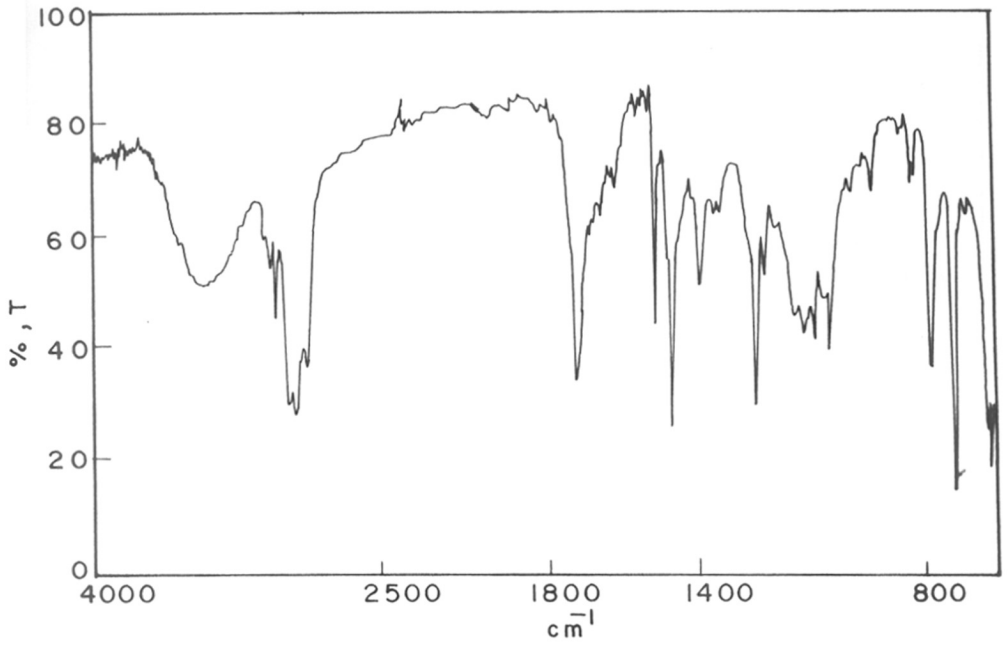


FIG. I.15 : IR OF BENZYL KETO ALCOHOL (46)

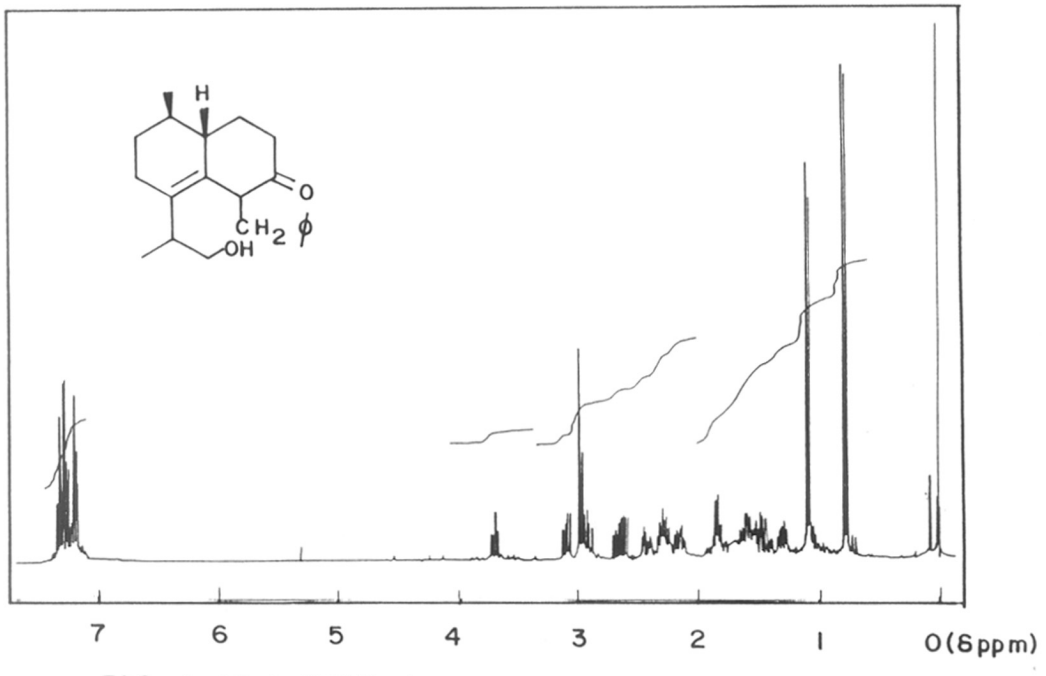


FIG. I.16 : NMR OF BENZYL KETO ALCOHOL (46)

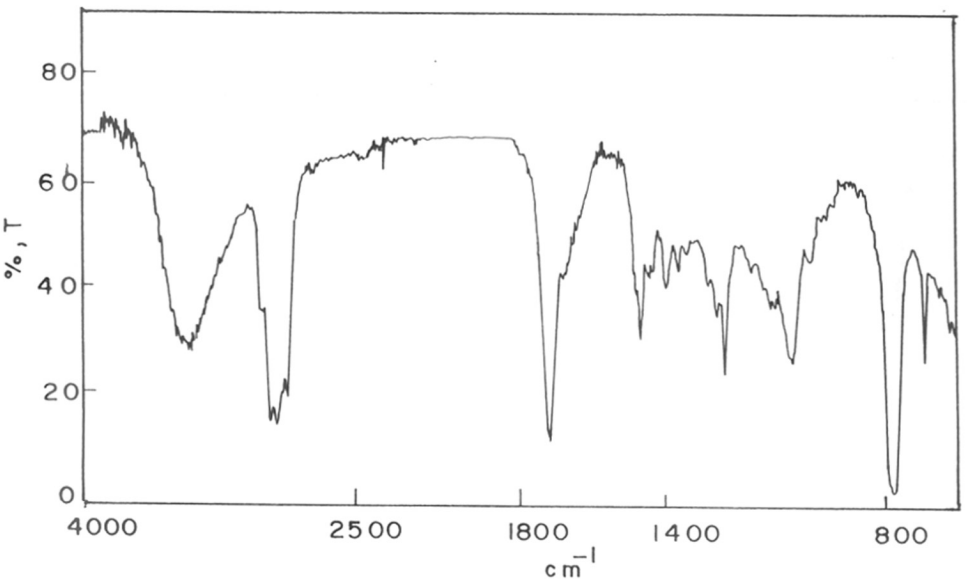


FIG. I.17 : IR OF SATURATED KETONE (50)

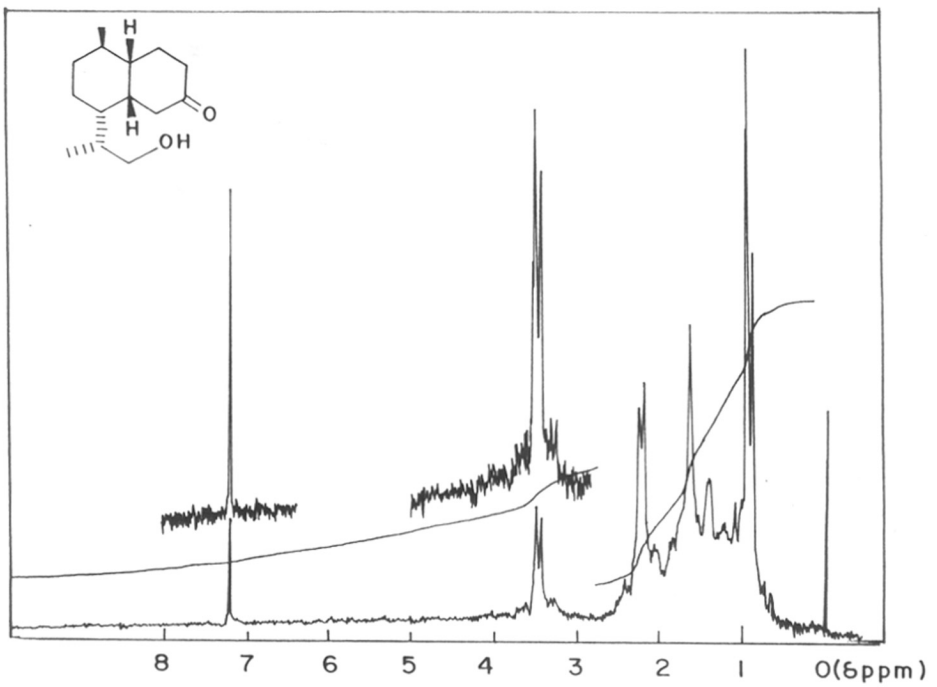


FIG. I.18 : NMR OF SATURATED KETONE (50)

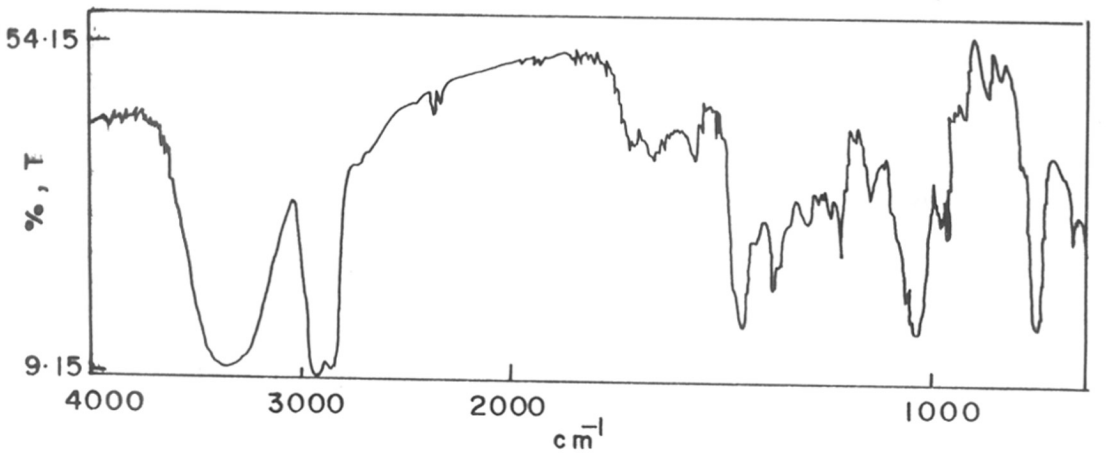


FIG. I.19: IR OF DIOL (52).

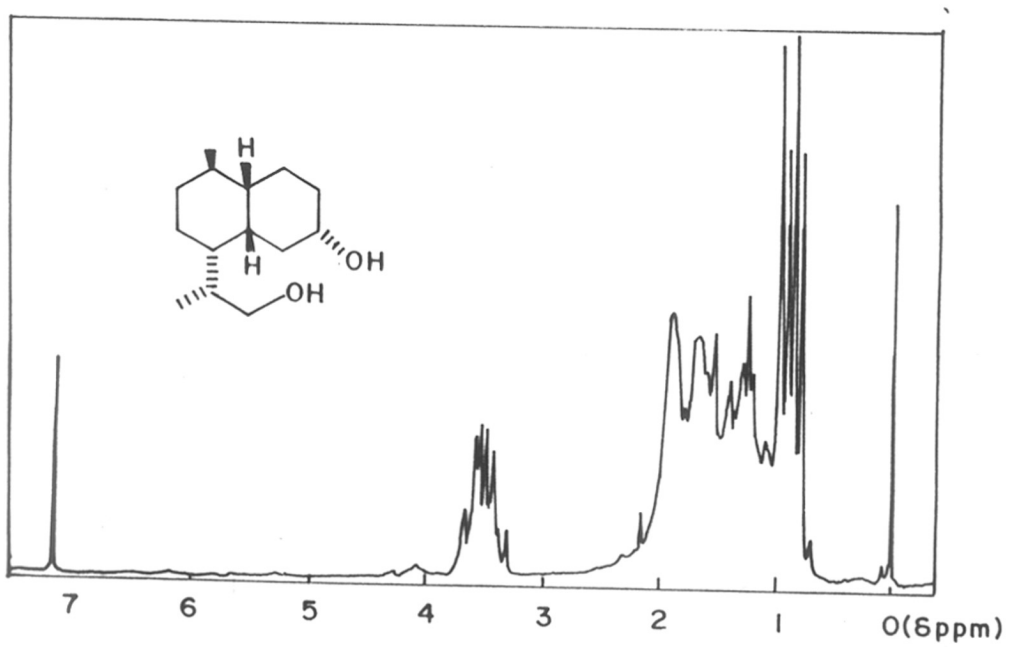


FIG. I.20: NMR OF DIOL (52)

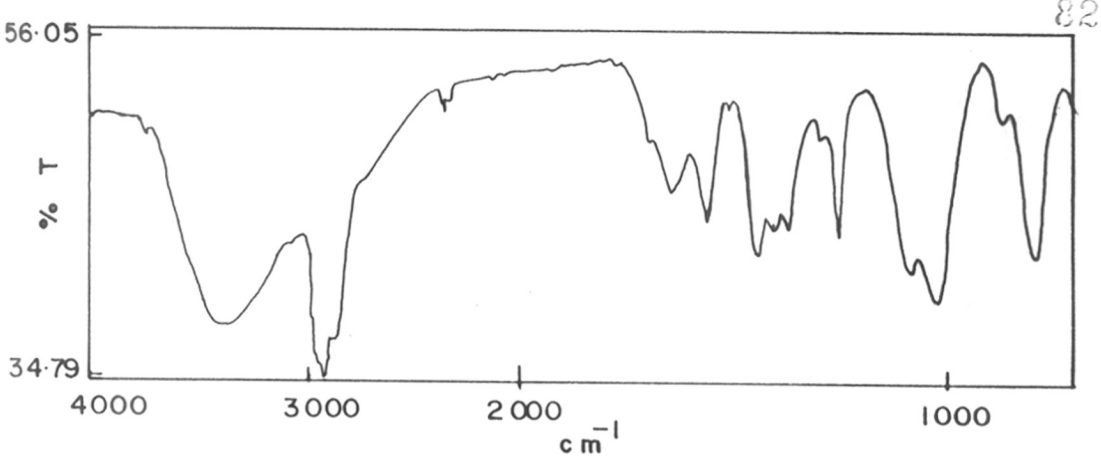


FIG. I.21: IR OF ARTEMISIOL (55)

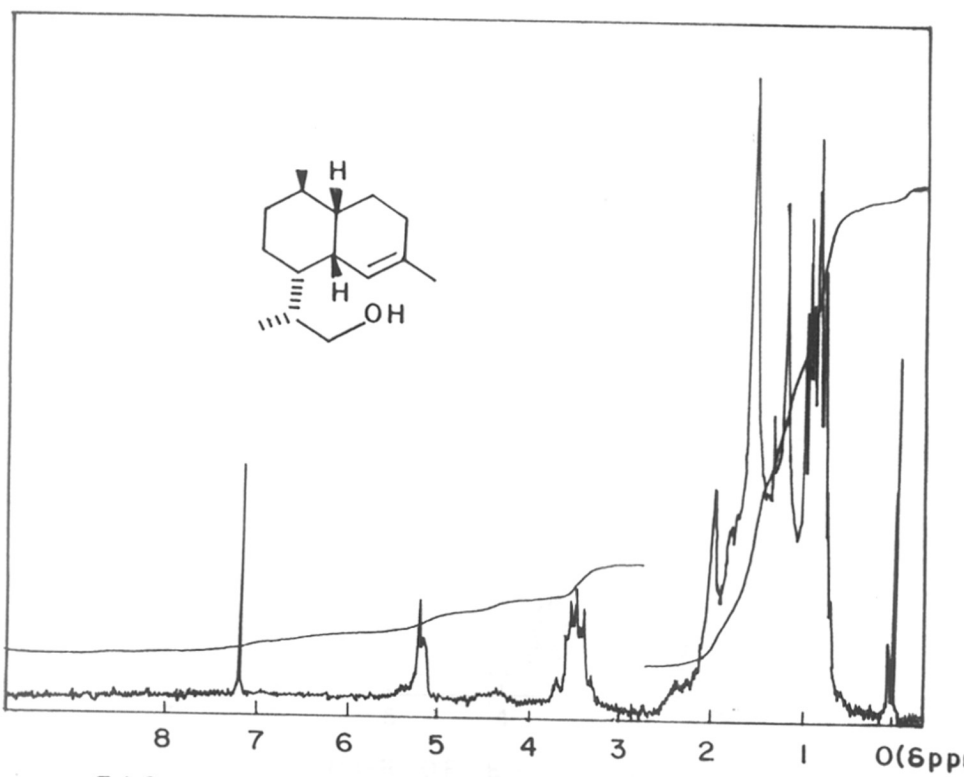


FIG. I.22: NMR OF ARTEMISIOL (55)

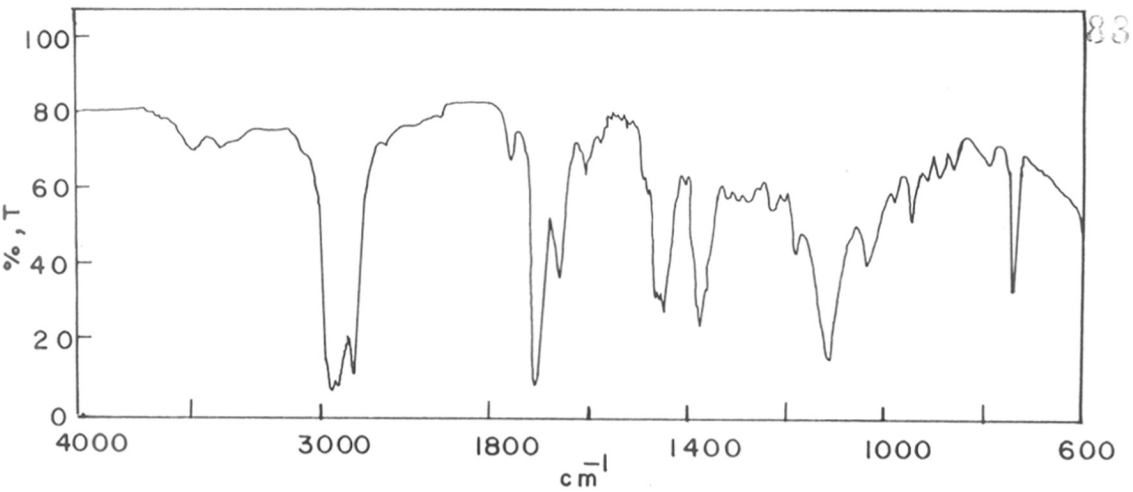


FIG. I.23: IR OF ESTER (17) + (18).

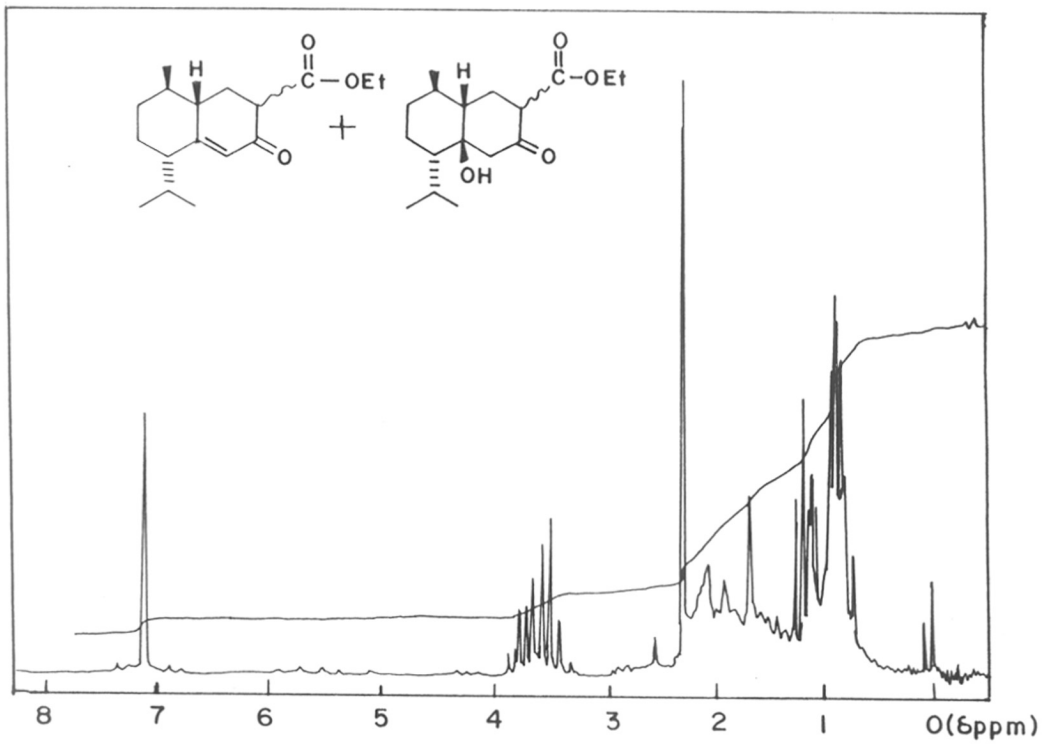


FIG. I.24: NMR OF ESTER (17) + (18)

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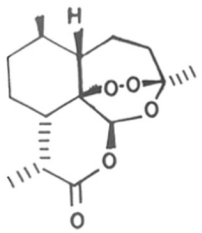
CHAPTER 2

PART A

A brief review of antimalarial
structure-activity relationship study
of Artemisinin and Parthenin derivatives.

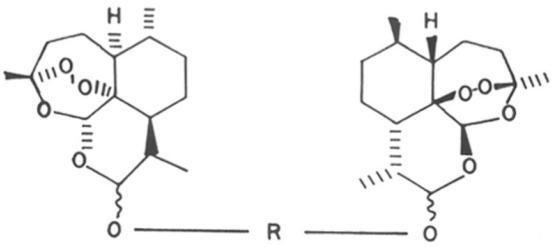
Malaria is still the most important parasitic and epidermic disease in the world. Resistance of Plasmodium falciparam to the drugs currently used has become a serious threat to effective control of the disease. Therefore, new antimalarials need to be devleoped, and artemisinin (qinghaosu) (1) (here after referred as QHS) and its derivatives may qualify for the successful candidates. The first report of *in vitro* and *in vivo* antimalarial efficacy of QHS(1) appeared in 1979[1]. In the last thirteen year phenomenal work has been done all over the world and several reviews on the antimalarial activity of QHS(1), its derivatives and analogues have appeared[2-5].

The antimalarial efficacy of QHS(1) against several strains was reported by several workers. Dutta et al[6] reported complete cure of P.berghei infection by 100 mg/kg for 7 days treatment of QHS(1) (for all IC_{50}, SD_{90}, ED_{50} and curative dose values of the hereafter following compounds see Table-I). Lin et al[7] reported IC_{50} values for Sierra Leone (D-6) strain and the Indochina (W-2) strain of P.falciparum as 2.93 and 0.66 ng/ml respectively and for complete cure of P.berghei infection 160 mg/kg. Brossi et al[8] reported ED_{90} and I_{90} values for P.berghi as 2.3 and 1.0 ng/ml respectively. Jung et al[9] found the IC_{50} values for Sierra Leone (D-6) origin and the Indochina (W-2) origin clones of P.falciparum as 2.33 and 1.21 ng/ml respectively. The IC_{50} values for the Sierra Leone (D-6) and the Indochina (W-2) clones of P.falciparum reported by Lin et al[10] were 2.35 and 2.60 ng/ml respectively.

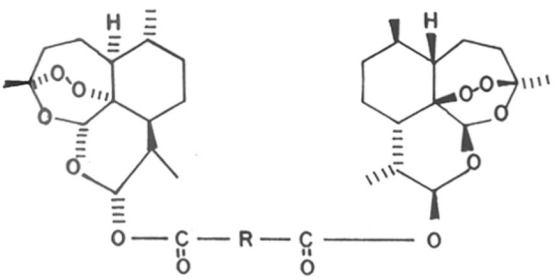


1

QHS

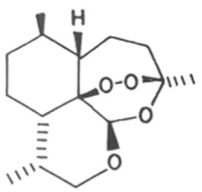


32



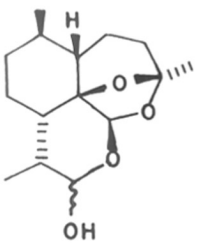
33 R : $(CH_2)_3$

34 R : $(CH_2)_5$



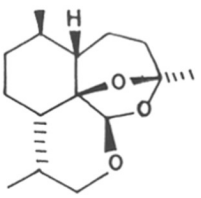
35

DEOXO QHS



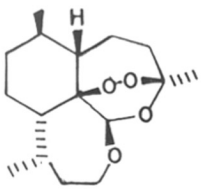
36

DEOXO DIHYDRO QHS



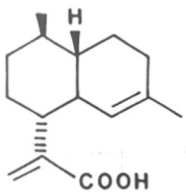
37

DEOXO DEOXY QHS



38

HOMODEOXO QHS



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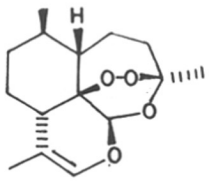
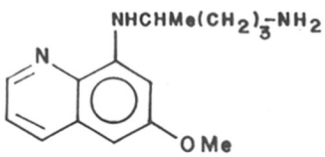
ARTEMISINIC ACID



40

11,12-DEHYDRO QHS



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PRIMAQUINE

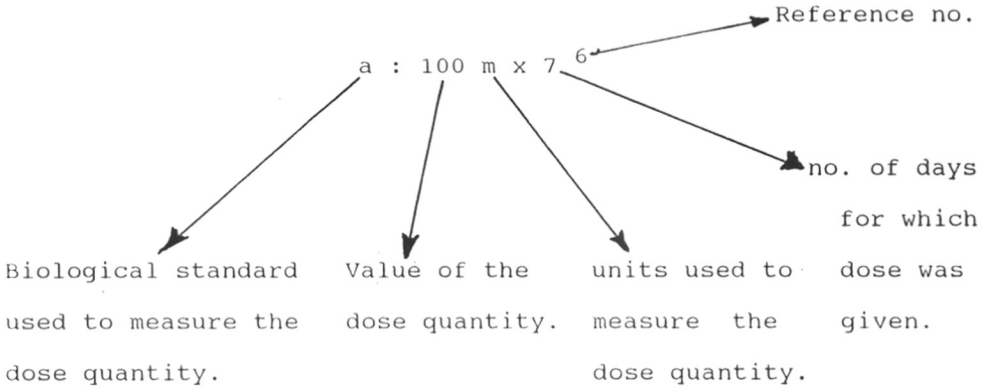
TABLE - 1

Comp no.	Activity Against P.berghei	P.falciparum D-6	P.falciparum W-2	P.falciparum --	P.cynomolgi B
1	a:100mx7[6]	b:2.93n[7]	b:0.66n[7]	c:1.99n[14]	a:10mx7[18]
	a:160m[7]	b:2.35n[10]	b:2.6n[10]		
	c:139m[13]	b:2.23n[9]	b:1.2n[9]		
		b:10.53M[8]	b:6.41M[8]		
2		b:0.41n[7]	b:0.69n[10]		
		b:1.83M[8]	b:1.79M[8]		
		b:5.75Q[8]	b:3.58Q[8]		
		b:0.11n[9]	b:0.04n[9]		
3	d:1.16m[13]	b:4.49M[8]	b:3.34M[8]	c:2.19n[14]	
	d:1.02m[13]	b:2.34Q[8]	b:1.92Q[8]		
	d:1.02m[19]				
4	a:5mx3[6]	b:4.13M[8]	b:3.07M[8]		
		b:2.52Q[8]	b:2.08Q[8]		a:5mx3[18]
		b:0.87n[9]	b:0.16n[9]		
5	a:160m[7]	b:4.07n[10]	b:1.38n[10]		
6		b:2.5n[10]	b:0.057n[10]		
7		b:0.36n[10]	b:0.015n[10]		
8		b:1.91n[10]	b:0.48n[10]		
9		b:0.44n[10]	b:0.071n[10]		
10	a:160m[7]	b:2.18M[8]	b:1.66M[8]	c:0.14n[14]	

		$b:4.83Q^{8}$	$b:3.86Q^{8}$
11		$b:0.6n^{7}$	$b:0.26n^{7}$
12		$b:1.84n^{7}$	$b:0.6n^{7}$
13		$b:0.77n^{7}$	$b:0.37n^{7}$
14	$d:1.20m^{13}$		
15	$d:0.66m^{13}$		
16	$d:0.65m^{13}$		
17	$d:0.50m^{13}$		
18	$d:0.51m^{13}$		
19	$d:0.48m^{13}$		
20	$d:0.67m^{13}$		
21	$d:0.46m^{13}$		
22	$d:0.51m^{13}$		
23	$d:0.48m^{13}$		
24	$d:0.78m^{13}$		
25	$d:0.63m^{13}$		
26	$d:0.50m^{13}$		
27	$d:0.49m^{13}$		
28	$d:0.60m^{13}$		
29	$d:0.64m^{13}$		
30	$d:0.67m^{13}$		
31	$d:0.63m^{13}$		
33	$d:0.65m^{13}$		
34	$d:0.96m^{13}$		
35		$b:0.58n^{9}$	$b:0.15n^{28}$

KEY TO TABLE - 1

Consider the example of the first compound no. 1 and entry in the first column. The explaination for each symbol in the entry made is as follows.



Sub-table - 1 for symbols for biological standards.

a : curative dose for complete cure from parasitemia.

b : inhibitory concentration for 50 % inhibition of parasitemia.

c : effective dose for 50 % cure of parasitemia.

d : suppression dose for 90 % suppression of parasitemia.

Sub-table - 2 for abbreviations used for units of dose quantity.

m : milligrams / kilograms

n : nanograms / milliliters

M : molar concentration

Q : no. of times more potent than artemisinine.

The antimalarial biological activity of QHS derivatives and analogues as compared to QHS (1) is as follows. Dihydroartemisinin (DHQHS) (2) (for all structures appearing hereafter see Table-2) is prepared by sodium borohydride reduction[7] of QHS(1) and is about three to four fold more potent[9,10] than QHS(1). The IC_{50} (50% inhibitory concentration) values of DHQHS(2) were reported by Jung et al[9], Lin et al[10] and Lin et al[7,11]. The ethers which have the advantage of being more lipid soluble than QHS(1) are prepared by treating DHQHS(2) with an alcohol in the presence of borontrifluoride etherate[12]. The methyl ether called artemether (3) or SM224 is about two to three times more potent[8] than QHS(1). The SD_{90} (the dose required for 90% suppression of the parasitemia) values were reported Luo et al[13] and Gu et al[19] for P.berghei infections, and treatment regimen of 600 mg/3days of artemether (3) was suggested for complete cure. The ED_{50} (effective dose for 50% cure) values were reported by Guan et al[14]. The antimalarial activity of artemether (3) was also reported by Gu et al[15], Gu et al[17] and Li et al[16] reported that artemether (3) has some modulating effect on red blood cell immunity other than its schizont killing action. The absolute stereochemistry of arteether (4) (ß-isomer) and its two to three fold more potency than QHS (1) was reported by Dutta et al[6]. The IC_{50} values were reported by Jung et al[9], Brossi et al[8] and Dutta et al[18]. Artelinic acid (5), is the most active of the water soluble derivatives of DHQHS (2)[10]. The IC_{50} value and curative dose value were reported by Lin et al[10] and Lin et al[7] respectively. The ester derivatives (6), (7), (8) and

(9) were prepared from DHQHS (2) by treatment with appropriate alcohols in presence of borontrifluoride etherate. The preparation and IC_{50} values were reported by Lin et al[10]. The superior activity of these esters than QHS (1), artemether (2) and arteether (3) is evident from the IC_{50} values.

Among the QHS derivatives the greatest promise is the DHQHS half ester of succinic acid[20], whose water soluble salt is known as sodium artesunate (10). Sodium artesunate (10) can be administered intravenously and shows 5.2 times more potency[10] than QHS(1) against P.berghei[21]. The IC_{50}, ED_{50} and curative dose values were reported by Brossi et al[8], Guan et al[14], Lin et al[7] and Luo et al[13] respectively. Lin et al[7] prepared a series of water soluble stable derivatives of DHQHS (2), compounds (11), (12) and (13) and reported their IC_{50} values against P.falciparum. The esters of DHQHS (2) (14) to (23) were prepared by Li et al[22] by treating DHQHS (2) with the appropriate acid anhydride or acid chlorides in pyridine with triethylamine, and reported their SD_{90} values against P.berghei. As a special group of esters, the carbonates(14) to (31) were prepared by treatment of DHQHS (2) with corresponding chloroformic esters in the presence of a Lewis base such as triethylamine or 4-dimethyl aminopyridine by Li et al[22] and Li et al[23]. The SD_{90} values against P.berghei of carbonates (24) to (31) were reported by China Co-operative Research group on QHS and its derivatives as antimalarials[24]. The ethers of bis(dihydroartemisinin) (32) were prepared by condensation of glycols with two moles of DHQHS (2) and their antimalarial activity was shown to be less than the

corresponding monoethers of DHQHS (2) by Chen et al[25]. The synthesis of diacid esters (33), (34) and their antimalarial activity (SD_{90}) against P.berghei was reported by Chen et al[26].

QHS (1) was converted to deoxoartemisinin (DOQHS) (35) by treatment of sodium borohydride and boron trifluoride etherate in THF by Jung et al[27] and found that it showed about eight times[28] the antimalarial in vitro activity of QHS (1) and in vivo more potent[9] than QHS (1). The 11-epi-deoxyarteether was prepared from deoxydihydroartemisinin (36) by treatment with ethanol saturated with hydrochloric acid by Gerpe et al[29] and reported to be less potent than QHS (1). The deoxo deoxyartemisinin (37) was prepared from deoxoartemisinin (35) by catalytic hydrogenation by Jung et al[9] and reported to be have no antimalarial activity. Bustos et al[30] synthesised homodeoxoartemisinin (38) from artemisinic acid (39) and reported that it showed twenty times less in vitro antimalarial activity than that of QHS (1). They prepounded the theory that the enlargement of the D-ring allows greater flexibility of the overall ring system including the biologically active endoperoxide, thus leading to poor receptor fit or more probably decreased reactivity of the endoperoxide and hence the decrease in the in vitro antimalarial activity. Lin et al[10] prepared 11,12-dehydroartemisinin (40) by treatment of DHQHS (2) with boron trifluoride etherate and reported its IC_{50} and curative dose values.

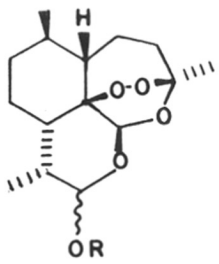
Several workers have reported preparation and antimalarial activity testing of several other QHS derivatives and analogues. Important work has been reported by Avery et al[31], Gu et al[32],

Peters et al[33] and Li et al[34]. Based on the observations of the change in activity with the change in the chemical structure of QHS (1) a qualitative structure-activity relationship was reported by Gu[3].

Based on the relative overall antimalarial potency Li et al[22] arranged QHS, and its derivatives in the following order of antimalarial activity. QHS(1) < DHQHS(2) < ethers (3) to (11) < carboxylic esters (14) to (23) < carbonates (24) to (31). The qualitative structure-activity relationship of QHS, its derivatives and analogues is briefly reviewed also by Luo et al[4]. The quantitative structure-activity relationship using Hansch analysis is reported by Wu et al[35].

The antimalarial activity was found to be potentiated when QHS (1) was used in combination with other antimalarial drugs. Wan et al[36] reported that the disappearence of malarial symptoms and survival time were increased and the recurrence of malaria diminished in experimental mice infected with P.berghei by combined use of QHS (1) and primaquine (41). Krungkrai et al[37] reported that the in vitro activity of QHS derivative artesunate was synergistic with miconazole or doxorubicin, both of which increase oxidant stress. Ye et al[38] reported that in vitro tetradrine and QHS (1) act synergistically against chloroquine-sensitive and chloroquine-resistant P.falciparum.

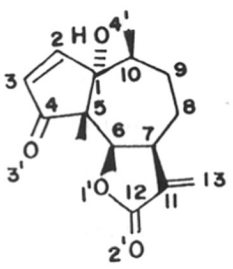
TABLE - 2



2-31

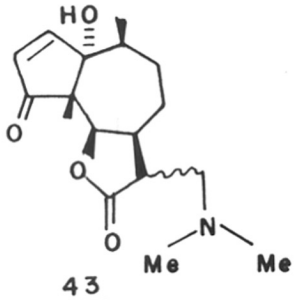
S.No	Compd No.	Name	R
1	2	DHQHS	H
2	3	Artemether	CH_3
3	4	Arteether	C_2H_5
4	5	Artelinic Acid	CH_2-C_6H_4-COOH
5	6	-	(R)-$CH_2CH(CH_3)$COOMe
6	7	-	(S)-$CH_2CH(CH_3)$COOMe
7	8	-	(S)-$CH(CH_3)CH_2$COOMe
8	9	-	(R)-$CH(CH_3)CH_2$COOMe
9	10	Sodium Artesunate	(R) $COCH_2CH_2COONa$
10	11	-	$CH_2COOCH_2CH_3$
11	12	-	$-CH_2CH_2$-$COOCH_3$
12	13	-	$CH_2C_6H_4COOCH_3$
13	14	-	$COCH_3(\alpha)$
14	15	-	$COCH_2CH_3(\alpha)$

15	16	-	CO-$CH_2CH_2CH_3$(α)
16	17	-	CO-$CH(CH_3)CH_3$(α)
17	18	-	CO-$CH_2CH_2CH_2CH_3$(α)
18	19	-	CO-CH_2-$CH(CH_3)Me$(α)
19	20	-	CO-C_5H_{11}(α)
20	21	-	CO-$CH=CH_2$(α)
21	22	-	CO-CH=CH-CH_3(α)
22	23	-	CO-Ph(α)
23	24	-	-$COOCH_3$(α)
24	25	-	$COOCH_2CH_3$(α)
25	26	-	$COOnC_3H_7$(α)
26	27	-	$COOiC_3H_7$(α)
27	28	-	$COOnC_4H_9$(α)
28	29	-	$COOiC_4H_9$(α)
29	30	-	$COOCH_2Ph$(α)
30	31	-	COOPh(α+ß)



42

PARTHENIN



43

Parthenin

Parthenin (42) is sequiterpene pseudoguianolide which occurs in Parthenium hysterophorus L.[39-41], a plant widely distributed in India. It has been declared a health hazard due to its potent allergy-including[42-43] properties, which affect the rural population. The molecule has a central seven membered saturated, twist-chair, carbocyclic ring (ring B) to which are fused two essentially planner five membered rings[44,45]. One of these incorporates an α, ß-unsaturated Γ-lactone with an exocyclic methylene group (ring C) and the other an endocyclic α, ß-unsaturated ketone group (ring A)[46,47]. The chemical abstract nomenclature of parthenin (42) is azuleno[4, 5-6]furan-2,9-dione, 3,3a,4,5,6,6a,9a,9b-octahydro-6a-hydroxy-6,9a-dimethyl-3-methylene[3aS-(3aα,6ß,6aα,9aß,9bα] and the registry number being 508-59-8.

Beside the allergy-including properties of parthenin (42) the CNS depressant[48] advernegic blocking[48] ameobicidal[49], allelopathic[50], cytotoxic[50] and recently antimalarial[51] activities are also reported. A computer graphic study[51] of parthenin (42) and the amphipathic QHS (1), by comparing the relationship between the oxygen atoms and the hydrocarbon frame work of parthenin (42) with that of QHS (1) showed the following results. In parthenin (42) the oxygen atoms O(2), O(1), O(3) and O(4) form a common cluster on one edge and face of the molecule, whereas in QHS (1)[4] the oxygen atoms form an L shaped cluster on the outside of the molecule set on an elongated

hydrocarbon frame work. The comparison of parthenin (42) and QHS (1) showed a very close coincidence of the O(2), O(1) and O(3) atoms of parthenin (42) with the O(5), O(4) and O(3) of QHS (see structure 1). Thus the antimalarial activity of parthenin (42) could be due to the above mentioned coincidence of oxygen atoms with those in QHS (1), not with standing the fact that the peroxy bridge oxygen atoms, which are reported to be essential[4] for antimalarial activity, lie on the opposite side of the super imposed hydrocarbon framework. A possible mechanism imparting parthenin (42) its biological activity is the presence of the C=C-C=O moiety[52,53]. The water[54], methanol[54] and amine[55] adducts of parthenin (42) are reported to be unstable and decompose readily, though partially, under mild conditions. Hence, these adducts of parthenin (42) could act as pro-drugs which can be degraded to cyto toxic parthenin (42) after transport into the plasmodium[51]. Vennerstrom et al[56] and Ellis et al[57] reported that amphipathic molecules enter membranes causing leakage of small ions and hydrophillic molecules, and the selectivity of the drug between the host and the parasite cells is due to the difference in the lipid composition of the respective cell membranes. Hooper et al[51] reported a nearly two fold increase in antimalarial activity of parthenin (42) by increasing its amphipathic nature by converting parthenin (42) to its dimethyl amine mono adduct (43). Thus the secondary amine adduct of parthenin (42) appears to be a promising potential antimalarial drug.

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CHAPTER II

PART B

SYNTHESIS OF SOME ARTEMISININE LIKE POTENTIAL ANTIMALARIAL COMPOUNDS

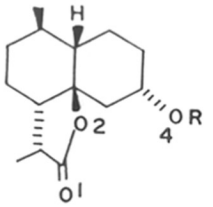
INTRODUCTION

As described in the review of biological activity of artemisinine (1), its derivatives and analogues, several workers have reported several derivatives and analogues of artemisinine (1). The common rationale for the synthesis and preparation of various artemisinine derivatives and analogues was the requirement of the unique C-O-O-C-O-C-O-C=O moeity[1,2] for antimalarial activity as is present in artemisinine (1).

On close examination of the molecular model of artemisinin (1), it is easy to appreciate the amphipathic nature of the molecule. One can see that five polar oxygen atoms are clustered on one side of the rather flattened molecule while the other side marks a non polar hydrocarbon skeleton. This forms a basis for the explanation of differences in the passage through and association with different bio-membranes, *in vitro* and *in vivo*[3,4]. Thus compounds with oxygen atoms forming an array similar to that in artemisinine could exhibit antimalarial activity and hence the following work was undertaken to design, synthesise and test for antimalarial activity some of these compounds.

Present Work

In 1980, the Qinghaosu research group[5] reported the crystal structure of artemisinin (1), and in 1988, Leban et al[6] reported a redetermination of the crystal and molecular structure of

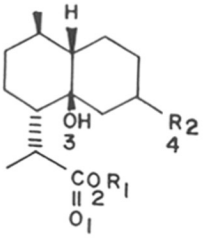


2 R : $COCH_3$

3 R : H

4 R : COOEt

5 R : $COOCH_2CH=CH_2$

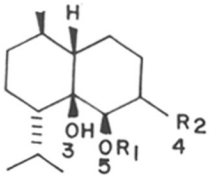


6 R_1: H ; R_2: OH (α)

8 R_1: H ; R_2: OH (β)

7 R_1: Me ; R_2: OH (α)

9 R_1: Me ; R_2: OH (β)



10-15

10,16,22 R_1: H ; R_2: OH (β)

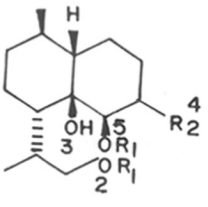
11,17,23 R_1: Me ; R_2: OMe (β)

12,18,24 R_1: Et ; R_2: OEt (β)

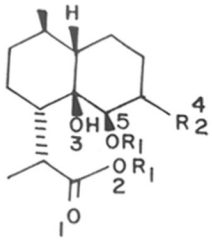
13,19,25 R_1: H ; R_2: OH (α)

14,20,26 R_1: Me ; R_2: OMe (α)

15,21,27 R_1: Et ; R_2: OEt (α)



16-21



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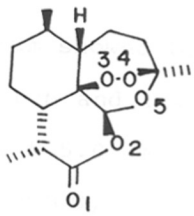


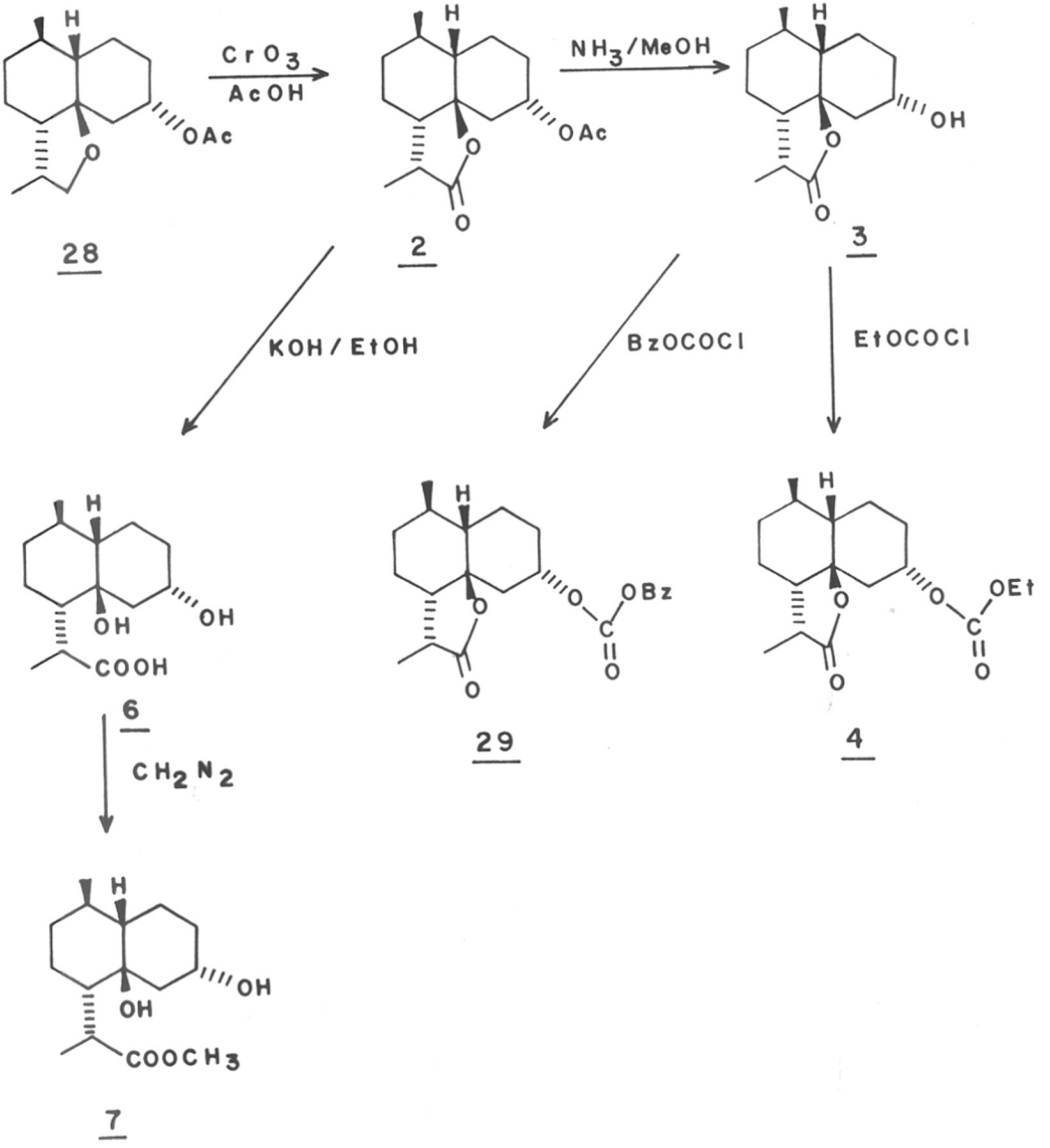
ARTEMISININ (QHS) - 1

artemisinin (1). The atomic coordinates of artemisinin were fed into the computer equipped with 'QUANTA 2' molecular modelling software[7]. Puranik et al[8] reported the crystal structure of the lactone acetate (2). The atomic co-ordinates of the lactone acetate (2) were also fed into the computer, compound (3) to compound (26) were made using the software in the computer and their energies minimised. The minimum energy molecules of compound (3) to compound (26) were compared for best fit with artemisinin (1). The criteria used for determining the best fit was the sum of the squares of the distances between the compared individual oxygen atoms. (see Table I). The molecular modelling study showed (see SD^2 values) that the oxygen atoms array in compounds (2), (4), (7), (8), (9), (10), (14), (15), (16), (19), (20) and (21) shows a reasonably good fit with the corresponding oxygen atom array in artemisinin(1). Thus the synthesis of compounds (2), (4), (7), (10) and (16) which was relatively easy and straight forward was attempted as follows.

Salunkhe[9] reported an unsuccessful attempt of oxidation of cyclic ether acetate (28) by chromium trioxide in acetic acid. Following an identical procedure, cyclic ether acetate (28) was treated with chromiun trioxide in acetic acid and stirred at RT for 3 days to yield after work up a solid, which was identified as the lactone acetate (2) by its IR, NMR and mass spectra (see scheme-1). IR spectrum showed bands at 1770 lactone C=O stretch, 1735 acetate C=O stretch and 1245 cm^{-1} acetate C-O stretch. NMR displayed signals at δ 5.0 (m, 1H, J=5Hz, $CH_2\underline{CH}(OAc)CH_2$), 2.26 (m, 1H, J=7Hz, $CH_3\underline{CH}COO$) and 2.00 (s, 3H, O-CO-$C\underline{H}_3$). Mass

spectrum showed molecular ion peak at m/e 280. Hydrolysis of the lactone acetate (2) with potassium hydroxide in ethanol gave the two compounds, one of which was very polar and was the major product of the reaction, whereas the other was relatively less polar but more polar than the starting lactone acetate (2) and was the minor product of the reaction. The more polar compound was identified as the dihydroxy acid (6) by its IR, NMR and mass spectra. IR spectrum showed bands at 3400 (very broad) assignable to the acid O-H stretch, 1720 C=O stretch, 1060 C-O stretch and 1085 cm^{-1} C-O stretch. NMR displayed signals at δ 3.44-4.18 (m, 2H, $CH_2C\underline{H}(OH)CH_2$ and $CH_3CHCOO\underline{H}$-D_2O exchangeable), 2.4 (m, 1H, J=7Hz, $CH_3C\underline{H}COOH$) and 2.0 (1H, D_2O exchangeable, $CH_2CH(O\underline{H})\ CH_2$. Mass spectrum showed molecular ion peak at m/e 256. The less polar compound was identified as lactone alcohol (3) by its IR, NMR and mass spectra. IR showed bands at 3403, O-H stretch, 1763 lactone C=O stretch and 1255 cm^{-1} C-O stretch. NMR showed signals at δ 3.88 (m, 1H, $CH_2C\underline{H}(OH)CH_2$) and 2.4 (m, 1H, J=7Hz, $CH_3C\underline{H}COO$). Mass spectrum showed showed molecular ion peak at m/e 238. Treatment of dihydroxy acid with diazomethane prepared from nitrosomethyl urea[10] furnished the methyl ester (7), which was identified by its IR, NMR and mass spectra. IR showed bands at 3380 O-H stretch, 3440 O-H stretch, 1725 C=O stretch and 1175 cm^{-1} C-O stretch. NMR displayed signals of δ 3.6 (s, 3H, $CH_3CHCOOC\underline{H}_3$), 3.86 (m, 1H, $CH_2C\underline{H}(OH)CH_2$), 3.33 (1H, D_2O exchangeable, $CH_2CH(O\underline{H})CH_2$ and 2.35 (m, 1H, $CH_3C\underline{H}COOCH_3$). Mass spectrum showed molecular ion peak at m/e 270.

SCHEME – I


H
OAc
O
28
CrO_3
AcOH
2
NH_3/MeOH
OH
3
KOH / EtOH
BzOCOCl
EtOCOCl
OH
COOH
6
CH_2N_2
COOCH3
7
OBz
29
OEt
4

The lactone alcohol (3) was obtained in good yields by treating the acetate lactone (2) by saturated solution of ammonia in anhydrous methanol[11]. In an attempt to epimerise the C_{14} methyl of the acetate lactone (2) by reported procedure[12], (see chapter 1 part B) using sodium methoxide in anhydrous methanol, the lactone alcohol (3) was obtained in good yields. Matzner et al[13] reviewed the synthesis of carbonates by chloro esters. Using the procedures recommended by Matzner et al[13] the lactone alcohol (3) was treated with benzyl chloroformate in pyridine, as solvent, to yield the desired lactone benzyl carbonate (29). The lactone benzyl carbonate (29) was characterised by its IR, NMR and mass spectra. IR showed bands at 1775 carbonate C=O stretch, 1755 lactone C=O stretch, 3030 aromatic C-H stretch, 1610 aromatic C=C stretch, 1260 C-O stretch and 1275 cm^{-1} C-O stretch. NMR displayed signals at δ 7.0-7.36 (m, 5H, aromatic protons), 4.7 (s, 2H, Ph-C$\underline{H}_2$O), 3.93 (m, 1H, CH_2 C$\underline{H}$(OCOOBz)CH_2), 1.18 (d, 3H, J=7Hz, C$\underline{H}_3$CHCOO), 0.94 (d, 3H, J=7Hz, CHCH(C$\underline{H}_3$)CH_2) and 1.2-2.5 (14H, rest of the methylene and methine protons). Mass spectrum showed a very weak molecular in peak at m/e 372. On treating the lactone alcohol (3) with ethylchloro formate in pyridine, as solvent, the lactone ethyl carbonate (4) was obtained, which was identified by its IR, NMR and mass spectra. IR showed bands at 1775 carbonate C=O stretch, 1760 lactone C=O stretch, 1262 C-O stretch and 1215 cm^{-1} C-O stretch. NMR displayed signals at δ 5.0 (m, 1H, CH_2C$\underline{H}$(O-COOEt)CH_2), 4.2 (q, 2H, J=7Hz, CH_3C$\underline{H}_2$O-COO), 2.5 (m, 1H, J=8Hz, CHCOO) and 1.3 (t, 3H, J=7Hz, C$\underline{H}_3$$CH_2$OCOO). Mass spectrum showed no molecular ion

peak, but the fragment ion at m/e 222 ($M^+-CO_2-CH_3CHO$), 207 ($M^+-CO_2-CH_3CHO-CH_3$), 179 ($M^+-CO_2-CH_3CHO-CH_3-C_2H_4$) and 69 ($C_3H_3O_2$) as base peak.

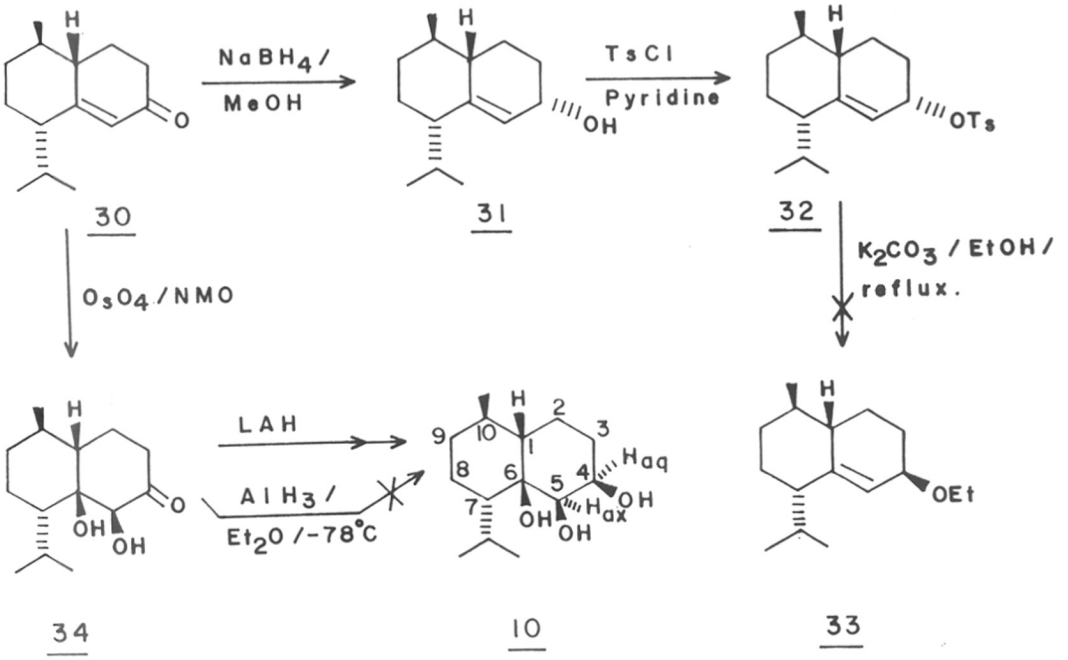
The triol (10) could be obtained by first reducing the ketone selectively to alcohol, and then hydroxylating the double bond. Sodium borohydride reduction of solid ketone (30) (see chapter 1) in methanol gave the allylic alcohol (31), which was identified by its IR, NMR and mass spectra. IR showed bands at 3340 O-H stretch, 1650 C=C stretch and 1075 cm^{-1} C-O stretch. NMR displayed signals at δ 5.45 (bs, 1H, C=C<u>H</u>-CH(OH)-CH_2) and 4.17 (bs, 1H, $W_{\frac{1}{2}}$=14Hz, C=CH-CH_{ax}(OH)CH_2). Mass spectrum showed molecular ion peak at m/e 208. The allylic proton on C_4 is axial[14] as the half width of the proton signal is 14Hz, hence the hydroxyl group is α-equitorial. The allylic alcohol (31) was converted to its tosyl derivative (32) by treatment with p-toulene sulphonyl chloride in pyridine. The tosyl derivative was identified by its IR, NMR and mass spectra. IR showed bands at 3040 aromatic C-H stretch, 1640 aromatic C=C stretch, 1360, 1140 S=O stretch and 1200 cm^{-1} C-O stretch. NMR displayed signals at δ 7.76 (d, 2H, J=8Hz, ortho aromatic protons), 7.1 (d, 2H, J=8Hz, meta aromatic protons), 5.28 (bs, 1H, C=C<u>H</u>CH(OTs)CH_2), 2.44 (s, 3H, para methyl protons). Mass spectrum showed molecular ion peak at m/e 362.

Walden et al[15] reported that on refluxing in ethanol with potassium carbonate tosylates gave ethyl ether with inversion in absolute configuration. Thus using an identical procedure the tosyl derivative (32) was refluxed in ethanol with potassium

carbonate to yield a complex mixture of unidentified products but no ethyl ether (33). Presuming that the ethoxide anion is the attacking species, which displaces the tosyl group by SN_2 mechanism to effect inversion, the tosyl derivative was treated with sodium ethoxide in anhydrous absolute alcohol The reaction yielded again a mixture of unidentifiable compounds but no ethyl ether (33). Thus this approach was abandoned.

To obtain the triol (10), the double bond could also be first hydroxylated and then the ketone reduced to alcohol. Several workers have reported the hydroxylation of olefins to obtain vicinal glycols[16-19]. The procedure of Mori et al[19] was found to be appropriate, and the reagent N-methyl morpholine N-oxide (NMO) was prepared by reported procedure[20]. Using the procedure reported by Mori et al[19], the solid ketone (30) was treated with NMO and osmium tetroxide in catalytic amount, in tertiary butanol to yield diol ketone (34). The diol ketone (34) was identified by its IR, NMR and mass spectra. IR spectrum showed bands at 3442 O-H stretch, 1713 C=O stretch, 1184 C-O stretch and 1112 cm^{-1} C-O stretch. NMR displayed signals at δ 4.33 (s, 1H, $C(OH)C\underline{H}(OH)COCH_2$), 4.1 and 2.45 (2H, D_2O exchangeable hydroxyl protons). Mass spectrum showed molecular ion peak at m/e 240. IR, NMR and mass spectral data does not prove the ß orientation of the hydroxyl groups. The axial and equatorial substituent to ketones in cyclohexanones, show a bathochromic and hypsochromic shift respectively[21]. The unsubstituted cyclohexane shows UV λ_{max} at 285 nm in n-hexane solvent for the n-π^* transition (R-band). An α-axial hydroxyl

SCHEME – 2



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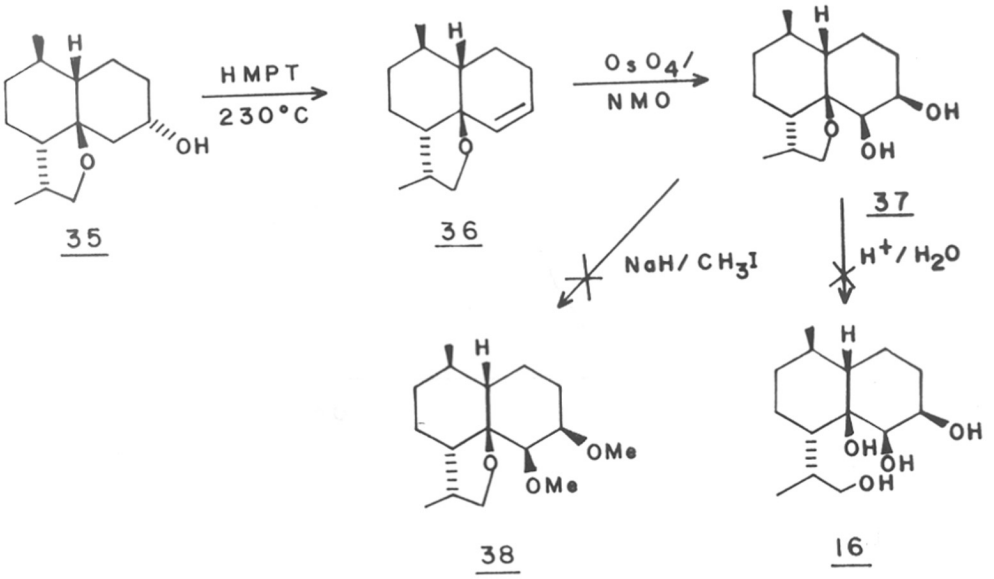
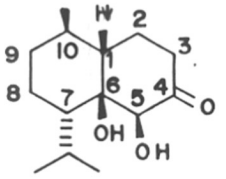
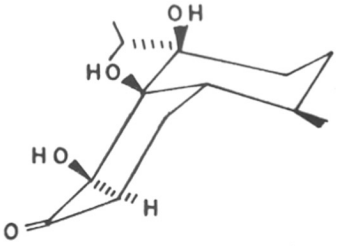


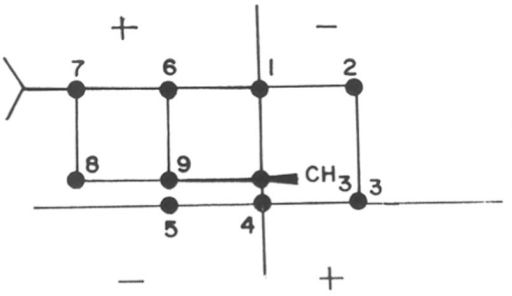
SCHEME – 3



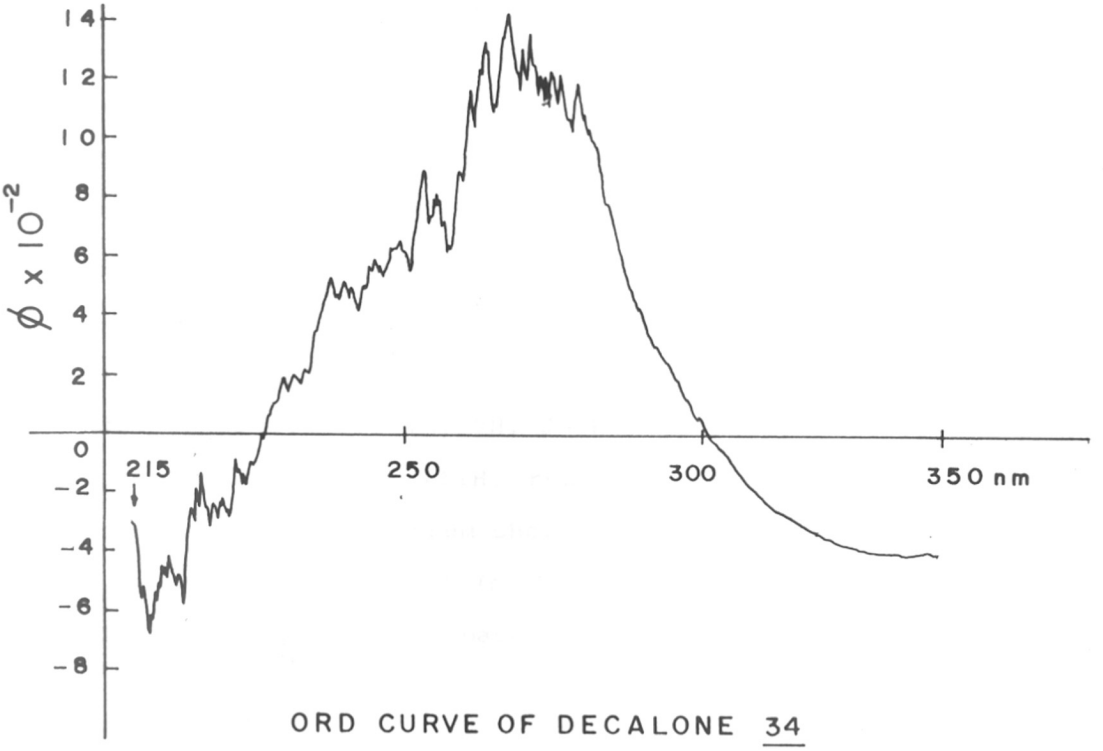
DIOL – KETONE 34



cis-nonsteriodal



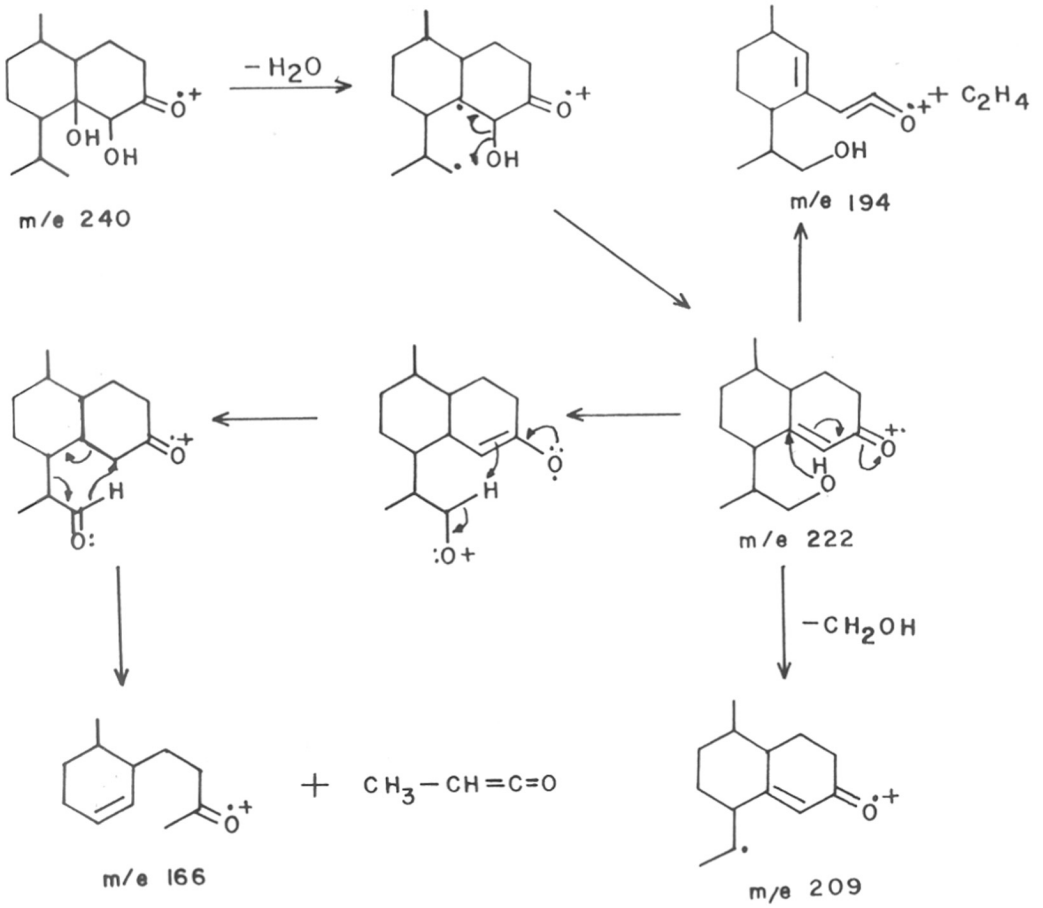
OCTANT DIAGRAM OF DECALONE 34

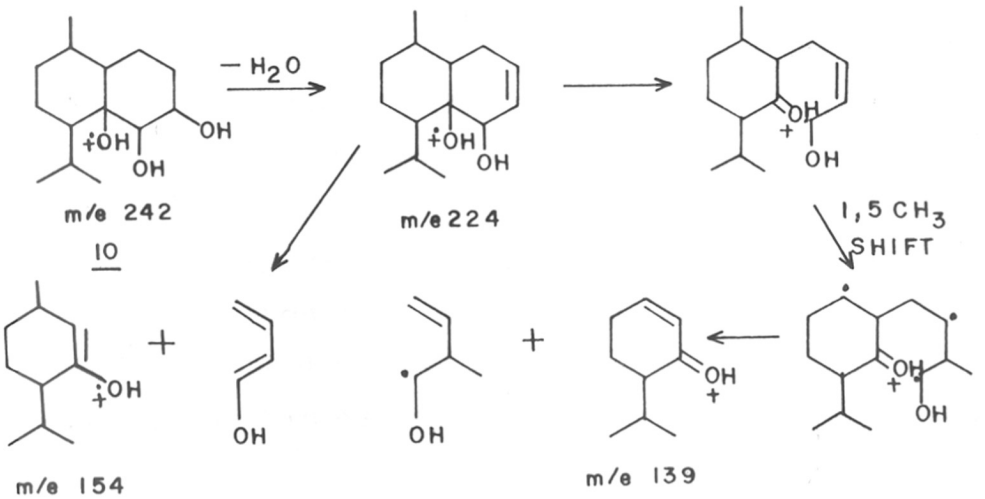


ORD CURVE OF DECALONE 34

substituent in cyclohexane would shift the UV λ_{max} to 302 nm, whereas an α-equitorial hydroxyl substitutent would shift the UV λ_{max} to 273 nm. The UV spectrum of diol ketone (34) was recorded in n hexane, which showed λ_{max} at 275 nm, thus proving the ß-orientation of the hydroxyl groups in diol ketone (35). The ORD spectrum showed a positive cotton effect where by the ß-orientation of the hydroxyl group is proved beyond doubt (see scheme-3). Aygres et al[22,23] reported stereo selective reduction of ketones by aluminium hydride to obtain axial alcohols preferentially. Aluminium hydride was prepared by procedure reported by Brown et al[24], and used for reaction with diol ketone (34) in diethyl ether at -78°C. The diol ketone (34) was retrieved unreacted from the reaction. Thus reduction of the diol ketone (34) was attempted with lithium aluminium hydride in refluxing dry diethyl ether to yield triol (10). The triol (10) was characterised by its IR, NMR and mass spectra. IR showed bands at 3408 O-H stretch, 3300 O-H stretch, 1094 C-O stretch, 1070 C-O stretch and 1053 cm^{-1} C-O stretch. NMR displayed signals at δ 4.0 (d, 1H, J=2Hz, $C(OH)C\underline{H}(OH)CH(OH)CH_2$), 3.76 (dd, 1H, J=2Hz and J=7Hz, $C(OH)CH(OH)C\underline{H}(OH)CH_2$), 3.45 and 3.10 (2H, D_2O exchangeable, $C(O\underline{H})CH(O\underline{H})CH(OH(CH_2)$, 2.9 (d, 1H, J=7Hz, D_2O exchangeable, $C(OH)CH(OH)C\underline{H}(OH)CH_2$), 2.85 (m(7lines), 1H, J=7Hz, $CH_3C\underline{H}CH_3$), 0.8-1.1 (d, 9H, J=7Hz, isopropyl methyl and methyl protons), 1.1-2.15 (11H, rest of the methylene and methine protons). Mass spectrum showed peaks at m/e 242 (M^+), 224 (M^+-H_2O), 206 (M^+-H_2O), 154 (m^+-H_2O-CH_2=CH-CH=CHOH) and 139 (M^+-H_2O-CH_2=CH=$C(CH_3)$=CHOH) as base peak. (see scheme-5). The ß-axial

SCHEME – 5


−H2O
m/e 240
m/e 194
+ C2H4
m/e 222
−CH2OH
m/e 166
+ CH3−CH=C=O
m/e 209

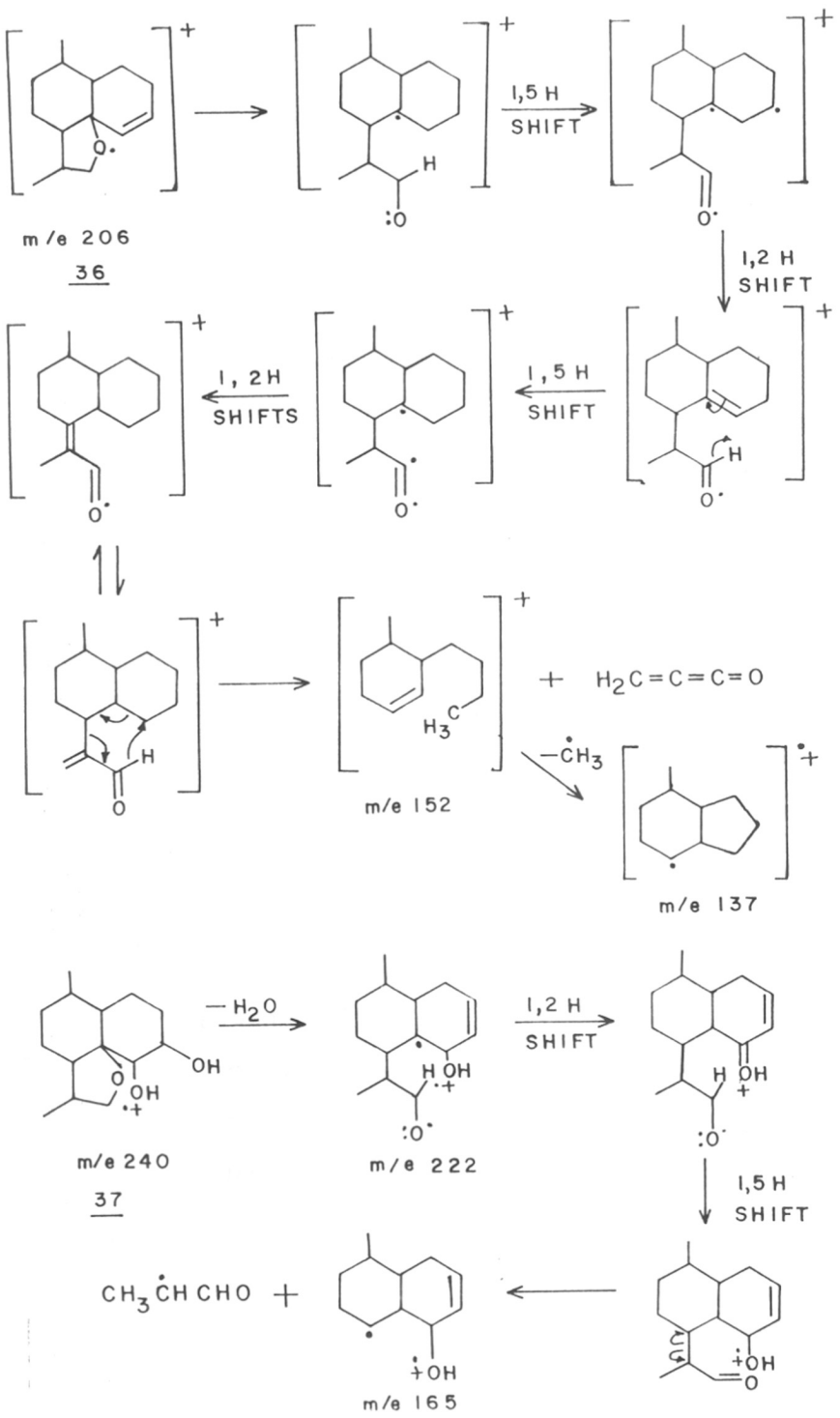

−H2O
m/e 242
m/e 224
1,5 CH3 SHIFT
m/e 154
m/e 139

10

orientation of the hydroxyl group at C_4 is proved by NMR. The coupling constants of protons in cyclohexanes are reported[21] as follows. If the protons are diaxial then they show coupling constant of 8-11 Hz, whereas if the protons are axial-equitorial then they show coupling constant of 2-4 Hz. The protons on C_4 and C_5 of the triol (10) show a coupling constant of 2Hz, hence they must be axial-equitorial orientation. Thus the ß-axial orientation of the hydroxyl group at the C_4 carbon.

The compounds (16) (tetra-alcohol) could be synthesised from hydroxy cyclic ether (35) as shown in scheme-4. Monson et al[25,26] reported the dehydration of secondary alcohols to the corresponding olefin by heating in hexamethylphosphorustriamide (HMPT) to 230°C. Accordingly the hydroxy cyclic ether acetate (35) was heated in HMPT to 230°C for one hour to yield after column chromatography alkene ether (36). The alkene ether (36) was identified by its IR, NMR and mass spectra. IR showed bands at 3021 olefinic C-H stretch, 1654 C=C stretch, 1113 C-O stretch and 1054 cm^{-1} C-O stretch. NMR showed signals at δ 5.6 (bs, 2H, $CH_2C\underline{H}=C\underline{H}-C-O$), 4.1 (t, 1H, J=9Hz, $CH_3CHCH\underline{H}CO$), 3.36 (t, 1H, J=9Hz, $CH_3CHC\underline{H}HCO$). Mass spectrum showed molecular ion peak at m/e 206. The ether diol (37) was obtained from alkene ether (36) by treatment with NMO and catalytic amount of osmium tetroxide in tertiary butanol. The ether diol (37) was identified by its IR, NMR and mass spectra. IR showed bands at 3418 O-H stretch, 1170 and 1128 C-O stretch of alcohols, 1075 and 1046 cm^{-1} C-O stretch of ether. NMR displayed signals at δ 4.5 and 2.67 (2H, D_2O exchangeable, hydroxyl protons), 4.2 (m, 1H, J=9Hz, $CH_3CHCH\underline{H}CO$),

SCHEME – 6


1,5 H SHIFT
m/e 206
36
1,2 H SHIFT
1,5 H SHIFT
1, 2H SHIFTS
+ H2C=C=C=O
m/e 152
m/e 137
– H2O
1,2 H SHIFT
m/e 240
37
m/e 222
1,5 H SHIFT
CH3ĊHCHO +
m/e 165

4.1 (bd, 1H, J=2Hz, $W_{\frac{1}{2}}$=17Hz, CO-C$\underline{H}_{ax}$(OH)CH(OH)CH_2), 3.4 (m, 1H, CO-CH(OH)C$\underline{H}$(OH)CH_2), 3.36 (t, 1H, J=9Hz, CH_3CHC$\underline{H}$HO). Mass spectrum showed molecular ion peak at m/e 240. The half width of proton on C_5 is 17 Hz and hence it is axial proton[14], thus the hydroxyl group on C_5 is ß-equitorial and the hydroxy group on C_4 is ß-axial. Attempts to hydrolyse the tetrahydrofuran moiety of ether diol (37) by acid catalysis failed. Attempts to obtain the triether (38) by sodium hydroxide and methyl iodide also failed. Further work on this scheme and the biological activity testing are in progress.

CONCLUSION

Molecular modelling studies using 'QUAWTA 2' showed compounds (2), (4), (7), (10) and (16) to be promising potential antimalarial compounds. Compounds (2), (4), (7) and (10) were successfully synthesised, whereas attempts to synthesise compound (16) did not succeed. Biological testing for antimalarial activity is in progress.

EXPERIMENTAL

Lactone acetate (2) from cyclic ether acetate (28).

To a stirred solution of cyclic ether acetate (28, 500 mg, 1.9 mmoles) in freshly distilled acetic acid (10 ml) was added chromium trioxide (500 mg, 5 mmoles) in one portion and stirred for 3 days. The reaction was poured in ice-water and neutralised by careful additon of potassium hydroxide solution. The aqueous layer was worked up as usual to yield a solid (400 mg, 76% yield) M.P.=155-157°C. TLC (Solvent C). NMR ($CDCl_3$) : δ 5.00 (m, 1H, J=5Hz, $CH_2C\underline{H}(OAc)CH_2$), 2.26 (m, 1H, J=7Hz, $CH_3C\underline{H}CO\text{-}O$), 2.00 (s, 3H, $CH_2C(O\text{-}CO\text{-}C\underline{H}_3)HCH_2$), 1.17 (d, 3H, J=7Hz, $C\underline{H}_3CHCOO$), 0.93 (d, 3H, J=7Hz, $CHCH(C\underline{H}_3\underline{3})CH_2$) and 1.25-2.25 (13H, rest of the methylene and methine protons). IR showed bands at 1770 lactone C=O stretch, 1735 acetate C=O stretch and 1245 acetate C-O stretch. MS:m/e 280 (M^+), 220 (M^+-CH_3COOH), 205 ($M^+-CH_3COOH-CH_3$), 192 ($M^+-CH_3COOH-C_2H_6$) and 176, 147. $(\alpha_D)^{26}$= -8°(c, 0.525), GC, HP-1, 200°C, r.t.=2.58 min.

Lactone alcohol (3) from lactone acetate (2).

To a stirred cooled saturated solution of methanol and ammonia (10 ml) was added lactone acetate (2, 250 mg, 0.9 mmoles) in one portion. The flask was securely stoppered, the reaction brought to room temperature and stirred for 12 hours. The solvent was removed in vacuo, and water added to the residue. The aqueous layer was worked up as usual to yield an oil (200 mg, 94% yield). TLC (Solvent D). NMR ($CDCl_3$) : δ 3.88 (m, 1H, $CH_2C\underline{H}(OH)CH_2$), 2.4 (m, 1H, J=7Hz, $CH_3C\underline{H}COO$), 1.14 (d, 3H, J=7Hz, $C\underline{H}_3CHCOO$), 0.9 (d, 3H, J=7Hz, $CHCH(C\underline{H}_3)CH_2$) and 1.25-1.22 (14H,

rest of the methylene and methine protons). IR ($CHCl_3$) showed bands at 3403 O-H stretch, 1763 C=O stretch and 1255 cm^{-1} C-O stretch. MS:m/e 238 (M^+), GC, HP-1, 200°C, r.t.=1.67 min.

Lactone ethyl carbonate (4) from lactone alcohol (3)

To a cooled stirred solution of lactone alcohol (3, 75 mg, 0.3 mmoles) in pyridine (5 ml), ethyl chloro formate (0.1 ml , 0.93 mmoles) was added in one portion. The reaction was stirred for 12 hours and worked up as usual to yield an oil (90 mg, 92% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 5.10 (m, 1H, $CH_2\underline{CH}$(OCOOEt) CH_2), 4.2 (q, 2H, J=7Hz, $CH_3\underline{CH_2}OCOO$), 2.5 (m, 1H, J=8Hz, $CH_3\underline{CH}COO$), 1.3 (t, 3H, J=7Hz, $OOCOCH_2\underline{CH_3}$), 1.2 (d, 3H, J=8Hz, $\underline{CH_3}CHCOO$), 0.99 (d, 3H, J=7Hz, $CHCH(\underline{CH_3})CH_2$) and 1.2-2.2 (13H, rest of the methylene and methine protons). IR ($CHCl_3$) showed bands at 1775 carbonate C=O stretch, 1769 lactone C=O stretch, 1262 C-O stretch and 1215 C-O stretch. MS:m/e 222 (M^+-CO_2-CH_3CHO), 207(M^+-CO_2-CH_3CHO-CH_3), 179 (M^+-CO_2-CH_3CHO-CH_3-C_2H_4) and 69 ($C_3H_3O_2^+$) as base peak. $(\alpha_D)^{26}$= -3.9° (c, 0.83), GC, 200°C, r.t.=7.1 min.

Dihydroxy acid (6) from cyclic ether acetate (2)

To a stirred solution of cyclic ether acetate (2, 250 mg, 0.9 mmoles) in absolute alcohol (10 ml) potassium hydroxide (250 mg, 4.5 mmoles) was added in one portion. The reaction was stirred for 4 hours, neutralised, solvent removed in vacuo and worked up as usual to yield an oil (200 mg, 87% yield), chromatographed on a silica-gel column to yield pure (150 mg)

dihydroxy acid (6). TLC (solvent D). NMR ($CDCl_3$) : δ 3.44-4.18 (3H, $CH_2C\underline{H}(OH)CH_2$, $CH_2CH(O\underline{H})CH_2$ and $CH_3CHCOO\underline{H}$), 2.4 (m, 1H, J=7Hz, $CH_3C\underline{H}COOH$), 2.0 (1H, D_2O exchangeable, $CHC(O\underline{H})CH_2CH(OH)CH_2$), 1.18 (d, 3H, J=7Hz, $C\underline{H}_3CHCOOH$), 0.9 (d, 3H, J=7Hz, $CHCH(C\underline{H}_3)CH_2$) and 1.25-2.2 (13H, rest of the methylene and methine protons). IR showed bands at 3400 O-H stretch, 1720 C=O stretch, 1060 C-O stretch and 1085 cm^{-1} C-O stretch. MS:m/e 256 (M^+), 238 (M^+-H_2O), 220 (M^+-2H_2O) and 205 ($M^+-2H_2O-CH_3$). $(\alpha_D)^{26}$= +2.0° (c, 0.815). GC, 200°C, r.t.=6.79 min.

Methyl ester (7) from dihydroxy acid (6)

To a cooled solution of nitrosomethyl urea (1.078g, 7.8 mmoles), in diethyl ether (50 ml) was added slowly with shaking, ice cold potassium hydroxide (50%) solution. The ether layer was transferred to test tubes with potassium hydroxide pellets. The aqueous layer was washed with diethyl ether (3x10 ml). The pooled ether layers with diazomethane was decanted off into a cooled stirred solution of dihydroxy acid (6, 400 mg, 1.56 moles) in methanol (20 ml). As much diazomethane in ether was added, until a pale yellow color persisted. The reaction was stirred for 15 minutes and solvent removed in vacuo to yield oil (350 mg, 83% yield). TLC (solvent D).NMR ($CDCl_3$) : δ 3.6 (s, 3H, $CH_3CHCOOC\underline{H}_3$), 3.86 (m, 1H, $CH_2C\underline{H}(OH)CH_2$), 3.33(1H, D_2O exchangeable, $CH_2CH(O\underline{H})CH_2$), 2.35 (m, 1H, $CH_3C\underline{H}COOCH_3$), 1.1 (d, 3H, J=7Hz, $C\underline{H}_3CHCOOCH_3$), 0.96 (d, 3H, J=7Hz, $CHCH(C\underline{H})_3CH_2$) and 1.25-2.2 (14H, rest of the methylene and methine protons). MS:m/e 270 (M^+), $(\alpha_D)^{26}$= +8.8° (c, 0.705).

Diol Ketone (34) from solid ketone (30)

To solid ketone (30, 500mg, 2.4 mmoles) in an inert atmosphere of ultra pure argon gas was added osmium tetroxide (308 mg, 1.2 mmoles) dissolved in freshly distilled tertiary butanol (10ml). To the stirred solution under argon was added N-methyl morpholine N-oxide (NMO)(568 mg, 4.9 mmoles) dissolved in distilled water (5 ml). The reaction was further stirred for 9 hours and saturated solution of sodium bisulphate (1.5 ml) was added. The reaction was filtered through a celite column, which was washed subsequently with tertiary butanol (100 ml). The filtrate was dried over anhydrous sodium sulphate and solvent removed in vacuo, to yield an oil (490 mg, 84% yield). TLC (Solvent D). NMR ($CDCl_3$): δ 4.33 (s, 1H, C(OH)C<u>H</u>(OH)C=OCH_2), 4.1 (1H, D_2O exchangeable, C(OH)CH(O<u>H</u>)C=OCH_2), 2.45 (1H, D_2O exchangeable, C(O<u>H</u>)CH(OH)C=OCH_2), 0.8-1.2 (d, 9H, J=7Hz, <u>CH_3</u>-CH-<u>CH_3</u> and CHCH(<u>CH_3</u>)CH2) and 1.2-2.5 (14H, rest of the methylene and methine protons). IR shows bands at 3442 O-H stretch, 1713 C=O stretch, 1184 C-O stretch and 1112 cm^{-1} C-O stretch. MS: m/e 240 (M^+), 222 (M^+-H_2O), 209(M^+-CH_2OH), 194 ($M^+-H_2O-C_2H_4$), 180 ($M^+-H_2O-CH_2CO$) and 166 ($M^+-H_2O-CH_3CHCO$) as base peak. UV: λ_{max}=275nm. $(\alpha_D)^{26}$ = -3.4° (c, 2.03). GC, 200°C, r.t. = 2.67 min.

Triol (10) from diol ketone(34)

To a stirred, cooled suspension of lithium aluminium hydride (24 mg, 0.63 mmoles) in dry diethyl ether (10 ml) was added slowly diol ketone (34, 300 mg, 1.25 mmoles) dissolved in dry ethyl

ether (5 ml). The reaction was brought to room temperature and refluxed with aid of an infra-red lamp for 10 hours. To the reaction mixture distilled water (0.1 ml) was added under vigorous stirring, followed by 15% sodium hydroxide (0.1 ml) and followed by water (0.1 ml). The reaction was filtered through a buchner funnel and the filterate extracted with dichloro methane (3x100 ml). The organic layer after usual work up yielded a solid (200 mg, 66% yield). M.P.=76-78°C, TLC (Solvent D). IR (Neat) showed bands at 3408 O-H stretch, 3300 O-H stretch, 1094 C-O stretch, 1070 C-O stretch and 1053 cm^{-1} C-O stretch. NMR($CDCl_3$3) : δ 4.0 (d, 1H, J=2Hz, C(OH)C<u>H</u>(OH)CH(OH)CH_2), 3.76 (dd, 1H, J=2Hz and J=7Hz, C(OH)CH(OH)C<u>H</u>(OH)CH_2), 3.45 and 3.10 (2H, D_2O exchangeable, C(O<u>H</u>)CH(O<u>H</u>)CH(OH(CH_2), 2.9 (d, 1H, J=7Hz, D_2O exchangeable, C(OH)CH(OH)C<u>H</u>(OH)CH_2), 2.85 (m(7lines), 1H, J=7Hz, $CH_3C\underline{H}CH_3$), 0.8-1.1 (d, 9H, J=7Hz, isopropyl methyl and methyl protons), 1.1-2.15 (11H, rest of the methylene and methine protons). MS :m/e 242 (M^+), 224 (M^+-H_2O), 206 (M^+-H_2O), 154 ($m^+-H_2O-CH_2$=CH-CH=CHOH) and 139 ($M^+-H_2O-CH_2$=CH=C(CH_3)=CHOH) as base peak. (see scheme-5). $(\alpha_D)^{26}$= -10.7° (c, 0.805). GC, 200°C, r.t.= 3.68 min.

Alkene ether (<u>36</u>) from hydroxy cyclic ether (<u>35</u>)

A solution of hydroxy cyclic ether (<u>35</u>, 500 mg 2.2 mmoles) in hexa methyl phosphorus triamide (10 ml) was heated to 230°C for one hour. Usual work up yielded an oil (450 mg, 100% recovery). The oil was chromatographed on a silica-gel column to yield the alkene ether (<u>36</u>, 200 mg, 44% yield) in the 10% ethyl

acetate : 90% benzene eluate. TLC (Solvent B). NMR ($CDCl_3$) : δ 5.6 (bs, 2H, C(O)C<u>H</u>=C<u>H</u>CH_2), 4.1 (t, 1H, J=9Hz, $CH_3CHCH\underline{H}CO$), 3.36 (t, 1H, J=9Hz, $CH_3CHC\underline{H}HCO$), 0.83-1.13 (d, 6H, J=7Hz, $C\underline{H}_3CHCH_2O$ and $CHCH(C\underline{H}_3)CH_2$) and 1.13-2.24 (12H, rest of the methylene and methine protons). IR showed bands at 3021 olefinic C-H stretch, 1654 C=C stretch, 1113 C-O stretch and 1054 cm^{-1} C-O stretch. MS:m/e 206 (M^+), 191 (M^+-CH_3), 152 ($M^+-CH_2=C=C=O$) and 137 ($M^+-CH_3CH_2=C=C=O$) as base peak. $(\alpha_D)^{26}$=-45.3°C (C, 0.875), GC, 170°C, r.t.=3.00 min.

Ether diol (<u>37</u>) from alkene ether (<u>36</u>)

The alkene ether (<u>36</u>, 88 mg, 0.43 mmoles) was subjected to reaction with osmium tetroxide (57 mg, 0.22 mmoles), N-methyl morpholine N-oxide (118 mg, 1.0 mmoles) water (2 ml) in tertiary butanol (5 ml) using the procedure described for conversion of solid ketone (<u>30</u>) to diol ketone (<u>34</u>). Usual work up yielded an oil (90 mg, 87% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 4.5 and 2.67 (2H, D_2O exchangeable, hydroxyl protons), 4.2 (m, 1H, J=9Hz, $CH_3CHCH\underline{H}CO$), 4.1 (bd, 1H, J=2Hz, $W_{\frac{1}{2}}$=17Hz $COC_{Hax}(OH)CH(OH)CH_2$), 3.4 (m, 1H, $COC_{Hax}(OH)C_{Heq}(OH)CH_2$), 3.36 (t, 1H, J=9Hz, $CH_3CHC\underline{H}HCO$) 0.95-1.1 (d, 6H, J=7Hz, $C\underline{H}_3CHCH_2O$ and $CHCH(C\underline{H}_3)CH_2$) and 1.1-2.3 (12H, rest of the methylene and methine protons). IR showed bands at 3418 O-H stretch, 1170 alcohol C-O stretch, 1128 alcohol C-O stretch, 1075 ether C-O stretch, and 1046 cm^{-1} ether C-O stretch. MS:m/e 240 (M^+), 225 (M^+-CH_3), 222 (M^+-H_2O) and 165 ($M^+-H_2O-CH_3CHCHO$) as base peak. $(\alpha_D)^{26}$= -14.7° (c, 0.925). GC, 200°C, r.t.= 4.12 min.

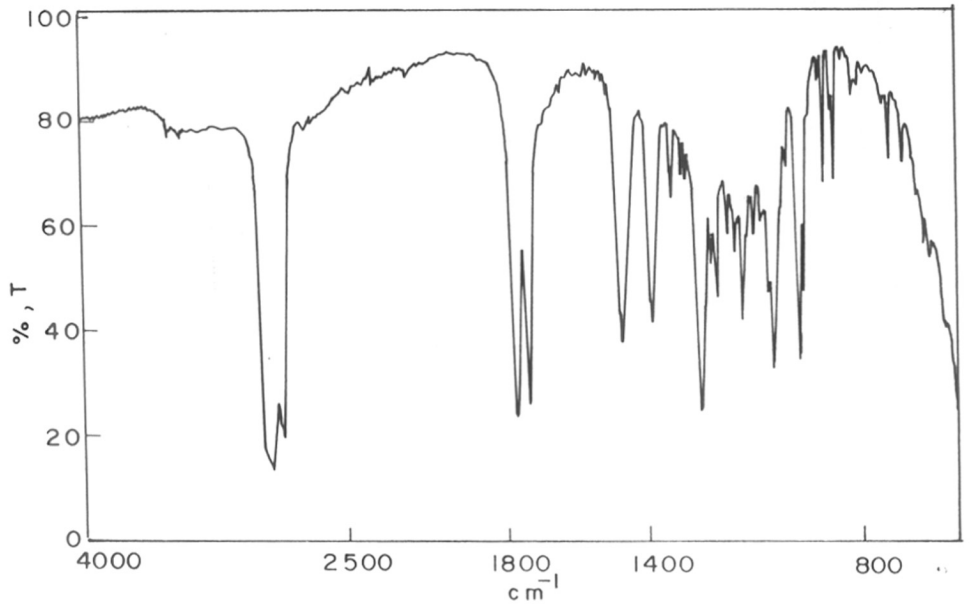


FIG.2B.1 : IR OF COMPOUND ACETATE LACTONE (2)

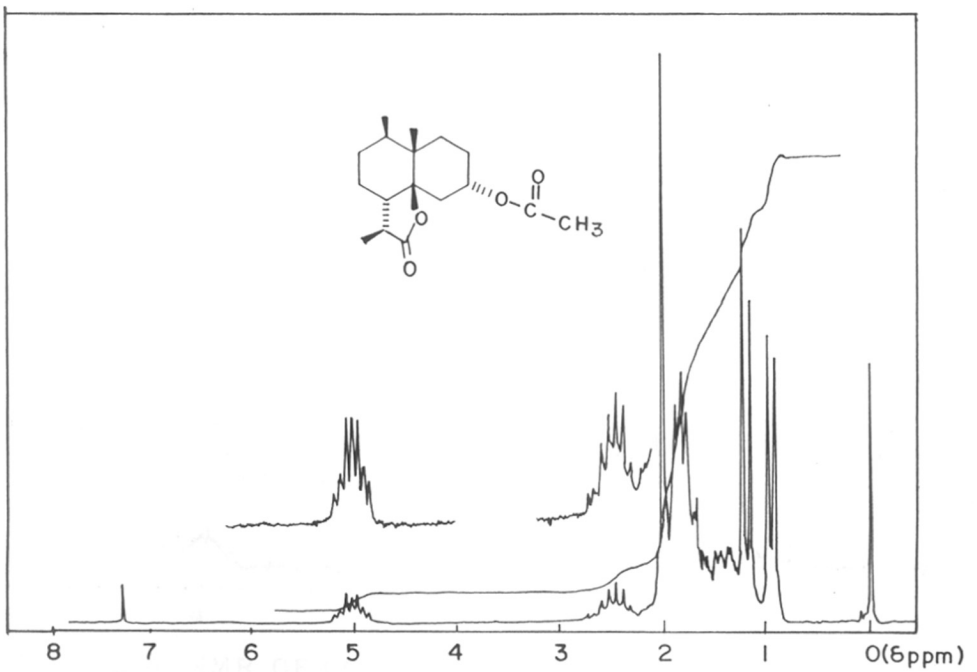


FIG. 2B.2 : NMR OF COMPOUND ACETATE LACTONE (2)

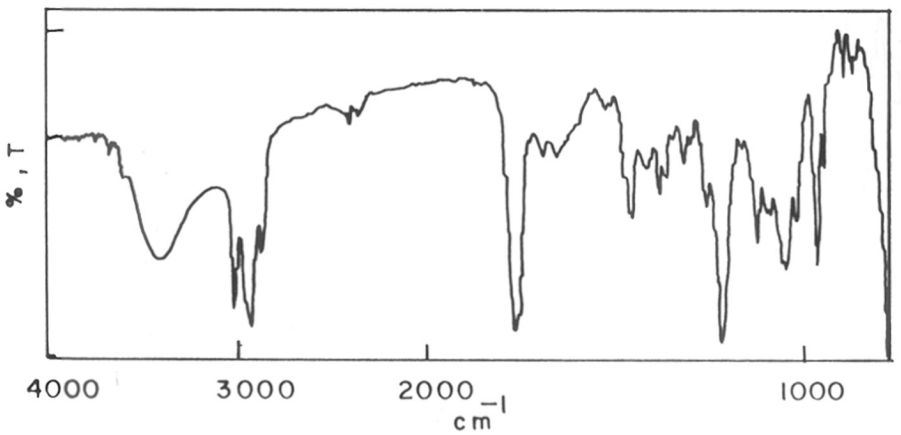


FIG. 2 B.3 : IR OF COMPOUND LACTONE ALCOHOL (3)

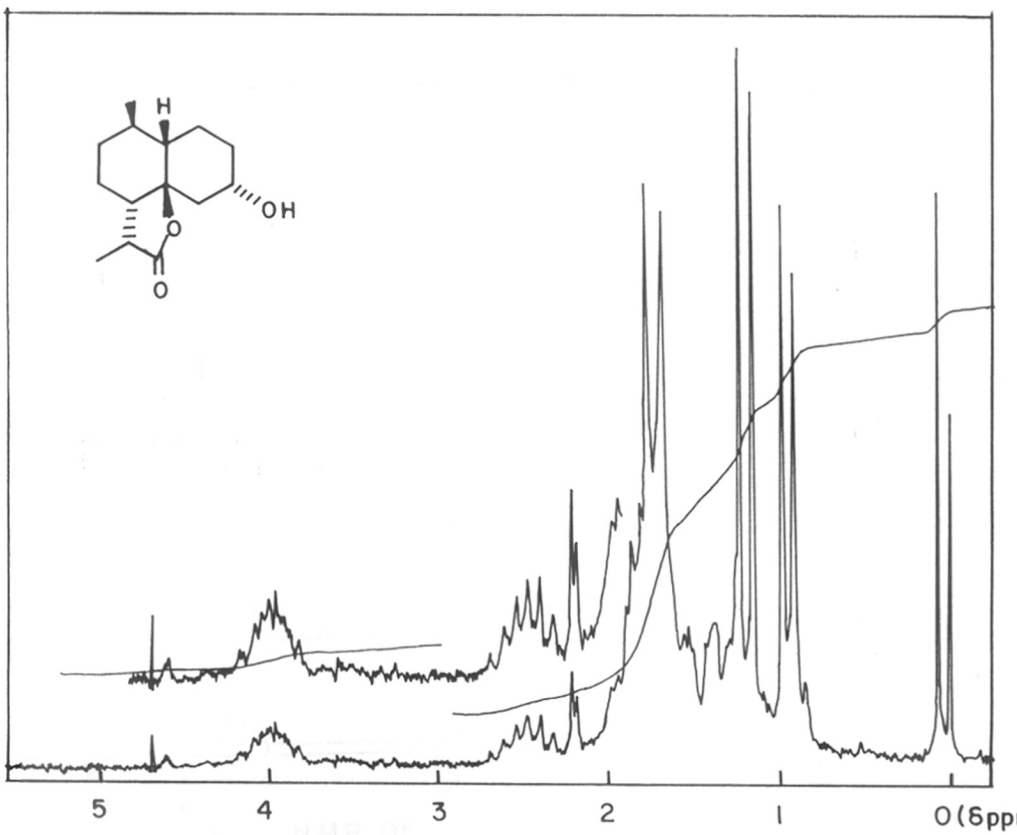


FIG. 2 B.4 : NMR OF COMPOUND LACTONE ALCOHOL (3)

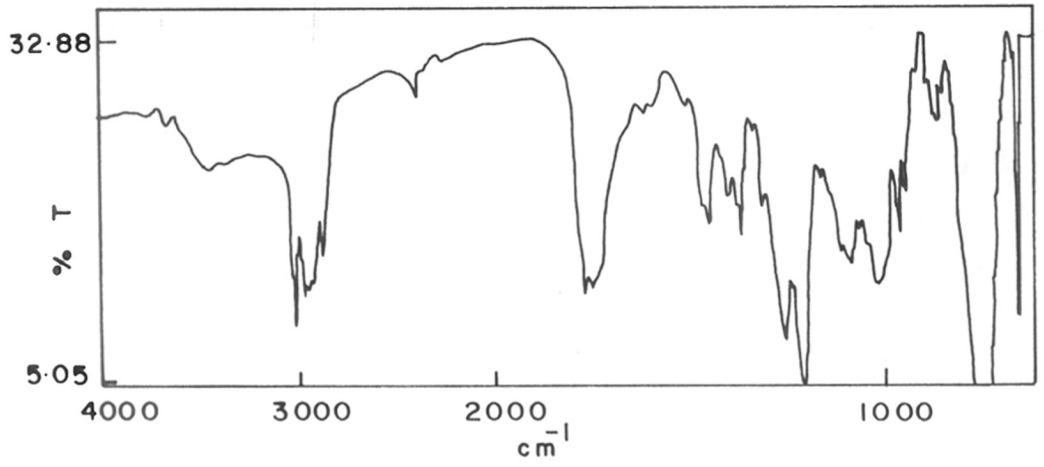


FIG. 2 B.5 : IR OF LACTONE ETHYL CARBONATE (4)

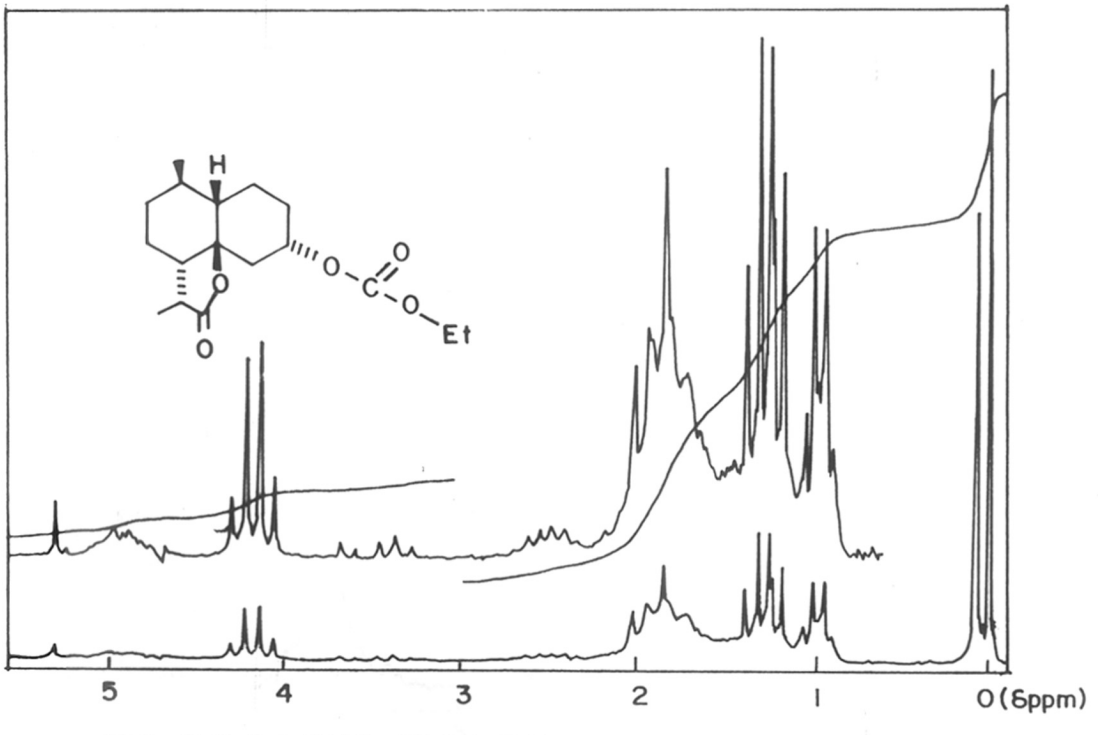


FIG. 2 B.6 : NMR OF LACTONE ETHYL CARBONATE (4)

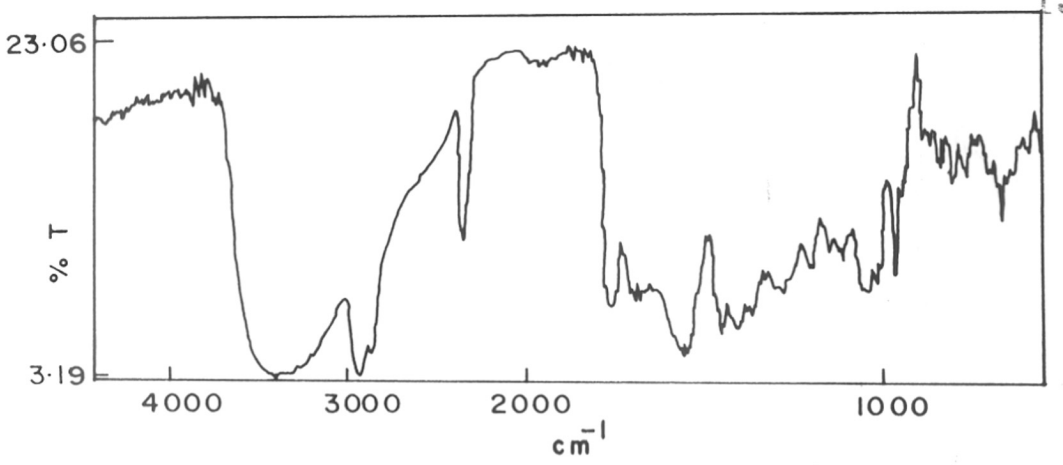


FIG. 2 B.7 : IR OF DIHYDROXYACID (6)

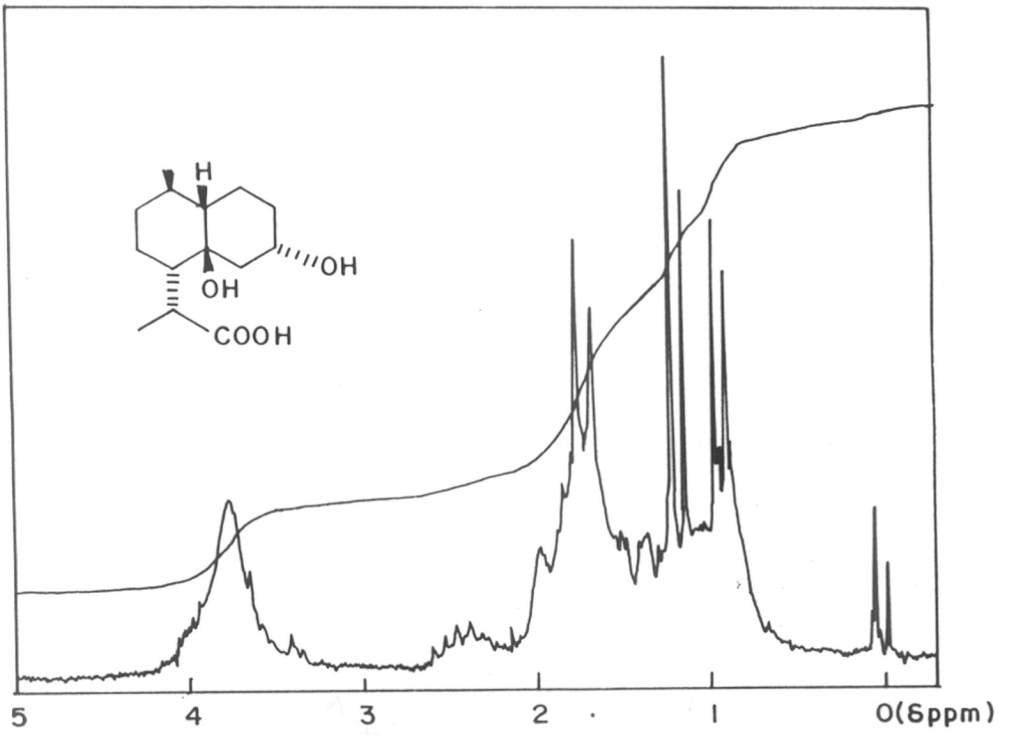


FIG. 2 B.8 : NMR OF DIHYDROXYACID (6)

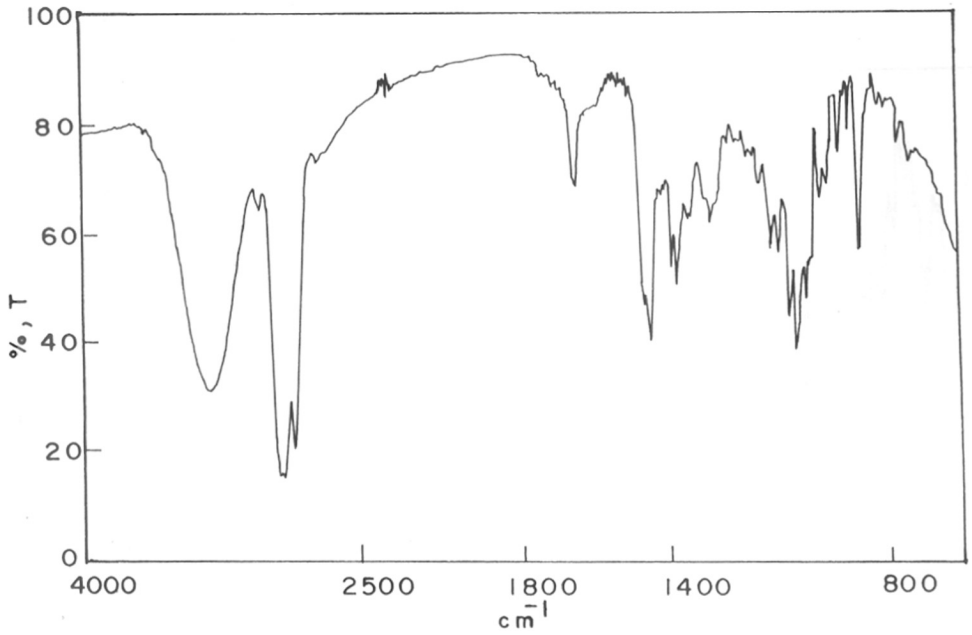


FIG. 2B.9: IR OF ALLYLIC ALCOHOL (31)

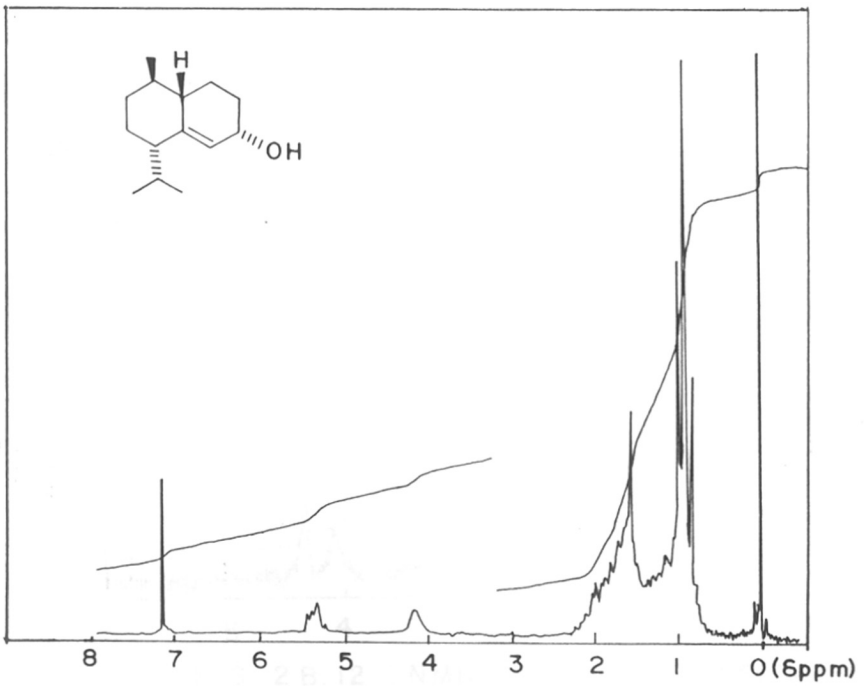


FIG. 2B.10: NMR OF ALLYLIC ALCOHOL (31)

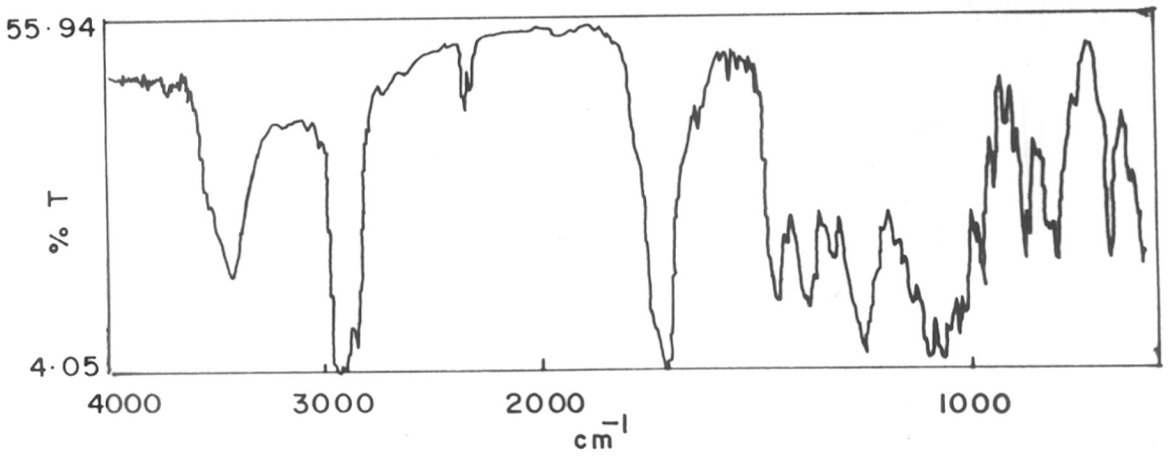


FIG. 2B.11 : IR OF DIOL KETONE (34)

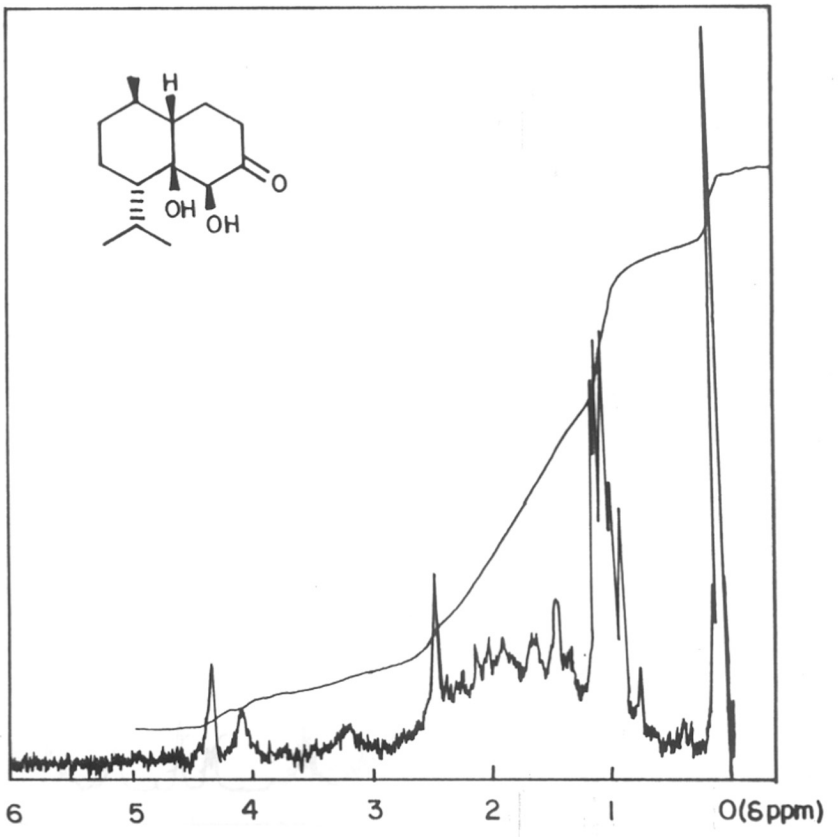


FIG. 2B.12 : NMR OF DIOL KETONE(34)

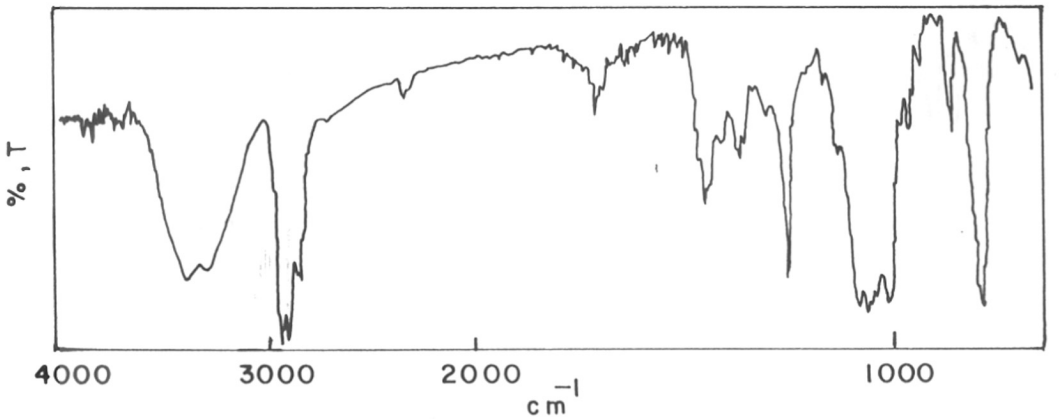


FIG. 2B: 13 : IR OF TRIOL (10)

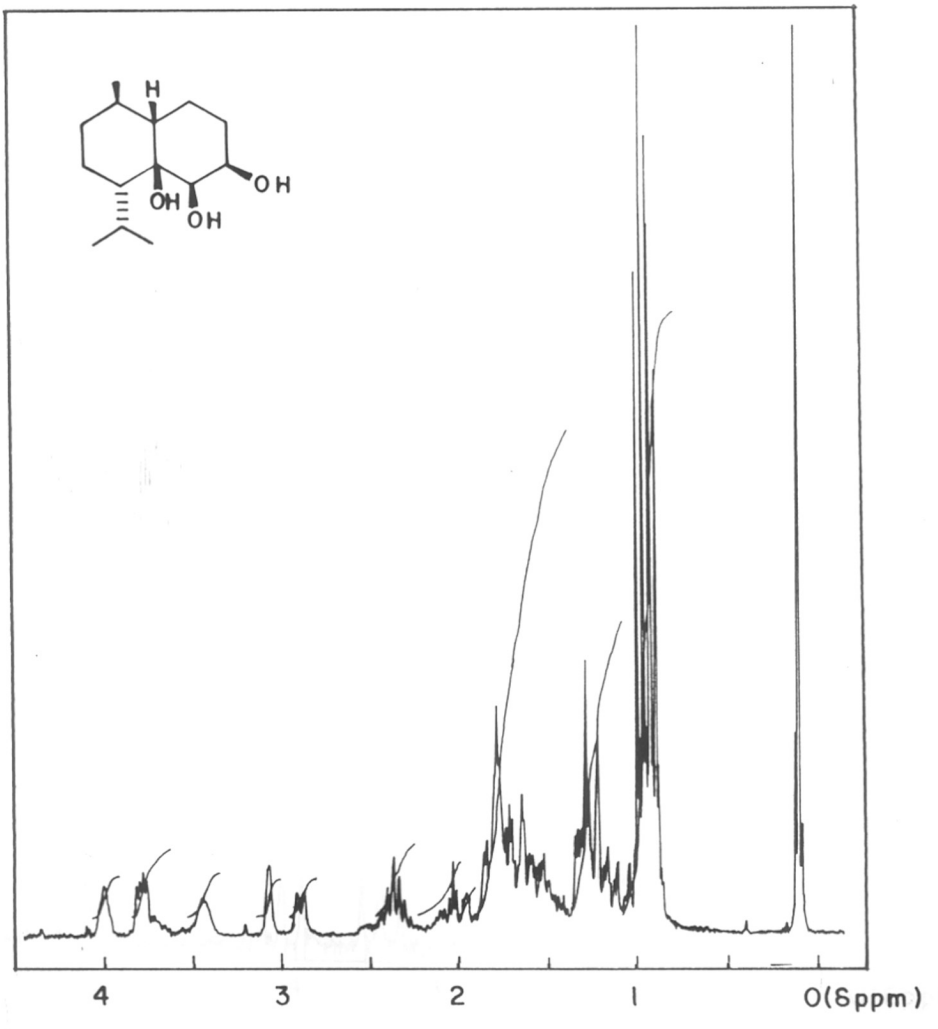


FIG. 2 B. 14 : NMR OF TRIOL (10)

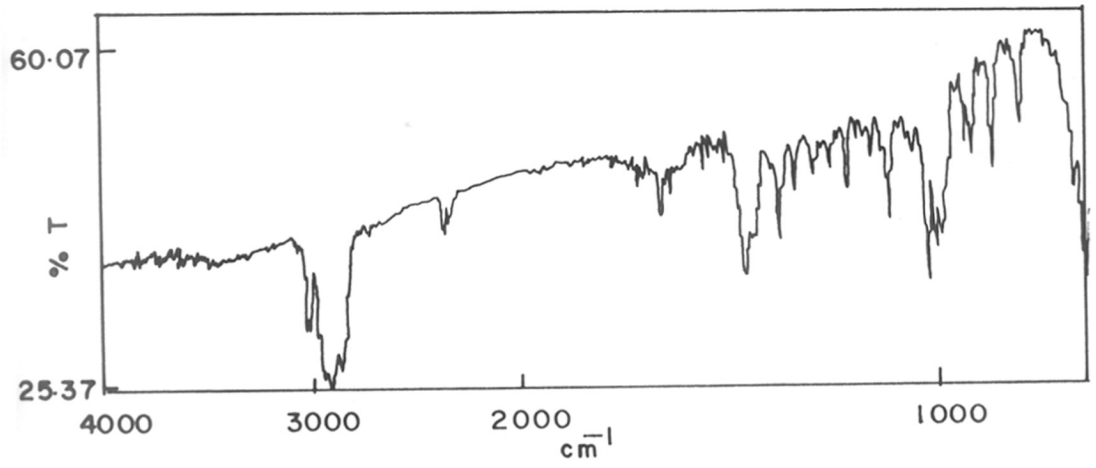


FIG. 2B. 15 : IR OF ALKENE ETHER (36)

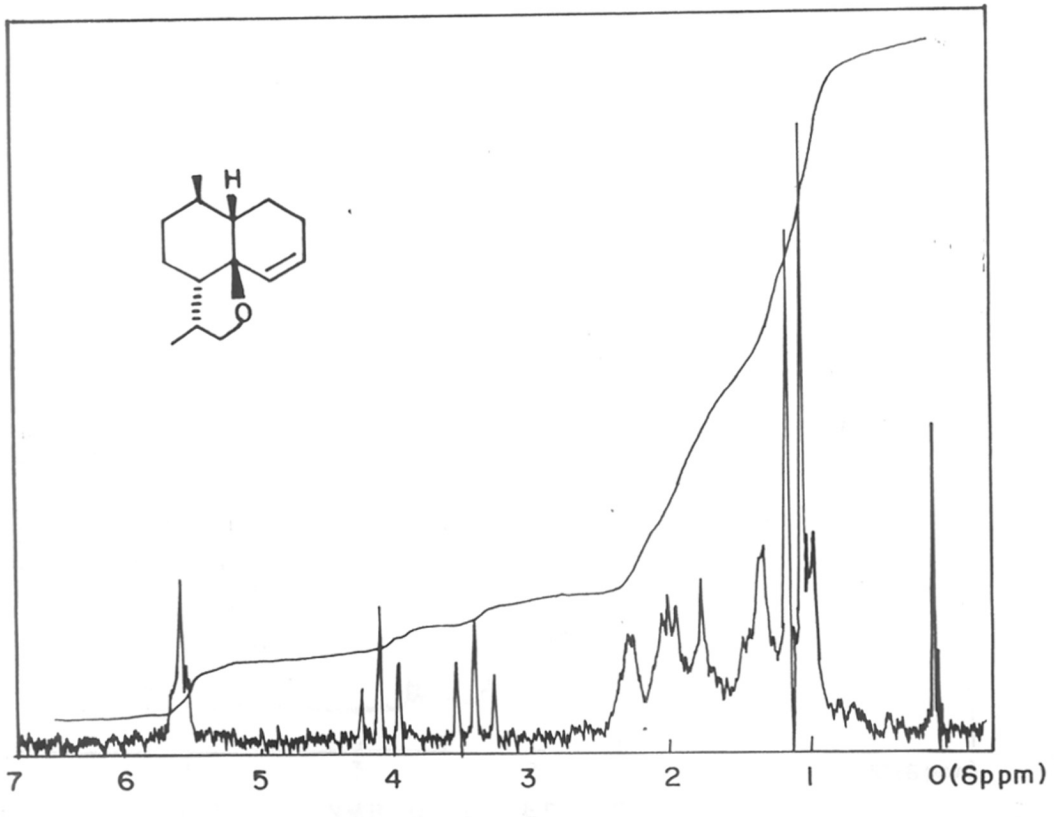


FIG. 2B. 16 : NMR OF ALKENE ETHER (36)

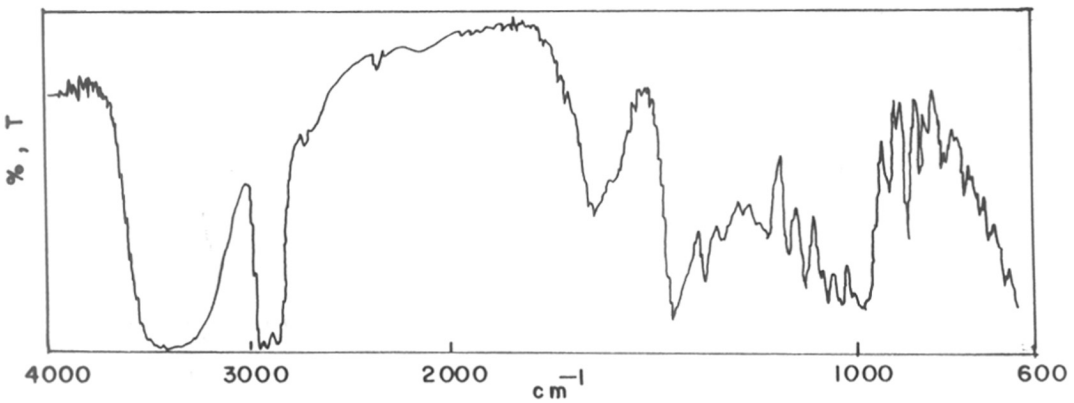


FIG. 2B.17 : IR OF ETHER DIOL (37)

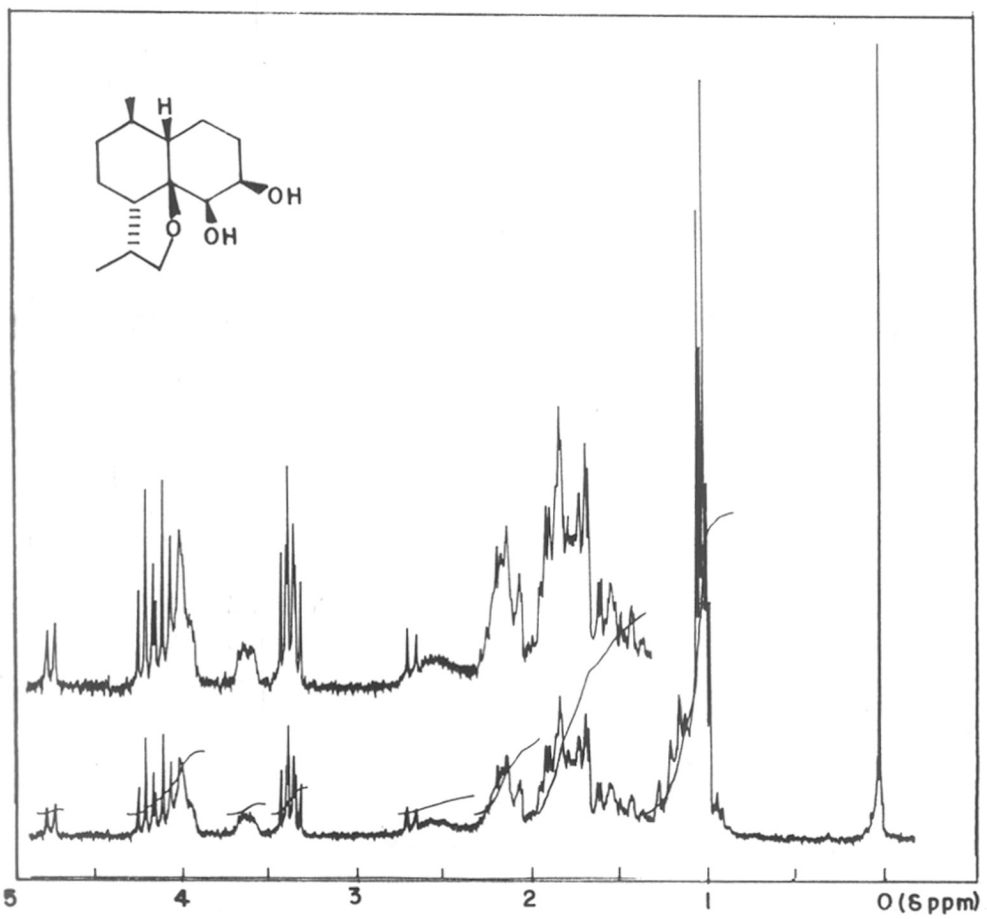


FIG. 2B.18 : NMR OF ETHER DIOL (37)

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CHAPTER II

PART C

SYNTHESIS OF PARTHENIN DERIVATIVE POTENTIAL ANTIMALARIAL COMPOUNDS

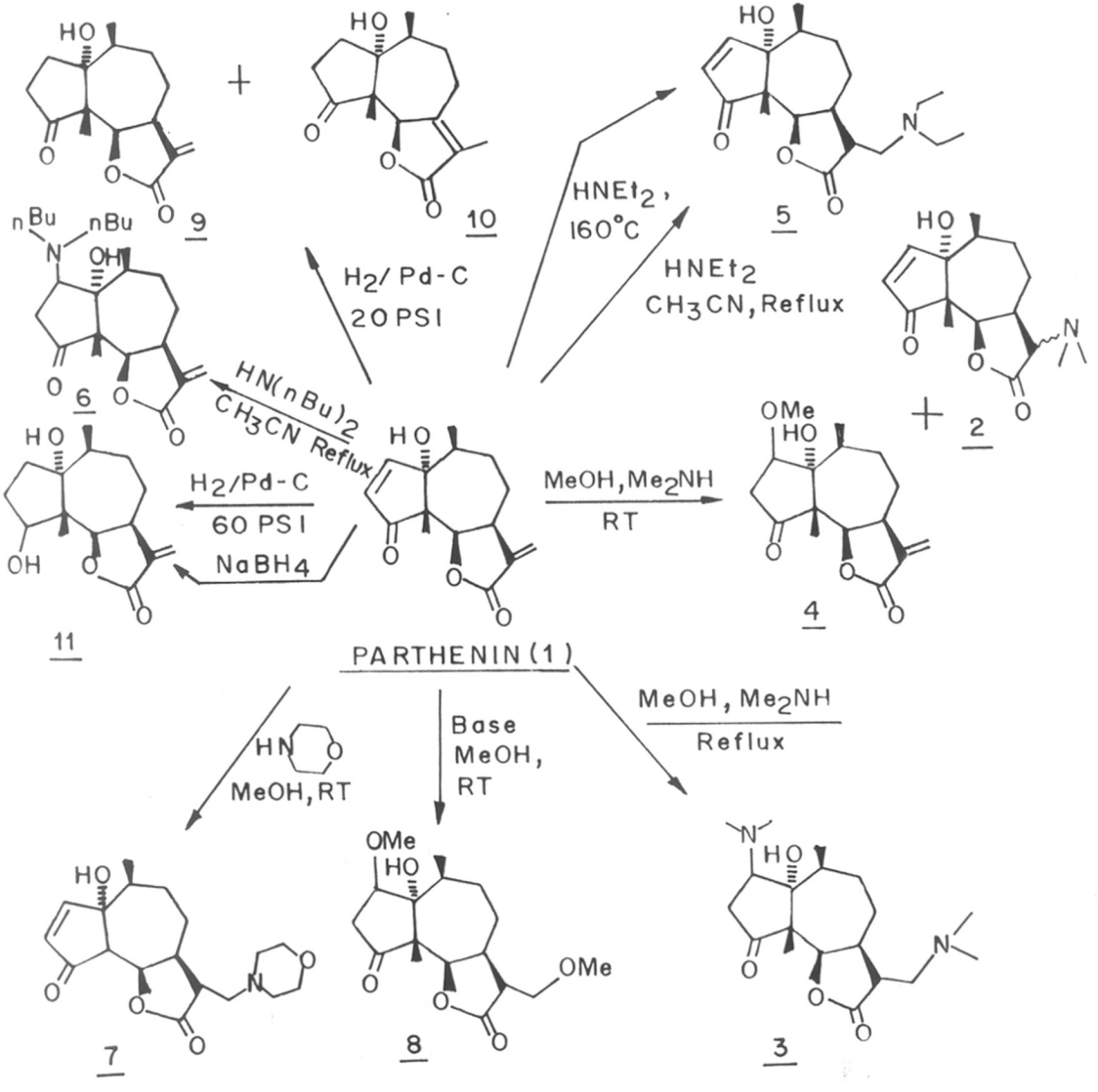
Introduction

As described earlier, in the brief review of biological activity of parthenin (1), the dimethyl amine mono adduct (2) showed nearly twice the antimalarial activity than that of parthenin (1). The dimethyl amine diadduct (3) was hence expected to be more active, and so also the other secondary amine diadducts. Thus, the work of conversion of parthenin (1) to its various derivatives was undertaken.

Present Work

Parthenin (1) was isolated from Parthenium hysterophorous L by solvent extraction and purified by repeated column chromatography. Crystalline parthenin so obtained was used for the preparation of the derivatives as described below. Hooper et al[1] reported the conversion of parthenin (1) to the dimethylamine mono adduct (2) by treatment of dimethyl amine. Using an identical procedure the dimethyl amine mono adduct (2) was prepared and characterised by its IR, NMR and mass spectra. IR showed bands at 3446 O-H stretch, 1755 lactone C=O stretch, 1725 C=O stretch and 1161 cm^{-1} C-O stretch. NMR displayed signals at δ 7.5 (d, 1H, J=6Hz, H-2), 6.1(d, 1H, J=6Hz, H-3), 5.93(d, 1H, J=8Hz, H-6), 2.2(s, 6H, ß-$CH_2N\underline{Me}_2$), 2.1(s, 3H, α-CH_2-N-$\underline{Me}_2$), 1.35 (s, 3H, ß-methyl on C-5), 1.2 (s, 3H, α-methyl on C-5), 1.1(d, 3H, J=8Hz, methyl on C-10) and 1.3-2.9 (10H, rest of the methylene and methine protons). Mass spectrum showed molecular ion peak at m/e 307. Treatment of parthenin (1) with

SCHEME - 1


HO
9
10
5
nBu
nBu
N
OH
6
HNEt2 ,
160°C
HNEt2
CH3CN, Reflux
H2/ Pd-C
20 PSI
HN(nBu)2
CH3CN Reflux
2
OMe
HO
H2/Pd-C
60 PSI
NaBH4
MeOH,Me2NH
RT
OH
11
4
PARTHENIN (1)
MeOH, Me2NH
Reflux
HN
O
MeOH, RT
Base
MeOH,
RT
OMe
7
8
3

dimethylamine gas at room temperature in methanol did not yield the diadduct (3), but the monoadduct (2) and the mono methoxy adduct (4) reported by Bhat et al[2]. The spectral characteristics of mono methoxy adduct (4) (IR, NMR and mass spectra) were in complete agreement with those reported. In a modified procedure, methanol was saturated with anhydrous dimethyl amine gas at 0°C and then parthenin (1) added to it. This solution was refluxed, continuing the bubbling of dimethylamine gas simultaneously. After workup the reaction afforded the dimethyl amine diadduct (3), which was identified by its IR, NMR and mass spectra. IR showed bands at 3474 O-H stretch, 1748 C=O stretch and 1168 cm^{-1} C-O stretch. NMR displayed signals of δ 4.75(d, 1H, J=8Hz, H-6), 2.3 (s, 6H, $CH_2N(C\underline{H}_3)_2$), 2.15(s, 6H, $CHN(C\underline{H}_3)_2$). Mass showed molecular ion peak at m/e 352. Treatment of parthenin (1) with diethyl amine in methanol at room temperature gave again the monomethoxy adduct (4) instead of the desired diethylamine adduct (5). On refluxing parthenin (1) with diethylamine in acetonitrile furnished the diethyl amine adduct (5) in poor yields which was identified by its IR, NMR and mass spectra. IR showed bands at 3463 O-H stretch, 1759 lactone C=O stretch, 1716 C=O stretch, 1653 C=C stretch, 1244 lactone C-O stretch and 1162 cm^{-1} alcohol C-O stretch. NMR displayed signals at δ 7.5(d, 1H, J=6Hz, H-2), 6.16(d, 1H, J=6Hz, H-3), 4.98(d, 1H, J=8Hz, H-6), 2.71(q, 4H, J=7Hz, CH_2-N-($C\underline{H}_2CH_3$) and 1.24(t, 6H, J=7Hz, $CH_2N(CH_2C\underline{H}_3)_2$). Mass spectrum showed molecular ion peak at m/e 335. The mono adduct (5) was obtained in good yields by heating parthenin (1) with diethyl amine at 160°C. The di n-butyl amine

adduct (6) was obtained by refluxing parthenin (1) and di-n-butylamine in acetonitrile. The di-n-butylamine adduct (6) was identified by its IR, NMR and mass spectra. IR spectrum showed bands at 3500 O-H stretch, 1760 lactone C=O stretch , 1720 C=O stretch and 1655 cm^{-1} C=C stretch, NMR displayed signals at δ 6.2(d, 1H, J=3Hz, H-13), 5.54(d, 1H, J=3Hz, H-13), 4.94(d, 1H, J=8Hz, H-6), 4.24(t, 1H, J= 8Hz, H-2) and 0.9(t, 6H, J=7Hz, terminal methyl of n-butyl). Mass spectrum showed molecular ion peak at m/e 391. The monomorphilino adduct (7) was prepared by reported procedure[3], and the spectral characteristic were in complete agreement with those reported. Attempts to obtain either mono or diadduct with parthenin of diisopropyl amine and diphenyl amine in methanol failed and instead the dimethoxy adduct (8) was obtained. The spectral characteristics of the diadduct (8) were in total agreement with those reported[2]. The dihydro parthenin (9) and isodihydro parthenin (10) were obtained on catalytic hydrogenation of parthenin (1) at 20 PSI pressure. These compounds were separated by chromatography and well characterised by IR, NMR and mass spectra. All the spectral characteristics were in complete agreement with there reported[4,5,6]. The tetrahydro parthenin (11) was obtained by catalytic hydrogenation of parthenin (1) at 60 PSI pressure, and characterised by IR, NMR and mass spectra. The tetrahydro parthenin (11) was also obtained by treatment of parthenin (1) with sodium borohydride and boron trifluoride in tetrahydrofuran. The spectral characteristics of the tetrahydroparthenin (11) was in agreement with those reported[5]. All the previously reported

compound (4), (7), (8), (9), (10) and (11) were prepared for testing antimalarial activity and the subsequent use of the data so obtained for qualitative and quantitative structure activity relationship study by Hansch analysis.

Conclusion

Parthenin derivatives (3), (5) and (6) were prepared from parthenin (1) for the first time other reported derivatives were also prepared. Antimalarial activity testing of all the compounds is in progress.

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2. U.G. Bhat and B.A. Nagasampagi, Ind. J. Chem., 27B, 989 (1988).
3. U.G. Bhat, Ph. D thesis, Poona Univ. (1978).
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EXPERIMENTAL

Diethyl amine adduct (5)

A solution of parthenin (1, 50 mg, 0.19 mmoles) in freshly distilled diethyl amine (1 ml) was placed in a thick glass ampoule, sealed and heated to 160°C in an oil bath for 90 minutes. The reaction mixture was poured in water (10 ml) and worked up as usual to yield an oil (65 mg, 100% recovery), from which the diethylamine adduct (5) was separated by preparative TLC (25 mg, 39% yield). TLC (Solvent E). NMR ($CDCl_3$) : δ 7.5 (d, 1H, J=6Hz, H-2), 6.16 (d, 1H, J=6Hz, H-3), 4.98 (d, 1H, J=8Hz, H-6), 2.71 (q, 4H, J=7Hz, CH_2-N-($C\underline{H}_2CH_3)_2$), 1.28 (s, 3H, C-5 methyl), 1.24 (t, 6H, J=7Hz, CH_2-N($CH_2CH_3)_2$), 1.11 (d, 3H, J=8Hz, C-10 methyl) and 1.3-2.53 (10H, rest of the methylene and methine protons). IR shows bands at 3463 O-H stretch, 1759 lactone C=O stretch, 1716 cyclo penteone C=O stretch, 1653 C=C stretch, 1244 lactone C-O stretch and 1162 cm^{-1} alcohol C-O stretch. MS:m/e 335 (M^+), 320 (M^+-CH_3), 302 ($M^+-CH_3-H_2O$), 287 ($M^+-2CH_3-H_2O$) and 244 ($M^+-H_2O-HNEt_2$).

Dimethyl amine diadduct (3)

To a saturated solution of anhydrous dimethyl amine in methanol was added parthenin (1, 50 mg, 0.19 mmoles). The reaction was refluxed with continous bubbling of dimethyl amine gas for 1 hour. The solvent was removed in vacuo to yield a highly hygroscopic solid (65 mg, 97% recovery), which after

preparative TLC yielded dimethyl amine diadduct (3, 25 mg, 37% yield). TLC (Solvent E). NMR ($CDCl_3$) : δ 4.75 (d, 1H, J=8Hz, H-6), 2.3 (s, 6H, CH_2-N-C$\underline{H}_3)_2$), 2.15 (s, 6H, CH-N-(C$\underline{H}_3)_2$), 1.1 (s, 3H, C-5 methyl), 1.0 (d, 3H, J=8Hz, C-10 methyl) and 1.2-2.8 (25H, amine methyls and other methylene and methine protons). IR showed bands at 3474 O-H stretch, 1748 C=O stretch and 1168 cm^{-1} alcohol C-O stretch. MS:m/e 352 (M^+), 307 (M^+-$HNMe_2$), 292 (M^+-$HNMe_2$-CH_3) and 262 (M^+-$2HNMe_2$).

Di-n-butyl amine adduct (16)

To a solution of di-n-butyl amine (1 ml) in freshly distilled dry acetonitrile (10 ml) was added parthenin (1, 50 mg, 0.19 mmoles) in one portion and refluxed on a water bath for 36 hours. Usual work up yielded an oil (55 mg, 73% recovery), from which the di-n-butyl amine adduct (6, 25 mg, 33% yield) was obtained after preparative TLC. TLC (Solvent E). NMR ($CDCl_3$) : δ 6.2 (d, 1H, J=3Hz, H-13), 5.54 (d, 1H, J=3Hz, H-13), 4.94 (d, 1H, J=8Hz, H-6), 4.24 (t, 1H, J=8Hz, H-2), 1.16 (d, 3H, J=8Hz, C-10 methyl), 1.1 (s, 3H, C-5 methyl), 0.9 (t, 6H, J=7Hz, CHN($(CH_2)_3C\underline{H}_3)_2$) and 1.2-2.3 (21H, rest of the methylene and methine protons). IR showed bands at 3500 O-H stretch, 1760 C=O stretch and 1655 cm^{-1} C=C stretch. MS:m/e 391 (M^+).

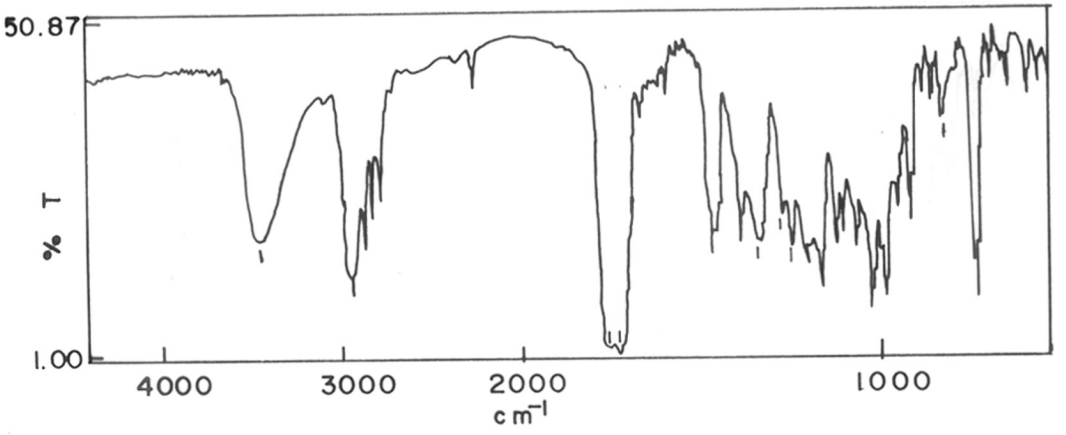


FIG. 2C.1: IR OF COMPOUND (2)

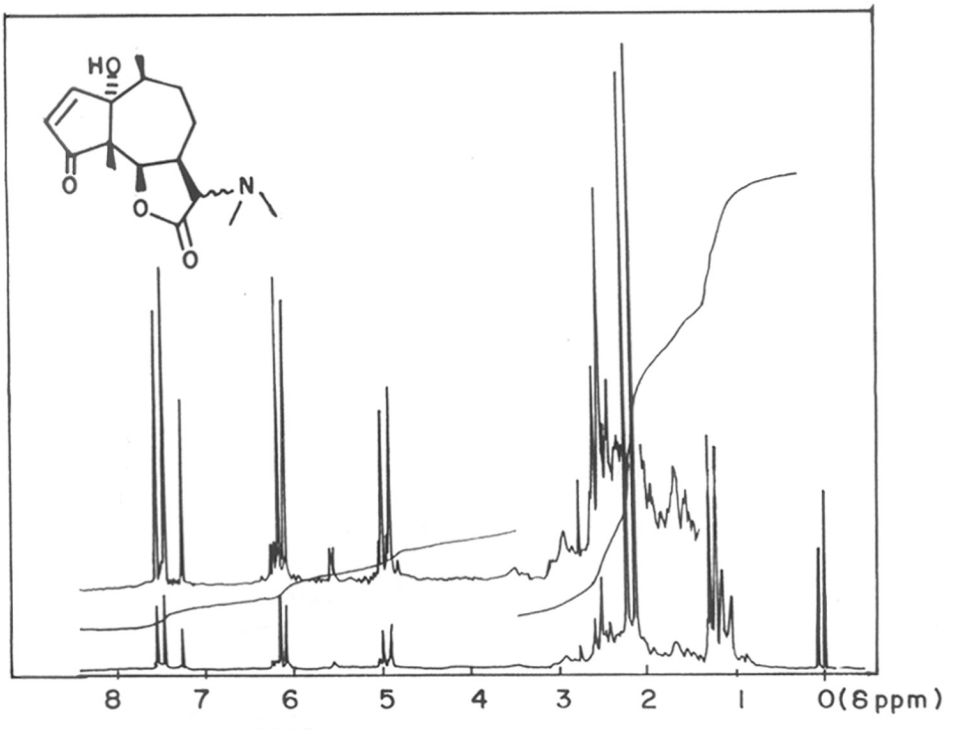


FIG. 2C.2 : NMR OF COMPOUND (2)

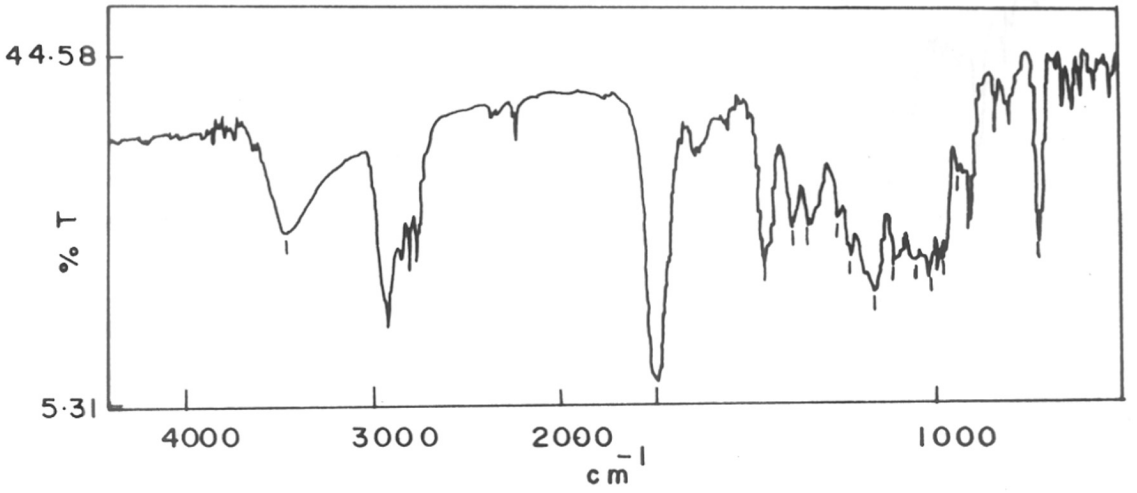


FIG. 2C.3 : IR OF COMPOUND (3)

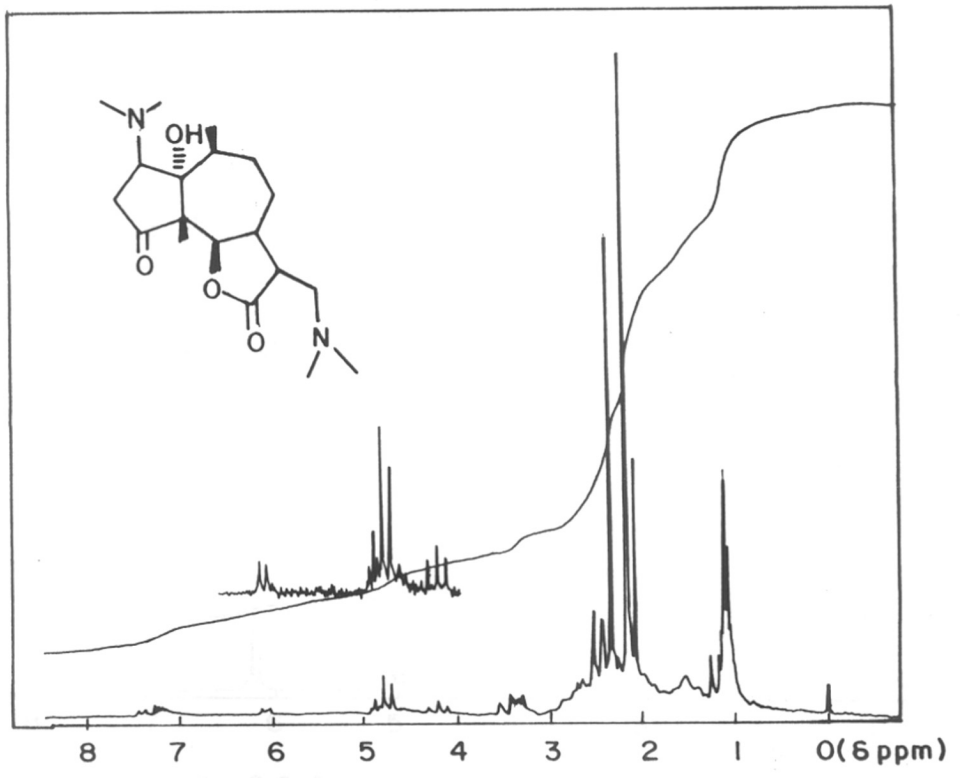


FIG. 2C.4 : NMR OF COMPOUND (3)

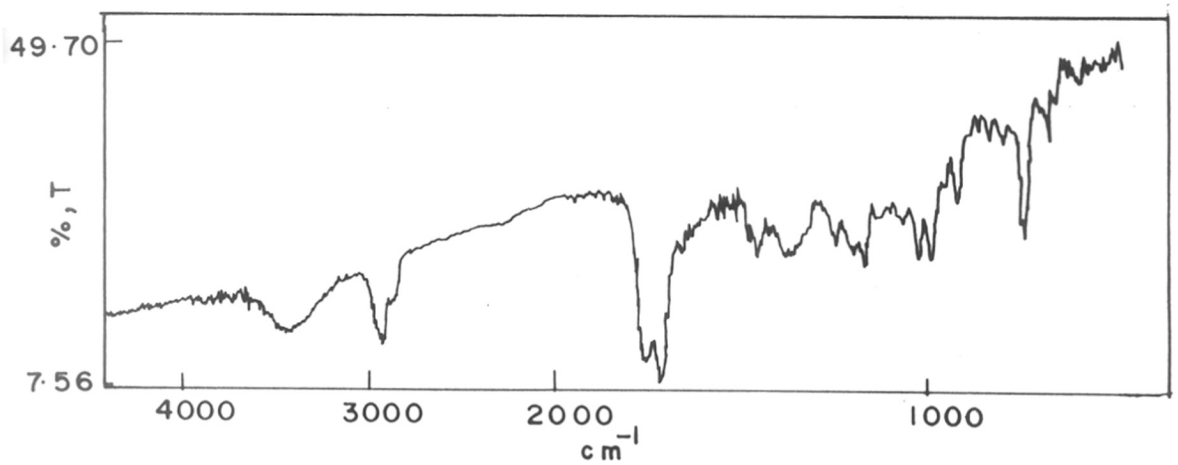


FIG. 2C.5 : IR OF COMPOUND(5)

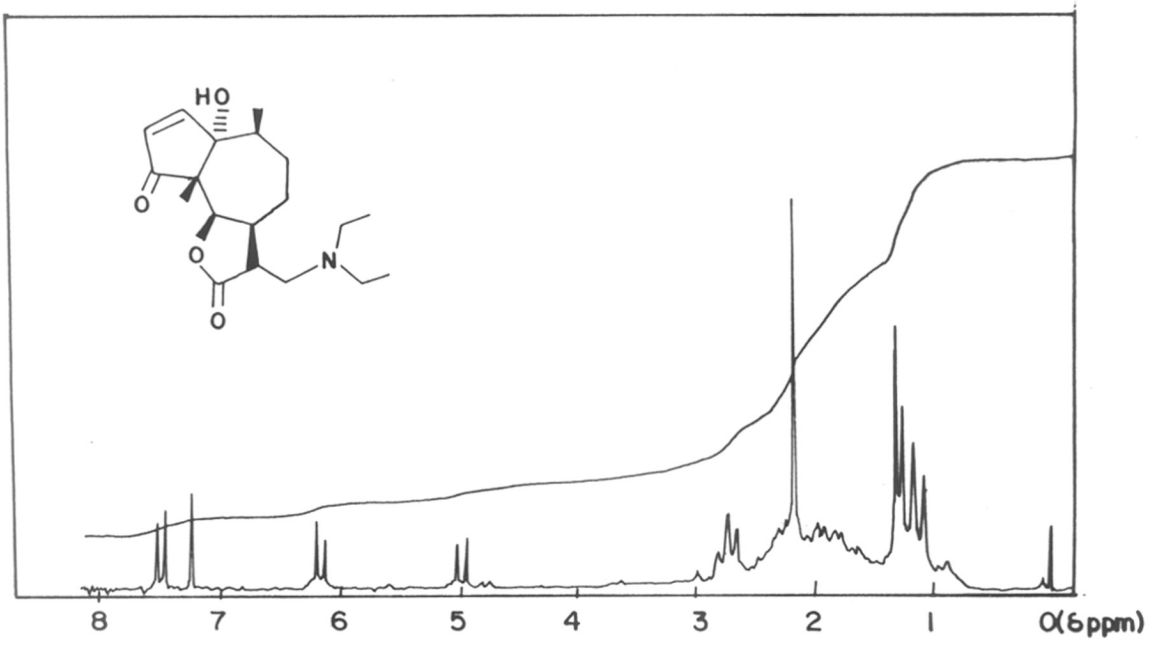


FIG. 2C.6 : NMR OF COMPOUND (5)

CHAPTER III

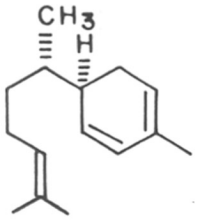
PART A

SYNTHESIS OF (+)-ZINGIBERENE

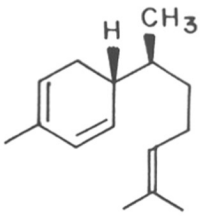
INTRODUCTION

(-)-Zingiberene (1) is a monocarbocyclic sesquiterpene related to the bisabolenes[1]. The chemical abstract nomenclature of (-)-zingiberene (1) is 1,3-cyclohexadiene,5-(1,5-dimethyl-4-hexenyl)-2-methyl-[S-(R*,S*)] and the chemical abstract registry number being 495-60-3. (-)-Zingiberene (1) occurs in large quantities in 'ginger oil' (rhizomes of Zingiber officinale)[2,3]. It has been isolated from various natural resources like essential oils as early as 1934[4,5] and from Zingiber officinale roscoe[6], Zingiber cassumuner roxb[7], Asarum species[8], Heterotropa species[8,9], Senecio species[10], Kleinia species[11], Curcuma species[12], Sideritis cretica[13], Levisticum officinale oils[14] and oil from Boswellia serrata[15]. Zingiberene is widely used in perfumes[16,17] and medicines. The reported therapeutic applications of (-)-Zingiberene (1) are as an absorption promoter for trans dermal pharmaceuticals[18], an antiulcer agent[3] and antifertility agent[19]. (-) Zingiberene (1) has been reported to possess insecticidal activity[20] and its ozonides have been reported to be useful in treatment of human immunodeficiency virus (HIV) and other virus infections[21]. The ozonides have also been reported to be useful with other pharmaceuticals for treatment of inflammations and other diseases[22].

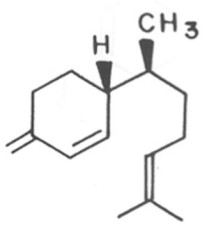
The structure of naturally occuring (-)-zingiberene (1) was first proposed by Ruzicka[23] and was later corrected by Eschenmoser[24]. (-)-Zingiberene (1) is shown to be a mixture of double bond isomers (1A) and (1B)[24,25]. (+)-Zingiberene (2) is



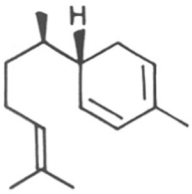
1



1 A



1 B



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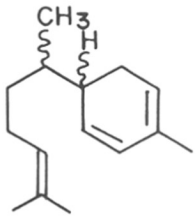

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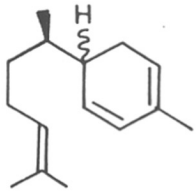
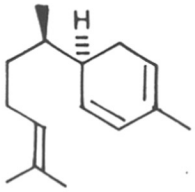
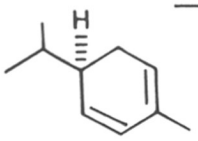


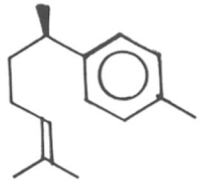
4



4 A



23

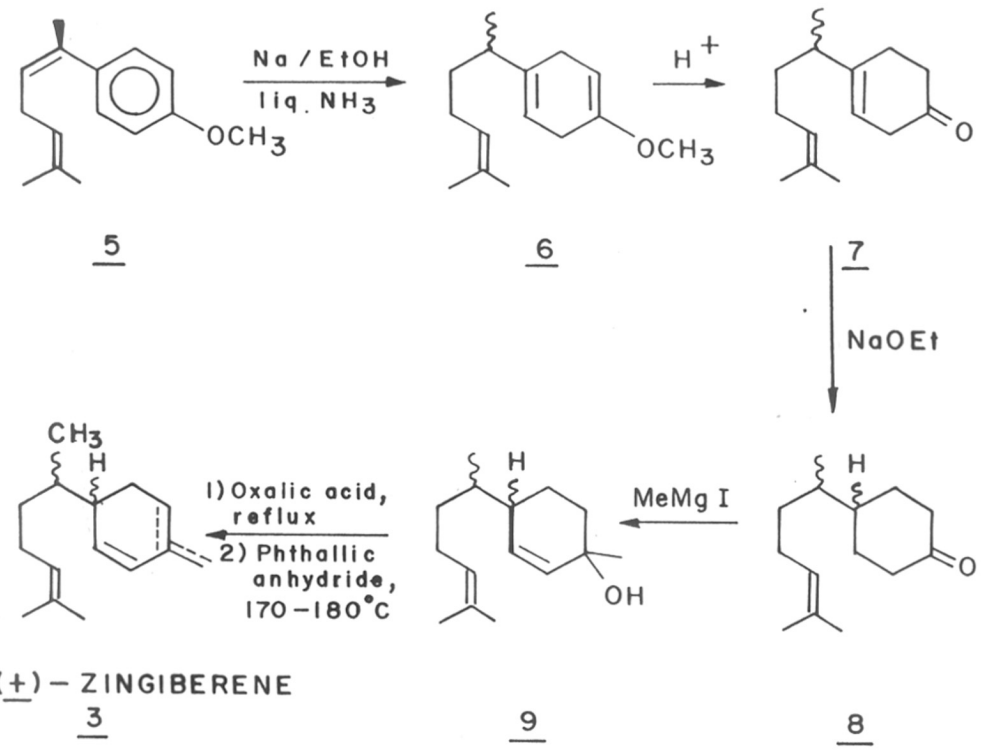


24

(−)∝− Phellandrene

(−)∝− Curcumene

SCHEME – I



5 6 7 8 9

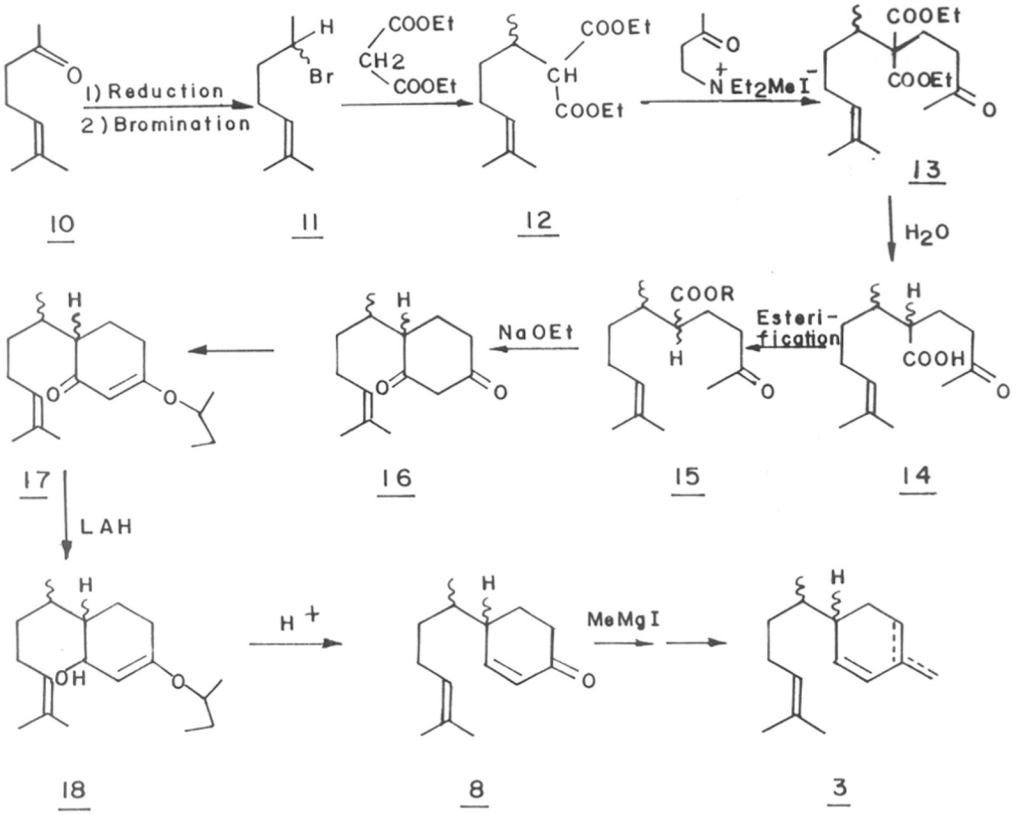
(±) – ZINGIBERENE
3

an enantiomer of the naturally occuring (-)-zingiberene (1). Till date two synthesis of (±)-zingiberene (3) and two syntheses of zingiberene (4) have been reported. The details of these syntheses are as follows.

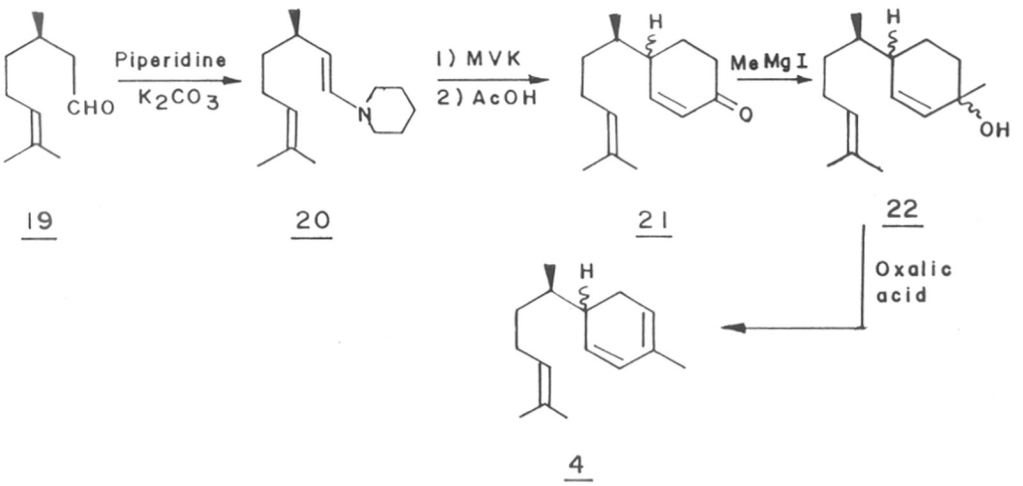
1. Mukherji and Bhattacharyya[25] reported synthesis of (+)-zingiberene (3) (see scheme-1) stating from 6-(p-methoxy phenyl)-2-methyl-2,5-heptadiene (5) which was converted to compound (6) in two steps using sodium in ethanol and liquid ammonia. The compound (6) was converted to ketone (7) by heating it with 5% sulphuric acid on steam bath for 40 minutes. The crucial α,ß-unsaturated ketone (8) was obtained by treating the ketone (7) with sodium ethoxide in absolute alcohol at 60°C for five minutes under nitrogen atmosphere. The α,ß-unsaturated ketone (8) was subjected to Grignard reaction with methyl magnesium iodide to yield carbinol (9) which was dehydrated in two steps using oxalic acid in water and refluxing for 2.5 hours and next by heating with phthallic anhydride in oil bath at 170-180°C for 20-25 minutes under nitrogen atmosphere to yield (±)-zingiberene (3.

2. Banerjee[26] reported the synthesis of (±)-zingiberene (3) (see scheme 2) starting from methyl heptenone (10) which on reduction and bromination gave bromide (11). The bromide (11) was condensed with diethyl malonate to obtain diester (12), which was condensed with methiodide of 4-diethyl aminobutan-2-one to yield ketodiester (13), On hydrolysis of the ketodiester (13), keto-acid (14) was obtained, which was esterified to keto-ester (15). On treatment of the keto-ester (15) with NaOEt the dihydroresorcinol derivative (16) was obtained, from which the

SCHEME - 2



SCHEME - 3



keto-isobutylenolether (17) was prepared. Reduction of the keto enolether (17) with LAH afforded the alcohol enolether (18), which on acid treatment gave the α,ß-unsaturated ketone (8). (±)-Zingiberene (3) was obtained from this α,ß-unsaturated ketone (8) by using the procedures reported by Mukherji and Bhattacharayya[24].

3. Joshi and Kulkarni[27] synthesised zingiberene (4) (see scheme 3) starting from R (+) citronellal (19) which was condensed with piperdine in presence of potassium carbonate to yield enamine (20). The enamine (20) on treatment with methyl vinyl ketone followed by acetic acid furnished the α,ß-unsaturated ketone (21), which on treatment with methyl magnesium iodide gave carbinol (22). Dehydration of the carbinol (22) was affected with oxalic acid to furnish zingerberene (4), which is stereochemically pure only at one stereochemical center.

4. Ni, Chen and Yan[19] reported the synthesis of zingiberene (4) starting from R (+) citronellal, (19) (unfortunately the details of this synthesis could not be obtained as the authors are reluctant to send reprints/photocopy of the publication). As shown in scheme-3, they must have obtained a mixture of (+)-zingiberene (2) and zingiberene (4A). It is very unlikely that Ni et al had obtained (-)-zingiberene (1) in their synthesis. The probable explanation for the negative rotation they have observed for the zingiberene they synthesised is as follows. (-) α-Phellandrene (23) has a rotation[28] of -241° and (-) α-curcumene (24) has a rotation[29] of -84°. As per the rule of shift[30], rule of optical superposition[31,32] and distance rule[33],

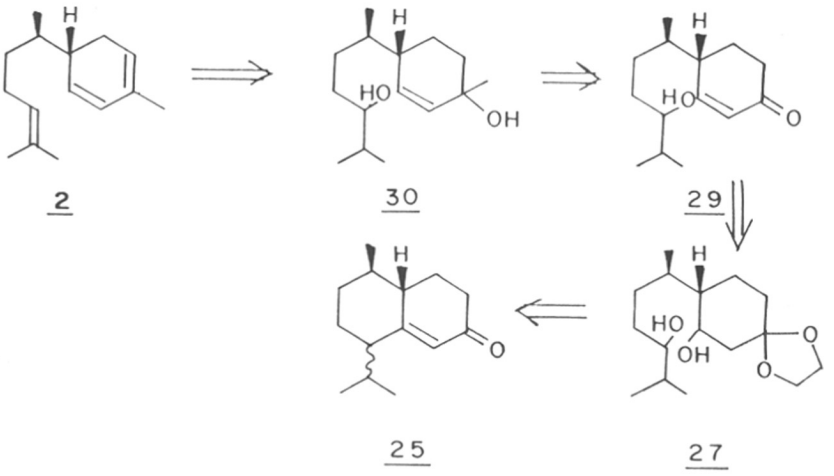
an approximate value of rotation for the various isomers of zingiberene can be guessed. Thus simple arithmetic calculations suggest that (-)-zingiberene (1) which has the (-)α-phellandrene moiety and (+)α-curcumene moiety would have a rotation of -152°, whereas the reported rotation is -150°. (+)-Zingiberene (2) which is an enantiomer of (-)-zingiberene (1) should have a rotation of +150°. Zingiberene (4A) which has the (-)α-phellandrene moiety and the (-)α-curcumene moiety would have approximately a rotation of -330°. Thus a 1:1 mixture of (2) and (4A), which Joshi and Kulkarni[27] and Ni, Chen and Yan[19] must have obtained in their synthesis would have a rotation of -45.5°, whereas the rotation reported by Joshi and Kulkarni is -50°. Thus the claim of Ni, Chen and Yan of the synthesis of (-)-zingiberene (1) may be incorrect.

To ascertain whether the use of stereochemically pure (+)-zingiberene (2), a component of the mixture for which antifertility activity has been reported[19], alone could enhance the antifertility acitivity and to explore other therapeutic applications, the synthesis of stereochemically pure (+)-zingiberene (2) was undertaken.

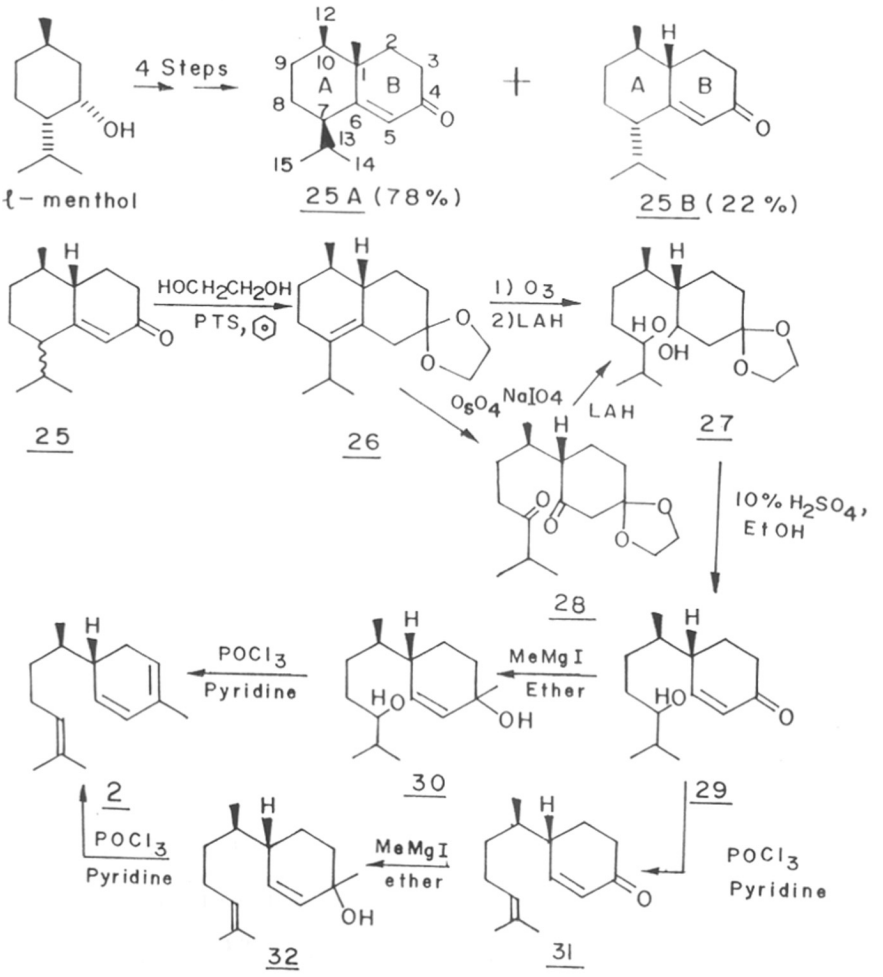
PRESENT WORK.

7(R,S)-isopropyl-10(R)-methyl-1(S)-4-oxobicyclo [4.4.0] dec-5-ene (liquid ketone) (25)[53] was synthesised from l-menthol (see scheme-5) and used for the synthesis of many

RETROSYNTHETIC SCHEME – 4



SCHEME – 5



sesquiterpenes[35,36,37]. (+)-Zingiberene (2) was planned to be synthesised from liquid ketone (25) as depicted in retrosynthetic scheme-4.

Rangaishenvi[36] reported that the double bond migrates to the A ring, when the ketone of the liquid ketone (25) is protected by ethanediol ketal (see scheme-5). Thus liquid ketone (25) on refluxing with ethanediol in benzene with catalytic amount of p-toulene sulphonic acid using Dean-Stark apparatus yielded the ketal (26) in almost quantitative yield. The ketal (26) was identified by its spectral characteristics. NMR showed signal at 3.9 (s, 4H, $O\underline{CH_2}\underline{CH_2}O$), IR showed C=C stretch at 1653, C-O stretch at 1117 and 1096 cm^{-1} and mass spectrum showed molecular ion peak at m/e 250. All the spectral characteristics were in agreement with those reported by Rangaishenvi[36].

As per the retrosynthetic scheme-4, ketal (26) was required to be converted to the diol ketal (27). Oxidation of the olefinic bond to the corresponding diketone or dialdehyde by use of sodium meta periodate as oxidant and osmium tetroxide[38] or ruthenium tetroxide[39,40] as catalyst is well known. Thus to obtain the diol-ketal (27), the ketal (26) could be converted to diketone-ketal (28), which on reduction with lithium aluminium hydride would have furnished the desired diol-ketal (27). However attempts to obtain diketone-ketal (28) by employing reported procedures failed and in all attempts the ketal (26) was recovered. Reductive in situ cleavage (without isolating the ozonide) of ozonides to alcohols have been reported to give excellent yields[41,42]. Hence the ketal (26) was subjected to

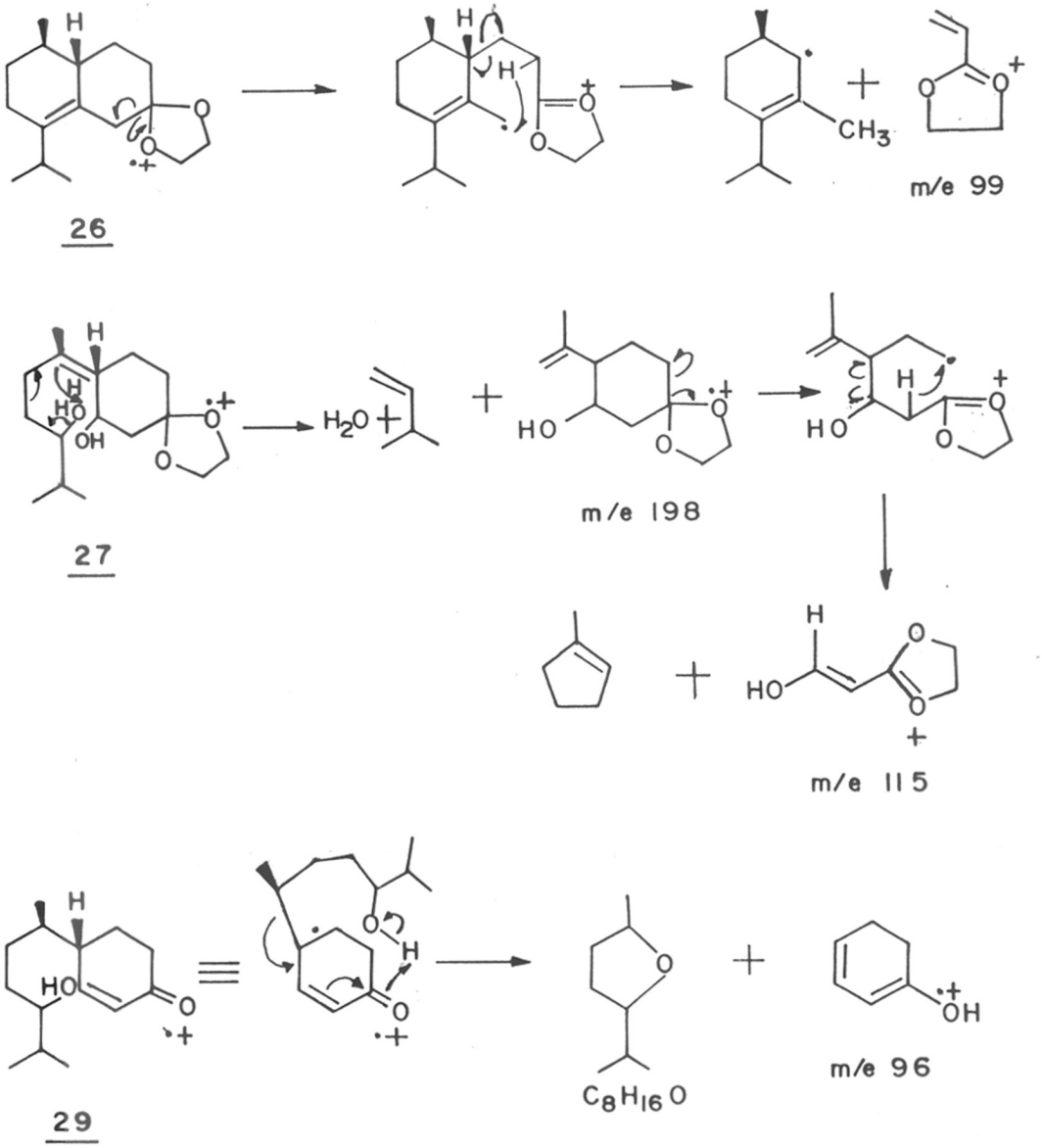
ozonolysis (estimation of ozone generated done by reported procedure[43]) in n-heptane and subsequent in situ reduction of the ozonide by lithium aluminium hydride yielded the diol ketal (27). The diol-ketal (27) was identified by IR spectrum which showed bands at 3480 O-H stretch and 1105 cm^{-1} C-O stretch, NMR spectrum displayed signals at δ 4.14 (m, 1H, HOCHCH$_2$COCH$_2$CH$_2$O), 3.95 (s, 4H, OCH$_2$CH$_2$O), 3.30 (m, 1H, CH$_2$(HO)CHCHMeMe) and 2.61 (D_2O exchangeable, 2H, 2 x OH) and mass spectrum showed molecular ion peak at m/e 286. The disappearence of the NMR signal at δ 2.85 (m, 1H, MeCHMe) of the ketal (26) confirmed the total consumption of the starting material.

The deprotection and dehydration was achieved in a single step when diolketal (27) was stirred at room temperature with 10% sulphuric acid in ethanol to yield the α,ß-unsaturated ketone alcohol (29). The keto alcohol (29) was identified by NMR which displayed signals at δ 6.83 (dd, 1H, J_{cis}=10 Hz, J_{ally}=1-2 Hz, C=CH-C=O) and 3.33 (m, 1H, CHOH), IR showed absorbance at 3450 O-H stretch, 1678 C=O stretch and 1098 cm^{-1} C-O stretch and mass spectrum showed molecular ion peak at m/e 224. Grignard reaction on the keto-alcohol (29) with methyl magnesium iodide furnished the diol (30) which was identified by its NMR, IR and mass spectra. The NMR of diol (30) displayed signals at δ 5.57 (bs, 2H, HC=CH), 3.34 (m, 1H, CHOH) and 1.28 (s, 3H, CH$_3$CO), IR showed bands at 3360 O-H stretch, 1670 C=C stretch, 1170 tertiary C-O stretch[44], 1080 secondary C-O stretch[44] and absence of the C=O stretching bands of the α,ß-unsaturated ketone (29) at 1678 cm^{-1}. Mass spectrum showed molecular ion peak at m/e 240.

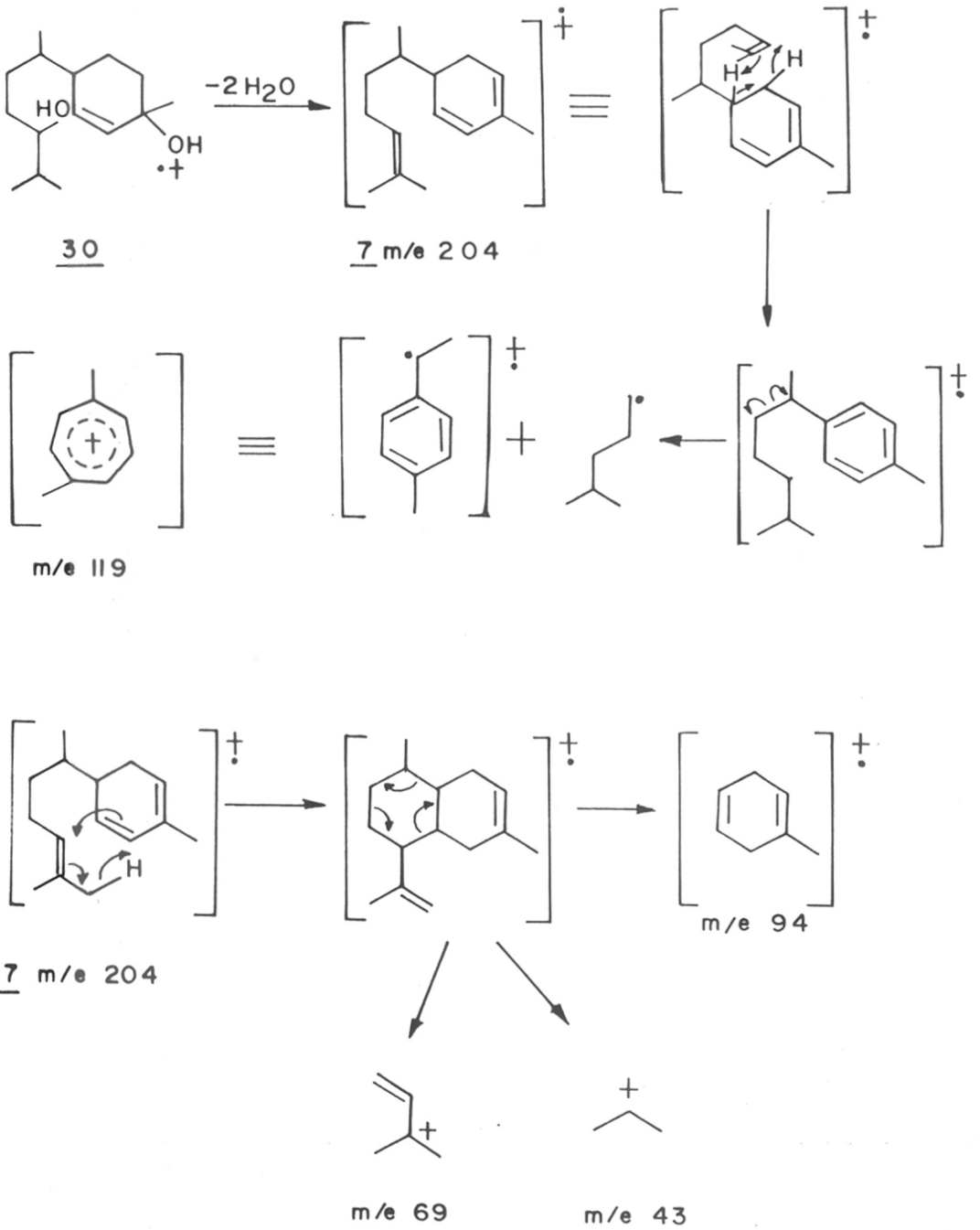
Stereochemically pure (+)-zingiberene (2) was obtained by stirring diol (30) with phosphorus oxychloride in pyridine for 12-13 hours at room temperature[45-48]. Pure (+)-zingiberene (2) was obtained after repeated purification on silver nitrate (15%) impregnated silica-gel preparative TLC with n-hexane as solvent. The (+)-zingiberene (2) so obtained was characterised by NMR, IR mass and UV spectra. NMR showed signals at δ 5.9 (dd, 1H, J_{cis}=10 Hz, J_{ally}=1-2 Hz, C=C<u>H</u>-CMe=C), 5.45 (bs, 1H, <u>H</u>C=CH-CMe=C) 5.1-5.2 (bs, 2H, HC=CHCMe=C<u>H</u> and $CH_2C\underline{H}=CMe_2$), 3.55 (m, 1H, ring junction methine), 2.2 (s, 3H, HC=CHC<u>Me</u>=C), 1.75 (s, 3H, =C<u>Me</u>Me), 1.65 (s, 3H, =CMe<u>Me</u>), 0.9 (d, 3H, J=7 Hz, methyl), 1.1-2.5 (7H, rest of the methylene and methine protons). IR showed band at 2962 =C-H stretch, 1653 cm^{-1} C=C stretch and the spectrum is in good agreement with that reported by Wenniger et al[49] for (-)-zingiberene (1). Mass spectrum displayed peaks at m/e 204 (M^+), 174 (M^+-2CH_3), 161 ($M^+-CH_3CHCH_3$), 119 (see scheme-6) and the spectrum is in agreement with that reported for (-)-zingiberene (1) by Moshonas and Lund[40]. UV (n-hexane) showed .max at 243 nm and shoulder at 263 nm, which was in complete agreement with that reported for (-)-zingiberene (1)[25,27,34]. Unfortunately the yield of pure (+)-zingiberene (2) obtained by this pathway was dismally poor (≈12%).

To improve upon the yields of (+)-zingiberene (2) an alternate pathway via the reported α,ß-unsaturated ketone (31)[25,26,27] was tried. Thus when the keto-alcohol (29) was stirred with phosphorous oxychloride in pyridine for 12-13 hours the α,ß unsaturated ketone alkene (31) was obtained. This was

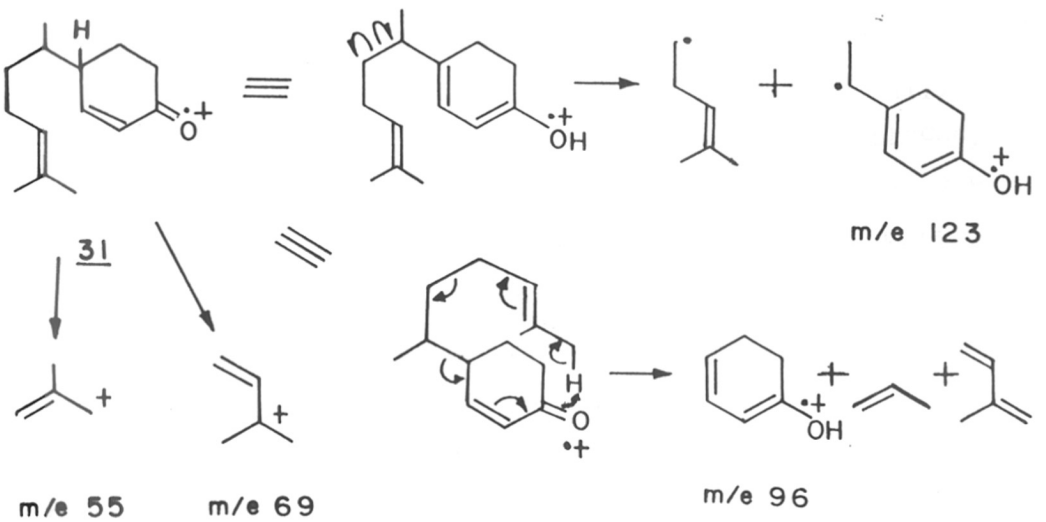
SCHEME — 6 [41, 51, 52]



SCHEME-6 Contd.



SCHEME – 6 CONTD



identified by NMR which showed signals at δ 6.84 (dd, 1H, J_{cis}=10 Hz, $J_{vic}\approx$0-1 Hz, HC=C-C=O), 5.96 (dd, 1H, J_{cis}=10 Hz), $J_{ally}\approx$1-2 Hz, C=CHC=O), 5.1 (dt, 1H, J_{vic}=6 Hz, J_{ally}=1-2 Hz, $CH_2CH=CMe_2$), 1.70 (s, 3H, $J_{ally}\approx$1-2 Hz, C=CMeMe) and 1.62 (s,3H, $J_{ally}\approx$1-2 Hz, C=CMeMe), IR showed bands at 1678 C=O stretch and 1635 C=C stretch and absence of the O-H stretching band of ketoalcohol (29) at 3450 cm^{-1} and mass spectrum showed molecular ion peak at m/e 206. Yield of $\approx$ 50% was obtained.

The alcohol (32) was obtained by Grignard reaction on the ketone alkene (31). The alcohol (32) was identified by NMR which showed signals at δ 5.47 (bs, 1H, $CH=CHCOCH_3$), 5.02 (dd, t, 2H, $HC=CHC(OH)CH_3$ and $CH_2CH=CMe_2$), IR showed bands at 3465 O-H stretch and 1609 C=C stretch and absense of the C=O stretching band of the ketone alkene (31) at 1678 cm^{-1}. The NMR and IR spectra were in fair agreement with those reported by Joshi[34]. (+)-zingiberene (2) was obtained by stirring the alcohol (32) with phosphorus oxychloride in pyridine for 4 hours[36] in 52% yield.

CONCLUSION

Stereochemically pure (+)-zingiberene (2) was synthesised as per scheme-5 in 9 steps from l-menthol.

EXPERIMENTAL

Ketal (26) from liquid ketone (25)

Liquid ketone (25, 11.0 gms, 0.054 mmoles) was dissolved in a solution of anhydrous benzene (400 ml), freshly distilled (over KOH), ethane diol (3.42 gms, 0.055 moles) and p-toulene sulphonic acid (0.067 gms, 0.39 mmoles) and refluxed using Dean-Stark separator until no water could be separated. Approximately 1 ml of water was separated in 12 hours. Benzene was remove in vacuo and water (150 ml) added to the reaction mixture. This was extracted with dichloromethane (3 x 200ml). The organic layer was washed with water (3 x 200 ml), brine (1 x 100 ml) and dried over anhydrous Na_2SO_4. Solvent was stripped at 40°C to yield thick viscous oil (13.0 gms, 97% yield), which was vaccum distilled 150-155°C at 0.5 mm vaccuum. TLC (solvent C). NMR ($CDCl_3$) : δ 3.9 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 2.75-2.9 (m, 3H, $CH_3C\underline{H}CH_3$) and $C{=}C{-}C\underline{H}_2{-}COCH_2CH_2O$), 0.65-1.1 (m. 9H, methyl and isopropyl methyl), 1.1-2.5 (10H, rest of the methylene and methine protons). IR (Neat) bands at 1653 C=C stretch, 1117 C-O stretch and 1096 cm^{-1} C-O stretch. MS:m/e 250 (M^+); 207 ($M^+-CH_3CHCH_3$); 235 (M^+-CH_3) and 99 ($M^+-C_{11}H_{19}$) (see scheme-6). $(\alpha_D)^{26}$= +3.7° (c, 3.90). GC, 175°C; r. t. = 5.49 minutes.

Diol ketal (27) from ketal (26)

Ketal (26, 500 mg, 0.002 moles) was dissolved in anhydrous n-heptane (100ml) and placed in the ozonolysis apparatus. After cooling to 0-5°C, ozone was bubbled in the solution for 30

minutes. (Ozone generation was estimated and found to be 0.027 moles per hour). After this oxygen was bubbled in the ozonolysis apparatus. Lithium aluminium hydride (380 mgms, 0.010 moles) in dry diethyl ether was added very slowly and carefully from a dropping funnel. After complete addition of the LAH, the solution was brought to room temperature and further stirred for 3 hours. Usual workup and removal of solvent furnished an oil. This was purified by silica-gel column chromatographed, when the desired compound was eluted in 30-40% ethylacetate in benzene. Concentration of the fractions yielded an oil (430 mgs, 75% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 4.14 (m, 1H, $HOC\underline{H}CH_2COCH_2CH_2O$), 3.95 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.30 (m, 1H, $HOC\underline{H}CHMe_2$) and 2.61 (D_2O-exchangeable, 2H, 2 x $O\underline{H}$), 0.79-1.06 (d, 9H, J=7Hz, 3 x CH_3), 1.06-2.26 (13H, other methylene and methine protons). IR (Neat) bands at 3480 O-H stretch and 1105 cm^{-1} C-O stretch. MS:m/e 286 (M^+), 268 (M^+-H_2O), 253 ($M^+-H_2O-CH_3$), 243 ($M^+-C_3H_7$), 225 ($M^+-H_2O-C_3H_7$), 207 ($M^+-2H_2O-C_3H_7$), 198 ($M^+-H_2O-C_5H_{10}$) and 115 ($M^+-CH_3C=CHCH_2CH_2CH_2$) as base peak (see scheme-6). $(\alpha_D)^{26}$= +24.0°(c, 0.744). GC, 200°C, r.t.= 10.54 minutes.

Ketone alcohol (29) from diolketal (27)

Diol ketal (27, 250 mgs, 0.87 mmoles) was dissolved in 10 ml distilled alcohol containing 0.1 ml concentrated sulphuric acid. This was stirred at room temperature for 2 hours. The alcohol was removed in vacuo at 40°C and water (25 ml) added to the reaction mixture. This was extracted with dichloromethane (3 x 50 ml). The combined organic portion was washed with water (2 x

50 ml), brine (1 x 50 ml), dried over anhydrous Na_2SO_4 and solvent removed to obtain a viscous oil. This was chromatographed on silica-gel column when the α,ß-unsaturated ketone (29) was eluted in 27% ethyl acetate : 83% benzene. Concentration of the fraction furnished an oil (145 mg, 73% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 6.83 (dd, 1H, J_{cis}=10Jz, J_{ally}=1-2Hz, C=C<u>H</u>-C=O), 3.33 (m, 1H, CHOH), 0.8-1.04 (d, 9H, J=7Hz, 3xCH_3), 1.04-3.0 (11H, other methylene and methine proton). IR (Neat) bands at 3450 O-H stretch, 1678 C=O stretch and 1098 cm^{-1} C-O stretch. MS:m/e 224 (M^+), 206 (M^+-H_2O), 181 ($M^+-C_3H_7$), 163 ($M^+-C_3H_7-H_2O$) and 96 ($M^+-C_8H_{16}O$) as base peak (see scheme-6). $(\alpha_D)^{26}$= +14.2° (c, 1.13). GC, 200°C, r.t.= 4.43 min.

Diol (30) from ketone alcohol (29).

The keto alcohol (29, 200 mgs, 0.97 mmoles) was taken in a 25 ml, two neck round bottom flask, equipped with magnetic needle, rubber septum and two way stopcock with ultra pure argon gas ballon. The apparatus was flushed with argon gas thrice by employing vaccum-argon gas release cycle. To this dry diethyl ether (7 ml) was added under stirring. The solution was cooled to 0-5°C by ice and standard 3M Grignard reagent (0.39 ml, 1.17 mmoles) added dropwise to it. This was stirred for 15 minutes and then brought to room temperature and further stirred for 9 hours. Excess of unreacted Grignard reagent was destroyed by cooling of the flask and dropwise careful addition of saturated aqueous ammonium chloride solution (1 ml). Usual workup furnished on oil (175 mg, 82% yield), TLC (Solvent C). NMR

($CDCl_3$) : δ 5.57 (bs, 2H, HC=CH-), 3.34 (m, 1H, CHOH), 1.28 (s, 3H, CH_3CO), 0.74-1.0 (d, 9H, J=7Hz, 3xCH_3), 1.0-2.07 (13H, other methylene and methine protons). IR (Neat) bands at 3360 O-H stretch, 1670 C=C stretch, 1170 C-O stretch and 1080 cm^{-1} C-O stretch. MS:m/e 240 (M^+), 222 (M^+-H_2O), 207 ($M^+-H_2O-CH_3$), 161 ($M^+-2H_2O-CH_3CHCH_3$), 119 as base peak, 94, 69 and 43 (see scheme-6). $(\alpha_D)^{26}$= +21.1° (c, 0.625).

(+)-Zingiberene (2) from Diol(30).

The diol (30, 150 mg, 0.63 mmoles) was taken in a two neck round bottom flask, equipped with magnetic needle, rubber septum and two way stopcock with ultra pure argon gas balloon. The apparatus was flushed with argon gas thrice by employing vaccum argon gas release cycle. To this dry pyridine (5ml) (distilled over lithium aluminium hydride) was added by aid of syringe. The solution was stirred and cooled to 0-5°C by ice. To this phosphorus oxychloride (0.12 ml, 1.125 mmoles) was added dropwise. The reaction was brought to room temperature after 15 minutes and stirred further for 12 hours. Usual workup furnished an oil (75 mgms, 59% yield). TLC (solvent A). This was purified by two successive preparative TLC run in pet-ether. NMR ($CDCl_3$) : δ 5.9 (dd, 1H, J_{cis}=10 Hz, J_{ally}=1-2 Hz, C=CH-CMe=C), 5.45 (bs, 1H, HC=CH-CMe=C) 5.1-5.2 (bs, 2H, HC=CHCMe=CH and $CH_2CH=CMe_2$), 3.55 (m, 1H, ring junction methine), 2.2 (s, 3H, HC=CHCMe=C), 1.75 (s, 3H, =CMeMe), 1.65 (s, 3H, =CMeMe), 0.9 (d, 3H, J=7 Hz, methyl), 1.1-2.5 (7H, rest of the methylene and methine protons). IR (Neat) showed band at 2962 =C-H stretch, 1653 cm^{-1} C=C

stretch. MS : m/e 204 (M^+), 174 (M^+-2CH_3), 161 ($M^+-CH_3CHCH_3$), 119 (see scheme-6) $(\alpha_D)^{26}$= +50.0° (c, 0.52).

Alcohol (32) from ketone alkene (31).

The α, ß-unsaturated ketone-alkene (31, 200 mg, 0.97 mmoles) was subjected to Grignard reaction in dry ether (7 ml) and 3M standard Grignard reagent (0.39 ml, 1.165 mmoles) using the procedure described for conversion of the keto-alcohol (29) to the diol (30). Usual work up furnished an oil. (172 mg, 80% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 5.47 (bs, 1H, $HC=C\underline{H}C(CH_3)(OH)CH_2$), 5.02 (m, 1H, $\underline{H}C=CH-CCH_3Me$), 5.01 (m, 1H, $CH_2C\underline{H}=CMe_2$), 11.6 (s, 3H, $CH_2CH=CCH_3Me$), 1.533 (s, 3H, $CH_2-CH=CMeC\underline{H}_3$), 1.19 (s, 3H, $HC=CHCC\underline{H}_3OH$), 0.88 (d, 3H, J=7Hz $CH_2CH-C\underline{H}_3-CH$)-1.1-2.5 (10H, rest of the methylene and methine protons). IR (Neat) bands at 3465 O-H stretch and 1609 cm^{-1} C=C stretch. $(\alpha_D)^{26}$= 27.0° (c, 0.862).

Ketone alkene (31) from keto alcohol (29).

The keto alcohol (29, 400 mg, 1.79 mmoles) was subjected to reaction with phosphorus oxychloride (0.3 ml, 3.2 mmoles) in dry pyridine (10ml) using the procedure described for conversion of the diol (30) to (+)-zingiberene (2). Usual work up furnished oil (185 mg, 50% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 6.84 (dd, 1H, J_{cis}=10Hz, J_{vic}=1Hz, $CH.C\underline{H}=CHCO-CH_2$), 5.96 (dd, 1H, J_{cis}=10Hz, J_{ally}=1Hz, $CH=C\underline{H}=COCH_2$), 5.10 (t, 1H, J_{vic}=6Hz, $CH_2C\underline{H}=CMe_2$), 1.70 (s, 3H, $CH=CC\underline{H}_3Me$), 1.62 (s, 3H, $CH=CMeC\underline{H}_3$), 1.03 (d, 3H, J=7Hz, CH_2CHCH_3CH), 1.06-1.60 and 1.72-2.60 (10H,

rest of the methylene and methine protons). IR (Neat) bands at 1678 C=O stretch and 1635 cm^{-1} C=C stretch. MS:m/e 206 (M^+), 191 (M^+-CH_3), 163 ($M^+-CH_3CHCH_3$), 123 ($C_8H_{11}O$), 96 (C_6H_8O) as base peak, 69 (C_5H_9) and 55 (C_4H_7) (see scheme-6). $(\alpha_D)^{26}$= +22.5° (c, 0.595), GC, 200°C, r.t.=2.27 min, DEGS/200°C, r.t.=2.97 min.

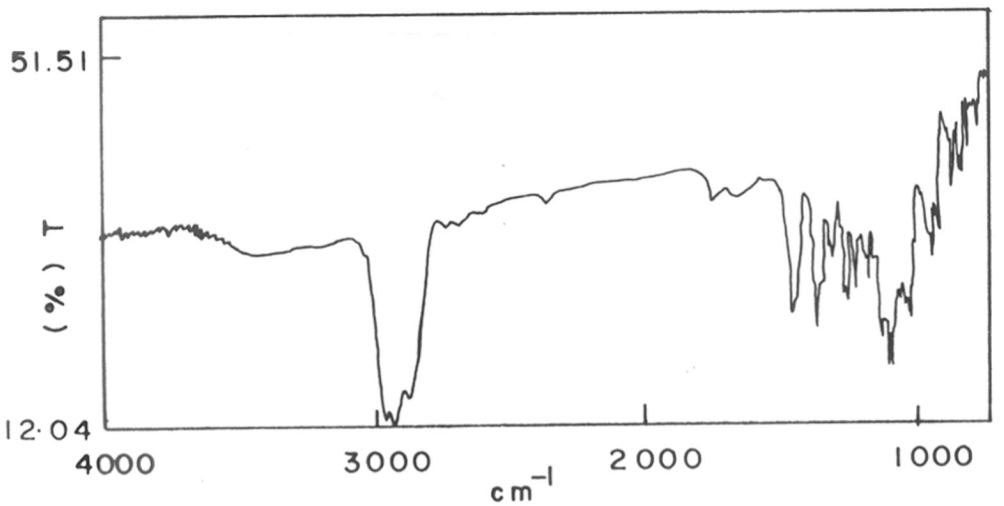


FIG. 3A.1 : IR OF KETAL (2)

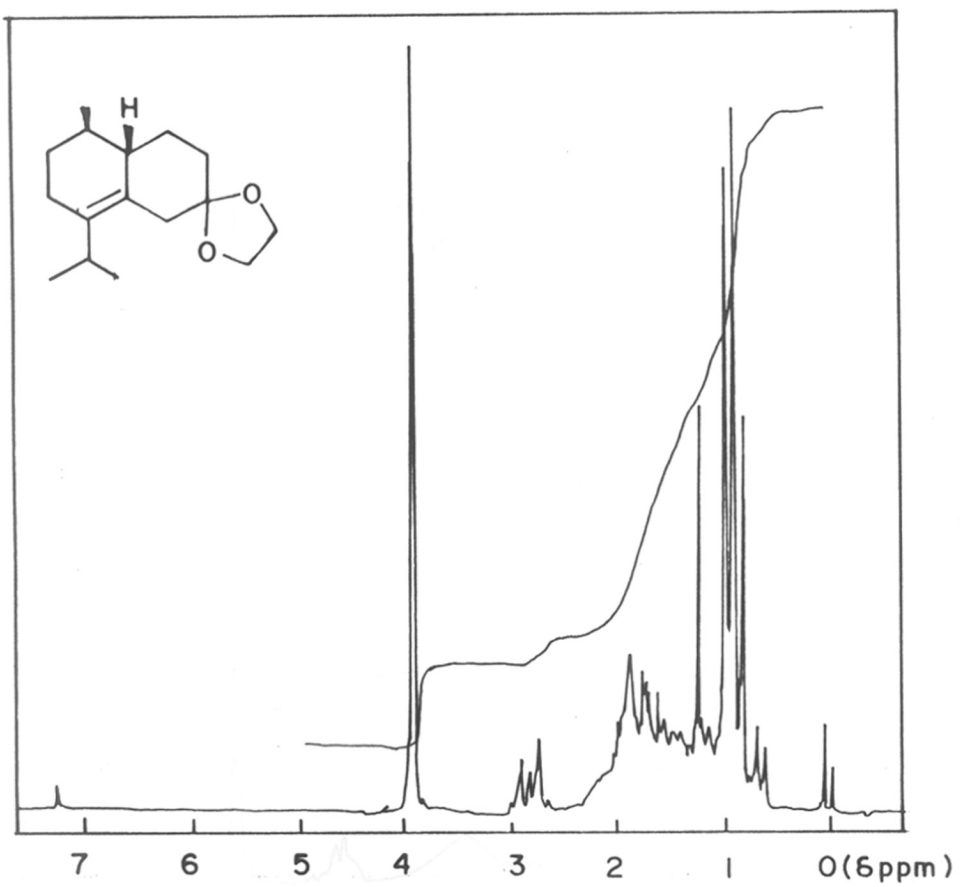


FIG. 3A.2 : NMR OF KETAL (2)

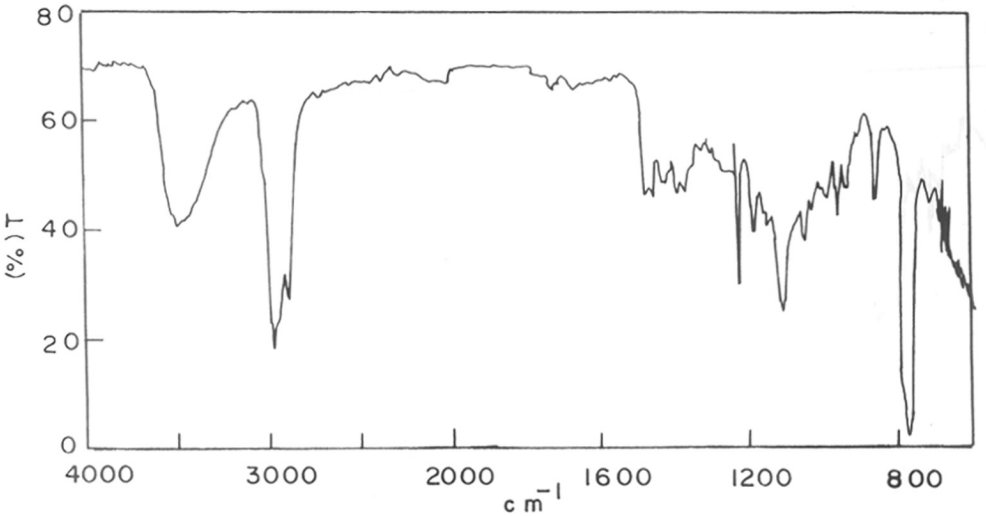


FIG 3A.3 : IR OF DIOL-KETAL (3)

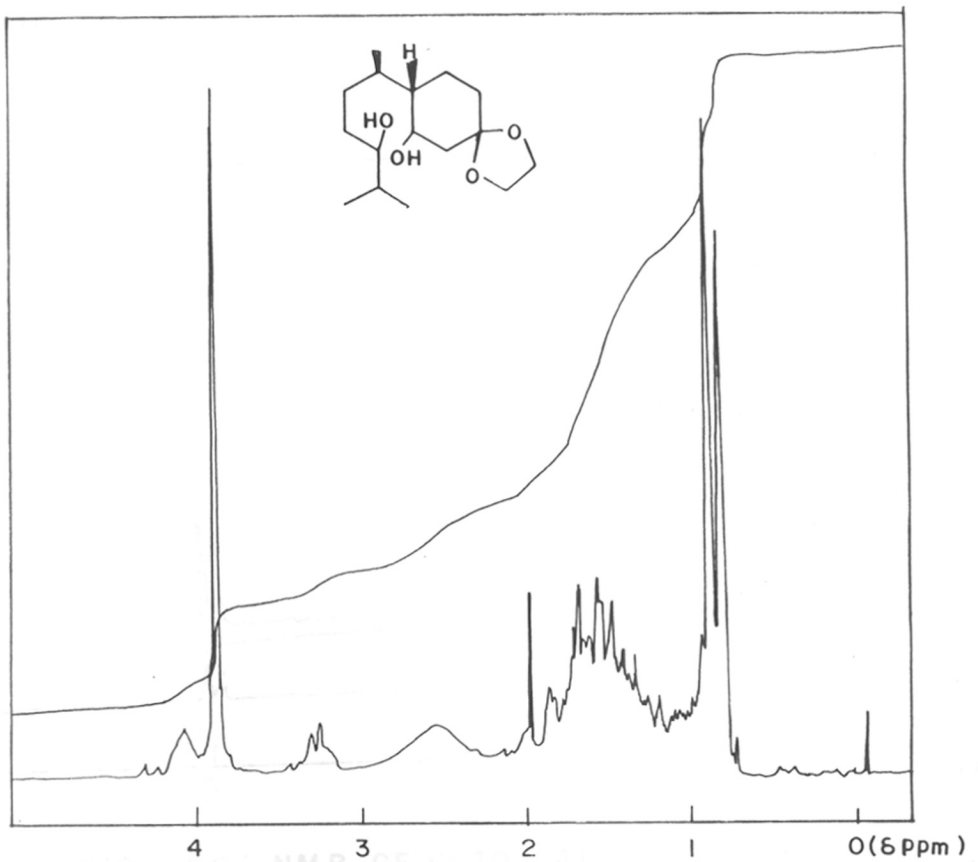


FIG. 3A.4 : NMR OF DIOL-KETAL (3)

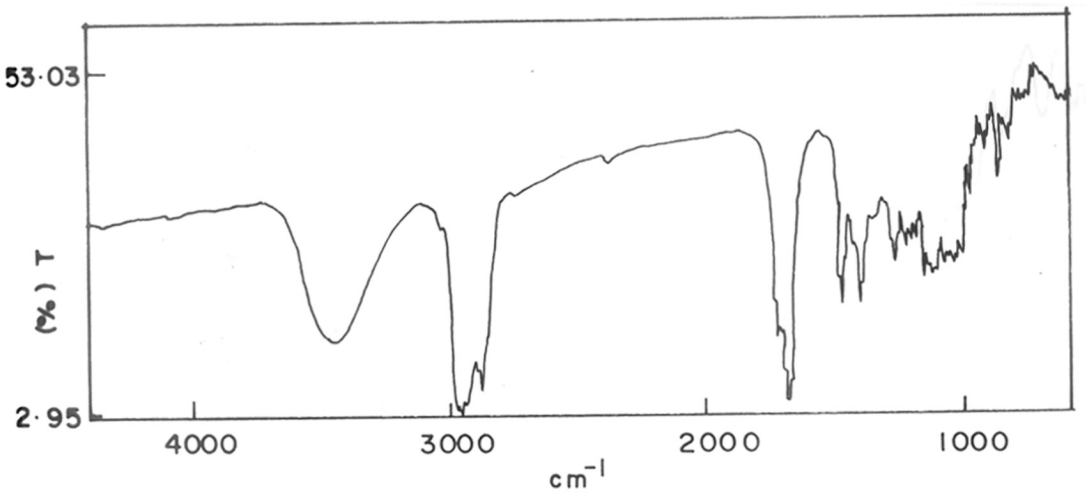


FIG.3A.5 : IR OF KETO – ALCOHOL (4)

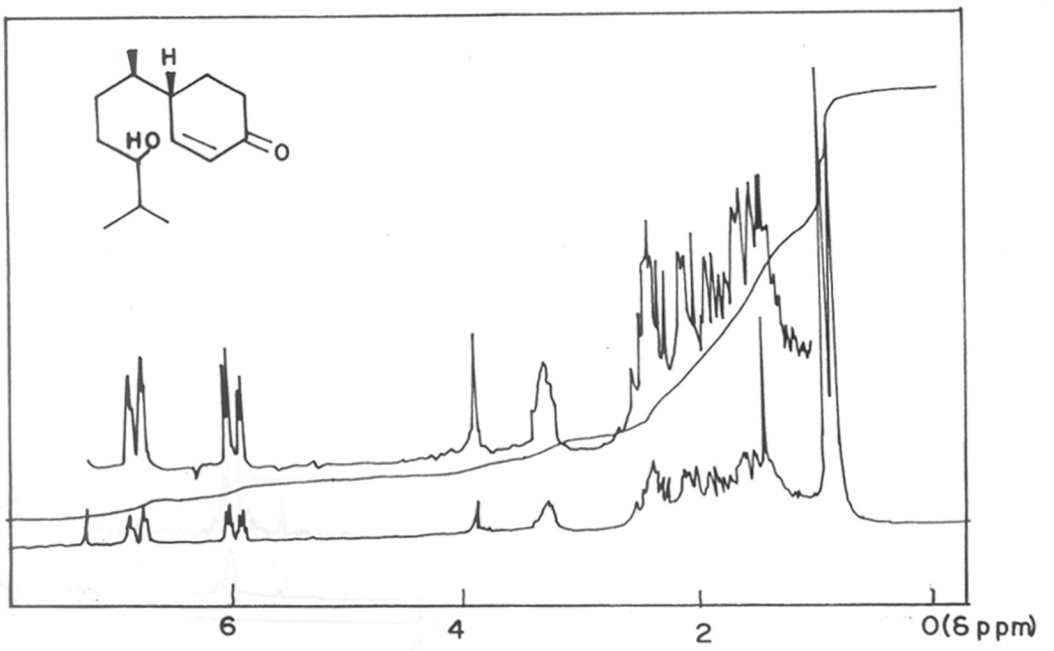


FIG.3A.6 : NMR OF KETO ALCOHOL (4)

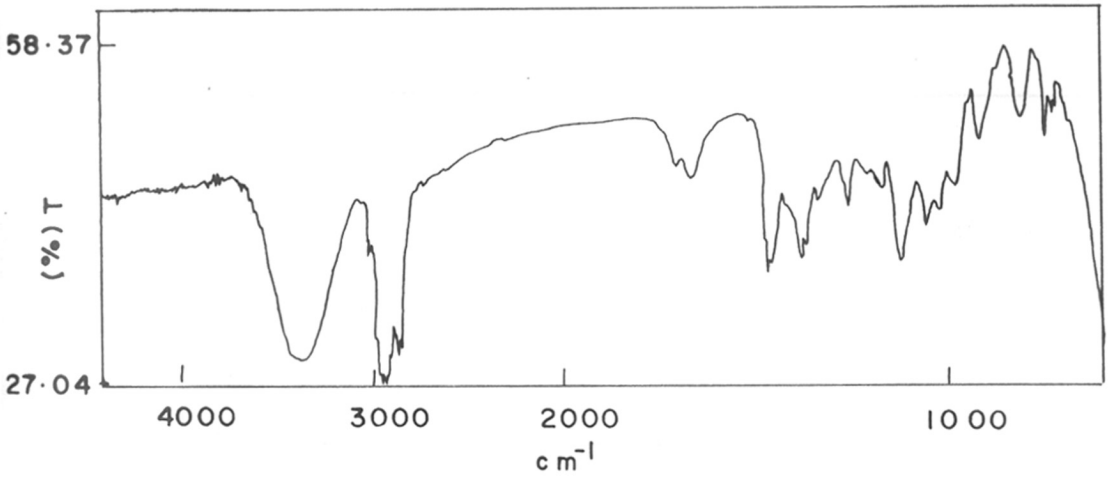


FIG. 3A.7 : IR OF DIOL (5)

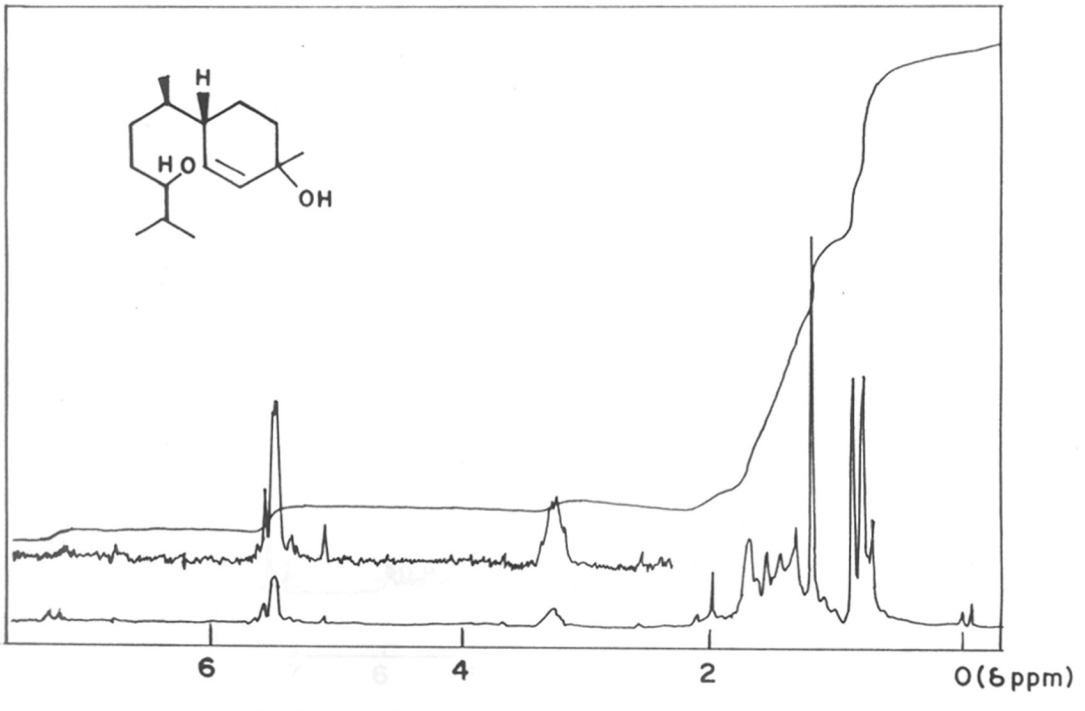


FIG. 3A.8 : NMR OF DIOL (5)

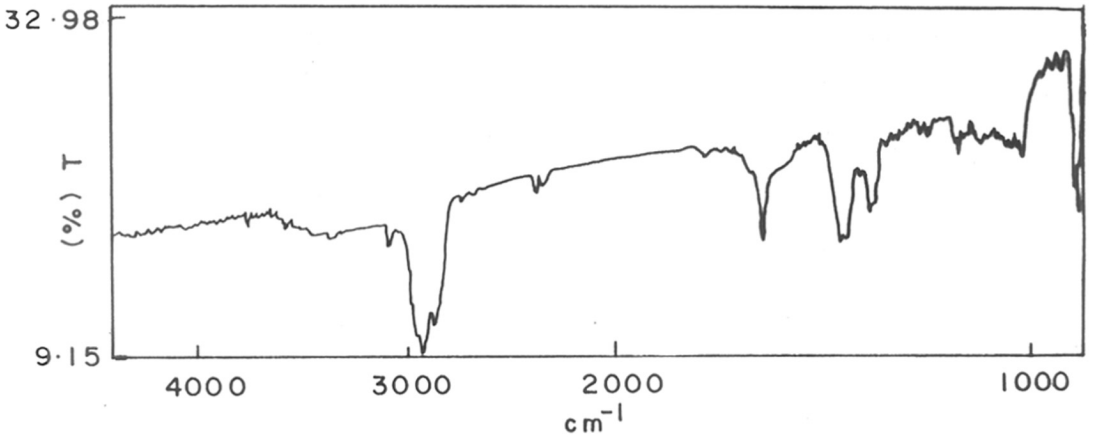


FIG. 3A.9: IR OF (−) − ZINGIBERENE (6)

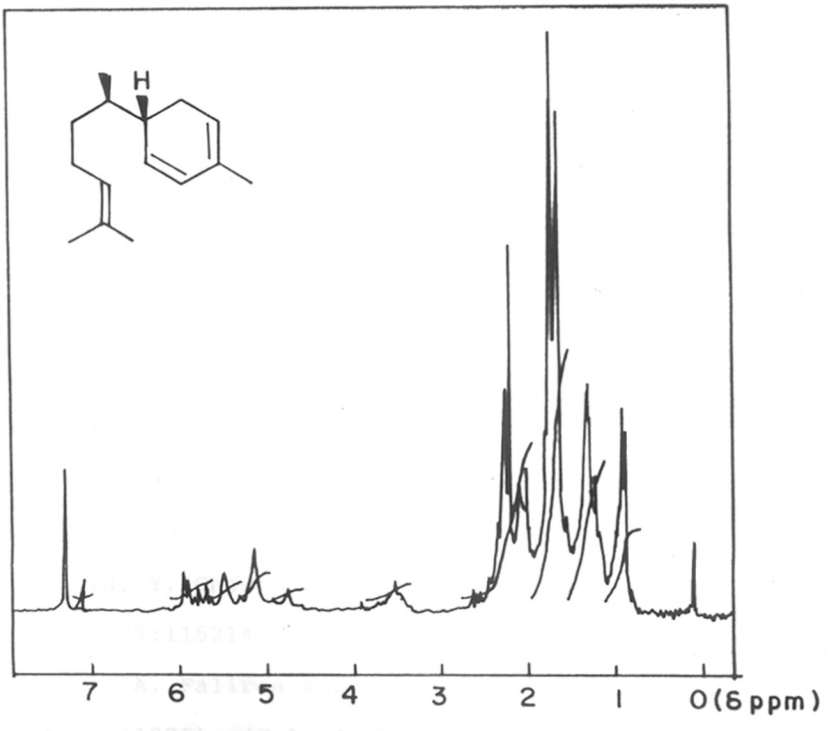


FIG. 3A.10: NMR OF(−) − ZINGIBERENE (6)

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CHAPTER 3

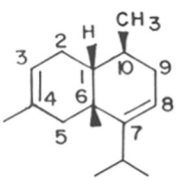
PART B

SYNTHESIS OF (+)-ISOZINGIBERENE

INTRODUCTION

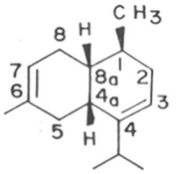
(-)-Isozingiberene (1) is a bicyclic sesquiterpene belonging to the muurolene series[1]. The chemical abstract nomenclature of (-)-isozingiberene (1) is napthalene-1,2,4a,5,8,8a-hexahydro-1,6-dimethyl-4-(1-methylethyl)-[1S-(1α,4aα,8aα)] and the chemical abstract registry number being 103739-12-4. (See formula (1A). The IUPAC nomenclature of (-)-isozingiberene (1) is 4,10(S)-dimethyl-7-isopropyl-1(R)-6(R)bicyclo[4.4.0]dec-3,7-diene (see formula 1B). As the total stereostructure of (-)-isozingiberene (1) was reported recently in 1985[2], all the stereoisomers, probably of isozingiberene without confirmed stereochemistry, were known by chemical abstract registry numbers 40388-35-0 and 57701-95-8. These compounds are isolated from various natural resources like bark oil[3], cinnamon oil [3], lemon and orange peels[4], laurel oils of Greece[5], extracts of Pinus edulis[6], Pinus monophylla[6], Hyssopus officinalis Linnaeus[7], Juniperus sabina[8], Pinus balfourana[9], Pinus longaeva[10], Pinus aristata[10], Pinus rzedowskii[10], Pinus pinaster[11], Bunium cylindricum[12], Sideritis funkiana[13], Leptactinia senegambia[14] and Piper Lancei[15].

The history of structure elucidation of (-)-isozingiberene (1) is spread over a period of about 70 years (1913-1985)[2,16] and involves several workers. The salient points are as follows. In 1913 Semmler and Becker[16] reported that isozingiberene has a bicyclic ring system and two unsaturated linkages, as they obtained a tetrahydro derivative on catalytic hydrogenation, whereas zingiberene under the same conditions absorbed 3 moles of

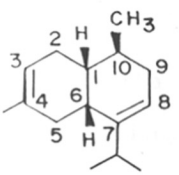


1

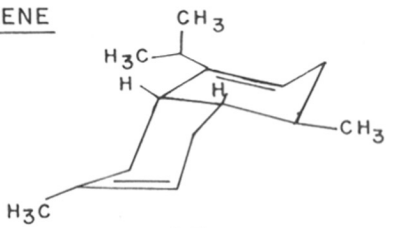
(−)− ISOZINGIBERENE



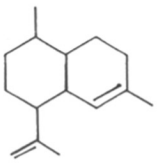
1A



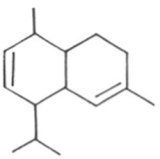
1 B



1 C



2 A



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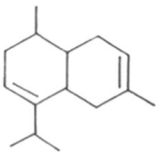
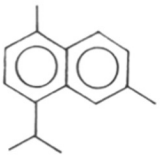
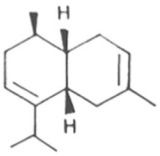


2 C

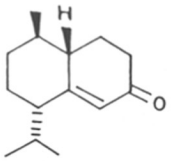


3



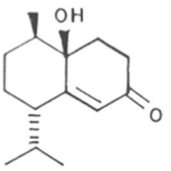
4

(+)− ISOZINGIBERENE



5

SOLID KETONE



7 B

hydrogen. Thus Semmler and Becker proposed formula (2A) for isozingiberene. In 1922, Ruzicka, Meyer and Mingazzini[17] established the skeletal structure of isozingiberene by dehydrogenation of 4-isopropyl-1,6-dimethyl napthalene (3), which was identified by synthesis. In 1931, Ruzicka, Koolhaus and Wind[19] reported on the basis of the physical properties of isozingiberene and tetrahydro isozingiberene, that isozingiberene has a cis configration between rings A and B. In 1932 Simonsen[20], in 1936 Stewart and Graham[21] and in 1937 Egloff[22] suggested formula (2B) for isozingiberene. In 1944 for the first time Soffer et al[23], proved that the structure of isozingiberene described by formula (2C), by action of methyl Grignard reagent on isozingiberene dioxide, to introduce methyl groups for marking the positions of the double bonds in isozingiberene. Isozingiberene dioxide was obtained by action of per benzoic acid on isozingiberene, which in turn is obtained by treating isozingiberene dihydrochloride by alcoholic potassium hydroxide. Isozingiberene dihydrochloride was obtained by action of dry hydrogen chloride gas on crude isozingiberene in glacial acetic acid. Crude isozingiberene was obtained by heating ginger oil with a mixture of glacial acetic acid and sulphuric acid for 6 hours. After this until 1985, there were no reports about the structure of isozingiberene. In 1985, Soffer et al[2] reported the complete stereostructure of (-)-isozingiberene (1) by X-ray crystallographic analysis of isozingiberene dihydrochloride. The stereochemical disposition of the ring junction carbons C_1, and C_6 is cis non-steriodal as shown in formula (1C).

There are no reports on the total synthesis of isozingiberene, as all the reported preparations are either from zingiberene or isozingiberene dihydrochloride. The histroy in brief of preparation of isozingiberene or its dihydrohalide is as follows. In 1916 Brooks[24] obtained a hydrocarbon $C_{15}H_{24}$ by heating sodium salt of zingiberol (obtained from ginger oil after repeated fractional distillations) with potassium bisulphate. This hydrocarbon on treatment with hydrochloric acid in glacial acetic acid yielded isozingiberene dihydrochloride. In 1929, Ruzicka and Van Veen[25] reported preparation of isozingiberene by treatment of zingiberene by sulphuric acid in glacial acetic acid. In 1944, Soffer et al[23] prepared for the first time pure isozingiberene from ginger oil, for determining its structure by the procedure explained earlier while discussing the history of structure elucidation of isozingiberene. In 1953, Zaoral[26] prepared isozingiberene by passing isozingiberene dihydrohalide through a chromatography column filled with alkaline alumina. In the same year Herout et al[27] reported synthesis of isozingiberene from zingiberene by acid catalysed cyclisation of zingiberene followed by treatment with hydrogen chloride gas to obtain isozingiberene dihydrochloride and filtration of this through alumina column.

The common problem with all these preparations of isozingiberene or its dihydrohalide detailed above is that they are all prepared form zingiberene which is isolated from ginger oil. It is very difficult and tedious, if not impossible to separate zingiberene from bisabolene which accompanies[25] it

during its purification from ginger oil. Thus isozingiberene prepared directly[16,25] by acid catalysed cyclisation of naturally occuring zingiberene contains a significant amount of bisabolene[23] or even the bicyclic hexahydrocadalene, a closely related isomer of isozingiberene, which results from direct acid catalysed cyclisation of bisabolene[28]. Thus pure isozingiberene can only be prepared by the procedure reported by Soffer et al[23].

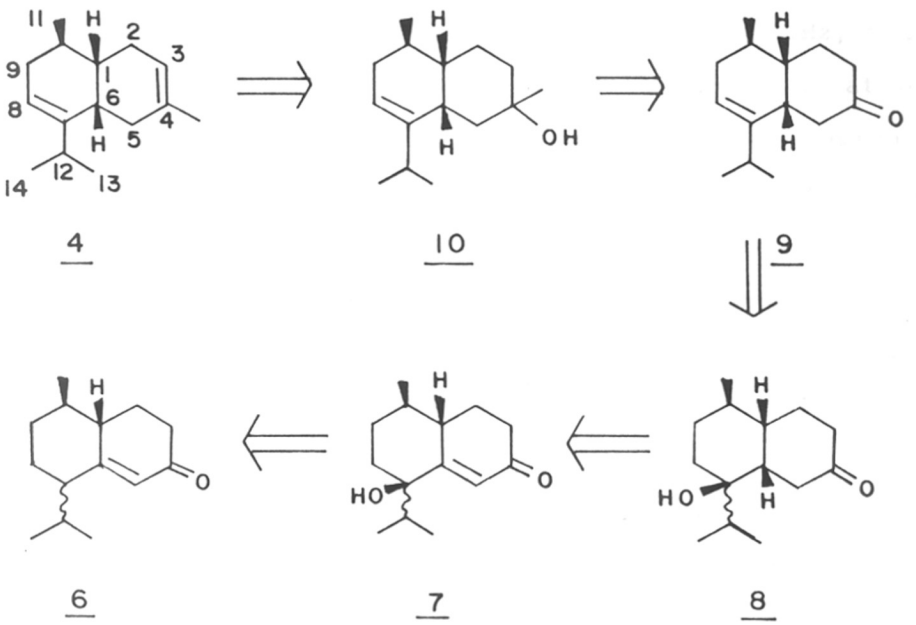
(+)-Isozingiberene (4), an enantiomer of the naturally occuring (-)-isozingiberene (1) is not reported so far in literature. The IUPAC nomenclature of (+)-isozingiberene is 4, 10(R)-dimethyl-7-isopropyl-1(S)-6(S)-bicyclo[4.4.0]dec-3,7-diene. Thus the synthesis of (+)-isozingiberene (4) was undertaken.

PRESENT WORK

A closer look at (+)-isozingiberene (4) and solid ketone (5) or liquid ketone (6) reveals that the stereochemical disposition of C_{11} and proton on C_1 is same in all three compounds. Thus solid ketone (5) or liquid ketone (6) could be good starting material for the synthesis of (+)-isozingiberene (4). The rationale behind the retrosynthetic scheme-1 is as follows. The double bond between C_3 and C_4 could be obtained by dehydration of an alcohol at C_4 position, thus the alkene alcohol (10). The methyl group and alcohol at C_4 can be obtained by Grignard if a ketone is present at C_4, hence the compound (9). Now turning to the double bond between C_7 and C_8, it could be obtained by elimination of mesylate by employing carbanion chemistry where the least substituted double bond would be obtained. The mesylate could be obtained from an alcohol, hence the alcohol ketone (8). A cis junction is desired at C_1 and C_6, which could be envisaged to be obtained by catalytic hydrogenation of a double bond, without affecting the ketone and tertiary alcohol thus the compound (7). This compound was in fact reported by Rangaishenvi.

Rangaishenvi[29] reported the prepartion of allylic alcohol (7) from solid ketone (5). Thus following the reported procedure the solid ketone (5) and selenium dioxide were refluxed in benzene for 6 hours to yield after column chromatography. α,ß-unsaturated ketone alcohol (7) and other compounds. This was identified by its IR spectrum which showed O-H stretch at 3438,

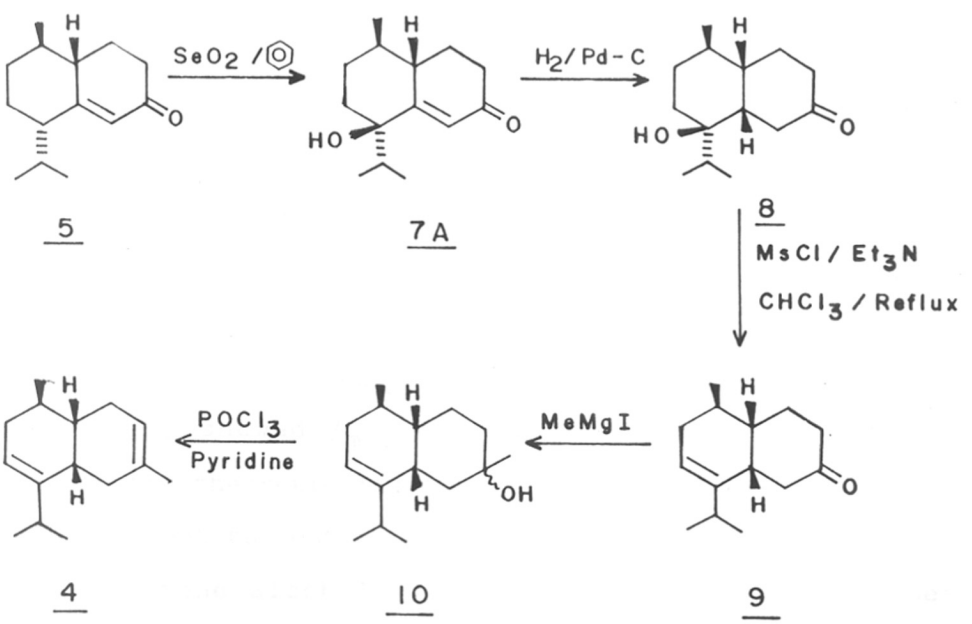
RETROSYNTHETIC SCHEME – I



4 10 9

6 7 8

SCHEME – 2

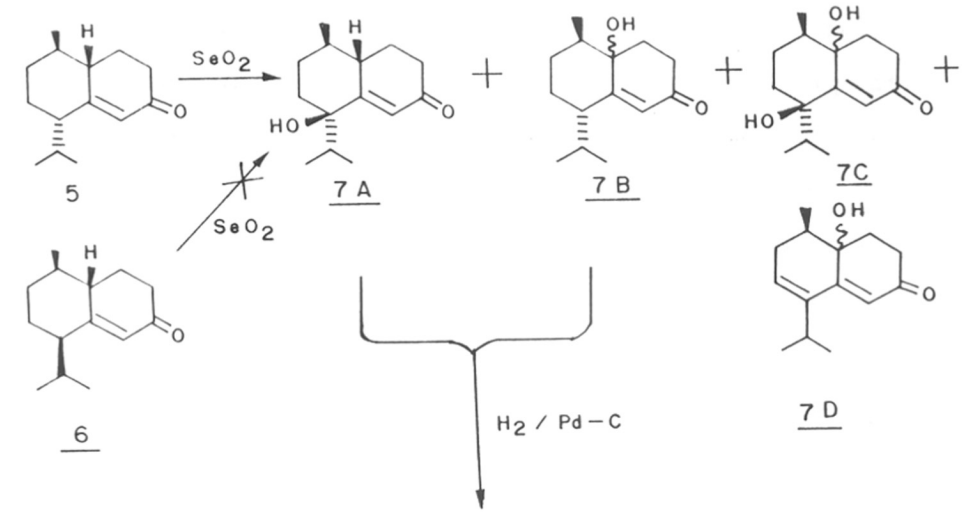


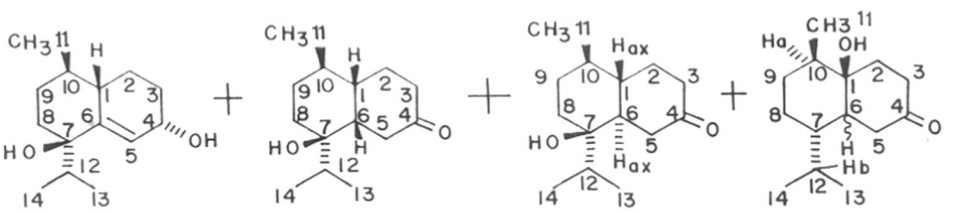
5 7A 8 4 10 9

C=O stretch at 1666 cm^{-1}, NMR spectrum which displayed signals at δ 5.9 (s, 1H, $J_{ally}\approx$1Hz, C=C<u>H</u>-C=O), 6.20 (s, 1H, $J_{ally}\approx$1Hz, C=C<u>H</u>-C=O) and mass spectrum which showed molecular ion peak at m/e 222. Though GC showed one single peak for the compound characterised for α,β-unsaturated ketone alcohol (<u>7</u>), the olefinic signals in the NMR spectrum suggest, which was also confirmed by later experiments, that the ketone alcohol (<u>7</u>) is a mixture of compounds (<u>7A</u>) and (<u>7B</u>). After the elution of ketone alcohol (<u>7</u>), another compound was eluted which showed IR absorbance at 3416 O-H stretch, 1661 C=O stretch, 1184 C-O stretch and 1113 cm^{-1} C-O stretch, NMR displayed signals of δ 5.96 (s, 1H, C-C<u>H</u>-C=O) and mass showed molecular ion peak at m/e 238. On the basis of these spectral characteristics the compound was assigned structure (<u>7C</u>) (See scheme-3). When the chromatographic column was washed with ethylacetate among other unidentifiable minor compounds, compound (<u>7D</u>) (see scheme-3) was eluted. Compound (<u>7D</u>) was identified by IR spectrum, which showed bands at 3426 O-H stretch and 1680 cm^{-1} C=O stretch, NMR spectrum which displayed signals at δ 5.85 (s, 1H, C=C-C=C<u>H</u>-C=O), 6.03 (t, 1H, J=5Hz, <u>H</u>C=C-C=CH-C=O), 2.45 (7 lines, 1H, $CH_3C\underline{H}CH_3$) and mass spectrum, which showed molecular ion peak at m/e 220. The Γ,δ- unsaturated system with OH group at the Γ position of compound (<u>7D</u>) would show a $/_{max}$ at 298nm[30], and the UV spectrum of compound (<u>7D</u>) showed $/_{max}$ at 290.2nm, which is in fair agreement with the theoretically calculated value.

It is pertinent to mention that in the column chromatography of the crude ketone alcohol (<u>7</u>), the benzene used must be

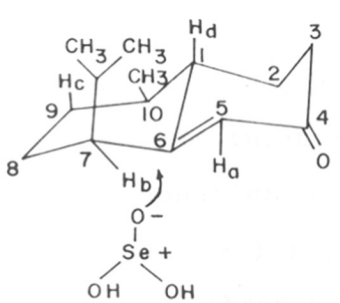
SCHEME – 3



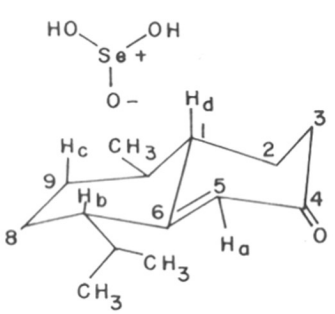


8C Ketoalcohol I 8 Ketoalcohol II 8A Ketoalcohol III 8B

SCHEME – 4



6



5

thiophene free (H_2SO_4 treatment before distillation[31]) or else the next step of catalytic hydrogenation fails, until the sulphur poison is removed (which was found to disappear on repeated attempts of hydrogenation by use of fresh catalyst at every attempt).

An identical experiment on liquid ketone (6) failed to yield the corresponding ketone alcohols, despite several attempts and modifications. The probable reason for the reluctance of liquid ketone (8) to undergo allylic oxidation lies in its stereochemistry. In liquid ketone (6) (see scheme-4), the approximate distances, measured from its molecular model, between equitorial proton on C_7 (H_b) and the olefinic proton on C_5(H_a) is 2.1A°. In the allylic oxidation by selenium dioxide the bulky selenious acid[32] H_2SeO_3 would have to attack from the equitorial face on H_b, where it would face severe steric interaction with H_a. However in solid ketone (5), where the approximate distances measured from its molecular model between the axial proton $C_7(H_b)$ and the axial protons on $C_1(H_d)$, $C_9(H_c)$ and the olefinic proton on C_5 (H_a) are 3.2 A°, 2.7 A° and 2.96 A° respectively, the bulky selenious acid H_2SeO_3 can easily attack on the proton H_b from ß-face as shown in scheme-4. This also explains the formation of compounds (7B), (7C) and (7D) alongwith the keto alcohol (7).

When the α,ß-unsaturated ketone alcohol (7) was subjected to catalytic hydrogenation a mixture of several components was obtained (see scheme-3) from which mainly four compounds were separated by column chromatography. The compound eluting first was tentatively identified as ketoalcohol I (8) by its IR

spectrum which showed bands at 3500 O-H stretch and 1720 cm^{-1} C=O stretch, NMR spectrum which displayed no signals in the olefinic region, and showed an exchangeable proton at 1.46 δ. Mass spectrum showed molecular ion peak m/e 224. The second compound, eluting very close to the first, was tentatively assigned structure (8B) and its NMR, IR and mass spectra closely resembled those of ketoalcohol I (8). The compound eluting third was tentatively assigned structure (8A) by its IR, NMR and mass spectra which again closely resembled those of keto alcohol I (8) except the chemical shifts of methyl and isopropyl methyl groups in NMR. The compound eluting last was identified as diol (8C) by its IR spectrum which showed band at 3600 sharp free O-H stretch[30], 3460 broad intermolecular bonded O-H stretch and absense of C=O stretch, NMR spectrum showed signals at δ 5.65 (s, 1H, C=C<u>H</u>-COH), 4.13 (bs, 1H, C=C-COH H_{eq})[33] and mass spectrum, which showed molecular ion peak at m/e 224.

As the NMR, IR and mass spectra of the compound (8B) were similar those of the ketoalcohol I (8), NMR decoupling experiments were undertaken to ascertain the location of the OH group. It has been reported[30] that methine protons would appear at δ 1.55 , whereas methine protons with OH group on the α-carbon would appear at δ 1.75. Thus when all the three methyl groups were irradiated, the effect was observed at δ 1.75 and 1.55. On irradiation of the C_{13} and C_{14} methyls of the isopropyl the effect was observed at δ 1.55, which was not very pronounced. To counter check the earlier observation irradiation at δ 1.5 was done by which the isopropyl C_{13} and C_{14} methyl, which were

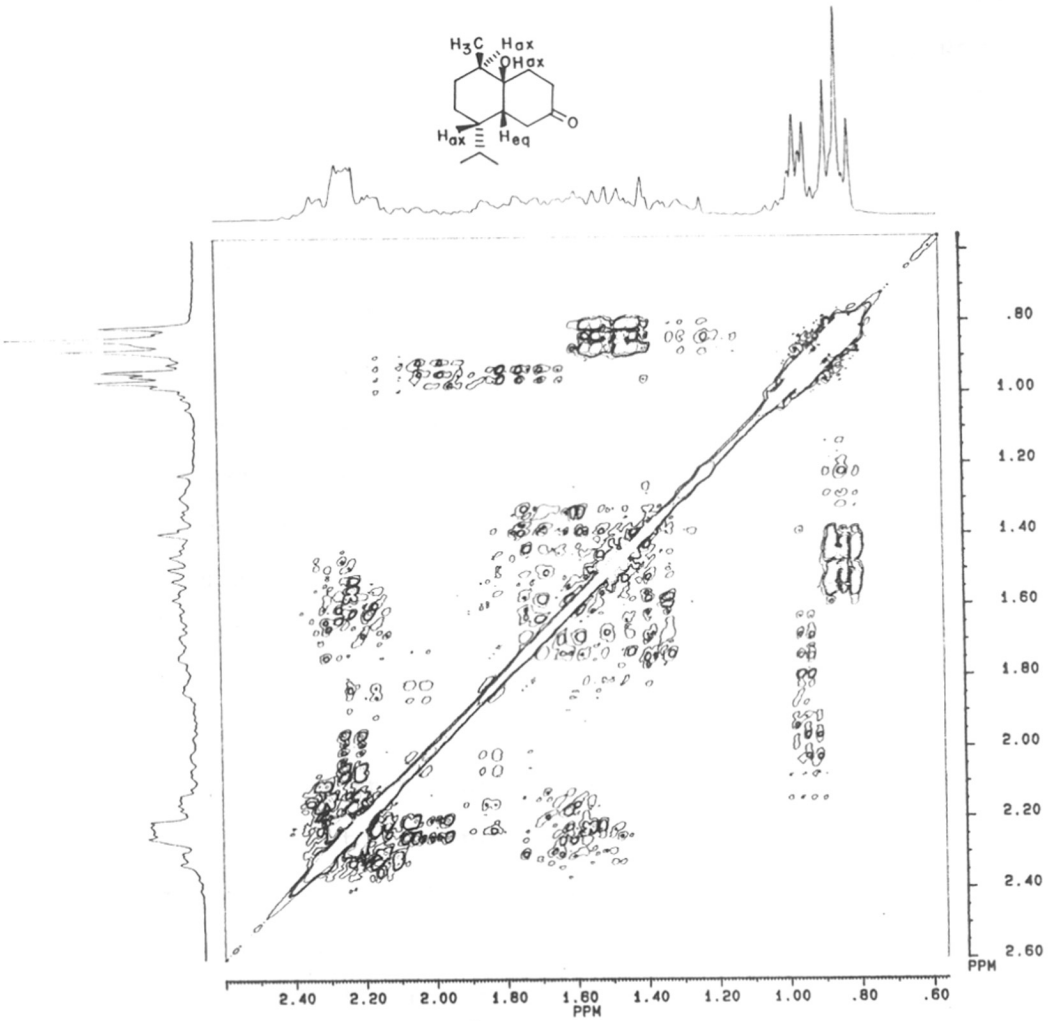
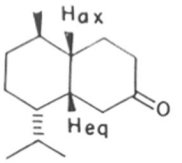


Fig. 1: 2D COSY H^1-NMR OF KETO-ALCOHOL III (8B).

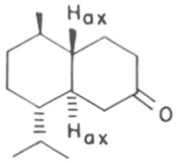
appearing as a triplet, collapsed to show a broad singlet. These experimental results thus rule out the possibility of the OH group being located at C_7 carbon. On irradiation of the C_{11} methyl group, the effect was observed at δ 1.70-1.75 by which it was confirmed that the OH group is at the C_1 position. However, the decoupling experiments did not give an undisputable picture about the structure of ketoalcohol III (8B), hence the 2D COSY experiment was undertaken. The 2D COSY spectrum of ketoalcohol III (8B) clearly shows (see Fig 1) that the isopropyl methyl C_{13} and C_{14} are coupled with a proton appearing at around δ 1.5, whereas the C_{11} methyl is coupled with a proton appearing around δ 1.80. This confirms the structure of ketoalcohol III (8B). As the compound was not of any synthetic value to the synthesis of (+)-isozingiberene (4) further studies like ORD-CD or C^{13} NMR were not done.

The NMR, IR and mass spectra of ketoalcohol I (8) and ketoalcohol II (8A) could not elucidate the stereochemical disposition of the ring junction and the location of the OH group. It is reported that the ketone I (11) and ketone II (12) exhibit a positive and negative Cotton effect curves respectively[29,34]. The octant projections of ketoalcohol I (8) ketoalcohol II (8A) (see scheme - 5) shows that keto alcohol I (8) should exhibit a positive Cotton effect whereas ketoalcohol II (8A) should exhibit a negative Cotton effect curve. Thus the ORD curves of the ketoalcohol I (8) and ketoalcohol II (8A) were recorded which shows (see Fig 2) as expected a small positive Cotton effect curve for ketoalcohol I (8) at 287nm, a = +14 and a

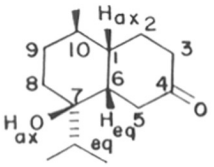
SCHEME – 5



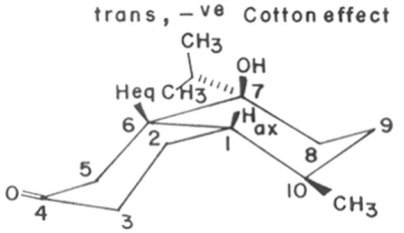
Ketone I (11)
cis – nonsteriodal
+ ve Cotton effect



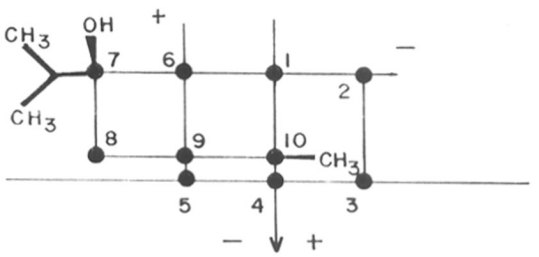
Ketone II (12)
trans, – ve Cotton effect



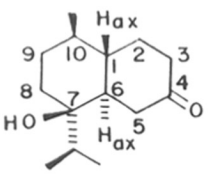
Ketone Alcohol I 8



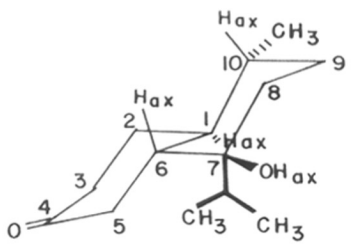
cis non-steriodal

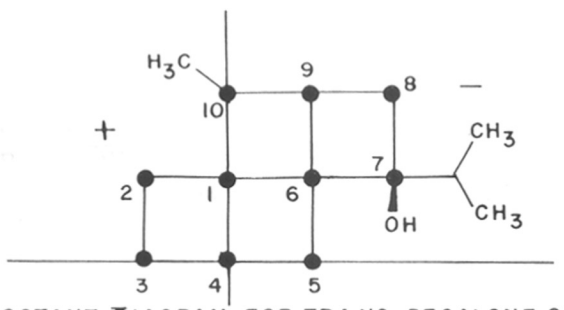


OCTANT DIAGRAM FOR CIS-NONSTERIODAL DECALONE 8
ORD Shows + ve Cottoneffect at 287nm with a = +14



Keto Alcohol II 8A

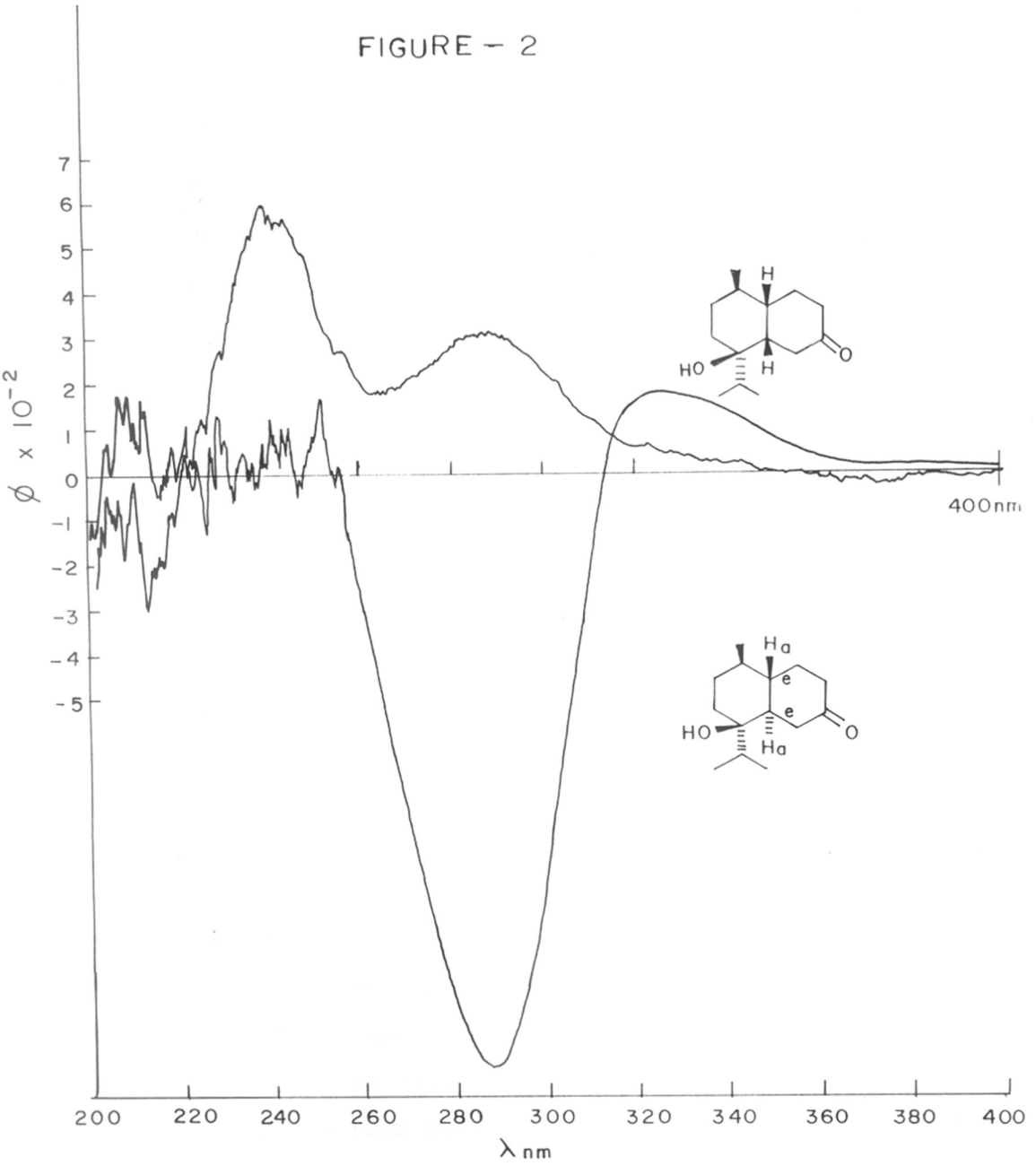




OCTANT DIAGRAM FOR TRANS-DECALONE 8A

ORD Shows – ve Cotton effect at 287 nm a = – 148

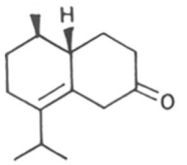
FIGURE – 2


7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
$\phi \times 10^{-2}$
400nm
H
HO
H
O
Ha
e
e
HO
Ha
O
200
220
240
260
280
300
320
340
360
380
400
λ nm

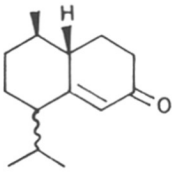
large negative Cotton effect curve for ketoalcohol II (8A) at 287nm, a = -148. The difference in magnitudes of the Cotton effects observed can be explained as follows. It is known[35] that the presence of several remote substituents in one of the octants may reflect itself in the amplitude of the Cotton effect. This is illustrated by the example of the positive Cotton effect of cholestan-2-one (15) which is considerably greater than that of cholestan-3-one (16). Thus on a closer evaluation of the octant projection of ketoalcohol I (8) one finds that since the whole bulk is concentrated close to the planes of projections the effective contribution to the Cotton effect is also small, whereas in case of ketoalcohol II (8A) as the bulk is spread far away into the negative quadrant, the amplitude of Cotton effect observed is large.

Now only the location of the OH groups remain to be confirmed in ketoalcohol I (8) and ketoalcohol II (8A). On dehydration of the tertiary alcohol by refluxing in benzene with p-toulene sulphonic acid as catalyst[29,34] keto alcohol I (8) should give alkene ketone I (AK-I) (13A), AK-II (13B) and AK-III (13C), (see scheme-6), whereas ketoalcohol II (8A) should give AK-I (13A), AK II (13B) and AK IV (13D), if the OH group is at C_7 position. If the OH group is at C_1 then AK V (14A), AK VI (14B) and AK VII (14C) or AK VIII (14D), AK IX (14E) and AK VII (14C) should be obtained from ketoalcohol I (8) and keto alcohol II (8A) respectively. However several attempts failed to effect dehydration of the alcohol and the starting ketoalcohol was recovered at all attempts.

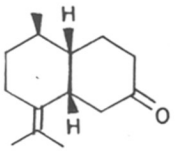
SCHEME – 6



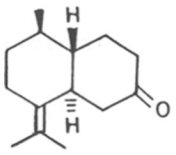
Alkene Ketone I
AK-I 13A



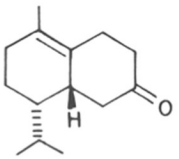
AK II 13B



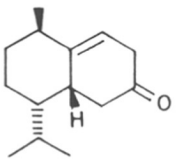
AK III 13C



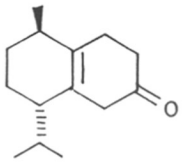
AK IV 13D



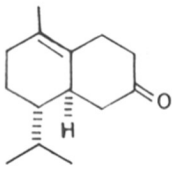
AK V 14A



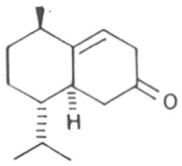
AK VI 14B



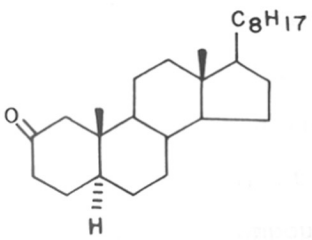
AK VII 14C



AK VIII 14D

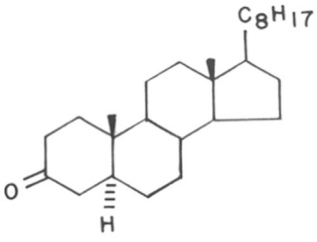


AK IX 14E



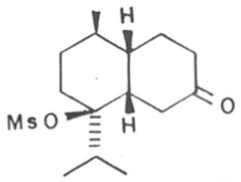
15

CHOLESTAN-2-ONE



16

CHOLESTAN-3-ONE

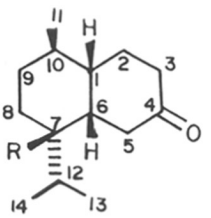


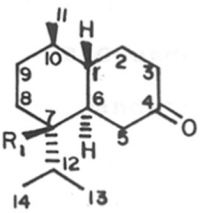
17

The location of the OH groups in ketoalcohol I (8) and ketoalcohol II (8A) was confirmed by the C^{13} NMR spectra. by exploiting the fact that due to the steric compression of a Γ-gauche interaction as upfield shift[30] is observed for carbon atoms Γ to the axial OH group. Thus as can be seen from the Table - I, the isopropyl methyl C_{13} and C_{14} have shifted upfield due to the axial OH at C_7, whereas the C_{11} methyl appears downfield in both the ketoalcohol I (8) and the ketoalcohol II (8A). For making the C^{13} assignments for the compounds[36] keto alcohol I (8), ketoalcohol II (8A) and ketoalcohol III (8B), the C^{13} NMR of ketone I (11) and ketone II (12) were recorded and their C^{13} NMR assignment values used.

As is evident from the retrosynthetic scheme-1 only ketoalcohol I (8) is of synthetic value for the synthesis of (+)-isozingiberene (4) and in which an Hoffman elimination is desired. Lundeen et al[37] reported that thoria (ThO) and other oxides of group III B elements catalyse the dehydration of alcohols to yield the least substituted olefins, as major products. Landeen et al[38] later in 1967 reported that dehydration of tertiary alcohols (t-amyl alcohol) over thoria at 306°C gave the least substituted olefin as major product. Thus as per the procedure of Landeen et al[38] dehydration of keto alcohol I (8) was attempted on a thoria (coated on glass beads and filled in a pyrolysis column) at various temperatures ranging from 250°C to 350°C to yield compounds ranging from the starting keto alcohol I (8) to some unidentifiable charred material but no alkene ketone (9).

Table-I





Carbon No.	R : H (ppm)	R : OH (ppm)	R_1 : H (ppm)	R_1 : OH (ppm)
1	42.9	25.3	47.8	42.0
2	27.8	29.1	35.3	30.8
3	36.8	35.2	41.0	40.6
4	211.7	211.5	211.1	211.3
5	37.8	38.9	44.9	44.0
6	47.9	43.9	48.8	55.0
7	39.9	38.9	44.8	74.0
8	24.5	29.1	24.0	31.8
9	35.7	25.8	30.5	31.8
10	28.8	31.5	37.0	37.5
11	19.5	17.9	14.8	19.6
12	27.0	35.5	26.1	37.2
13	20.4	13.8	21.3	19.6
14	21.1	14.5	20.1	18.7

Another methodology to obtain the Hoffmann elimination was by carbanion chemistry, where the order of ease of proton abstraction is CH_3 > CH_2 > CH. Thus treating keto alcohol I (8) with three moles of lithium diisopropyl amide at -78°C under argon did not yield the expected alkene-ketone (9), and the starting keto alcohol I (8) was recovered. The same reaction was tried at 0°C to yield similar results. To facilitate the elimination of the OH group (which by the previous experiments was known to be difficult) it was found essential to convert it to a better leaving group. (e.g., mesylate). Keto alcohol I (8) was stirred with methane sulphonyl chloride in dry pyridine for 7 days to recover the starting keto alcohol I (8). Prakash et al[39] reported a typical procedure for conversion of alcohols to mesylate, by stirring the alcohol with methane sulphonyl chloride and triethylamine in dichloromethane at room temperature.

The procedure reported by Prakash et al[39], when used for keto alcohol I (8) with 12 hours stirring gave only 50% yield, but with 7 days stirring at room temperature gave about 90% yield of the mesylate (17). The mesylate (17) was identified by IR spectrum which showed bands at 1715 C=O stretch, 1340 and 1150 cm^{-1} S=O stretch. NMR spectrum, which showed signals at δ 3.65 (s, 3H, $\underline{CH_3}SO_2$-) and mass spectrum showed molecular ion peak at m/e 302. The mesylate (17) on treatment with 2 moles of n-butyl lithium in tetrahydrofuran at various temperatures ranging from -78°C to 0°C gave complex mixtures, in which neither the starting mesylate (17), keto alcohol I (8) nor the desired alkene ketone (9) was found. Meanwhile in attempts to find a quicker procedure

to obtain the mesylate in good yields, the keto alcohol I (8) was refluxed in chloroform with methane sulphonyl chloride and triethylamine for 9 hours, when the complete consumption of the keto alcohol I (8) was observed. While monitoring the reaction by TLC (solvent D) a new spot with R_f value 0.8-0.9 was observed, evidently of a very non polar compound. The new compound was purified by chromatography and its NMR, IR and mass spectra recorded, which indicated the new compound to have the structure same as alkene ketone (9). The salient features, by which the alkene ketone (9) was identified, are NMR spectrum showed signals at δ 5.37 (bd, 1H, CH_2-CH=C-), IR spectrum showed bands at 1708 C=O stretch and 1615 cm^{-1} C=C stretch and mass spectrum showed molecular ion peak at m/e 206. Thus serendipitiously the much sought alkene ketone (9) was obtained. A possible explaination for the formation of alkene ketone (9) as sole product is as follows.

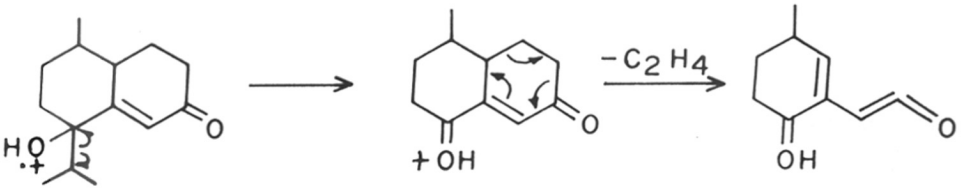
Yadav[40] et al reported a facile conversion of tertiary alcohols to olefins by employing methane sulphonyl chloride, triethylamine and catalytic amount of 4-dimethylaminopyridine in dichloromethane to obtain both the Zaitsev (most substituted olefin) and Hoffmann (least substituted olefin) products. However in the case of dehydration of keto alcohol I (8), where possibility of formation of Zaitsev products like alkene ketone I (AK I) (13A), AK II (13B) and AK III (13C) (see scheme-6) also did exist, only the Hoffmann product alkene ketone (9) was formed. This clearly indicates that the mechanism of the reaction is an anti E_2 mechanism[32]. In keto alcohol I (8) and

its mesylate (17) only C_8 has a proton trans to the axial OH group on C_7, thus only formation of double bond between C_7 and C_8 is possible by the anti E_2 mechanism, to yield alkene ketone (9).

Grignard reaction on the alkene ketone (9) with methyl-magnesium iodide furnished the alkene alcohol (10), which was identified by its IR, NMR and mass spectra. IR showed bands at 3365 O-H stretch, 1665 C=C stretch and 1107 cm^{-1} C-O stretch, NMR showed signals at δ 5.3 (bd, 1H, $CH_2C\underline{H}$=C-), 1.29 (s, 3H, CH_2-COH $C\underline{H}_{3(ax)}$), 1.20 (s, 3H, CH_2COH $C\underline{H}_{3(eq)}$) and mass spectrum showed molecular ion peak at m/e 222.

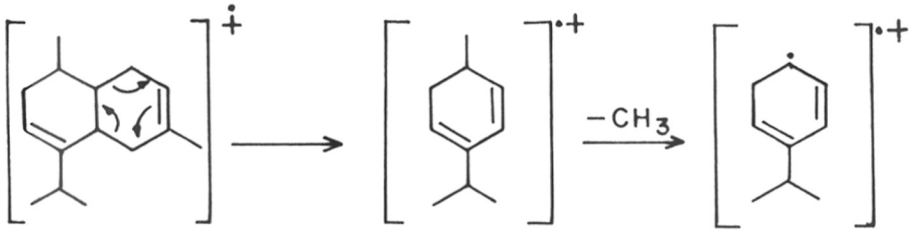
(+)-Isozingiberene (4) was obtained by stirring alkene alcohol (10) with phosphorus oxychloride in dry pyridine for 4 hours[29]. The crude (+)-isozingiberene (4) so obtained was purified by repeated preparative TLC to yield pure (+)-isozingiberene (4). The (+)-isozingiberene (4) was characterised by NMR, which showed signals at δ 5.35 (bs, 2H, $CH_2C\underline{H}$=C($CHMe_2$)C and $CH_2C(CH_3)C$=C$\underline{H}$), 1.67 (bs, 3H, CH_2-$\underline{CH}_3$-C=CH-), 0.87-1.08 (m, 9H, J=7hz, methyl and isopropyl methyls). IR showed band at 2958 C-H stretch, 1652 C=C stretch, 1447 C-H scissoring, and 1377 cm^{-1} C-H deformation. Mass spectrum showed peaks at m/e 204 (M^+), 205 (M^++1), 189 (M^+-CH_3), 161 (M^+-CH_3CHCH_3) as base peak and 136 (M^+-$CH_2CHC(CH_3)CH_2$) (see scheme-7). IR spectrum of (-)-isozingiberene (4) is reported by Pliva et al[41], but we could not procure it despite our much efforts.

SCHEME – 7



m/e 222 m/e 179 m/e 151

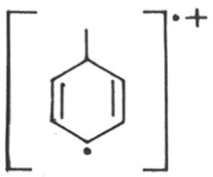
7



m/e 204 m/e 136 m/e 121

4

$-CH_3CHCH_3$



m/e 93

EXPERIMENTAL

Ketone alcohol (7) from solid ketone (5)

Solid ketone (5, 1.0 gm, 4.9 mmoles), and selenium dioxide (2.0 gm, 17.7 mmoles) was refluxed in benzene (150 ml) for 6 hours. The reaction mixture was cooled and filtered through a filter paper. The filterate was washed with water (2 x 100 ml), brine (1 x 50 ml), dried over anhydrous sodium sulphate and concentrated in vacuo to yield an oil (1.1 g, 100% yield). The crude product was subjected to column chromatography with silica-gel and eluted with pet-ether, benzene and ethylacetate with gradual increase in polarity. Compound (7) eluted in 20% ethylacetate : 80% benzene. Compound (7C) eluted in 35% ethylacetate :65% benzene and compound (7D) eluted in 50% ethylacetate : 50% benzene. TLC (solvent D). Compound (7) NMR ($CDCl_3$) : δ 5.91 (d, 1H, J_{ally} = 1Hz, C=C<u>H</u>-C=OCH_2), 6.20 (d, 1H, J_{ally} = 1Hz, C=C<u>H</u>-C=O-CH_2), 0.6-1.1 (d, 9H, J=7Hz, isopropyl methyl and methyl), 1.1-2.6 (12H, other methylene and methine protons). IR (Neat) showed bands at 3438 O-H stretch, 1666 C=O stretch and 1614 cm^{-1} C=C stretch. MS : m/e 222 (M^+), 223 (M^++1), 204 (M^+-H_2O), 179 ($M^+-CH_3CHCH_3$) and 151 ($M^+-CH_3CHCH_3-C_2H_4$) as base peak. $(\alpha_D)^{26}$ = + 70.6° (c, 0.564), GC, 200°C r.t = 4.92 min.

Keto-alcohol I (8) from ketone alcohol (7).

A solution of ketone alcohol (7, 1.5 gms, 6.8 mmoles) in

methanol was placed in the Paar hydrogenation bottle with 10% Pd-C (200 mg) and hydrogenated at room temperature for 8 hours at 20 PSI hydrogen gas pressure. The solution was then filtered and alcohol was removed in vacuo, to yield an oil (1.52 gms, 100% yield). The oil was then purified through silica-gel column, when keto alcohol I (8) was obtained in 10% ethyl acetate: 90% benzene eluate (850 mg). TLC (solvent D). NMR ($CDCl_3$) : δ 1.46 (1H, D_2O exchangeable, CH_2-C(O<u>H</u>) (isopropyl)-C), 0.82 (d, 6H, J=7Hz, CH_3CHCH_3), 0.9 (d, 3H, J=7Hz, CH-CH(C<u>H</u>$_3$)CH_2, 1.1-2.5 (15H, rest of the methylene and methine protons). IR (Neat) showed bands at 3500 O-H stretch and 1720 cm^{-1} C=O stretch. MS : m/e 224 (M^+), 206 (M^+-H_2O), 191 ($M^+-H_2O-CH_3$), 181 ($M^+-CH_3CHCH_3$) as base peak and 163 ($M^+-CH_3CHCH_3-H_2O$). $(\alpha_D)^{26}$ = 11.84° (c, 0.532). GC, 180°C, r.t.= 5.76 min.

Alkene ketone (9) from keto alcohol (8).

The keto alcohol (8, 250 mg, 1.25 mmoles) was taken in a two neck round bottom flask equipped with a magnetic needle, rubber septum, reflux condenser and 2 way stopcock with ultra pure argon gas balloon. The apparatus was flushed with argon thrice using the vaccum argon gas release cycle. To this dry chloroform (25 ml) and triethylamine (1.52 ml, 10.9 mmoles) was added by aid of syringe. The flask was cooled to 0-5°C by ice and mesyl chloride (0.75 ml, 9.7 mmoles) was added under stirring. After 15 minutes the apparatus was transferred into an oil bath and refluxed for 9 hours. Usual work up furnished a foul smelling oil (240 mg, 93%). The crude product was loaded onto a silica-gel column, and

eluted with pet-ether, benzene and ethylacetate. The alkene ketone (9) eluted in 2% ethylacetate in benzene. TLC (solvent B). NMR ($CDCl_3$) : δ 5.37 (bd, 1H, $CH_2C\underline{H}$=C-(isopropyl)-), 1.017 and 0.961 (d, 9H, J=7Hz, isopropyl methyl and methyl), 1.056-3.5 (12H, other methylene and methine protons). IR (Neat) showed bands at 1708 C=O stretch and 1615 cm^{-1} C=C stretch. MS:m/e 206 (M^+), 207 (M^++1), 191 (M^+-CH_3) and 163 ($M^+-CH_3CHCH_3$) as base peak. $(\alpha_D)^{26}$= +4.1° (c, 0.97). GC, 200°C r.t. = 2.11 min.

Alkene alcohol (10) from alkene ketone (9).

The alkene ketone (9, 128 mg, 0.62 mmole) was taken in a two round bottom flask equipped with a magnetic needle, rubber septum and two way stop cock with ultra pure argon gas ballon. The flask was finished with argon using the vaccum-argon gas release cycle. To this anhydrous diethyl ether (10 ml) was added. The solution was cooled to 0-5°C by ice and the standard 3M Grignard reagent (0.75 ml, 2.3 mmoles) was added dropwise under stirring. After 15 minutes the reaction was brought to room temperature and stirred further for 9 hours. Excess of unreacted Grignard reagent was destroyed by cooling the reaction mixture to 0-5°C by ice and dropwise addition of saturated ammonium chloride (1 ml). Usual work up furnished an oil (130 mg, 94% yield). TLC (Solvent C). NMR ($CDCl_3$) : δ 5.3 (bs, 1H, $CH_2C\underline{H}$=C-(isopropyl)), 1.29 (s, 3H, $CH_2CC\underline{H}_{3ax}OH$), 1.20 (S, 3H, $CH_2C\underline{H}_{3\ eq}OH$), 0.83-1.10 (d, 9H, J=7Hz, isopropyl methyls and methyl). 1.10-2.5 (16H, methyl and other methylene and methine protons). IR (Neat) shows bands at 3365 O-H stretch, 1665 C=C stretch and 1107 cm^{-1} C-O stretch. MS

: m/e 222 (M^+), 204 (M^+-H_2O), 189 ($M^+-H_2O-CH_3$) and 161 ($M^+-H_2O-CH_3CHCH_3$) as base peak. $(\alpha_D)^{26}$= +10.1° (c, 0.812).

(+)-Isozingiberene (4) from alkene alcohol (10).

The alkene alcohol (10, 102.0 mg, 0.46 mmoles) was taken in a two neck round bottom flask, equipped with magnetic needle, rubber septum and two way stop cock with ultra pure argon gas balloon. The apparatus was flushed with argon gas thrice by employing vaccum-argon gas release cycle. To this dry pyridine (5 ml) (distilled over lithium aluminium hydride) was added by aid of syringe. The solution was stirred and cooled to 0-5°C by ice. To this phosphorus oxychloride (0.1 ml, 1.07 mmoles) was added dropwise. The reaction was stirred for 12 hours and worked up as usual to furnish an oil (50 mg, 53% yield). TLC (Solvent A) This was purified by two successive preparative TLC run in pet ether. NMR ($CDCl_3$) : δ 5.35 (bs, 2H, $CH_2C\underline{H}=C(CHMe_2)C$ and $CH_2C(CH_3)C=C\underline{H}$), 1.67 (bs, 3H, $CH_2-\underline{CH}_3-C=CH-$), 0.87-1.08 (m, 9H, J=7hz, methyl and isopropyl methyls). IR (Neat) showed band at 2958 C-H stretch, 1652 C=C stretch, 1447 C-H scissoring, and 1377 cm^{-1} C-H deformation. MS : m/e 204 (M^+), 205 (M^++1), 189 (M^+-CH_3), 161 ($M^+-CH_3CHCH_3$) as base peak and 136 ($M^+-CH_2CHC(CH_3)CH_2$) (see scheme-7). $(\alpha_D)^{26}$= +30.0° (c, 0.428). GC, 200°C, r.t.=1.17 min.

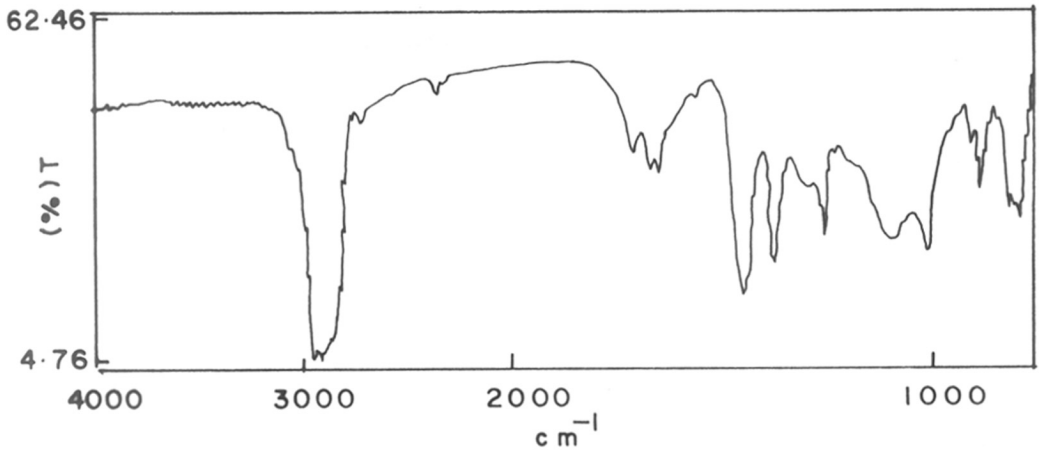


FIG. 3B.1 : IR OF (+) - ISOZINGIBERENE (4)

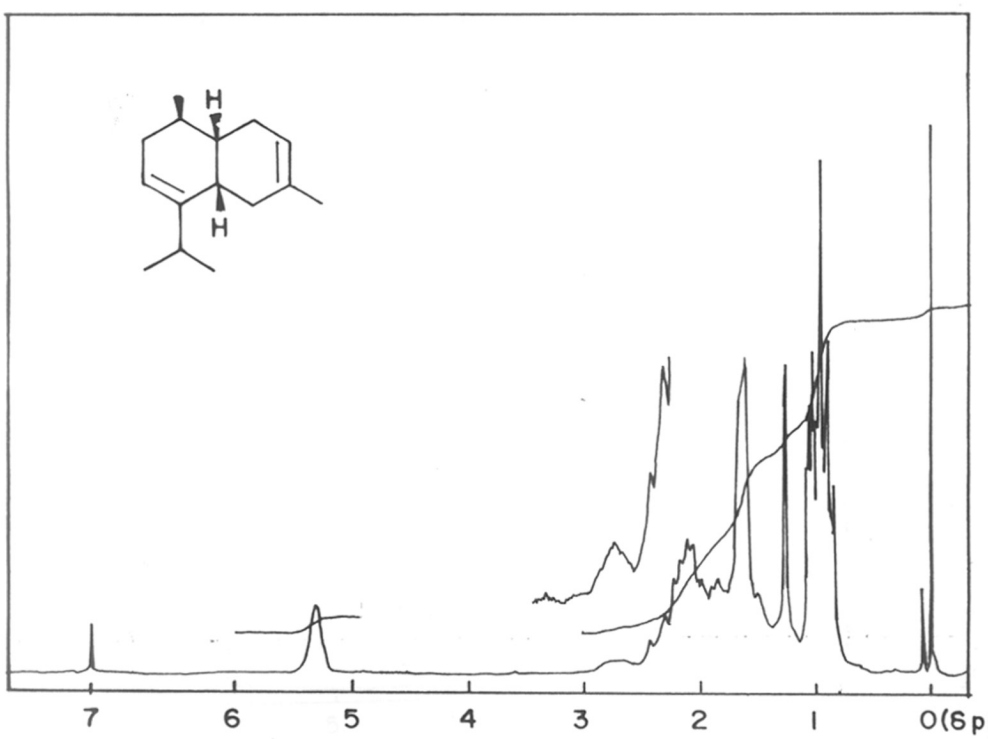


FIG.3B.2 : NMR OF(+) - ISOZINGIBERENE (4)

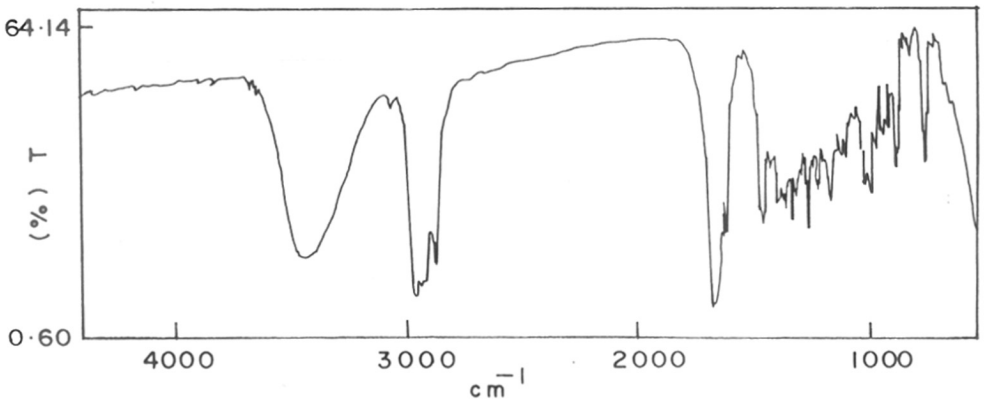


FIG. 3B.3 : IR OF KETONE ALCOHOL (7A) + (7B)

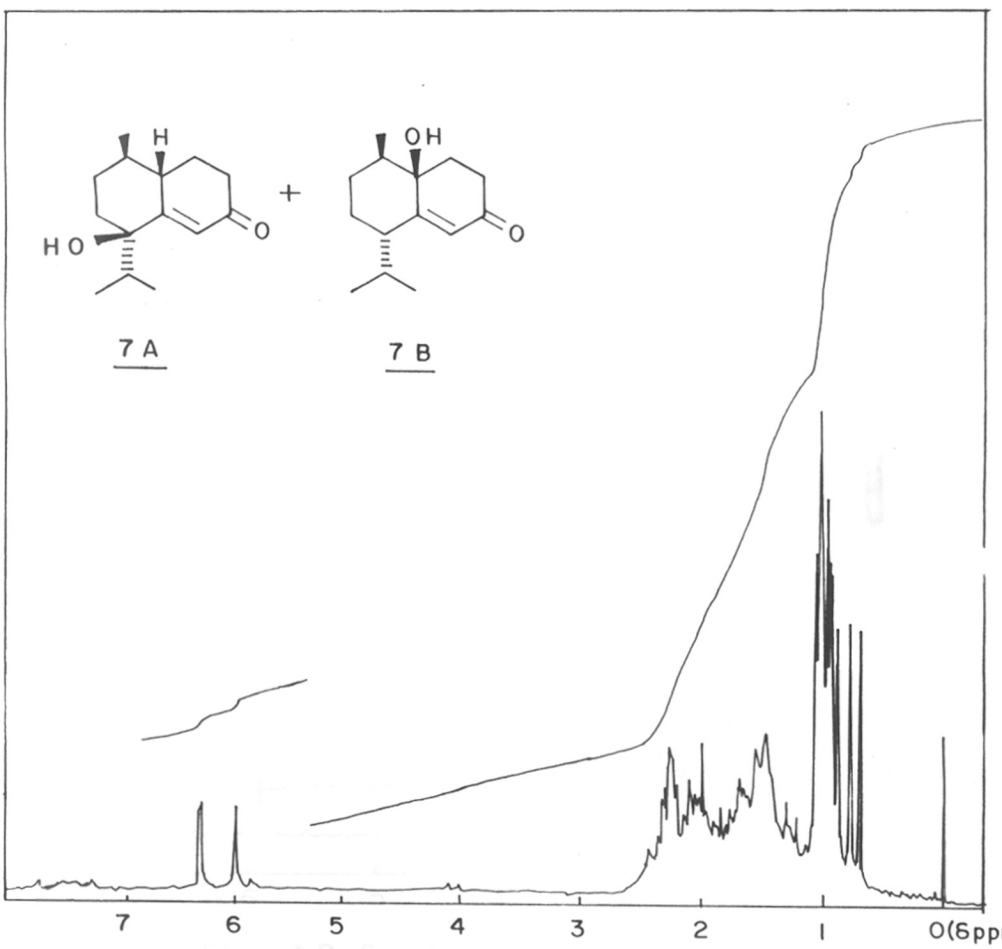


FIG. 3B.4 : NMR OF KETONE ALCOHOL (7A) + (7B).

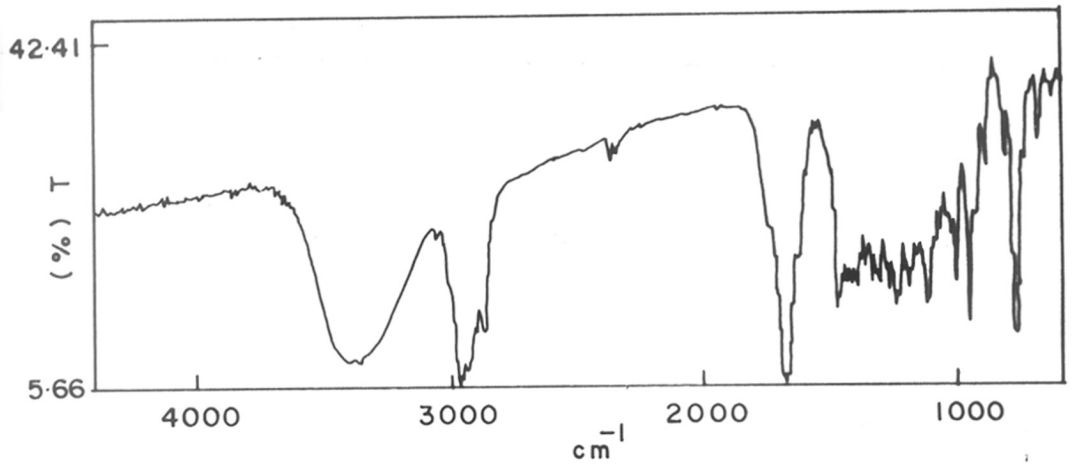


FIG. 3B.5 : IR OF COMPOUND (7C).

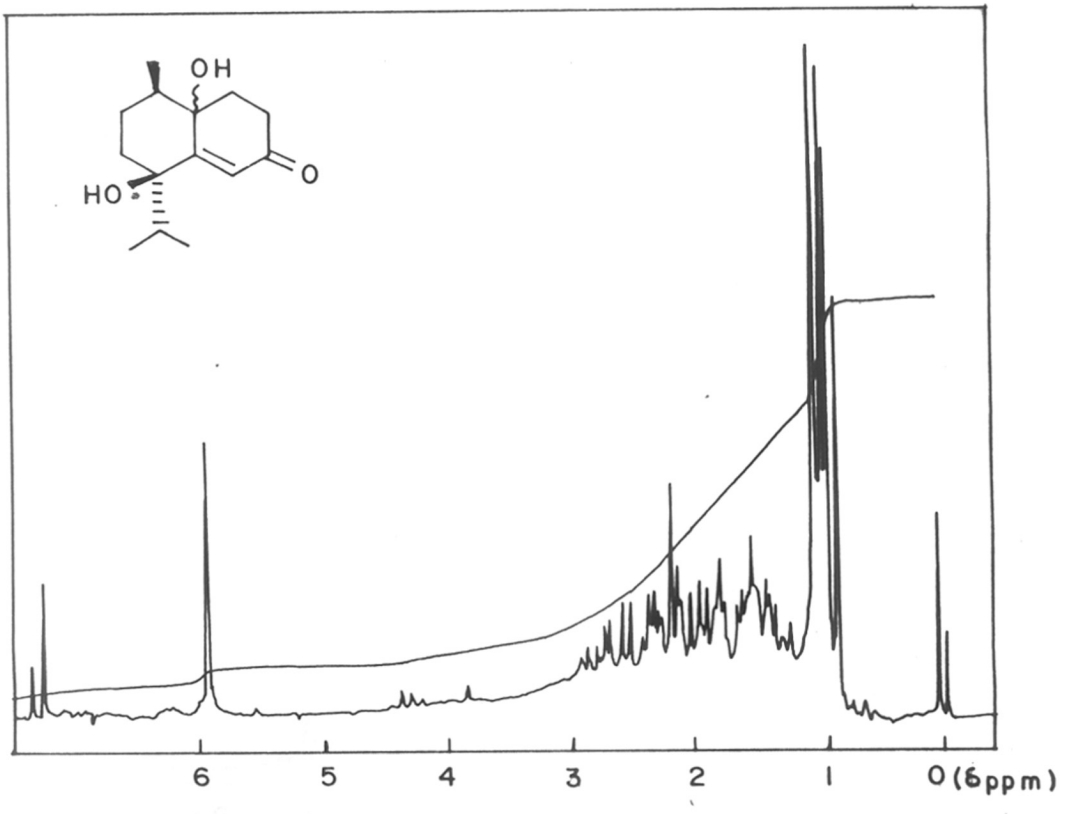


FIG .3B.6 : NMR OF COMPOUND (7C)

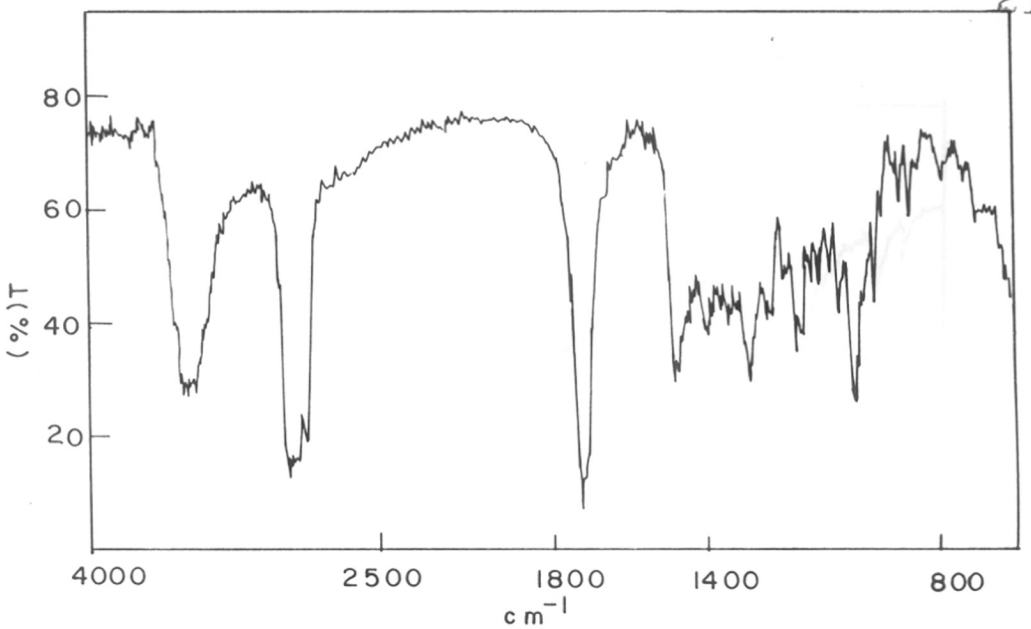


FIG. 3B.7 : IR OF KETO ALCOHOL I (8)

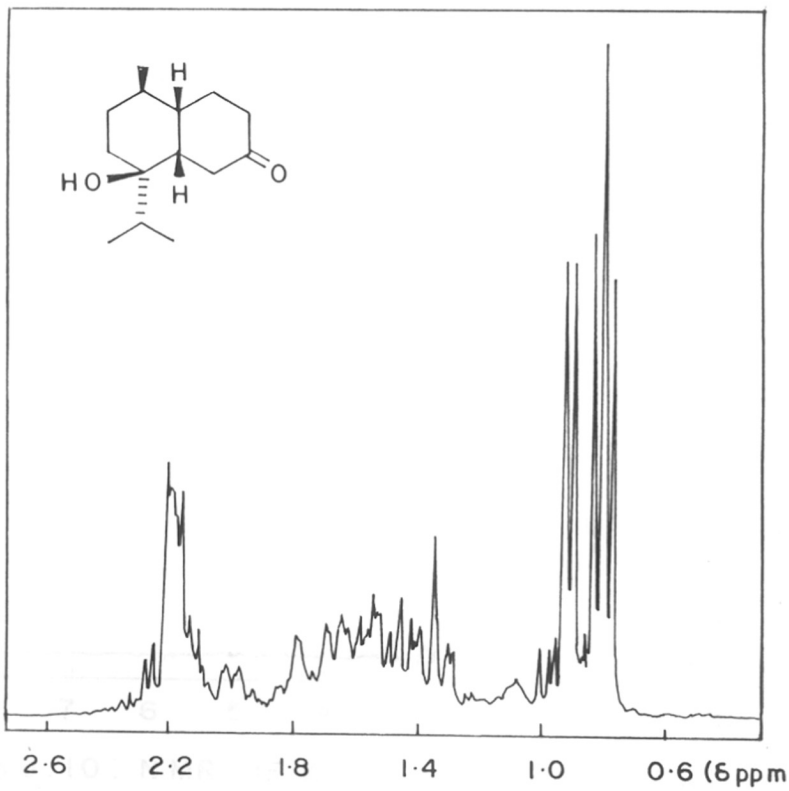


FIG. 3B.8 : NMR OF KETO ALCOHOL I (8)

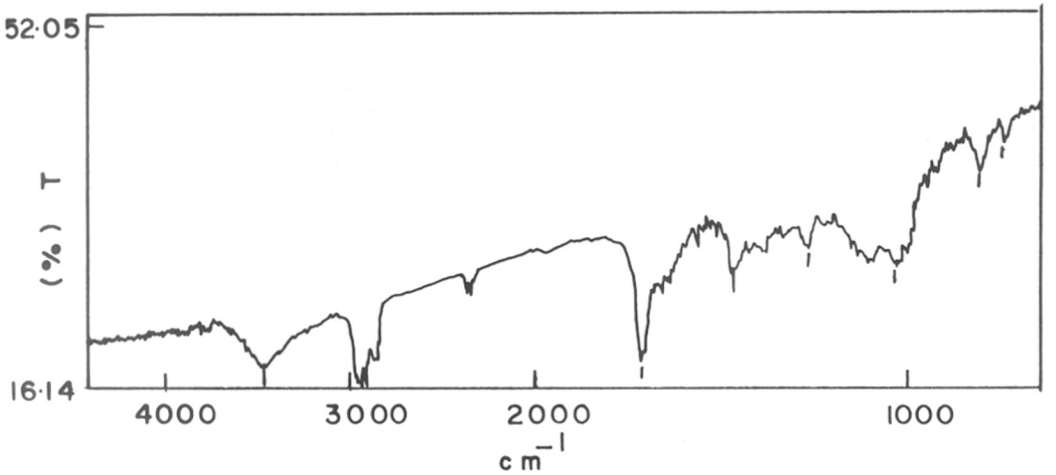


FIG. 3B.9 : IR OF KETO ALCOHOL II (8A)

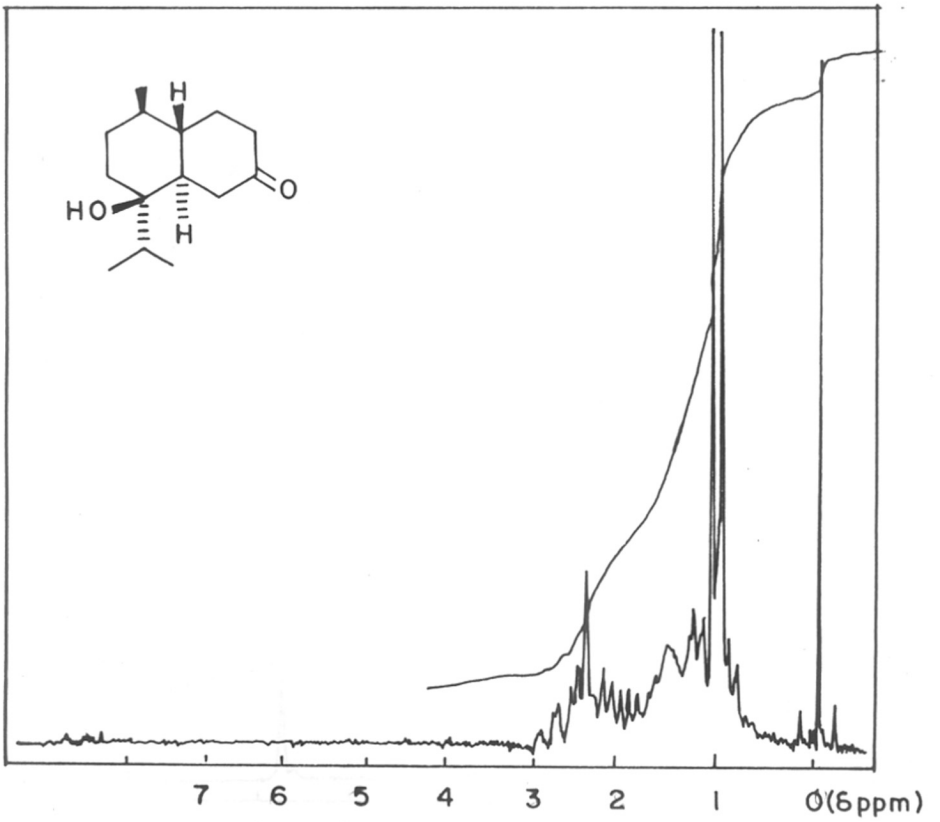


FIG. 3B.10 : NMR OF KETO ALCOHOL II (8A)

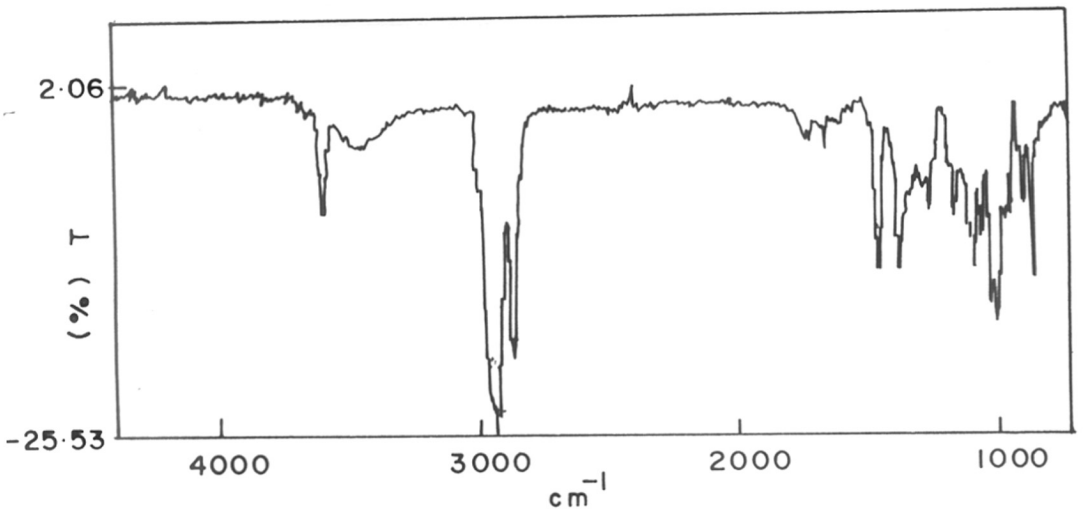


FIG. 3 B. II : IR OF DIOL (8C)

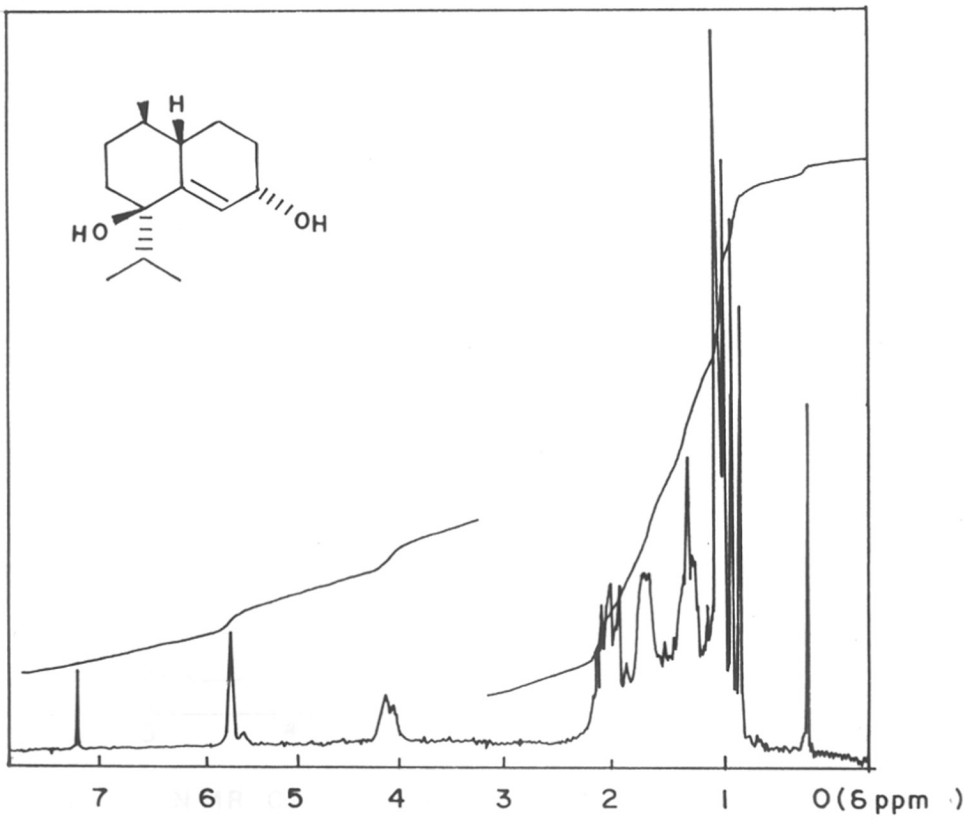


FIG. 3 B. I2 : NMR OF DIOL (8C).

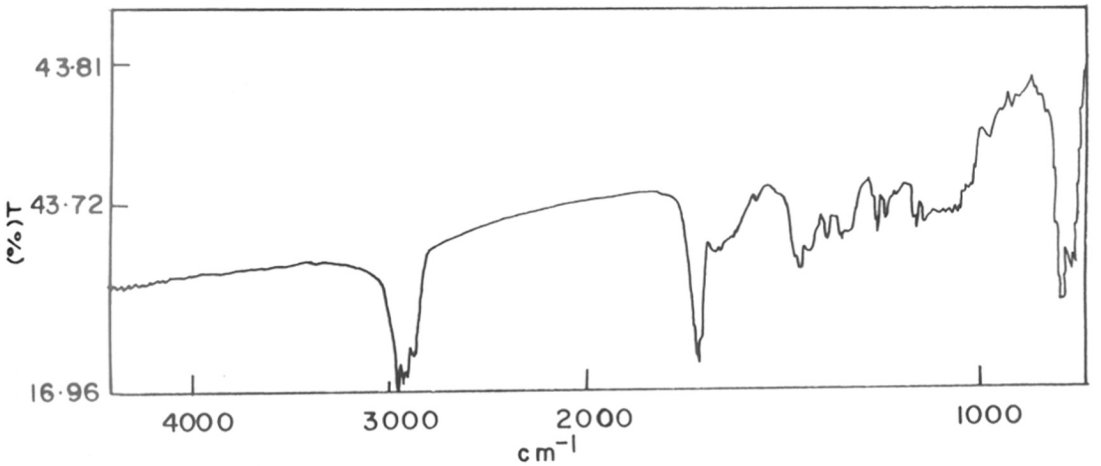


FIG.3B.13: IR OF ALKENE KETONE (9)

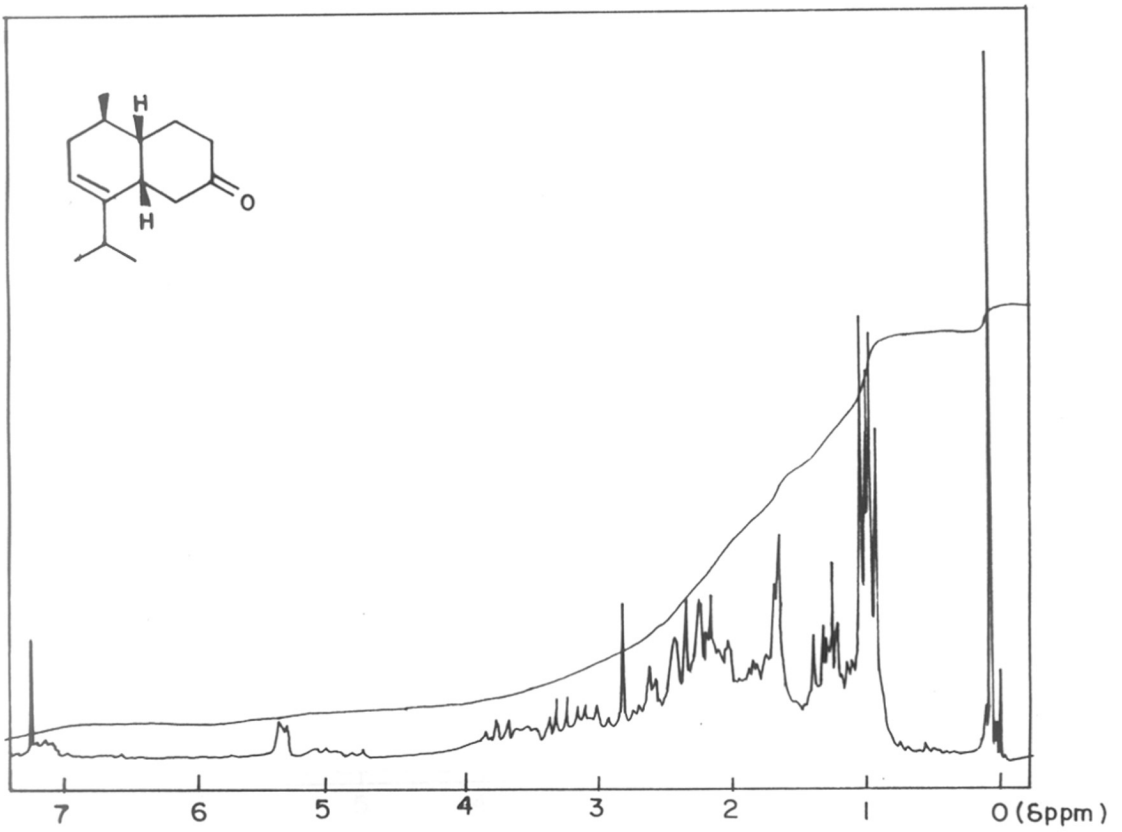


FIG. 3B.14: NMR OF ALKENE KETONE (9).

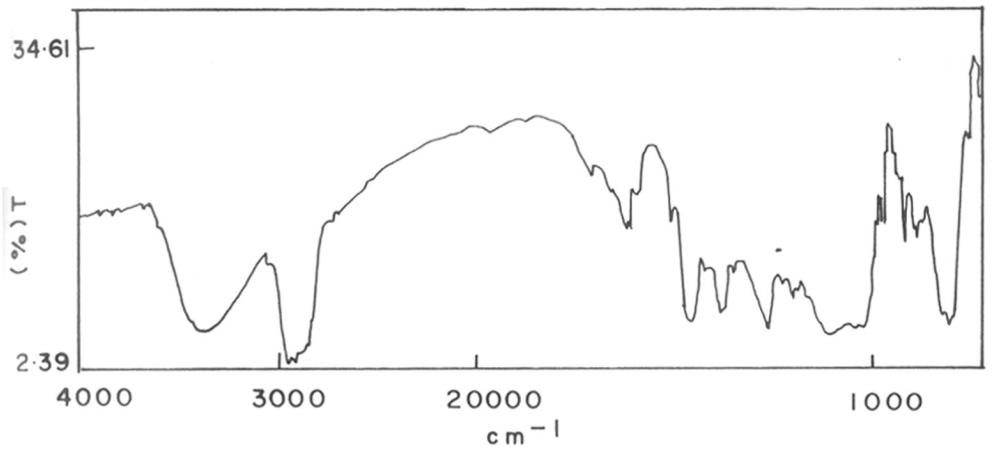


FIG. 3 B.15: IR OF ALKENE ALCOHOL (10)

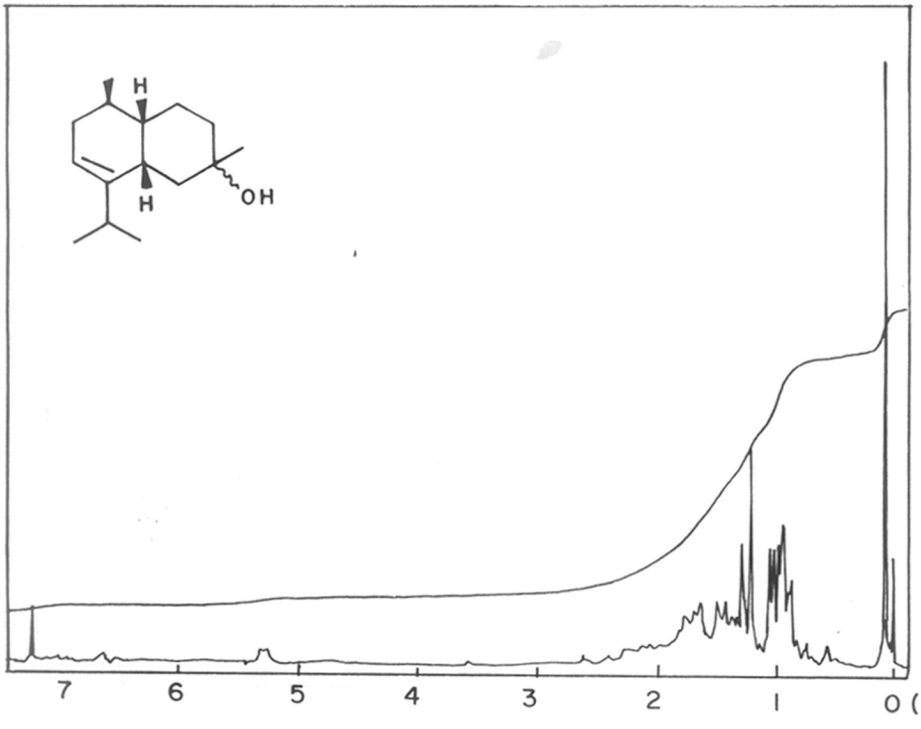


FIG. 3 B.16: NMR OF ALKENE ALCOHOL (10)

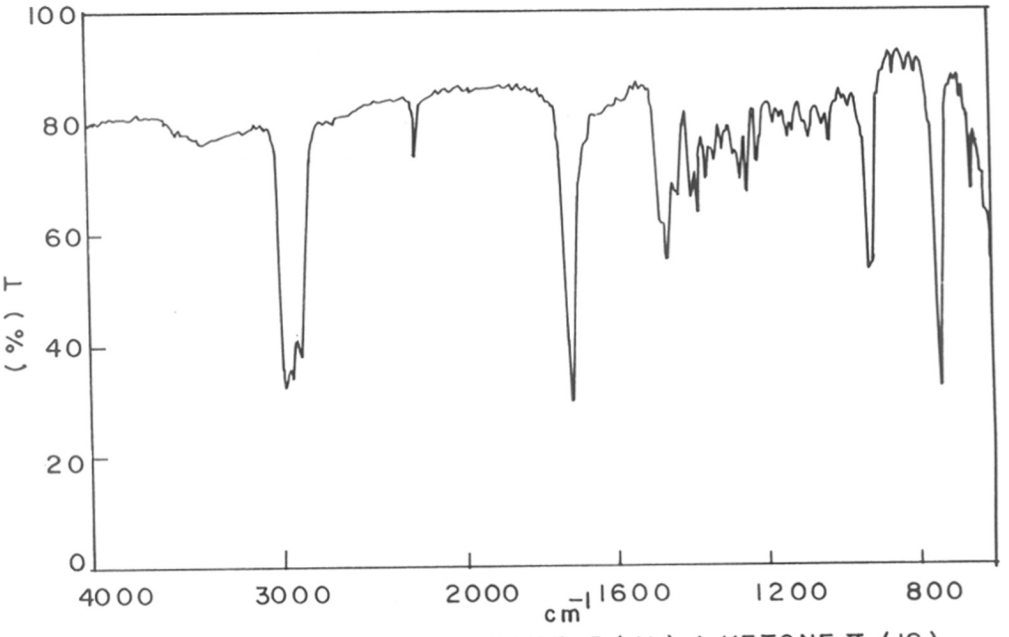


FIG.3B.17 : IR OF KETONE I (11) + KETONE II (12)

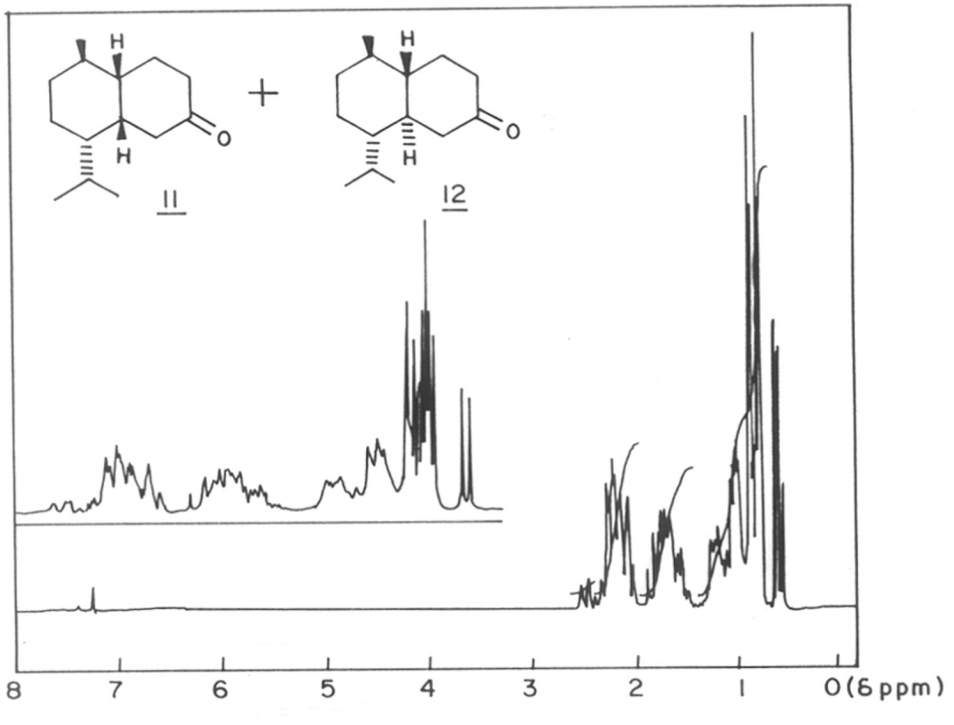


FIG.3B.18 : NMR OF KETONE I(11) + KETONE II(12).

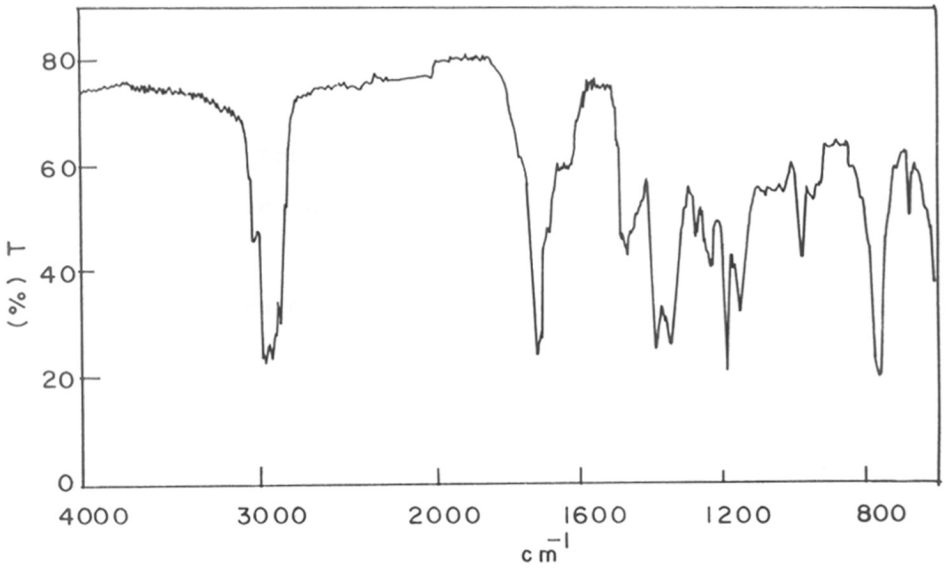


FIG. 3B.19 : IR OF MESYLATE (17)

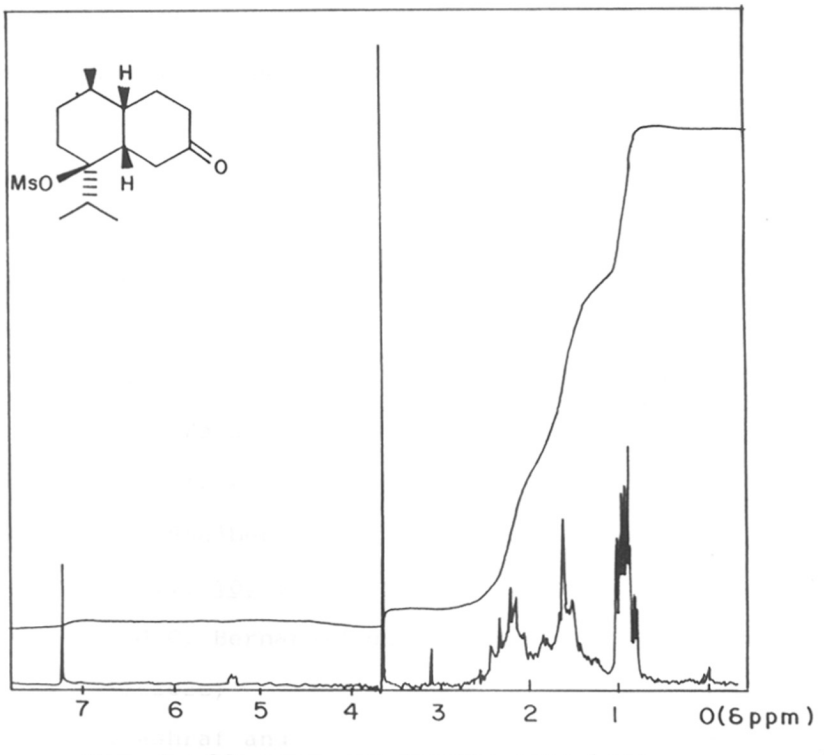


FIG. 3B.20: NMR OF MESYLATE (17)

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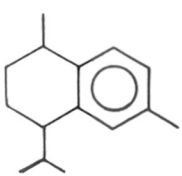
CHAPTER 3

PART C

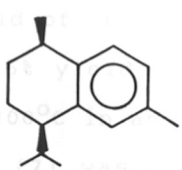
SYNTHESIS OF CALAMENENE, Γ-CALACORENE, CADALENE, EPIZONARENE AND EPIBICYCLOSESQUIPHELLANDRENE.

INTRODUCTION

Calamenene (1) is a naturally occuring aromatic sesquiterpene of the cadalene series[1-8]. It has been isolated from many natural resources like Cedrela toona roxb[1,2], berries of Piperubeba L[3], heartwood of Juniperus foestidissima[4], extract from fresh and fungus infested wood of Pinus silver strist[5], essential of kusunoki[6], oil of Amorpha frouticasa[7], wood of Cryptomeria japonica[8] and many others. Several synthesis of calamenene are reported in literature but only a few report stereochemically pure calamenene synthesis. Khusinol was transformed to pure cis-calamenene(2)[9], trans-calamenene(3)[9,10]. δ-Cadinene[11] and shyobunone[12] were transformed into a mixture of cis,trans-calamenene(4)[12]. Total synthesis of a mixture of cis,trans-calamenene(4) was reported from 2-methyl-6-(p-toyl)-2-heptanol[13], 6-methyl-hept-5-en-2-one[14], α-p-dimethyl styrene[15], 3,4-dihydro-4,7-dimethyl-1(2H)-naphalone[16], p-methyl acetophenone[17,18], p-bromotoulene[18] and (-)-menthone[19]. The total synthesis of stereochemically pure cis-calamenene was reported by Pednekar et al[20]. However the total synthesis of trans-calamenene has not been reported.



1



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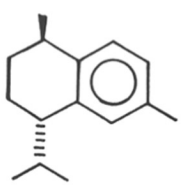

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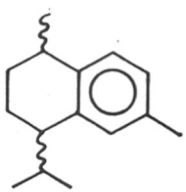


4

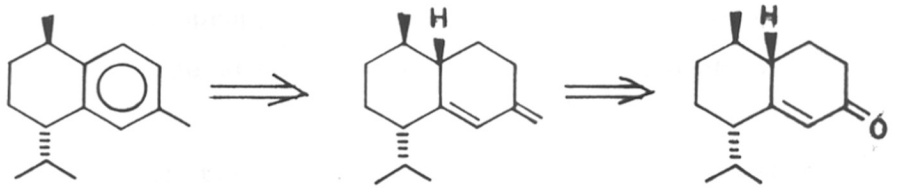
PRESENT WORK

l-Menthol was converted to 7-isopropyl-10-methyl-4-oxo-bicyclo[4.4.0]dec-5-ene[21] (Solid ketone) (5) and was extensively used for the synthesis of many sesquiterpenes[21,22,23]. Thus as per the retrosynthetic scheme (Scheme 1A) solid ketone (5) could be used for the synthesis of stereochemically pure trans-calamenene.

Ranghaishenvi et al[22] reported the conversion of solid ketone (5) to epibicyclosesquiphellandrene (EBSP) (6) in 33% yield. The procedure was modified by substituting the base potassium teritary butoxide by n-butyllithium, the solvent diethyl ether by tetrahydrofuran and by employing 50% excess of triphenylphosphine methyliodide [24] to get 94% yield of EBSP (6). (see scheme-1B)

Joshi et al [25] reported the synthesis of α-curcumene from zingiberene (see scheme-2A). The Diels-Alder adduct obtained from zingiberene and maleic anhydride was pyrolysed to furnish α-curcumene. The similar strategy was attempted for the synthesis of trans-calamenene from EBSP (6) as depicted in scheme-2B. A mixture of EBSP (6) and maleic anhydride in benzene or toulene gave poor yield of the desired adduct (7). The adduct (7) was obtained in 85% yield when EBSP (6) was heated with maleic anhydride at 200^{o}C in an inert atmosphere of argon. The Diels-Alder adduct (7) was characterised by IR cm^{-1} 1830, 1774 assignable to C==O and 1220 assignable to C--O stretch. NMR ($CDCl_3$) showed signals at δ 5.5 and 5.7 (singlet, 1H, olefinic

SCHEME - 1 A

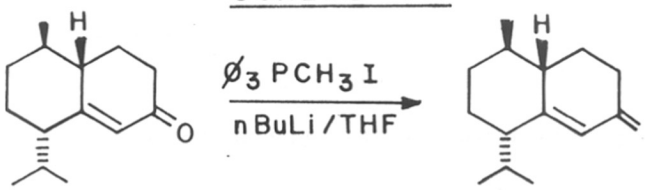


3
trans - Calamenene

6

5

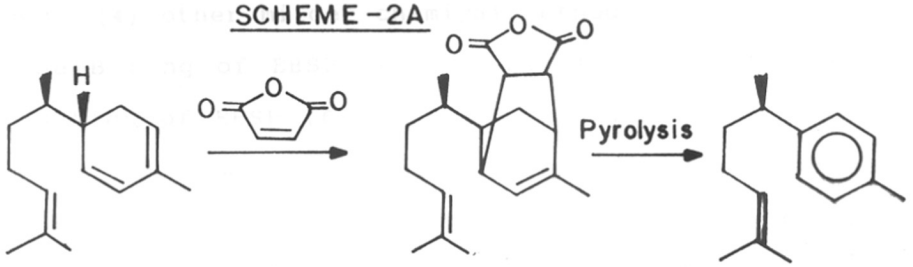
SCHEME - 1 B



5

EBSP 6

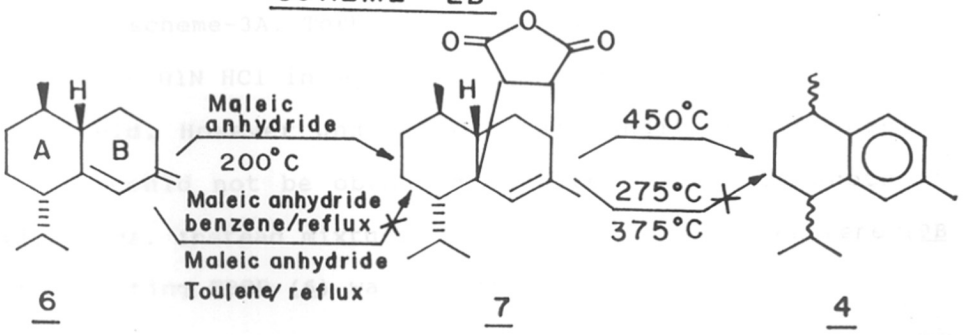
SCHEME - 2A



(—) - Zingiberene

∝- Curcumene

SCHEME - 2B



6

7

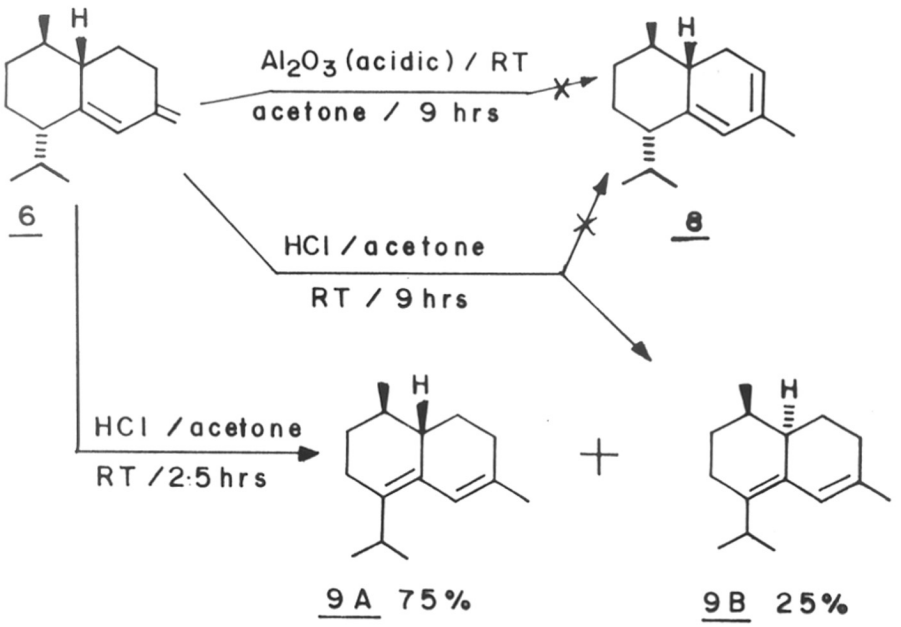
4

proton), 1.6 and 1.5 (singlet, 3H, allylic methyl) and 0.75-1.2 (multiplet, 9H, isopropyl methyls and C_{10}-methyl). Mass spectrum showed peaks at m/e 302(M^+), 204(M^+-maleic anhydride), 259 (M^+-isopropyl).

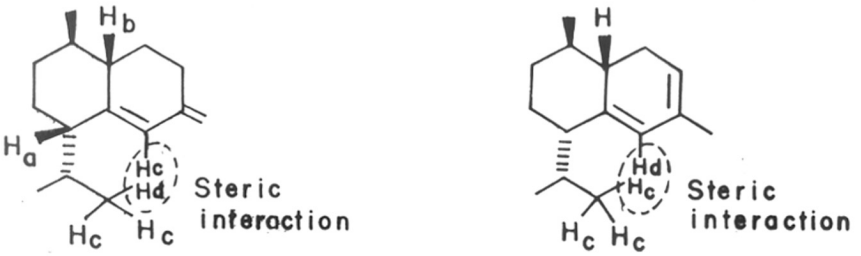
Pyrolysis of the Diels-Alder adduct (**7**) at temperatures 275°C and 375°C could not be effected and furnished the starting Diels-Alder adduct (**7**). Thus Diels-Alder adduct (**7**) was pyrolysed at 450°C to yield a complex mixture from which calamenene was isolated in ≈ 15% yield after elaborate argentic (15% - silver nitrate impregnated silica-gel) chromatography. This was found to be a mixture of cis,trans-calamenene (**4**) as shown by NMR spectrum.

As this methodology yielded a mixture of cis,trans-calamenene (**4**) other milder chemical methods were envisaged to aromatise B ring of EBSP (**6**). To facilitate aromatisation, isomerisation of EBSP (**6**) to diene (**8**) was attempted. Thus treatment of EBSP (**6**) with acidic alumina in acetone (scheme-3A) furnished a mixture of epizonarene (**9A**) - zonarene (**9B**) in low yield alongwith starting EBSP (**6**). Under a stronger acidic condition EBSP (**6**) did not yield the desired diene (**8**) and furnished a mixture of epizonarene (**9A**) - zonarene (**9B**) as depicted in scheme-3A. Terhune et al[27] reported that EBSP (**6**) in presence of 0.01N HCl in aqueous dioxane at 50°C yields diene (**8**) in 21% yield. However under identical conditions the desired diene (**8**) could not be obtained despite several attempts and modifications. Instead mixtures of epizonarene (**9A**)-zonarene (**9B**) and the starting EBSP (**6**) was obtained.

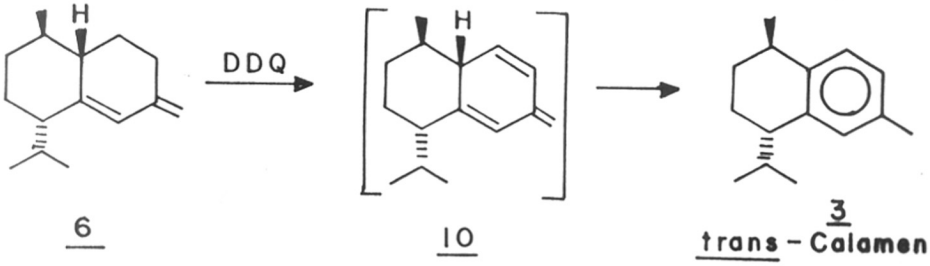
SCHEME – 3 A



SCHEME – 3 B



SCHEME – 4



The undue reluctance of EBSP (**6**) to isomerise to diene (**8**) and its facile isomerisation to epizonarene (**9A**) - zonarene (**9B**) prompted us to look into their molecular models to propound an explaination. On constructing the molecular model of EBSP (**6**) and diene (**8**), it was found that there is severe steric interaction between protons H_c and H_d (see scheme-3B) which severely restricts the free rotation of the isopropyl group, thus reducing its entropy and thereby increasing its ground state energy. This is the prime reason for the anomalously high acidic nature of the proton H_a in EBSP (**6**), which is lost readily to make the isopropyl group planar and relieve the steric strain. This relief from steric strain is not possible in diene (**8**) and hence EBSP (**6**) gets isomerised to epizonarene (**9A**) - zonarene (**9B**) preferentially. Proton H_b being allylic also has some acidic character and hence isomerisation takes place at the ring junction to yield ≈25% of zonarene (**9B**).

As isomerisation of EBSP (**6**) to diene (**8**) failed, conversion of EBSP (**6**) to (**10**) as depicted in scheme-4, was envisaged, which would readily aromatise in situ to furnish the desired trans-calamenene. Bhatwadekar et al[9] reported the use of chloranil at room temperature condition to synthesise stereochemically pure cis-calamenene. It is known that dichlorodicyanobenzoquinone (DDQ) is more reactive than chloranil and that the stereochemistry of the isopropyl group is temperature sensitive, thus reaction of EBSP (**6**) with DDQ (both in equimolar quantities) in tetrahydrofuran (THF) at -10°C was tried, which furnished the starting EBSP (**6**) [Entry no.1, Table - I]. The same reaction

TABLE - I

S.No.	Solvent	SP/DC[a]	Temp	RxT[b]	Products (see scheme-5)
1	T.H.F.[x]	7.6	-10°C	6	**6** ≈100%
2	Chloroform	4.8	0-5°C	36	**4** <10% ; **9** 37% ; **11** 37%
3	Dioxane	2.2	R. T.	12	**4** 16% ; **11** 33% ; **12** 10% ; **13** 14%
4	Ether	4.3	R. T.	1	**4** 18% ; **11** 18%
5	Benzene	2.3	Reflux	4	**4** 17% ; **9** 53%
6	Xylene	2.3	Reflux	9	**4** 10%
7	T.C.E.[y]	>7[z]	Reflux	2	**4** 16% ; **9** 33%
8	T.C.E.[y]	>7[z]	Reflux	9	**4** 30% ; **12** 22% ; **13** 20%

a = Solvent polarity / dielectric constant[33]

b = Reaction time in hours.

x = Tetrahydrofuran

y = 1,1,2,2-Tetrachloroethane

z = Dielectric constant of 1,1,2,2-dibromoethane is 7.0[33].

NOTE : - i) The percentages mentioned above are approximate and relative as they are calculated from NMR (see N. H. Anderson et al[26]).

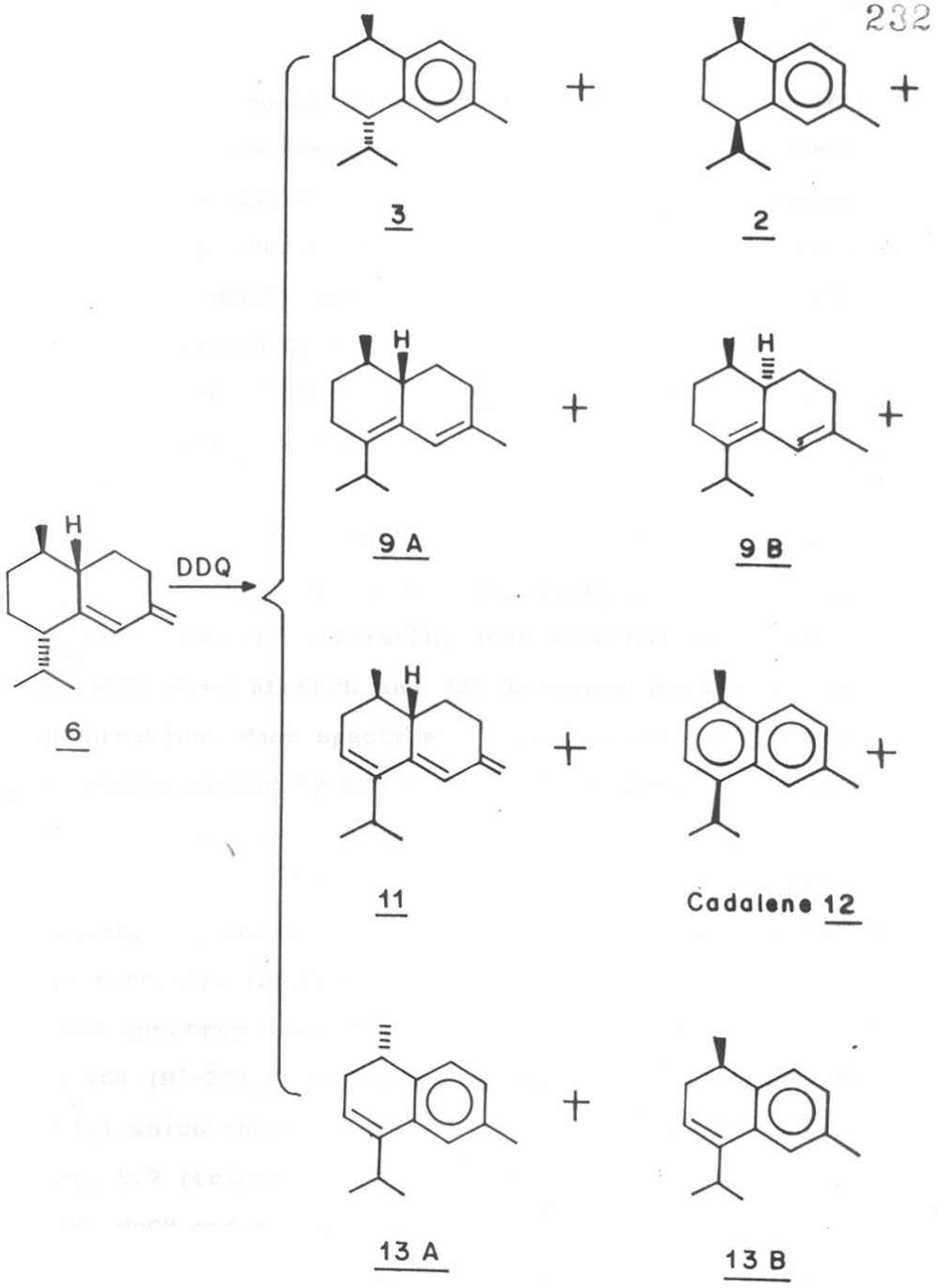
ii) Except entry no. 1 in all other cases complete consumption of EBSP (**6**) was observed which was used as a criteria for the reaction time.

was attempted in chloroform at 0-5°C [Entry no.2, Table - I] and the reaction was monitored by silver nitrate impregnated silica-gel TLC (solvent system A). After 36 hrs it showed complete consumption of EBSP (**6**). The dihydrodichlorodicyano-benzoquinone formed was filtered off and the residue washed thoroughly with pet-ether. The combined organic extract was washed successively with water, brine, dried over anhydrous Na_2SO_4 and recovery of 98% yield was obtained. The NMR spectrum[26] of the crude product was used to determine the percentages of the various products formed. The crude product was found to comprise of calamenene (**4**) ≈10%, epizonarene (**9A**) - zonarene (**9B**) ≈37% and compound (**11**) ≈37%.

As calamenene was formed in poor yields at low temperatures and the fact that the stereochemistry of the calamenene was not affected in reactions carried out at room temperatures[9]. The reaction was repeated at room temperature in diethyl ether [Entry no. 4, Table -I] to yield calamenene (**4**) ≈18%. Isolation of pure trans-calamenene from the mixture in reasonable quantities for its characterisation could not be achieved and hence other methods were explored to improve the yield of calamenene.

The consistent low yield of the desired calamenene and the formation of (**9**) and (**11**) indicated that the $-C=C-C=CH_2$ system was getting unduly polarised thereby increasing the acidity of proton H_a (see scheme-3B) in polar solvents. Thus use of non-polar solvent like dioxane was envisaged (see Table-I solvent dielectric constant). Fu et al[28] and Naidu et at[29] used DDQ in dioxane for aromatisation of cyclohexene moeities. Thus EBSP (**6**)

SCHEME – 5



was stirred with an equimolar quantity of DDQ in dioxane (Entry no.3, Table-I) at room temperature for 12 hrs to yield calamenene (**4**) ≈16%, compound (**11**) ≈33%, cadalene (**12**) ≈10% and Γ-calacorene (**13**) ≈14%. These products were isolated by elaborate and careful argentic chromatography and characterised as follows. Compound (**11**) was characterised by its NMR ($CDCl_3$) which showed signals at δ 6.95 (singlet, 1H, C=C**H**-C=CH_2), 6.43 (triplet, J=6Hz, 1H, **H**C=C-C=CH_2), 5.14 (broad singlet, 1H, C=CH-C=C**H**H), 5.05 (broad singlet, 1H, C=CH-C=CH**H**), 3.06 (septet, J=7Hz, 1H, $CH_3C\underline{H}CH_3$), 1.18 (doublet, J=7Hz, 3H, $\underline{CH_3}CHCH_3$), 0.92 (doublet, J=7Hz, 3H, $CH_3CH\underline{CH_3}$), 0.92 (doublet, J=8Hz, 3H, $CH\underline{CH_3}$). IR (Neat) shows bands at cm^{-1} 3043 =C--H stretch, 3085 terminal methylene C--H stretch, 1613 C==C stretch and 885 terminal methylene out of plane deformation. Mass spectrum showed m/e 202 (M^+). Cadalene (**12**) was characterised by NMR ($CDCl_3$) which showed signals at δ 7.85-8.0 (2H, aromatic), 7.2 (broad singlet, 3H, aromatic), 3.7 (septet, J=7Hz, 1H, MeC**H**Me), 2.6 (singlet, 3H, aromatic methyl), 2.5 (singlet, 3H, aromatic methyl) and 1.3 (doublet, J=7Hz, 6H, isopropyl methyls). IR (Neat) shows aromatic ring stretch at 1625 cm^{-1}. Mass spectrum showed m/e 198 (M^+), 183 (M^+-CH_3) as base peak and 168 (M^+-2CH_3). Γ-Calacorene (**13**) was characterised[16] by NMR ($CDCl_3$) which showed signals at δ 6.85-7.05 (multiplet, 3H, aromatic), 5.7 (triplet, J=6Hz, 1H, olefinic), 2.75 (multiplet, J=7Hz, 2H, MeC**H** and $Me_2C\underline{H}$), 2.3 (singlet, 3H, aromatic methyl), 1.16 (doublet, J=7Hz, 3H, isopropyl methyl), 1.11 (doublet, J=7Hz, 3H, isopropyl methyl), 0.99 (doublet, J=7Hz, 3H, α-methyl), 0.7 (doublet, J=7Hz, 3H, ß-methyl). IR (Neat) shows

aromatic ring stretch at 1628 cm^{-1}. Mass spectrum showed m/e 200 (M^+), 185 (M^+-CH_3) and 157 ($M^+-CH_3CHCH_3$) as base peak.

Aromatisation reactions by use of DDQ are reported like tetralin to naphthalene, acenapthene to acenaphthylene by Brande et al[30], 1,1-dimethyltetrahydronaphthalene to 1,2-dimethylnapthalene by Linstead et al[31] and in refluxing benzene by Muller et al[32]. However no report of stereospecific reactions of DDQ in refluxing benzene was found. To ascertain the effect of refluxing benzene on the stereochemistry of EBSP (**6**) a model experiment was conducted. EBSP (**6**) was refluxed in dry benzene for 4 hrs and on usual work up furnished the starting EBSP (**6**), which was confirmed by NMR and GC. Thus EBSP (**6**) was refluxed in benzene (Entry no.5, Table-I) with equimolar quantity of DDQ, which yielded a mixture of epizonarene (**9A**) - zonarene (**9B**) ≈53% and calamenene (**4**) ≈17%. Scaling up of the reaction did not yield proportionately more amount of calamenene (**4**).

Exasperated with the elusive calamenene two other methods were tried at higher temperatures. EBSP (**6**) with DDQ in refluxing xylene for 8 hrs yielded only 10% calamenene (**4**) and with 1,1,2,2-tetrachloroethane (T.C.E.) refluxing for 2 hrs yielded calamenene (**4**) ≈16%, epizonarene (**9A**)- zonarene (**9B**) ≈33% and unreacted starting EBSP (**6**). Thus EBSP (**6**) with equimolar quantity of DDQ was refluxed in T.C.E. for 8 hrs. The reaction mixture after work up showed to comprise of about 30% calamenene (**4**), about 22% cadalene (**12**) and about 20% Γ-calacorene (**13**). Calamenene (**4**) was isolated after elaborate argentic chromatography and was characterised by NMR, IR and mass spectra

which showed it to be a mixture of cis,trans-calamenene (**4**). NMR ($CDCl_3$) showed signals at δ 7.05 (broad singlet, 3H, aromatic), 2.35 (singlet, 3H, aromatic methyl), 0.8-1.26 (multiplet, 16H, methyl, isopropyl methyls, and the rest). IR (Neat) showed aromatic stretching at 1613 cm^{-1}. Mass spectrum showed m/e 202 (M^+), 187 (M^+-CH_3) and 159 ($M^+-CH_3CHCH_3$) as base peak.

CONCLUSION

Stereochemically pure trans-calamenene (**3**) could not be synthesised via formation of maleic anhydride Diels Alder adduct of epibicyclosesquiphellandrene (**6**) and subsequent pyrolysis to effect retro Diels Alder and aromatisation.

Dehydrogenation of epibicyclosesquiphellandrene (**6**) with DDQ in various solvents and conditions did not yield stereochemically pure calamenene. It however gave other products like epizonarene (**9A**) - zonarene (**9B**), compound (**11**), cadalene (**12**) and Γ-calacorene (**13**). cis,trans-Calamenene (**4**) was obtained in fair yields in refluxing 1,1,2,2-tetrachloroethane.

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Epibicyclosesquiphellandrene (6) (EBSP)

To a cooled solution (-10°C) of triphenylphoshonium methyl iodide (3.11gms, 7.7mmoles) in dry THF (50ml) was added n-BuLi (4.8ml, 7.7mmoles) and stirred for 15 minutes. To this a solution of freshly crystallised solid ketone (see chapter 1) (1.05gms, 5.1mmoles) in THF (50ml) was added dropwise. Through out the experiment the whole setup was maintained under argon atmosphere. On complete addition of solid ketone the reaction was stirred for 15 minutes after which the reaction mixture was brought to room temperture. This was stirred for a further 2 hours period at room temperature. The reaction mixture was then poured in cold anhydrous pet-ether (500 ml). This was filtered through a buchner funnel, and the residue washed with cold anhydrous pet-ether (50mlx3). The combined organic layer was washed with water (200mlx3) until neutral, followed by brine (200ml), dried over anh.Na_2SO_4 and the solvent removed under vacuo. The crude compound was chromatographed over neutral alumina (60gms). The first pet-ether eluate furnished TLC (solvent A) pure epibicyclosesquiphellandrene (6) 2.9gms (94% yield). The spectral data was in complete agreement with the reported data[22].

Diels Alder adduct (7)

Epibicyclosesquiphellandrene (118 mg, 0.57 mmole) was heated with maleic anhydride (570 mg, 5.7 mmole) in oil bath at 200°C under

argon atmosphere for 8 hrs. The reaction mixture was then dissolved in dichloromethane (100 ml), filtered and the solvent removed under vacuo. Purification was done by chromatography (silica-gel) which furnished, an oil, the Diels Alder adduct (7) 150 mg (85% yield) . TLC (solvent A). IR (liq film) showed bands at cm^{-1} 1830, 1774 assignable to C==O and 1220 assignable to C--O stretch. NMR ($CDCl_3$) showed signals at δ 5.5 and 5.7 (singlet,1H,olefinic proton), 1.6 and 1.5 (singlet,3H,allylic methyl) and 0.75-1.2 (multiplet,9H,isopropyl methyls and C_{10}-methyl). Mass spectrum showed peaks at m/e 302(M^+), 204(M^+-maleic anhydride), 259 (M^+-isopropyl). $(\alpha_D)^{26} = -10.2^o$ (c, 0.72). TLC (Solvent B).

cis,trans-Calamenene (4)

The Diels Alder adduct (230 mg, 0.76 mmoles) was dissolved in dry pet-ether (5 ml) and was passed through a glass column packed with glass pieces maintained at 450°C with constant flow of argon gas. The pyrolysed product was chromatographed on silver nitrate impregnated silica gel (15% $AgNO_3$ in silica gel) to yield 23 mg of calamenene (4) (15% yield). NMR ($CDCl_3$) showed signals at δ 7.05 (broad singlet, 3H, aromatic), 2.35 (singlet, 3H, aromatic methyl), 0.8-1.26 (multiplet, 16H, methyl, isopropyl methyls, and the rest). IR (Neat) showed aromatic stretching at 1613 cm^{-1}. Mass spectrum showed m/e 202 (M^+), 187 (M^+-CH_3) and 159 ($M^+-CH_3CHCH_3$) as base peak. $(\alpha_D)^{26} = +0.84^o$ (c, 0.404). TLC

(Solvent A).

General Procedure for DDQ oxidations

Weighed amount of DDQ was dissolved in the requisite solvent (5 ml) which was stirred and brought to the desired temperature. To this solution weighed amount of Epibicyclosesquiphellandrene (6) (equimolar to DDQ) dissolved in the respective solvent (5 ml) was added slowly. The reaction was continued for the requisite time. (see Table - I) The reaction mixture was then poured in anhydrous pet-ether (100 ml) and filtered. The organic layer was washed with water (50 ml) thrice, followed by brine (50 ml), dried over anh. Na_2SO_4 and solvent stripped under vacuo. NMR of the crude compound so obtained was recorded. Careful chromatography on silver nitrate impregnated (15 %) silica gel yielded compounds as indicated in Table - I.

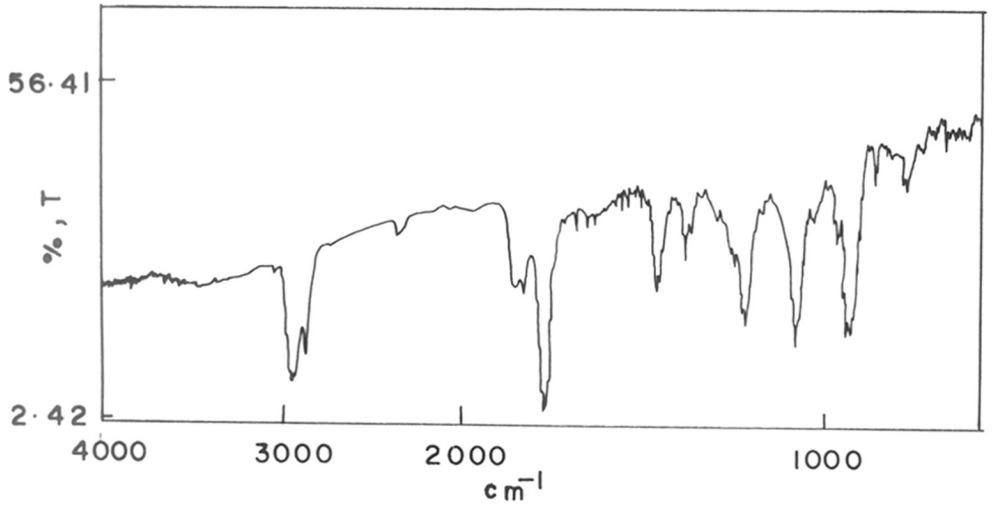

FIG. 3C. 1 : IR OF DIELS ALDER ADDUCT (7)

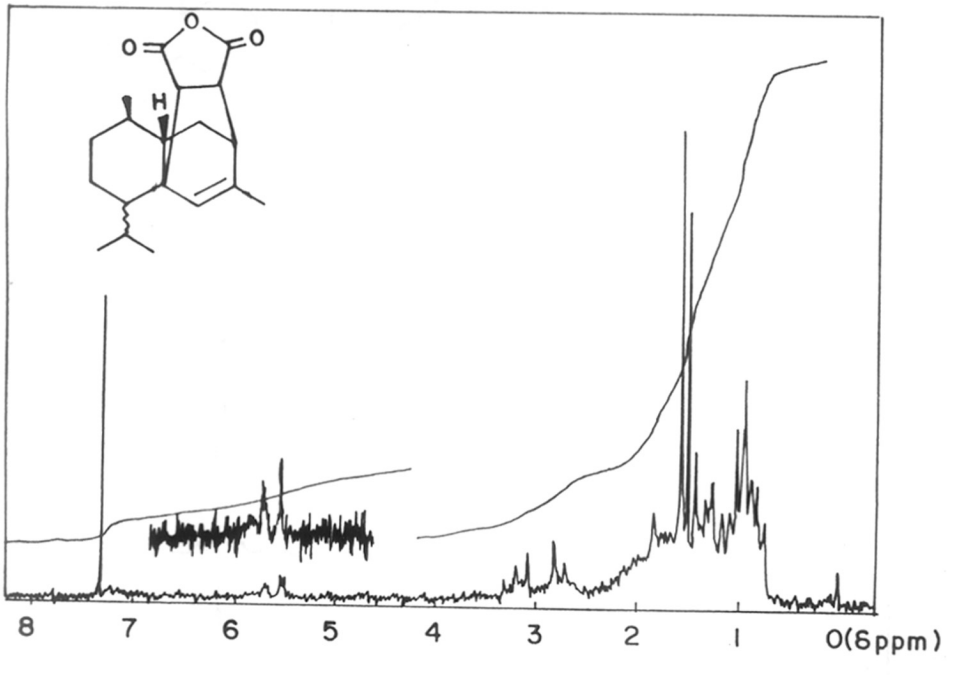

FIG. 3C. 2 : NMR OF DIELS ALDER ADDUCT (7)

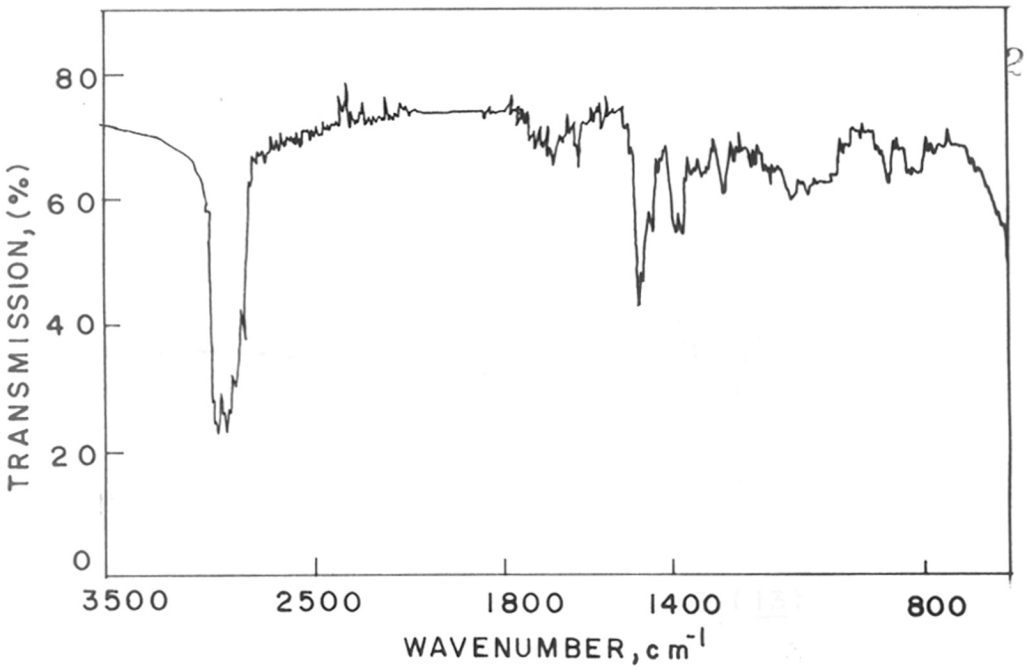

FIG. 3C.3 : IR OF EPIZONARENE (9A) + ZONARENE (9B)

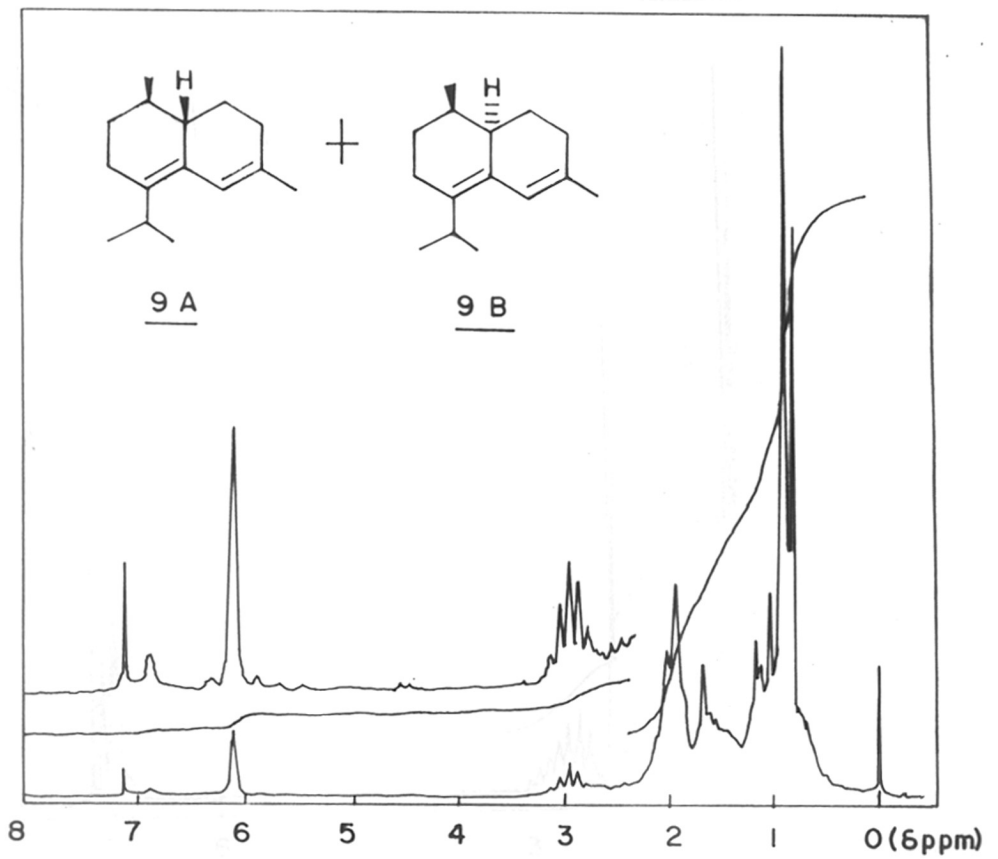

FIG. 3C.4 : NMR OF EPIZONARENE (9A) + ZONARENE (9B).

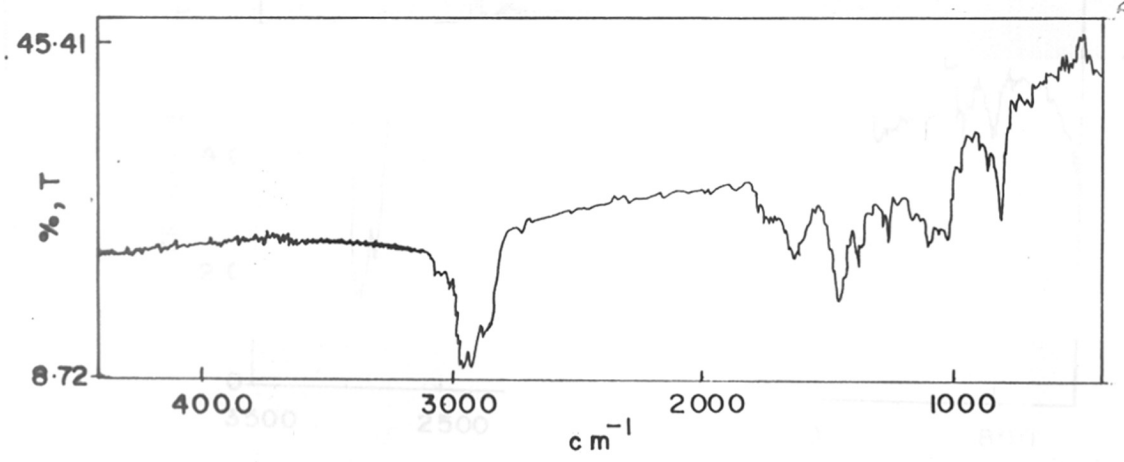

FIG. 3C.5 : IR OF r – CALACORENE (13)

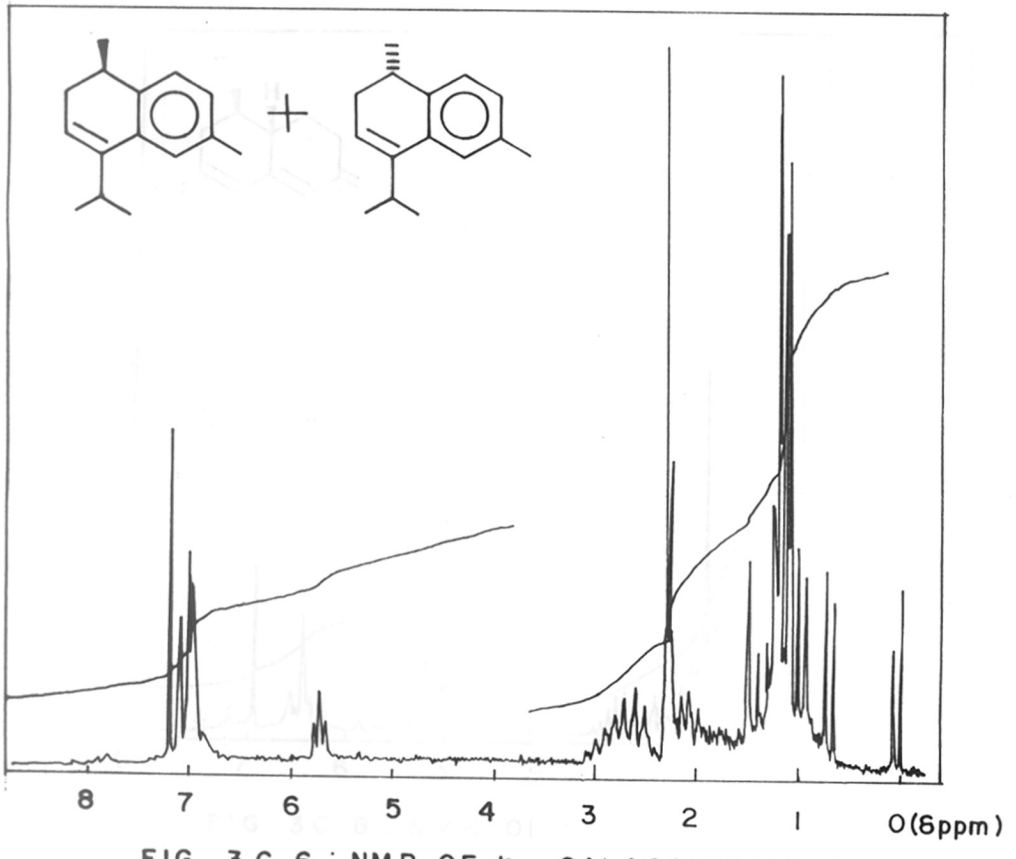

FIG. 3C.6 : NMR OF r - CALACORENE (13)

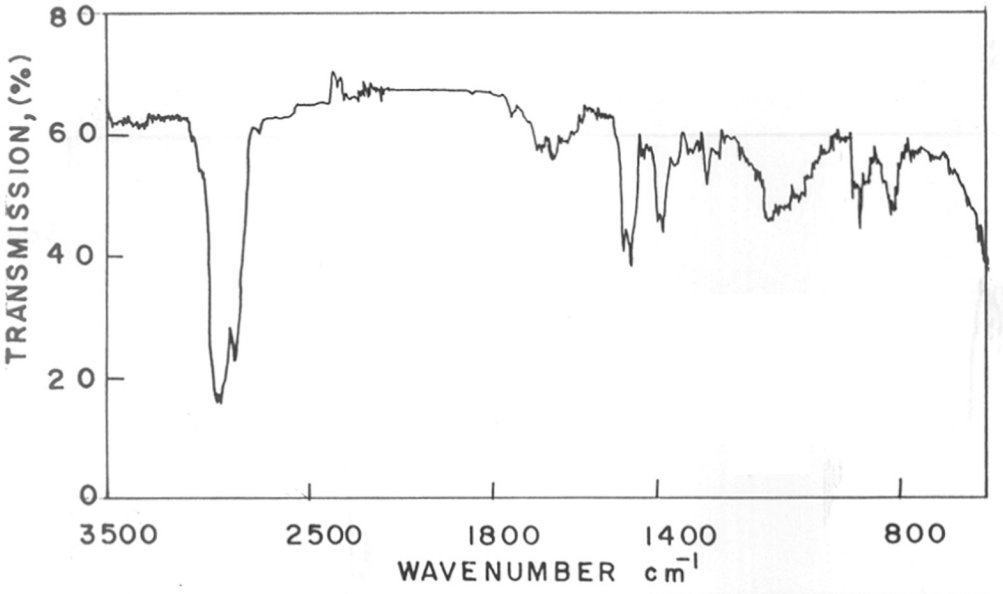

FIG. 3C. 7 : IR OF COMPOUND (11)

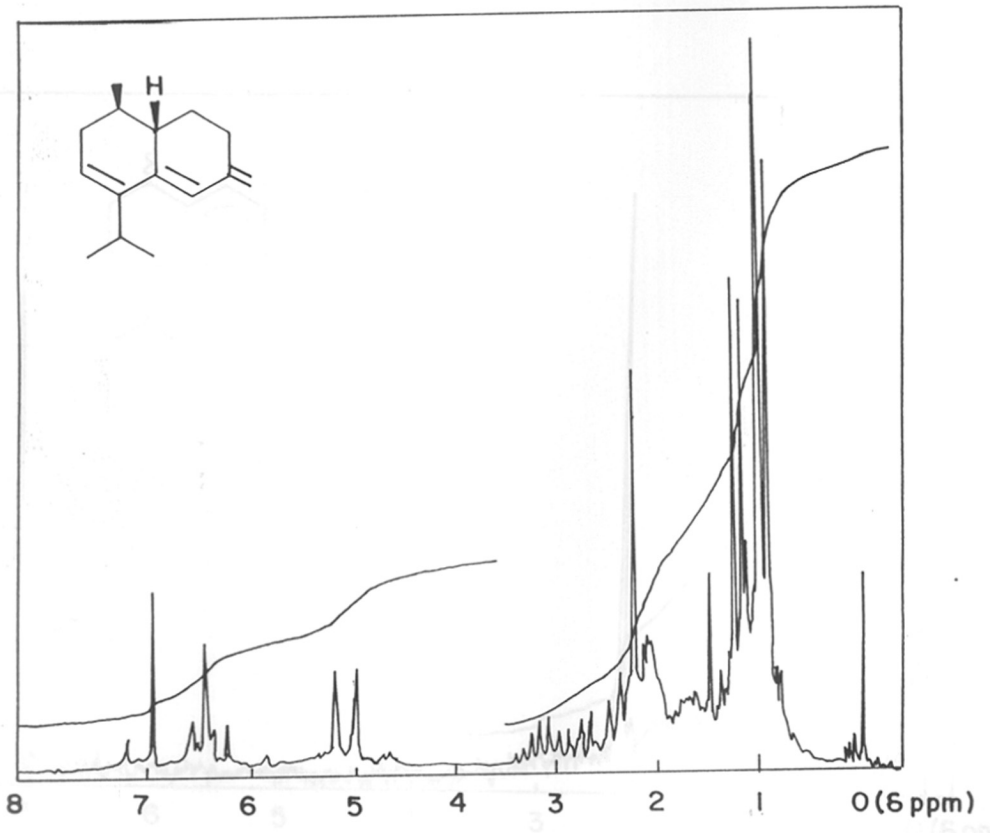

FIG. 3C. 8 : NMR OF COMPOUND (11)

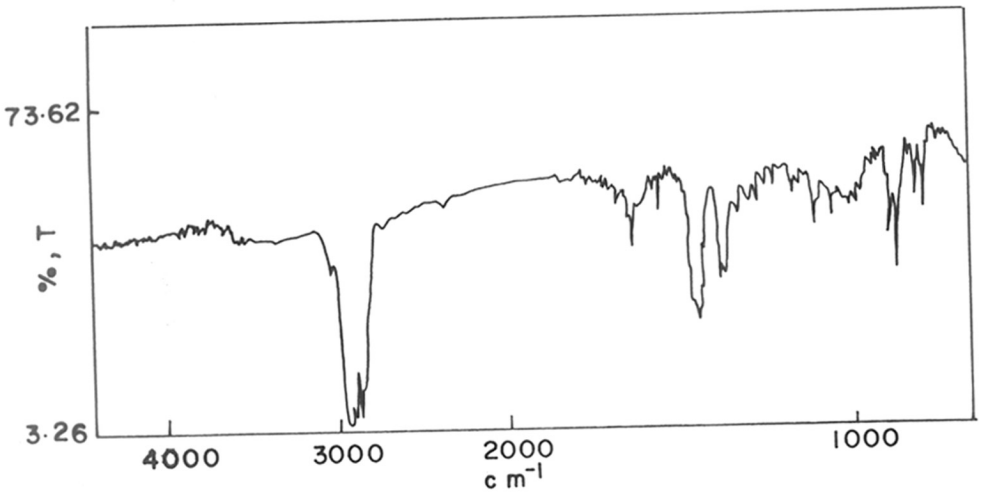

FIG. 3C. 9 : IR OF CALAMENENE (4)

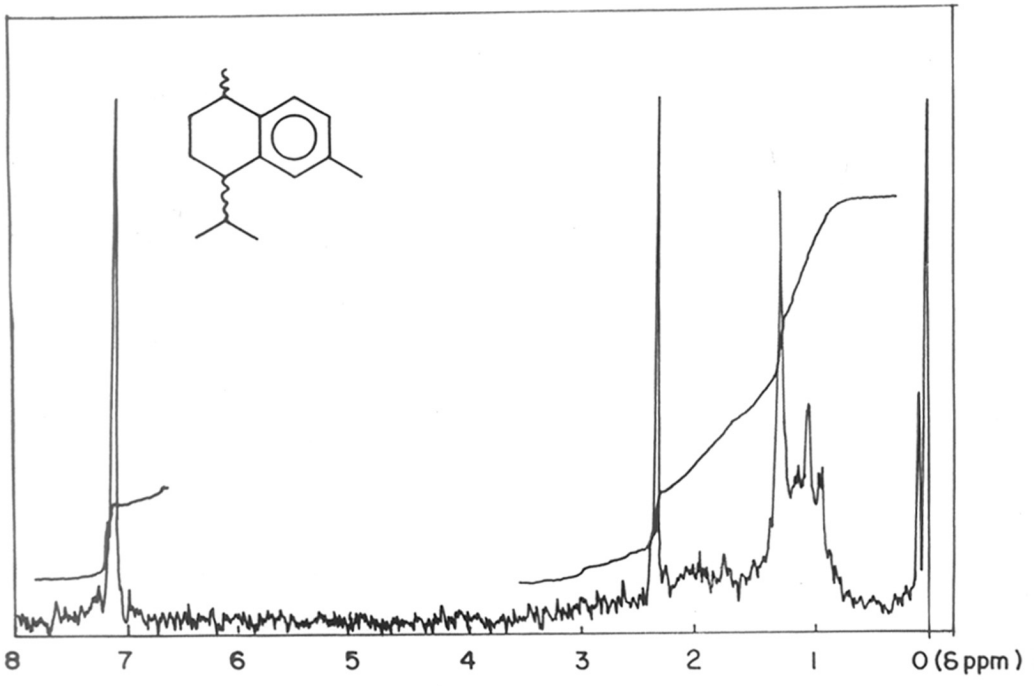

FIG. 3C. 10 : NMR OF CALAMENENE (4)