SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS
SUBMITTED TO THE

UNIVERSITY OF POO NA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

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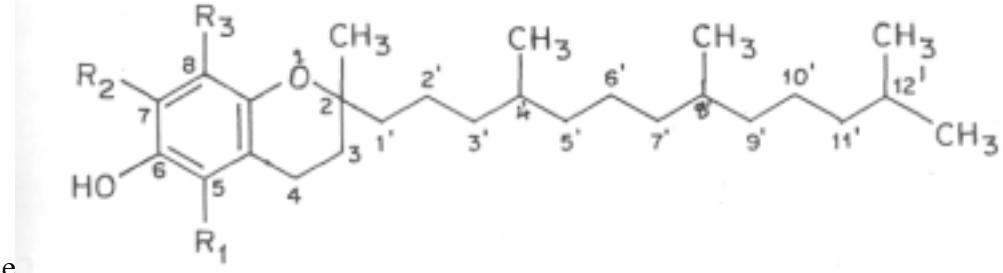
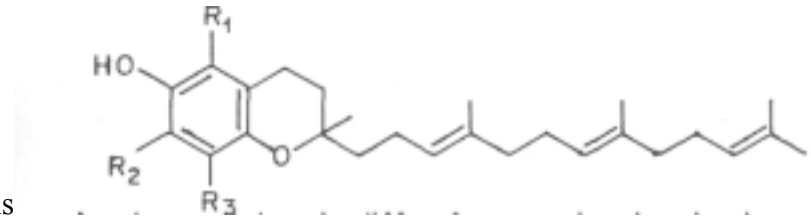
The correct structure was established by Fernholz by degradation studies of α-tocopherol using pyrolysis and chromic acid oxidation.



The structure for different tocopherols can be represented as follows.

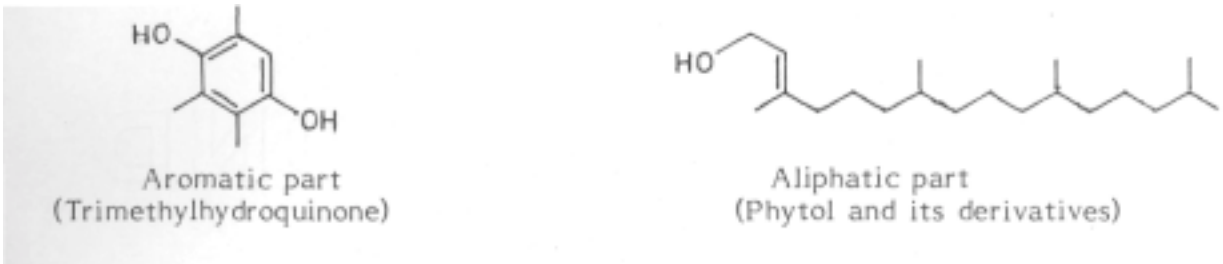
It was observed that of α,β,γ and δ -tocotrienols on hydrogenation gave respective tocopherols.

Compounds	R_1	R_2	R_3
α-tocopherol	CH_3	CH_3	CH_3
β-tocopherol	CH_3	H	CHL
γ -tocopherol	H	CH_3	CH_3
δ -tocopherol	H	H	CH_3



As the tocopherols ditier from each other in the number of methyls on the aromatic part they are regarded as derivatives of 2-methyl-6-chromanol. Tocopherols bear a saturated isoprenoid C_{16} side chain

and can be visualised as containing of an aromatic part and an aliphatic part as shown below.



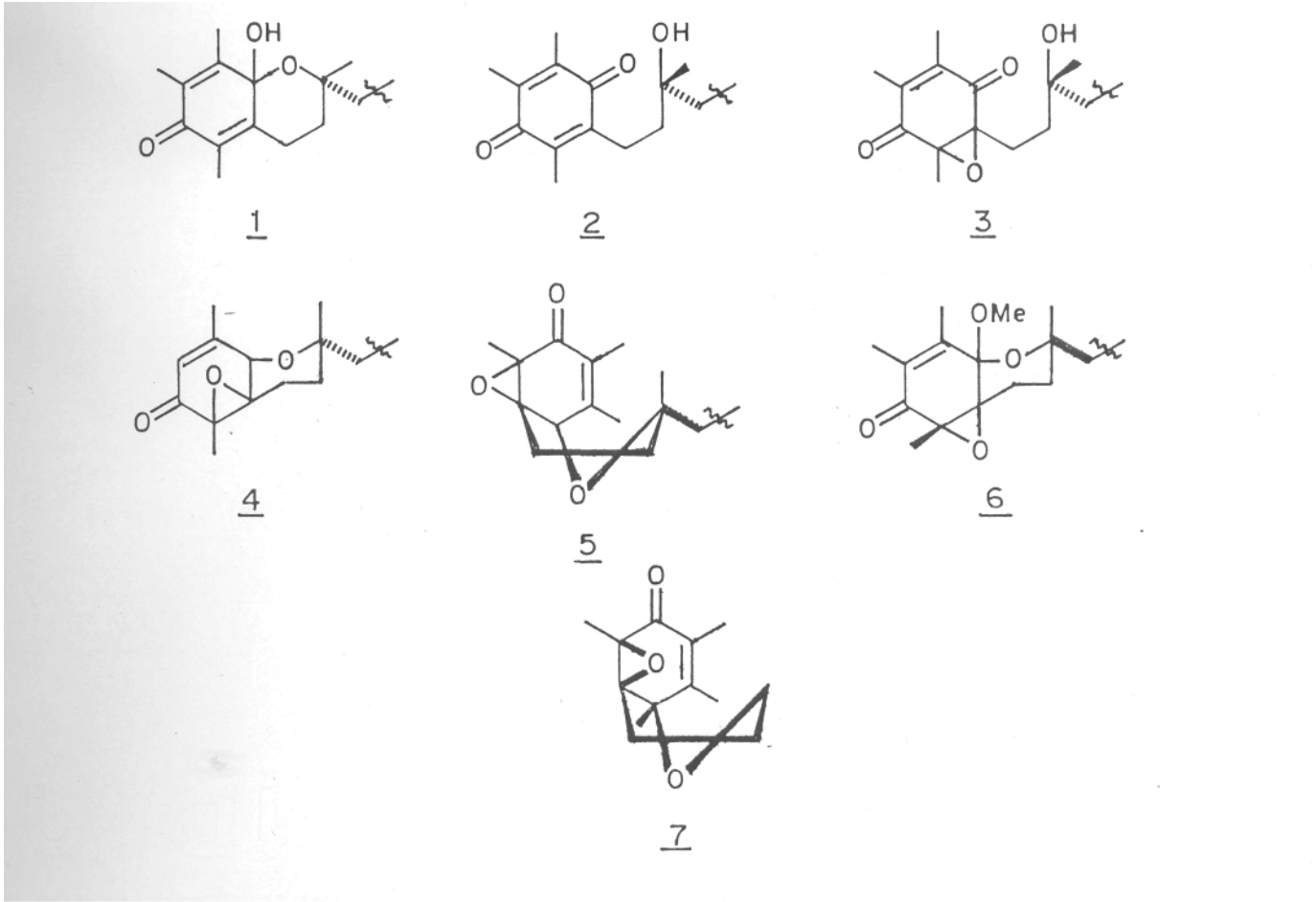
of free radicals by α-tocopherol will break the chain of events preventing lipid decomposition. In this process vitamin E itself becomes a free radical. Because the unpaired electrons are delocalised over its chrcmanol ring, it thereby stops the spread of free radical reaction.

Recently oxidation of tocopherols with singlet oxygen have been

studied in detail, because of plausible analogous mechanism by which tocopherols function as antioxidant in vivo or _in vitro. Grams et ai[7,8].

irradiated [dl]- α-tocopherol in methanol in pyrex vessel with a G.E. 300 W tungsten lamp in presence of proflavin and oxygen and established the structure of oxidation products as (1) and (2) (quinones) and the epoxides 3-7. It has been suggested that the reactivity of tocopherols with singlet oxygen is in correlation with their vitamin E activity and

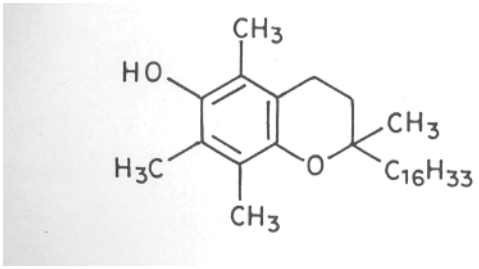
that the quenching of singlet oxygen by tocopherols is the mechanism by which the tocopherols inhibit lipid peroxidation[9].

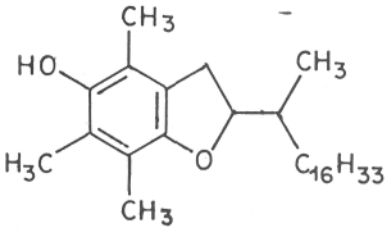


Investigators have already proved that antioxidants protect animals from chemically induced carcinoma as it is known fact that free radicals activates hydrocarbons to their carcinogenic state yielding H_2O_2, so the action of vitamin E as a free radical scavenger promises better protection. Vitamin E has received importance because of antiageing and antioxidant property. Nomenclature

The nomenclature accepted for this group of tocopherols is the one recommended by IUPAC-IUB Commission on Biochemical Nomenclature.[10] Structure and Stereochemistry

Two possible structures were assigned for α -tocopherol, i.e. chroman and coumarctn structure, on the basis of pyrolysis, selenium dehydrogenation and oxidation studies. Oxidation product of α-tocopherol can be better explained by its chroman structure and was supported by its UV" and by its synthesis.





Chroman Structure Coumaran Structure

α -Tocopherol is having three chiral centres at C_2, C_4. and C_8,

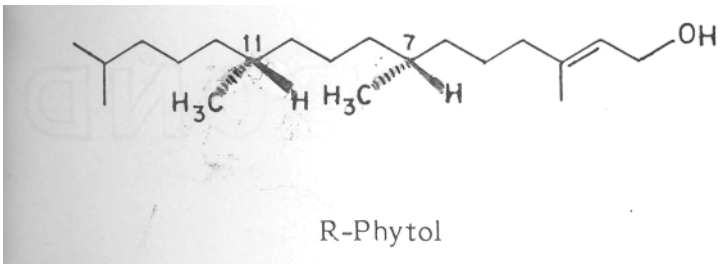
so eight stereo-isomers are possible. All have been synthesised recently[12]

and shown to be biologically active. The absolute configuration of α-tocopherol was determined by comparing natural α -tocopherol with phytol, whose absolute configuration at C_7 and C_{11} has been shown

to be R. by comparison with (-)-linalool of established R configuration.

Since natural phytols have 7R, 11R configuration[13,14],α -tocopherol

from natural phytol must be a mixture of two epimers; whereas with racemic phytol, a total of eight diastereomeric α-tocopherols must be considered. The specification of α-tocopherol is based on the positive

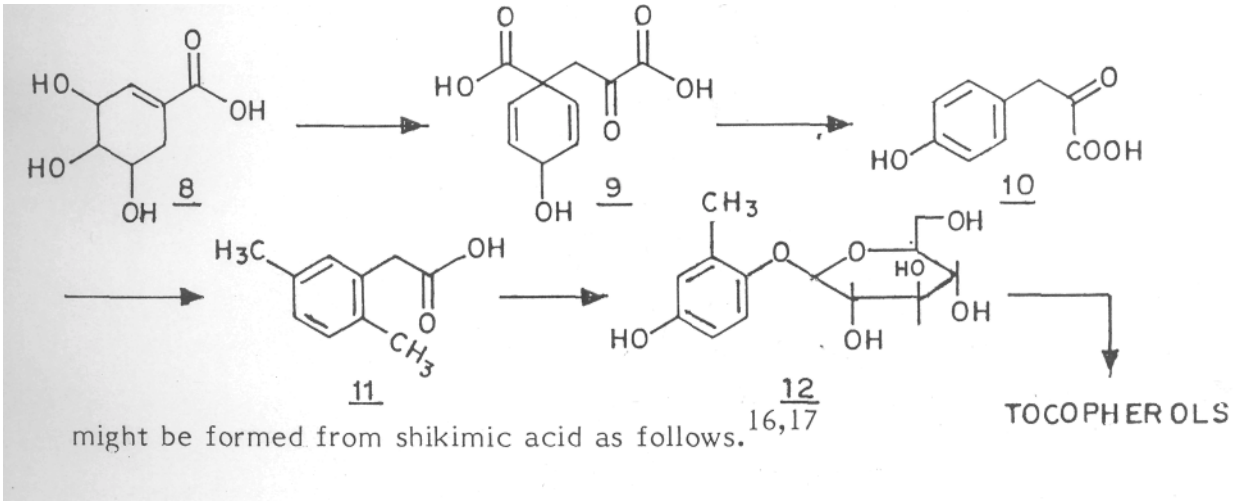


optical rotation in ethanol solution.[15a] The sign of rotation is solvent

dependant, as a negative optical rotation is observed in benzene solution.[15b]

Biogenesis; Experiments with radioactive material administered

to higher plants showed that the aromatic part of the tocopherol molecule

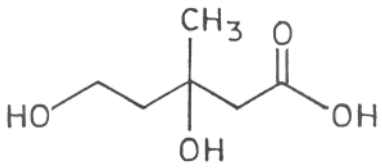


Shikimic acid (8) ------ > prephenic acid (9) -----> 4-hydroxyphenyl

pyruvicacid (10) ——> homogentisic acid (11) ----> homo-

arbutin (12) ——> tocopherols.

The isoprenoid side chain might be formed from mevalonic acid (13)[18,19,20]



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It has also been realised that tocotrienβls are formed first, followed by methylation and reduction of the side chain. The remaining aromatic methyl groups of tocopherol are derived from SAM (S-Adenosyl Methionine).

Synthesis: Synthetic methods described in literature for tocopherols and tocotrienols, can be classified as total and partial synthesis. (A) Total Synthesis

(i) One approach involves construction of the heterocyclic ring with isoprenoid side chain at C-2 using methylated hydroquinones and. aliphatic part as the starting materials.

(ii) In another approach, the isoprenoid side chain is introduced into the preformed methylated 1-benzopyran system by formation of C-C bond.

(a) Synthesis of Tocopherols by Construction of the Substituted Hetero-Cyclic Ring (Scheme I, Fig. 1)

Isler et al[21]. described the first attempt to synthesise (2RS,

4'R, 8'R)- α-tocopherol from trimethyl hydroquinone (14) and 1,3-dibromo-phytane. Later Karrer et al[22]. published a method for condensing

phytyl bromide, obtained from natural phytol, with trimethyl hydroquinone in petroleum ether using zinc chloride as a catalyst (Scheme-2). This method gives a mixture of diasteromers of α -tocopherol. Separation of these 2R and 2S epimers is reported[15] via a piperazine complex.

SCHEME-1

FIG. 1. TOTAL SYNTHESIS OF TOCOPHEROLS BY CONSTRUCTION OF SUBSTITUTED HETEROCYCLIC RING

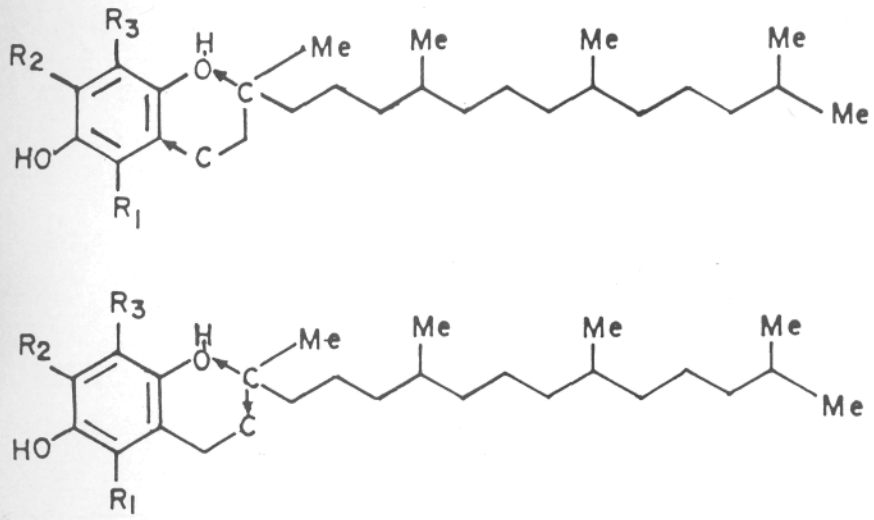
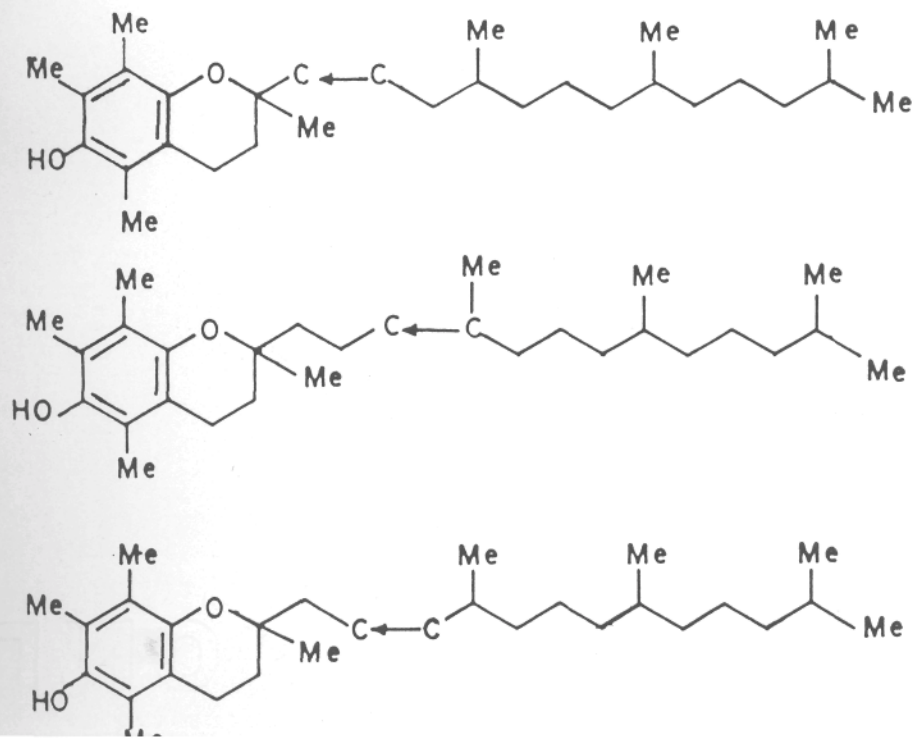


FIG. 2. TOTAL SYNTHESIS OF TOCOPHEROLS BY CONSTRUCTION OF ISOPRENOID SIDE CHAIN



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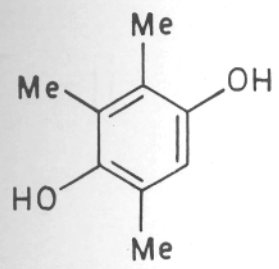

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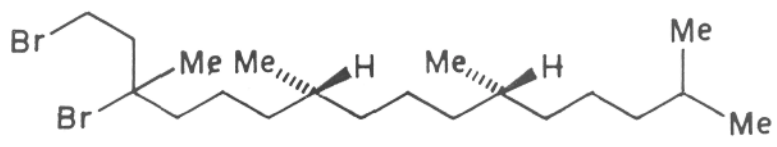
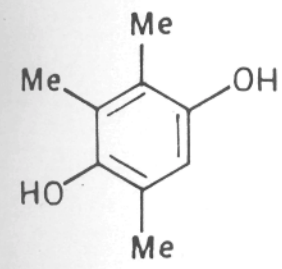
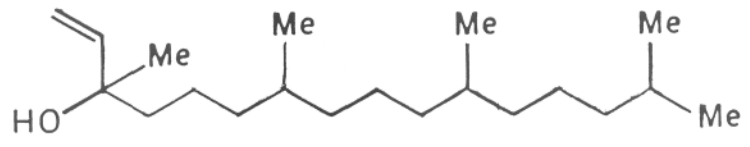


1, 3 – DIBROMOPHYTANE



14 +

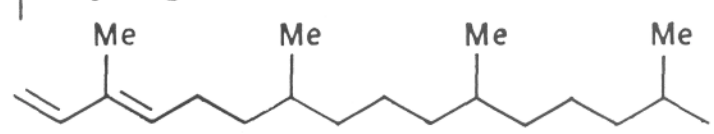


15

14 → $BF_3 – Et_2O$ → 15

ALL – RAC – α – TOCOPHEROL

14 + 16 → $BF_3 – Et_2O$ → ALL – RAC – α – TOCOPHEROL



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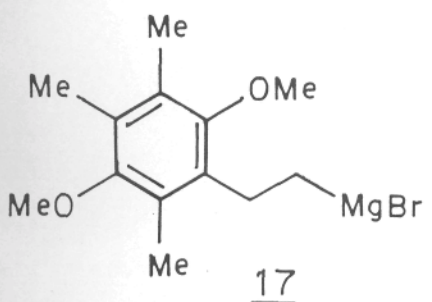
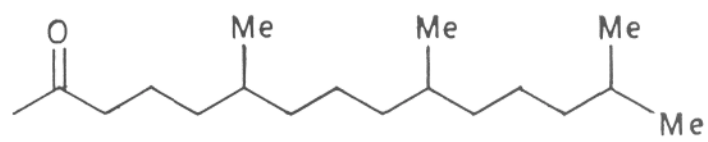
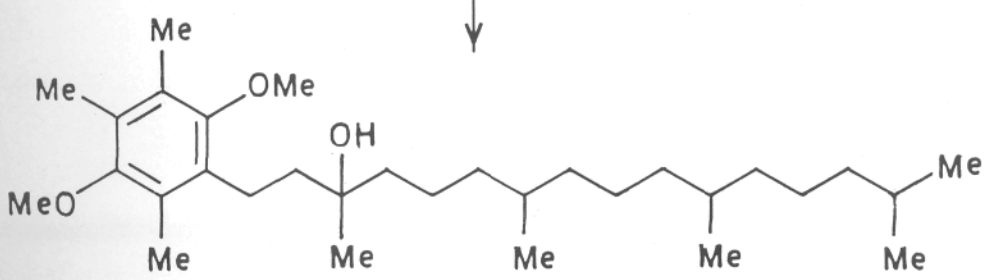


17 +



18

17 + 18 → 19



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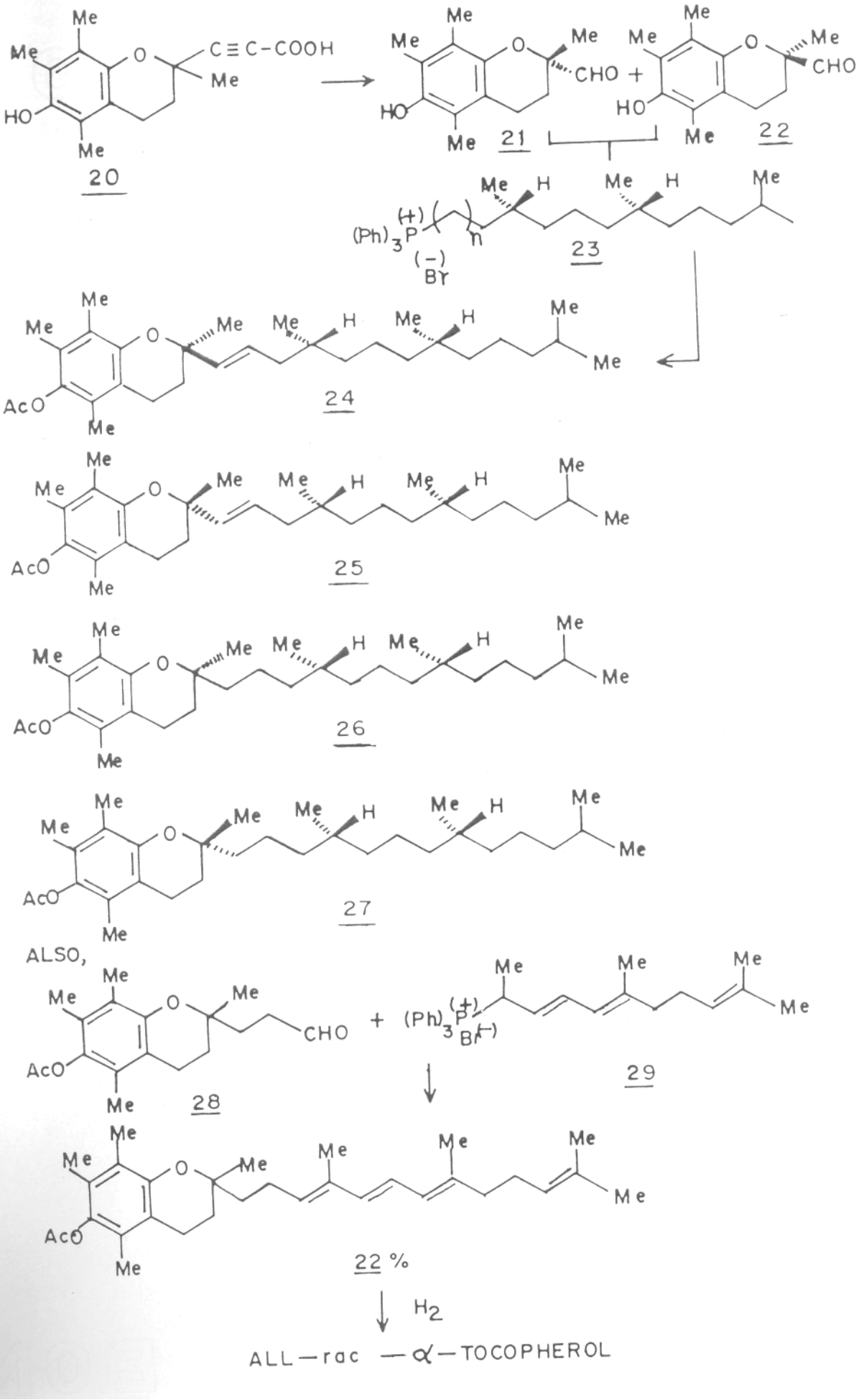
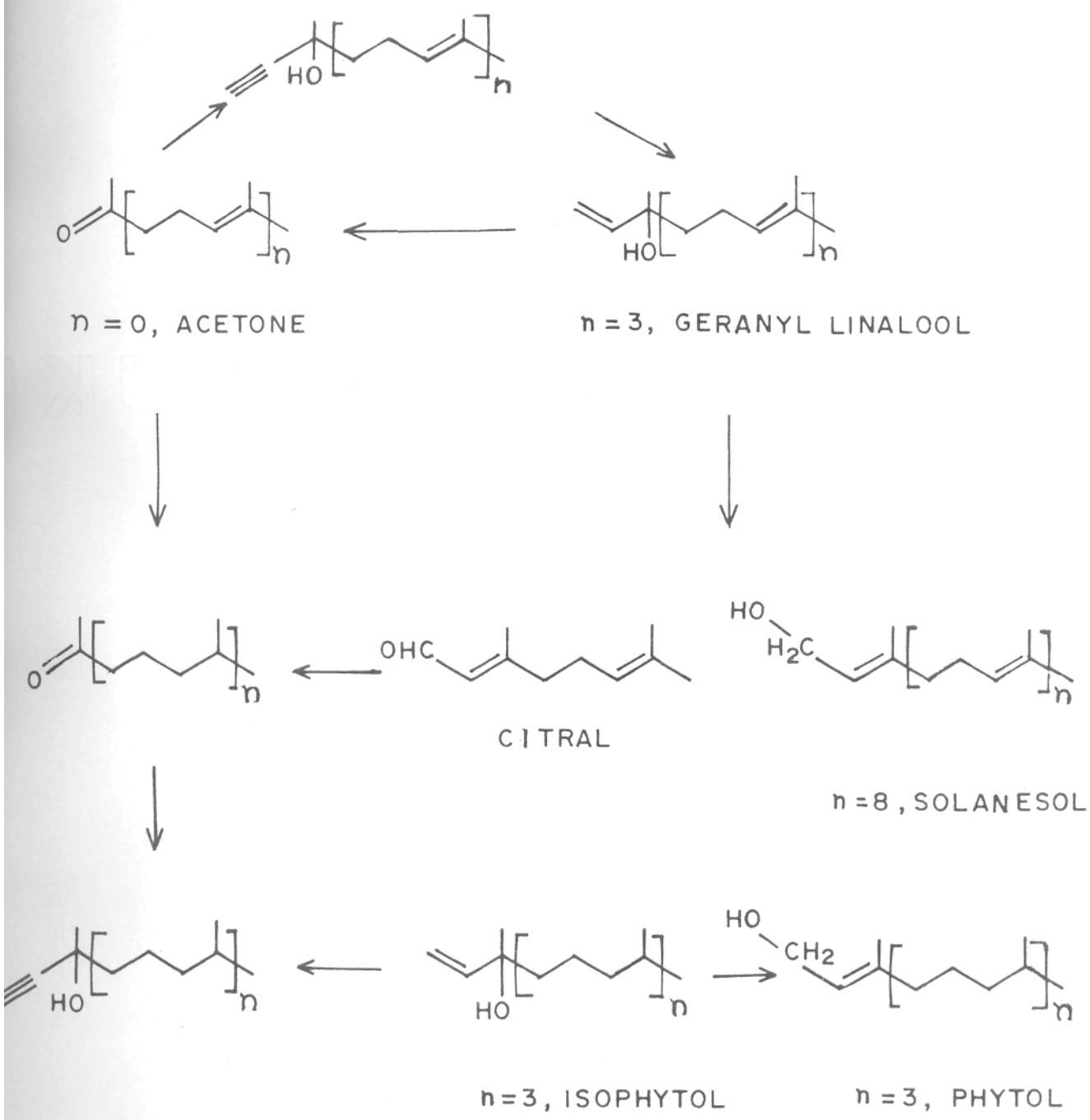
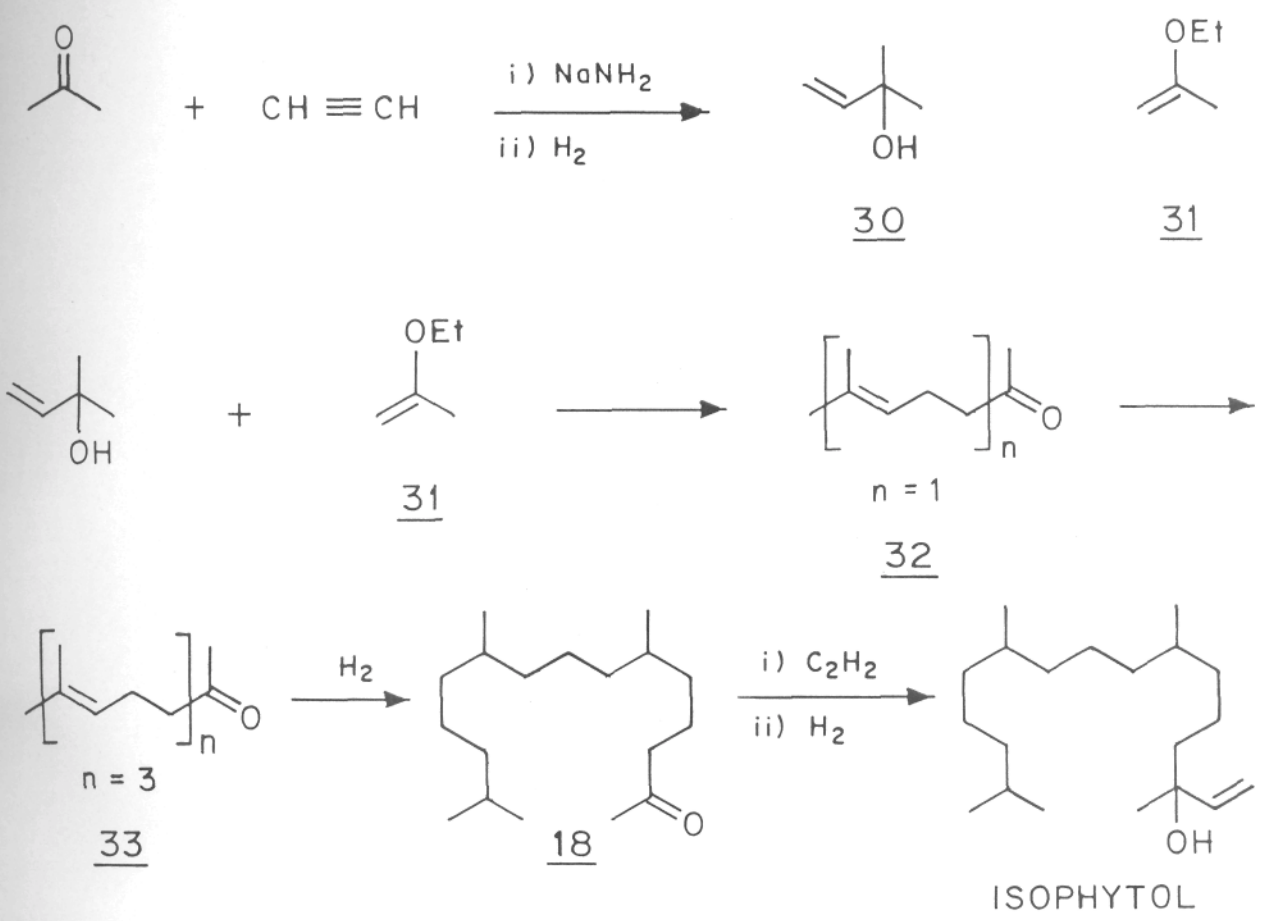
SCHEME–3


Me
Me
O
C≡C-COOH
Me
HO
Me
20
Me
Me
O
Me
CHO
HO
Me
21
+
Me
Me
O
Me
CHO
HO
Me
22
Me H
Me H
Me
(+)
(Ph)3P
n
(-)
Br
23
Me
Me
O
Me
Me H
Me H
Me
Me
AcO
Me
24
25
26
27
ALSO,
CHO
28
(Ph)3P
(+)
(-)
Br
29
22 %
H2
ALL–rac –α–TOCOPHEROL

SCHEME-4


HO
n
O
n
HO
n
n = 0, ACETONE
n = 3, GERANYL LINALOOL
OHC
CITRAL
HO
H2C
n
n = 8, SOLANESOL
HO
n
HO
n
HO
CH2
n
n = 3, ISOPHYTOL
n = 3, PHYTOL

SCHEME – 5



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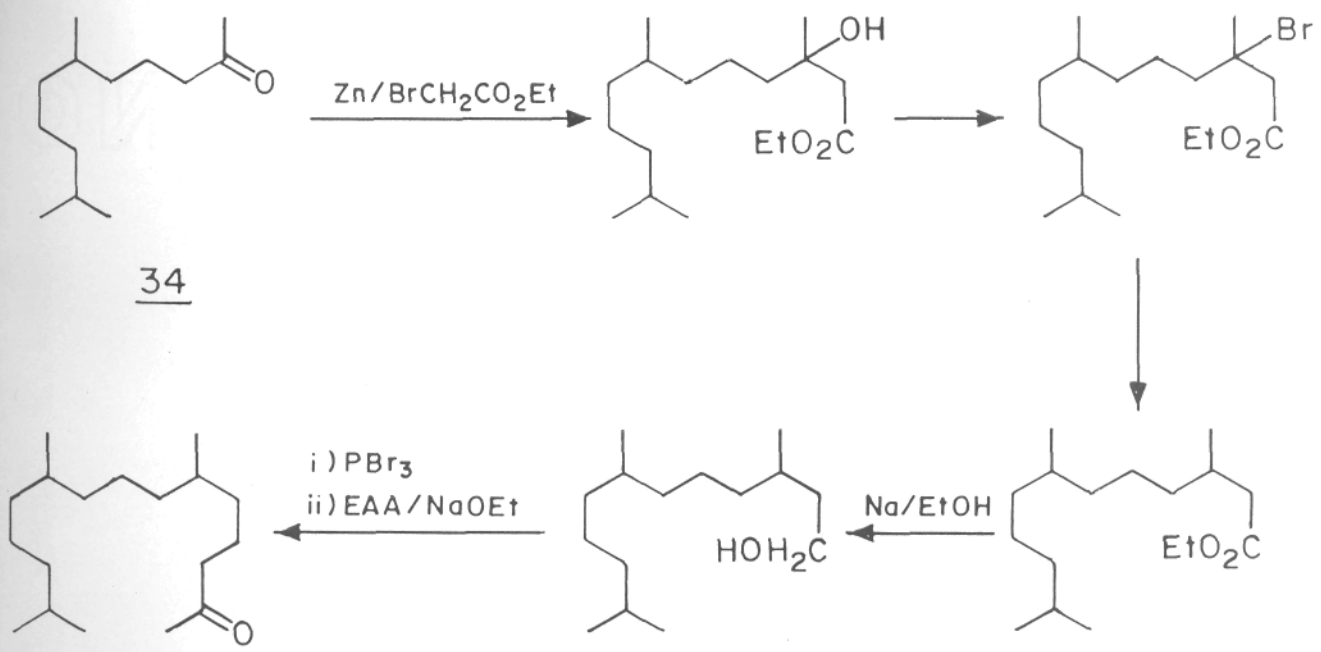

TH-508

547.9:577.16 E+615.7(043)

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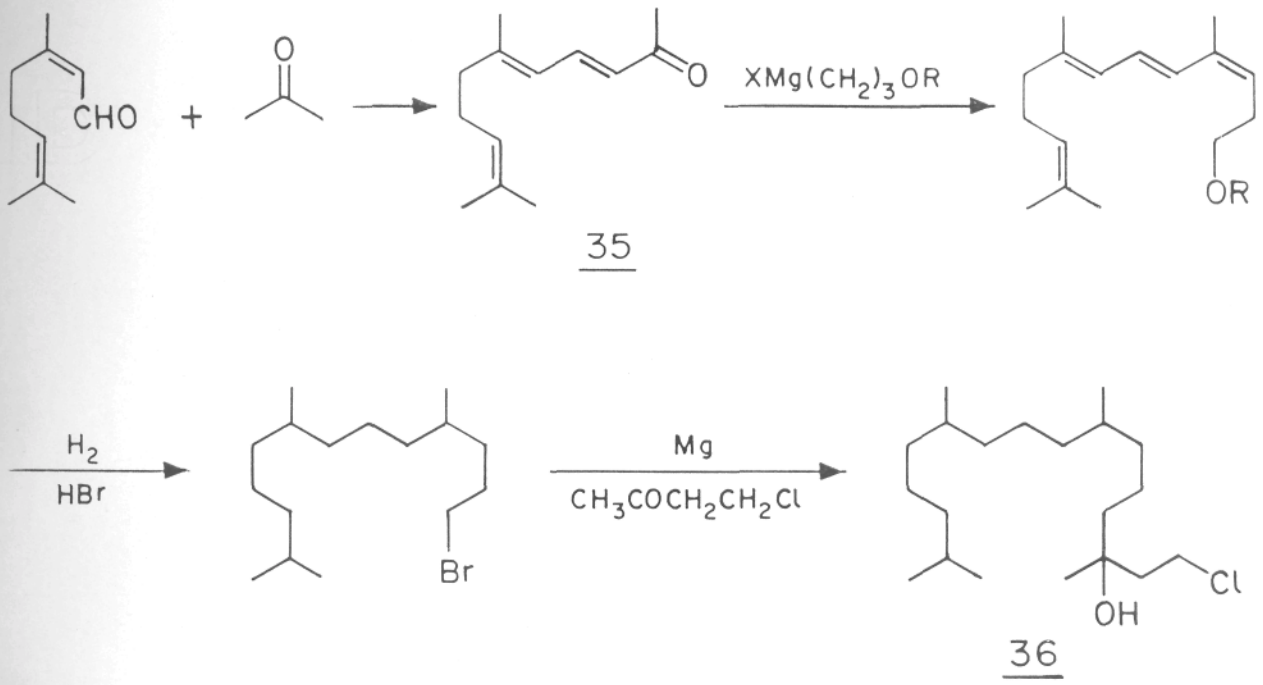

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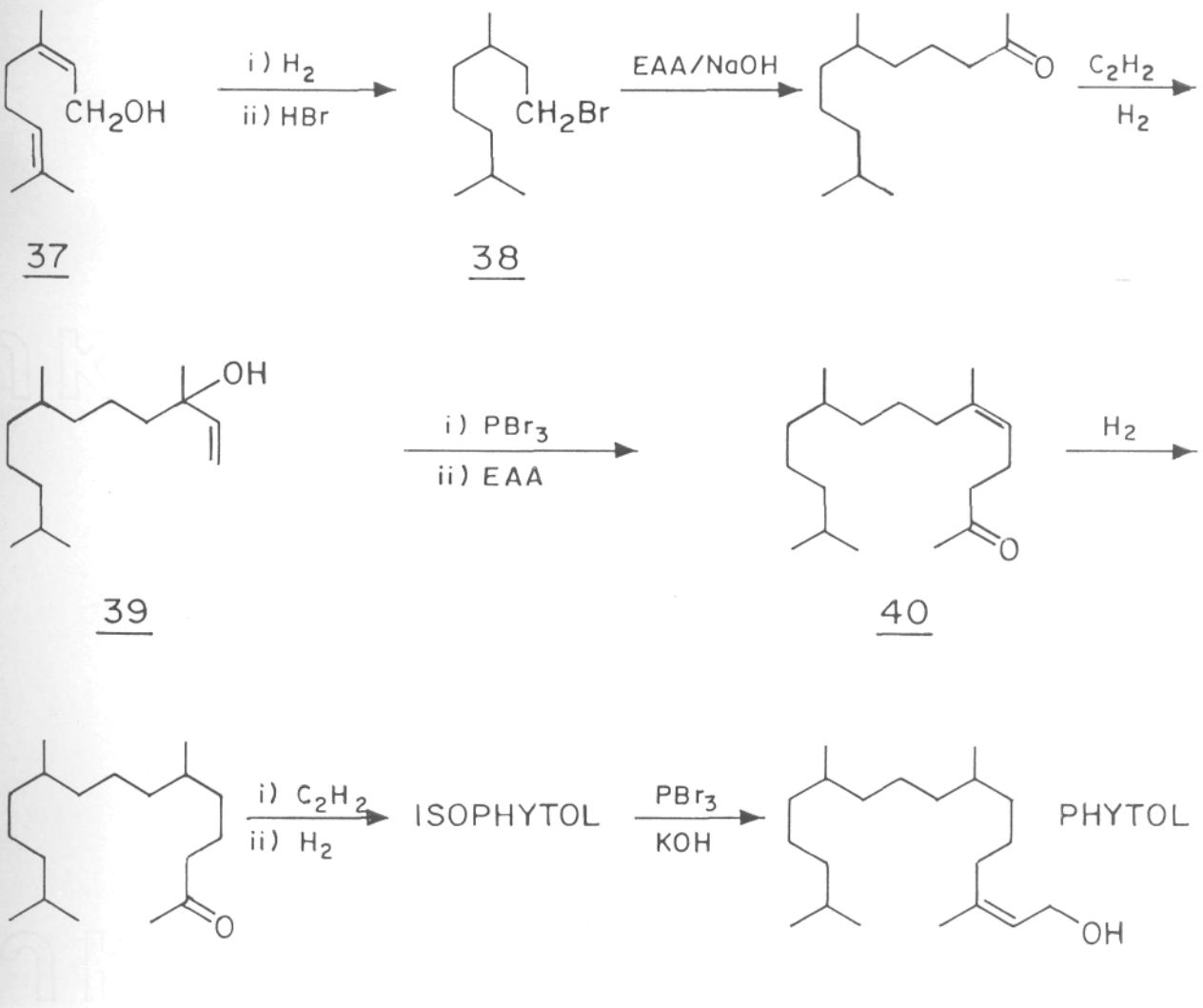

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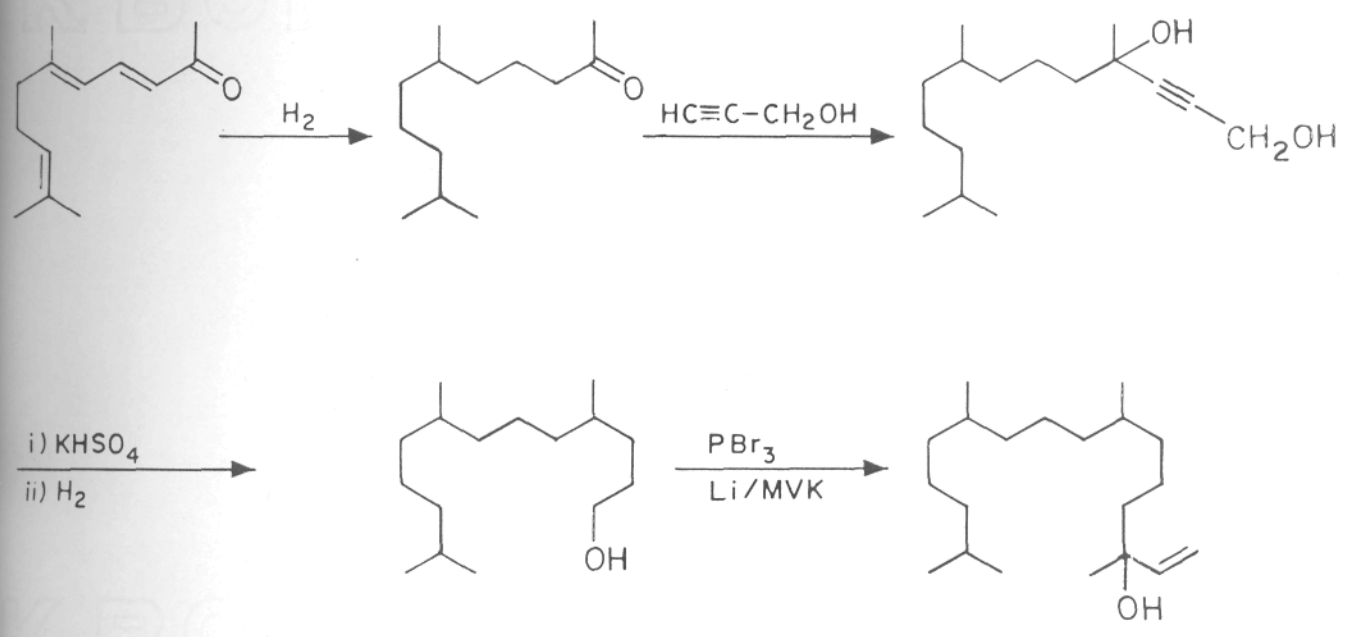

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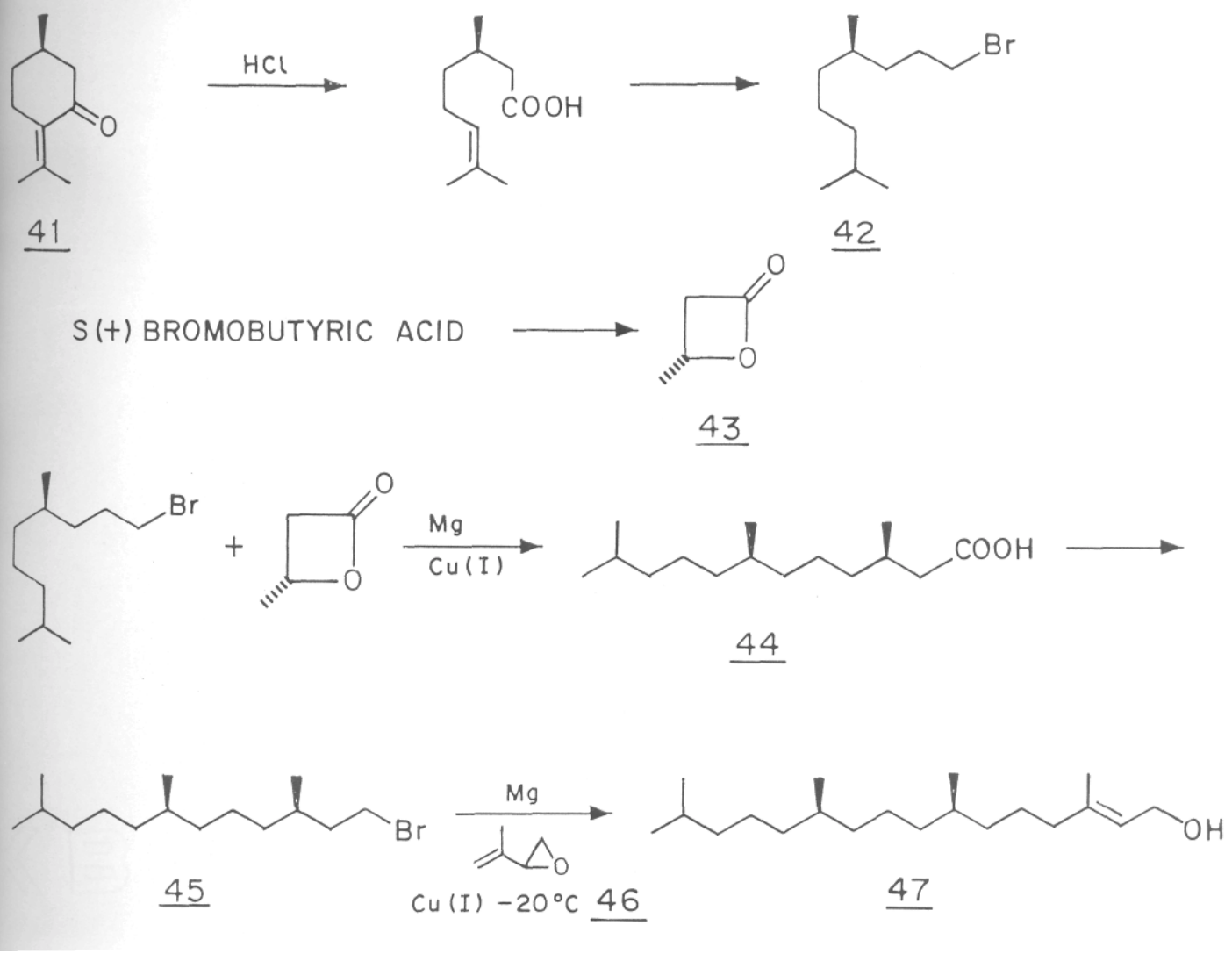

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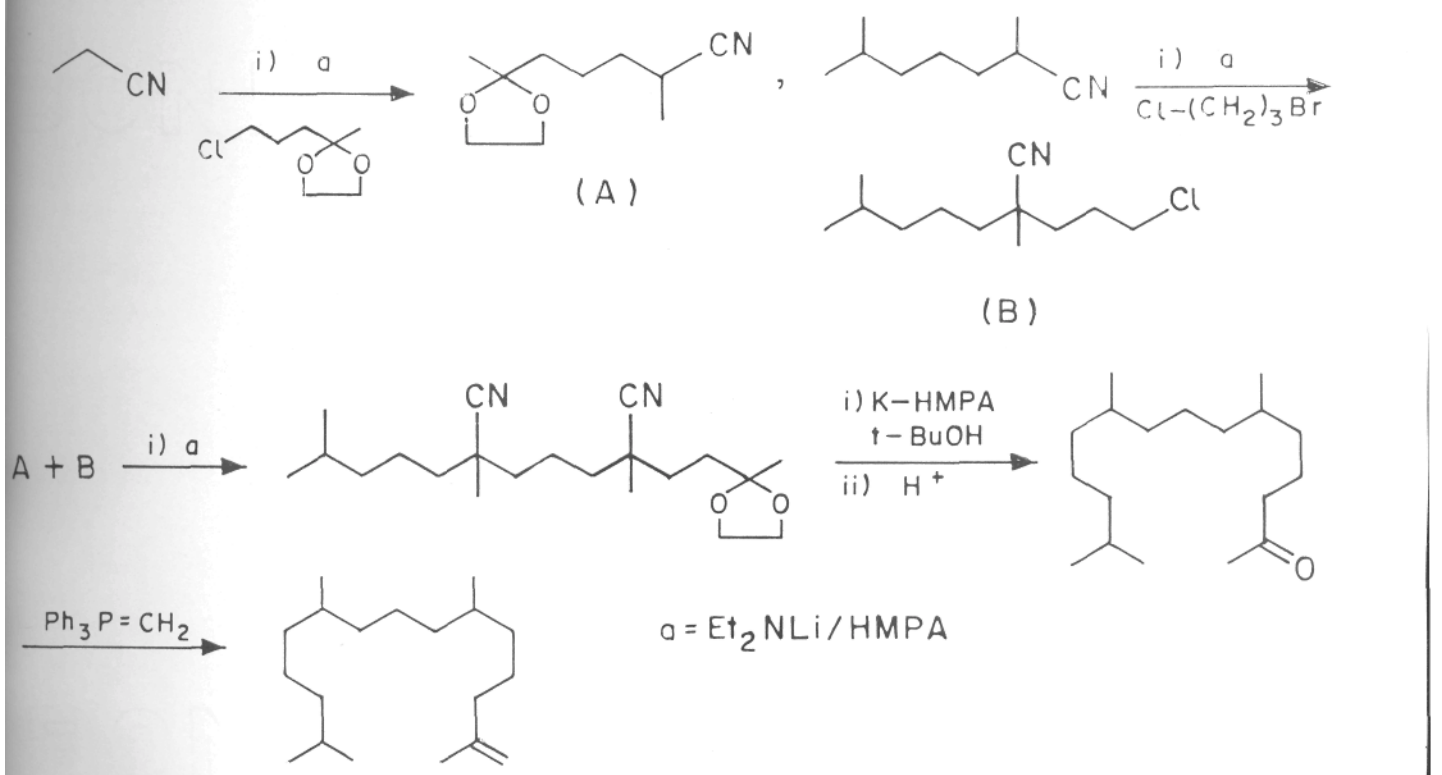

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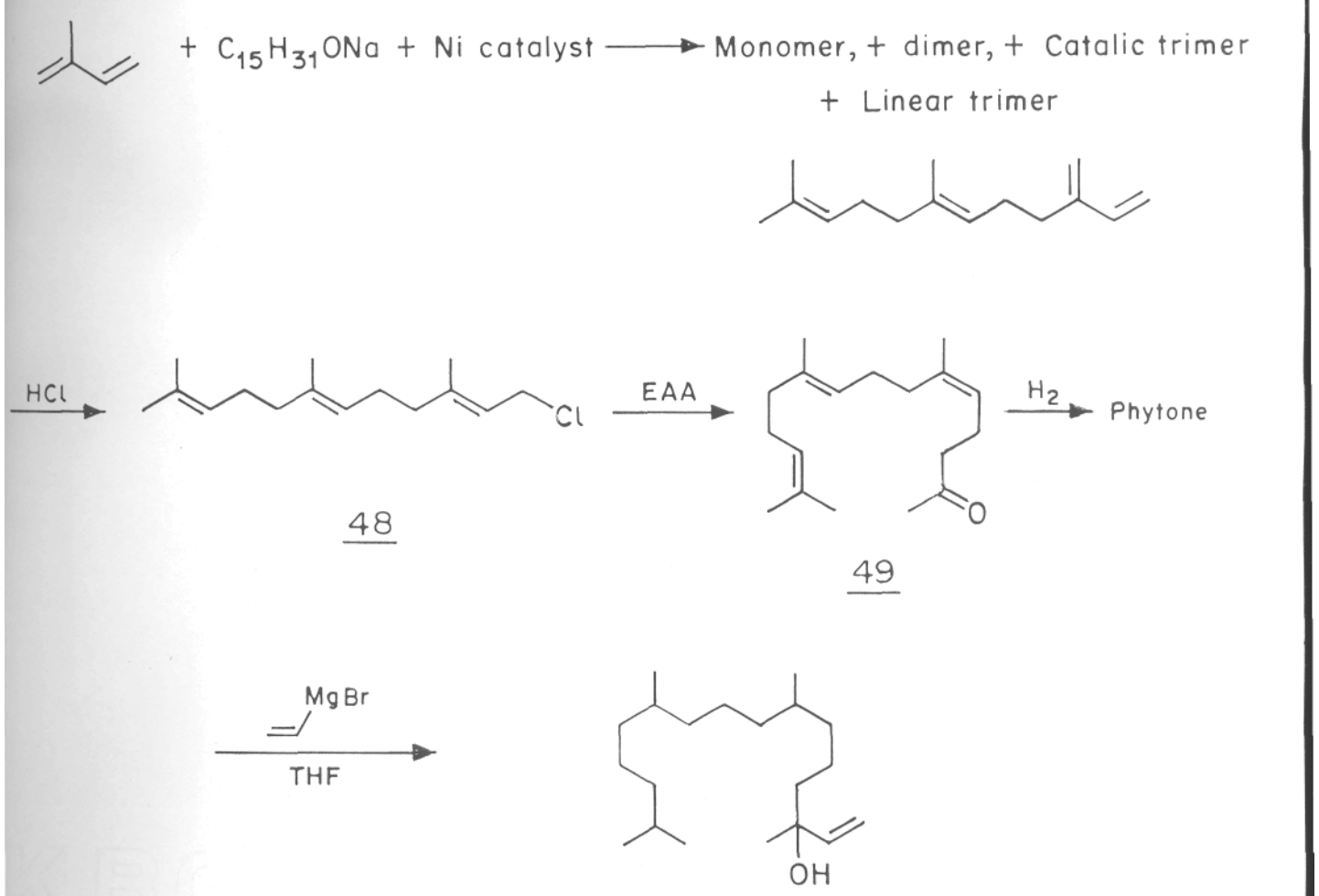

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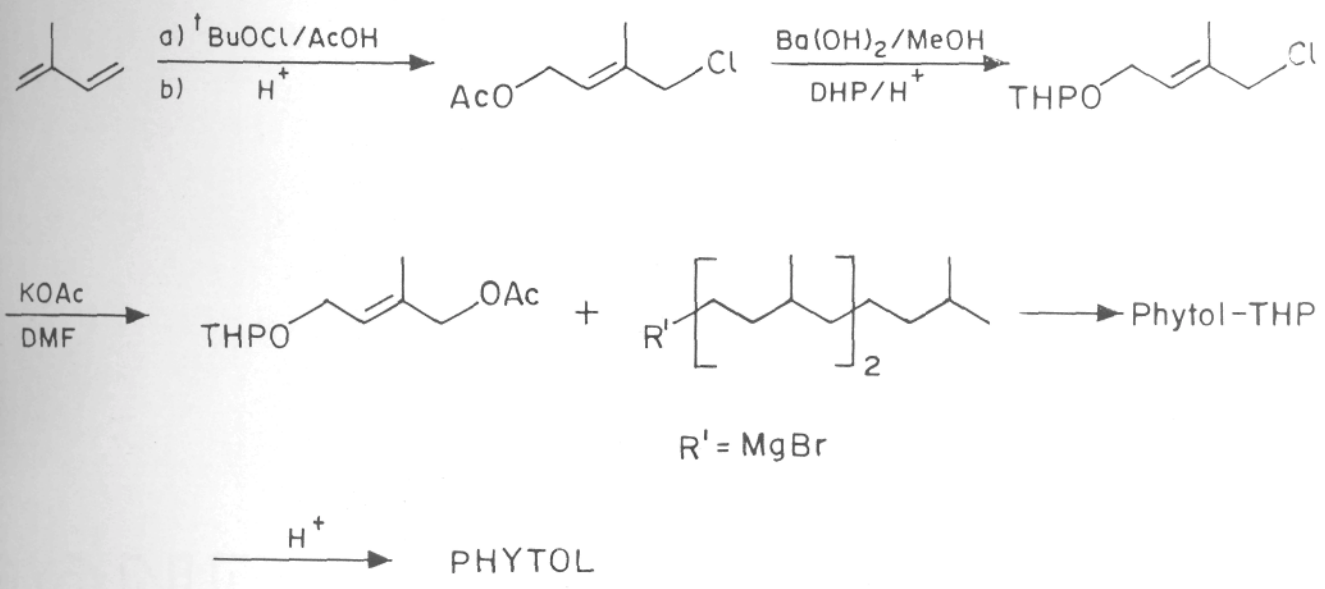

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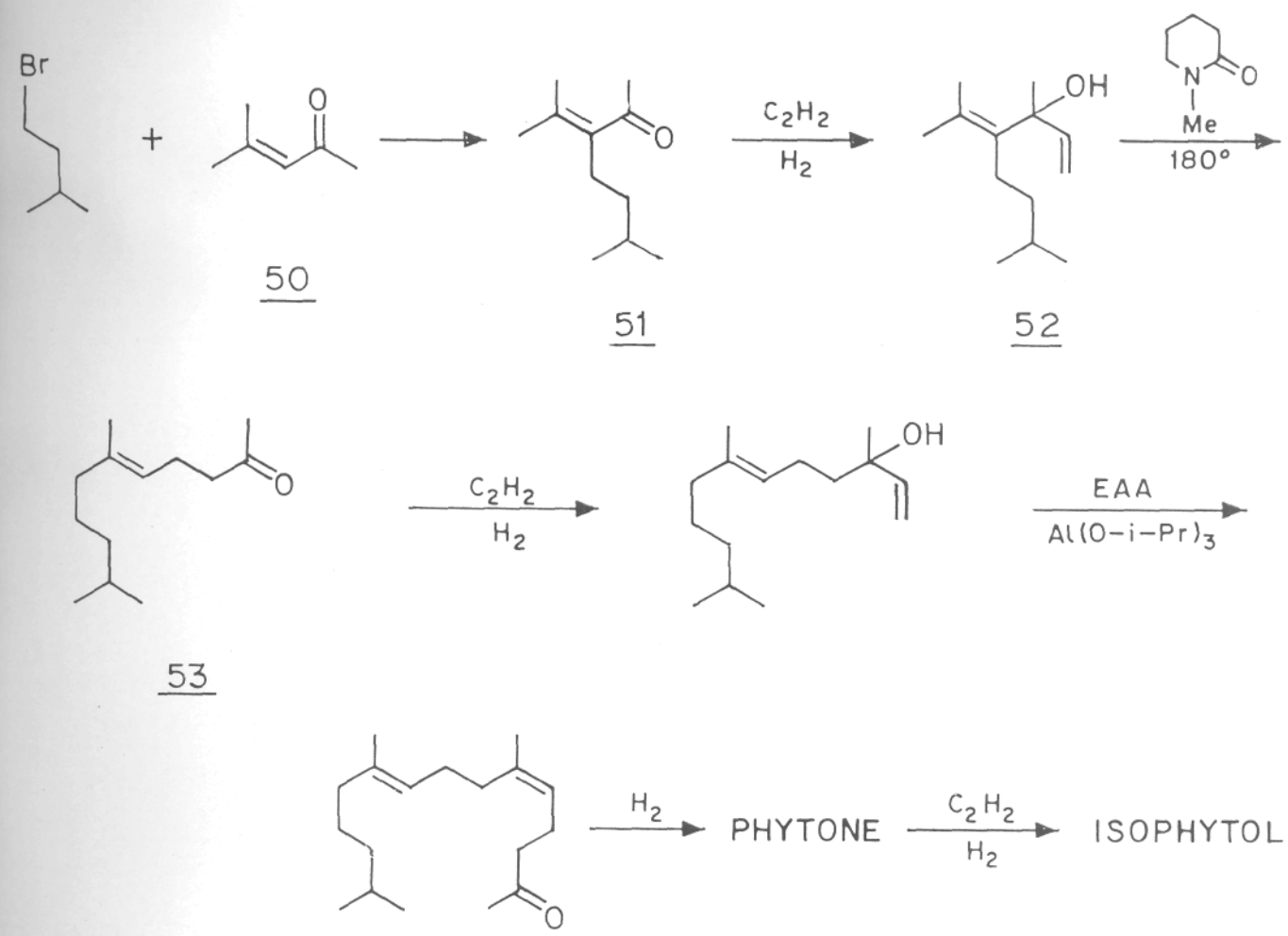

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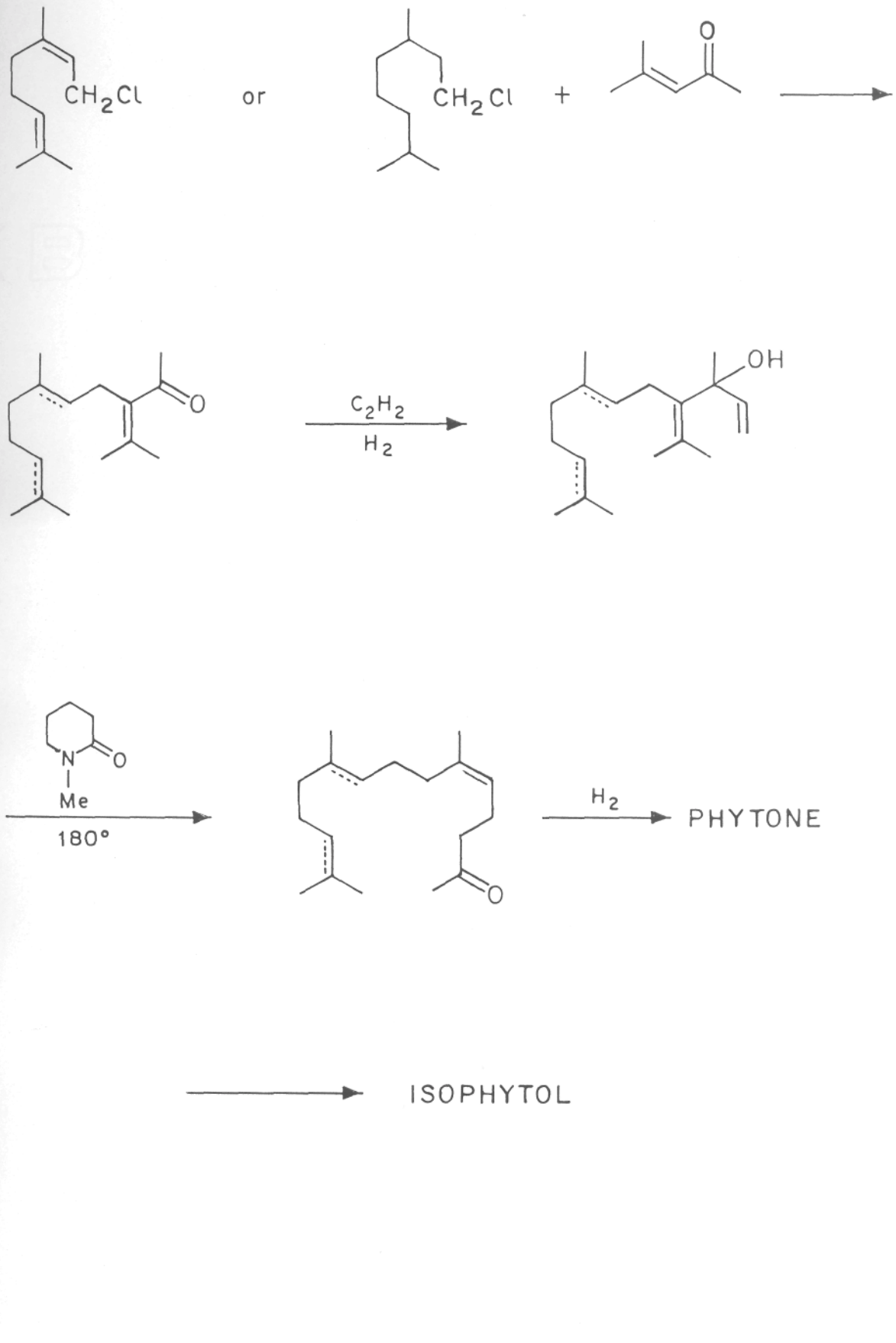

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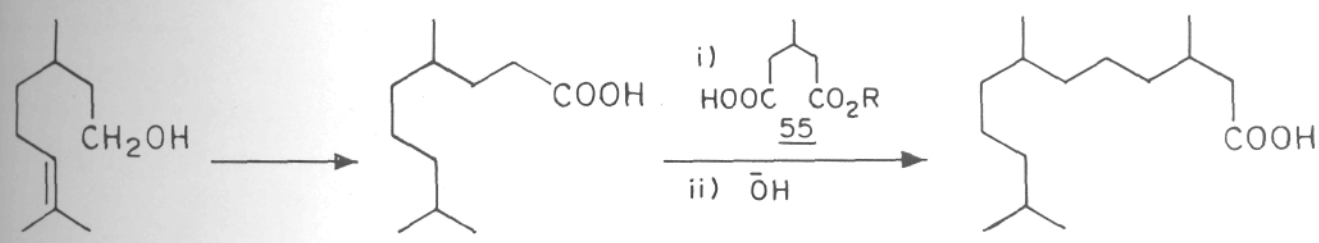

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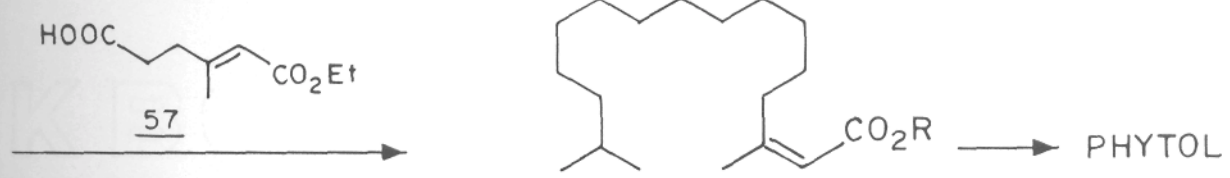
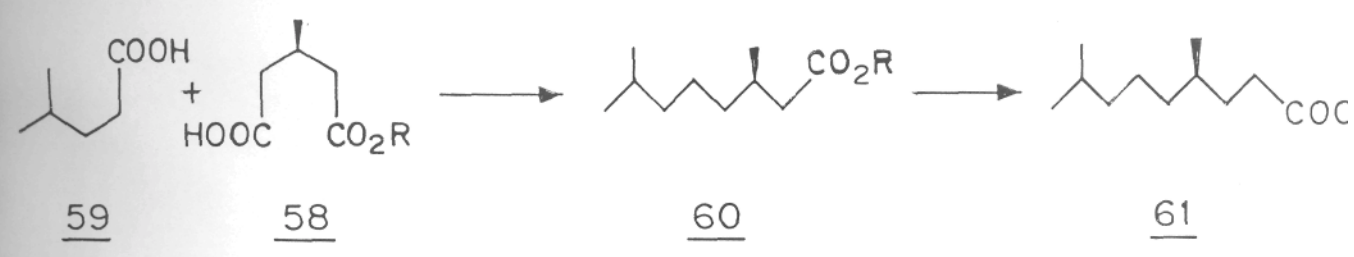
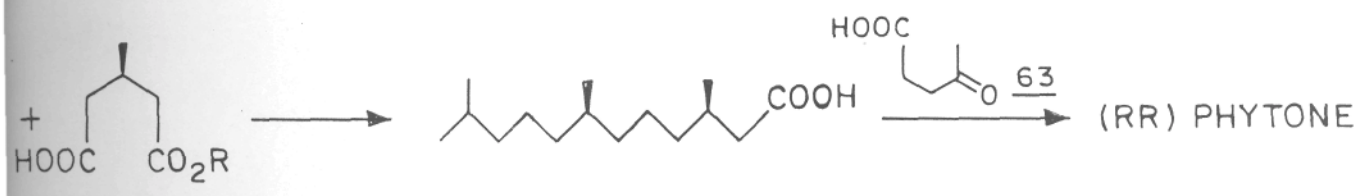




59 58 60 61



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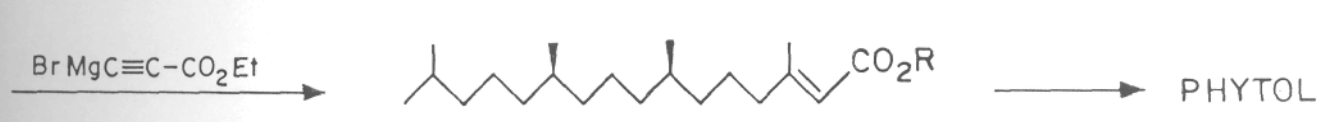

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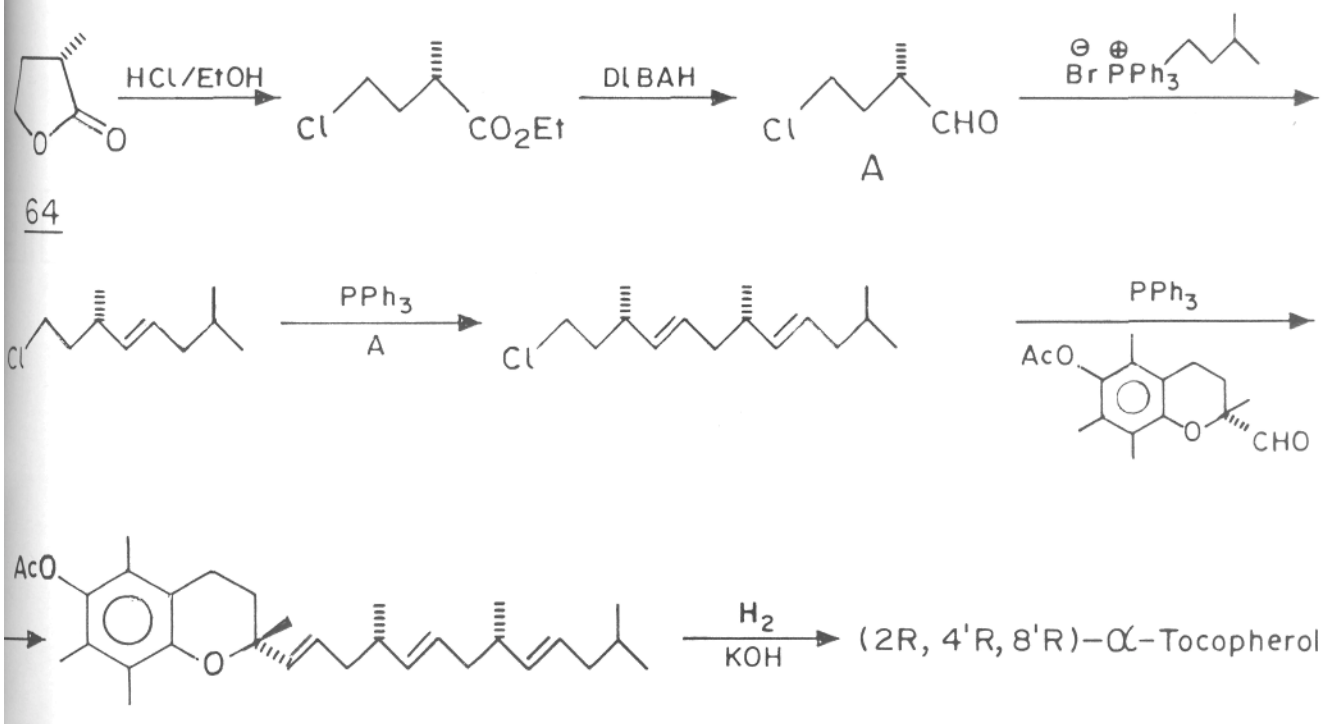

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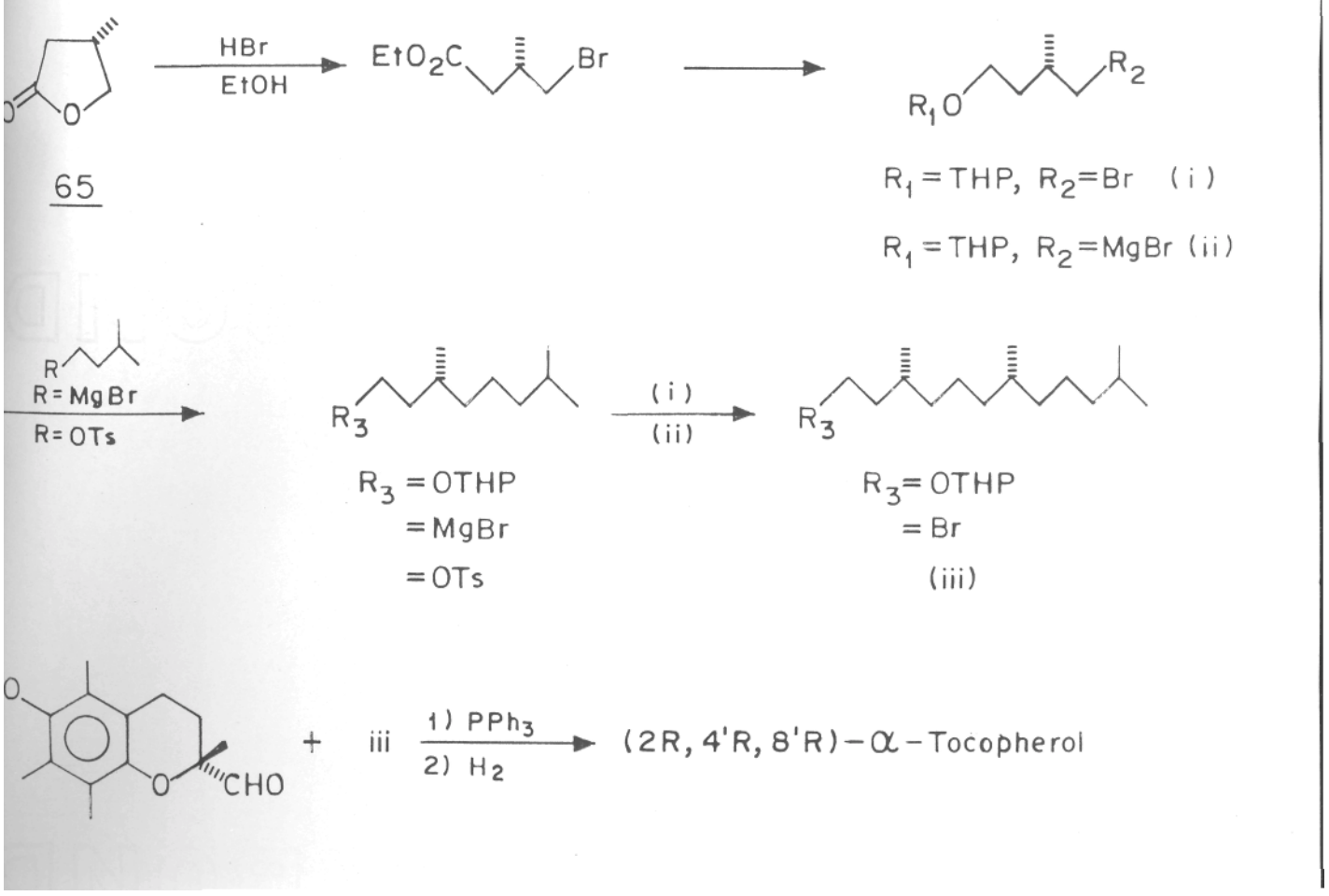

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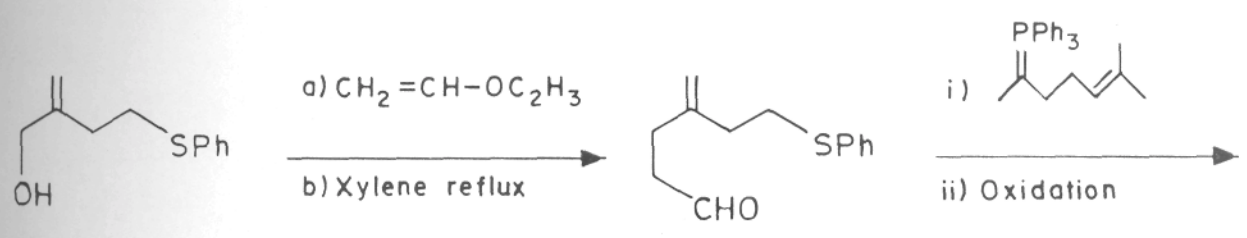
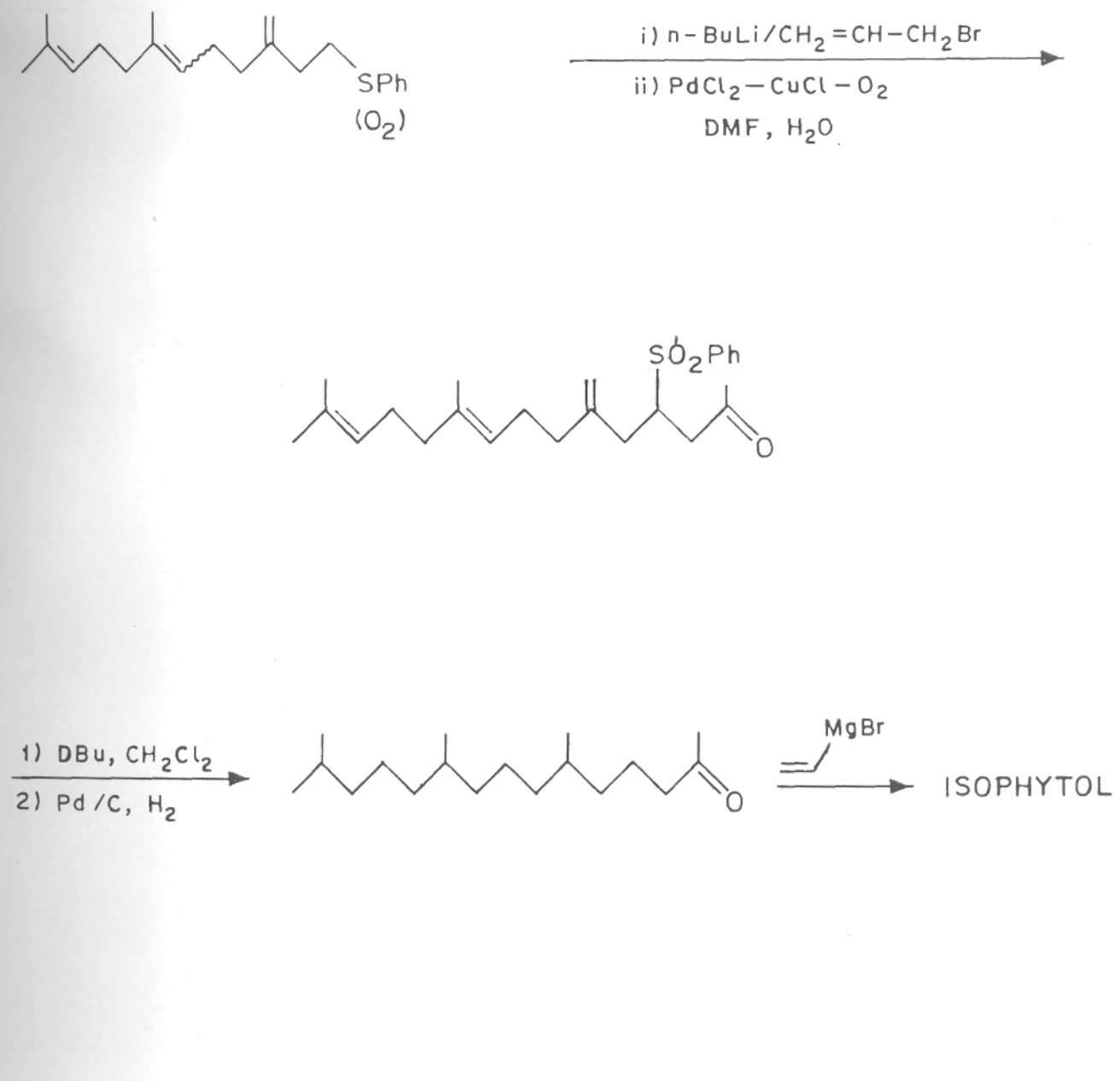
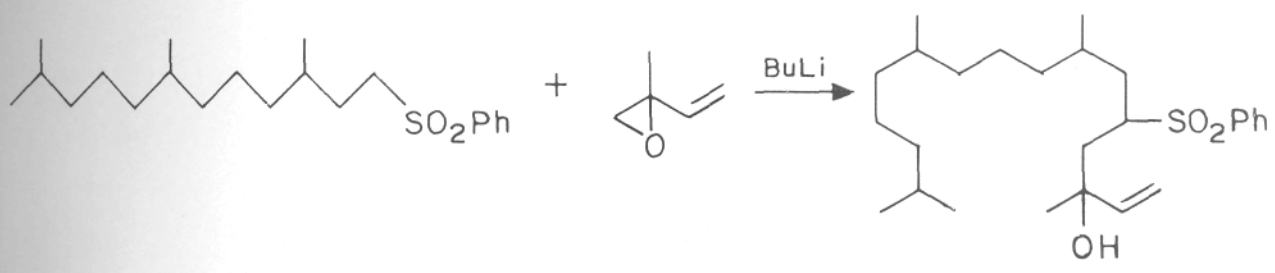

SPh
OH
a) $CH_2=CH-OC_2H_5$
b) Xylene reflux
SPh
CHO
PPh_3
i)
ii) Oxidation

66


SPh
(O_2)
i) n-BuLi/$CH_2=CH-CH_2Br$
ii) $PdCl_2-CuCl-O_2$
DMF, H_2O
SO_2Ph
O
1) DBu, CH_2Cl_2
2) Pd/C, H_2
O
MgBr
ISOPHYTOL

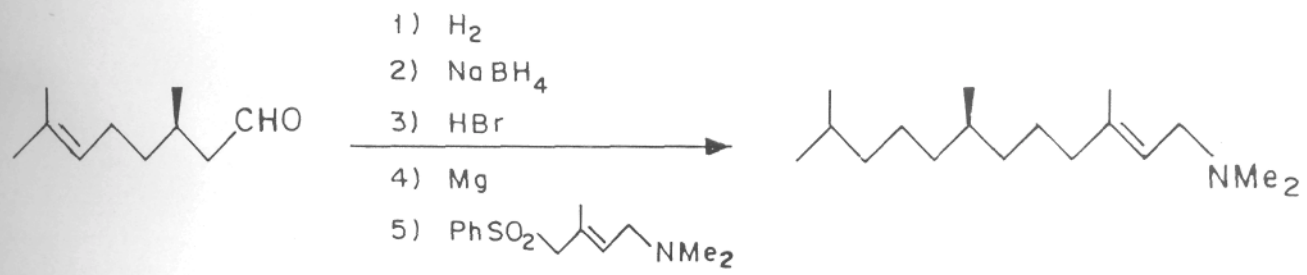
SCHEME – 20



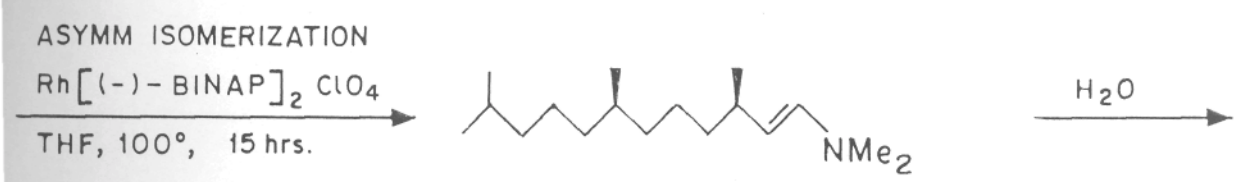
67 68 69

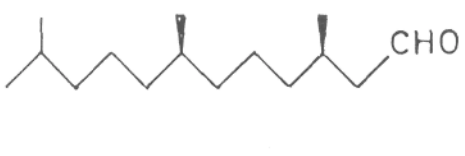
Na/Hg/EtOH → ISOPHYTOL

SCHEME – 21



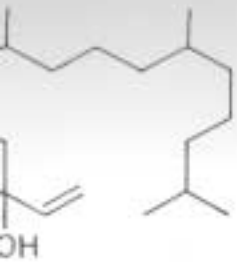
70





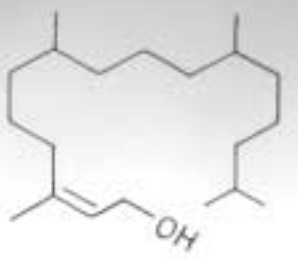
71

RETEROSYNTHETIC SCHEME

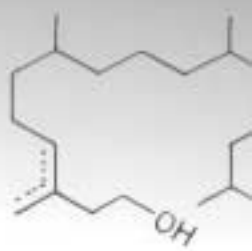


OH

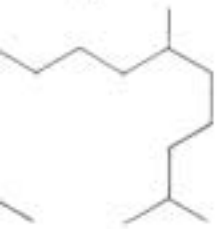
ISOPHYTOL



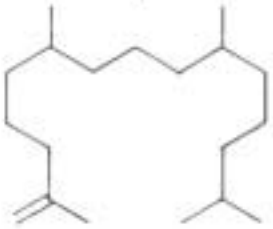
PHYTOL



PHYTOL ISOMER

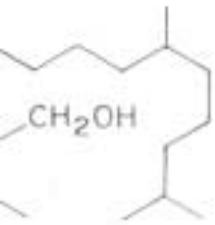


PHYTONE

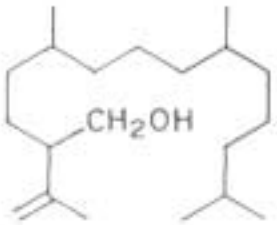


NORPHYENE

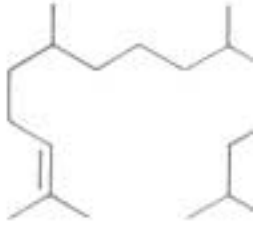
C_{19}-HYDROCARBON



CH_2OH



CH_2OH



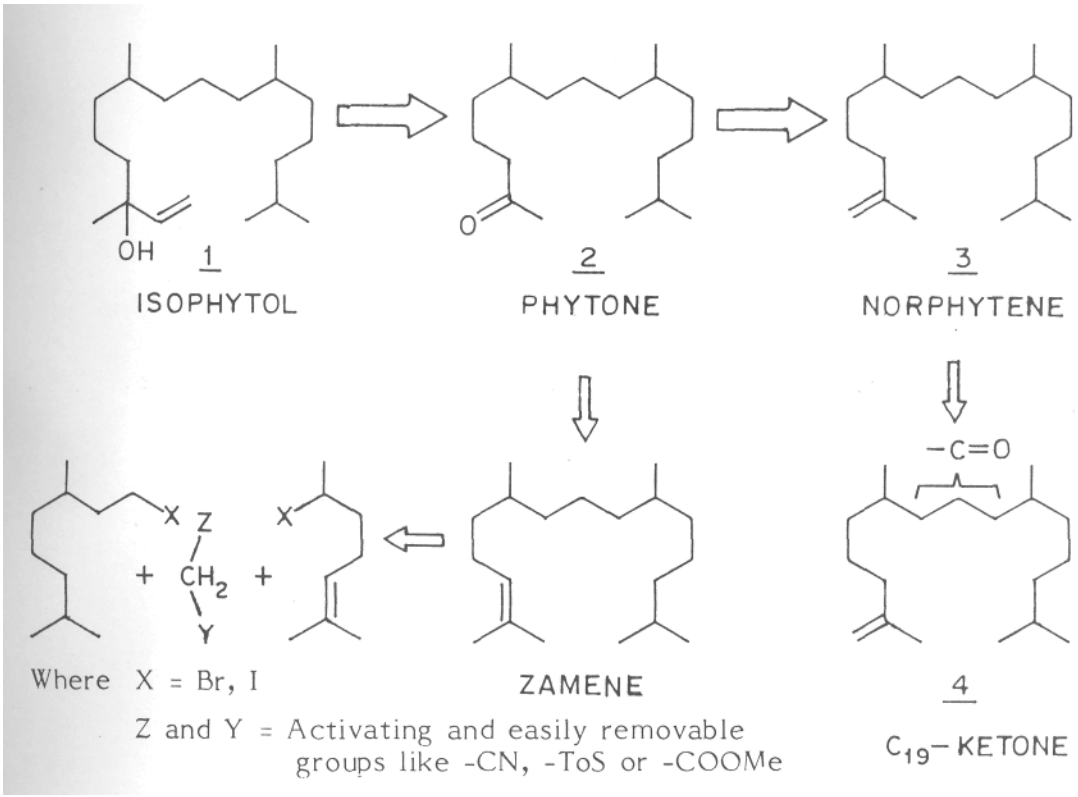
2,6,10,14-TETRAM

PENTA DEC-2-

C_{19}-HYDROCARE

PRESENT INVESTIGATION

In the past two decades very little attention has been given towards the development of a new commercial process for the synthesis of vitamin E, by new routes, for industrial exploitation, utilising cheap and indigenously available raw materials. As a part of this research programme, initially the work towards the synthesis of phytol, isophytol or any of their intermediates was undertaken in our laboratory. A retrosynthetic scheme for the synthesis of phytol, isophytol and its isomers is given below.

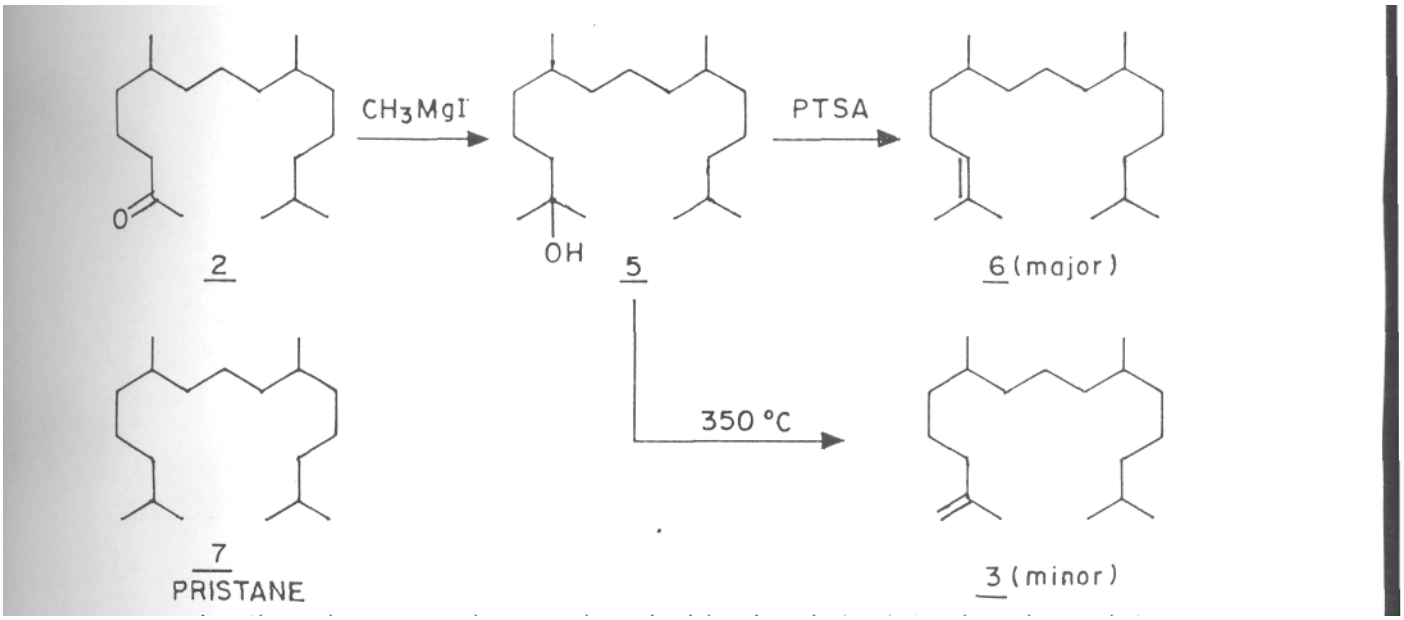


2,6,10,14-Tetramethylpentadec-2-ene and its positional isomer norphytene are important intermediates for the synthesis of phytone and phytol isomers (retrosynthetic scheme-22 in Introduction to vitamin-E, first chapter).

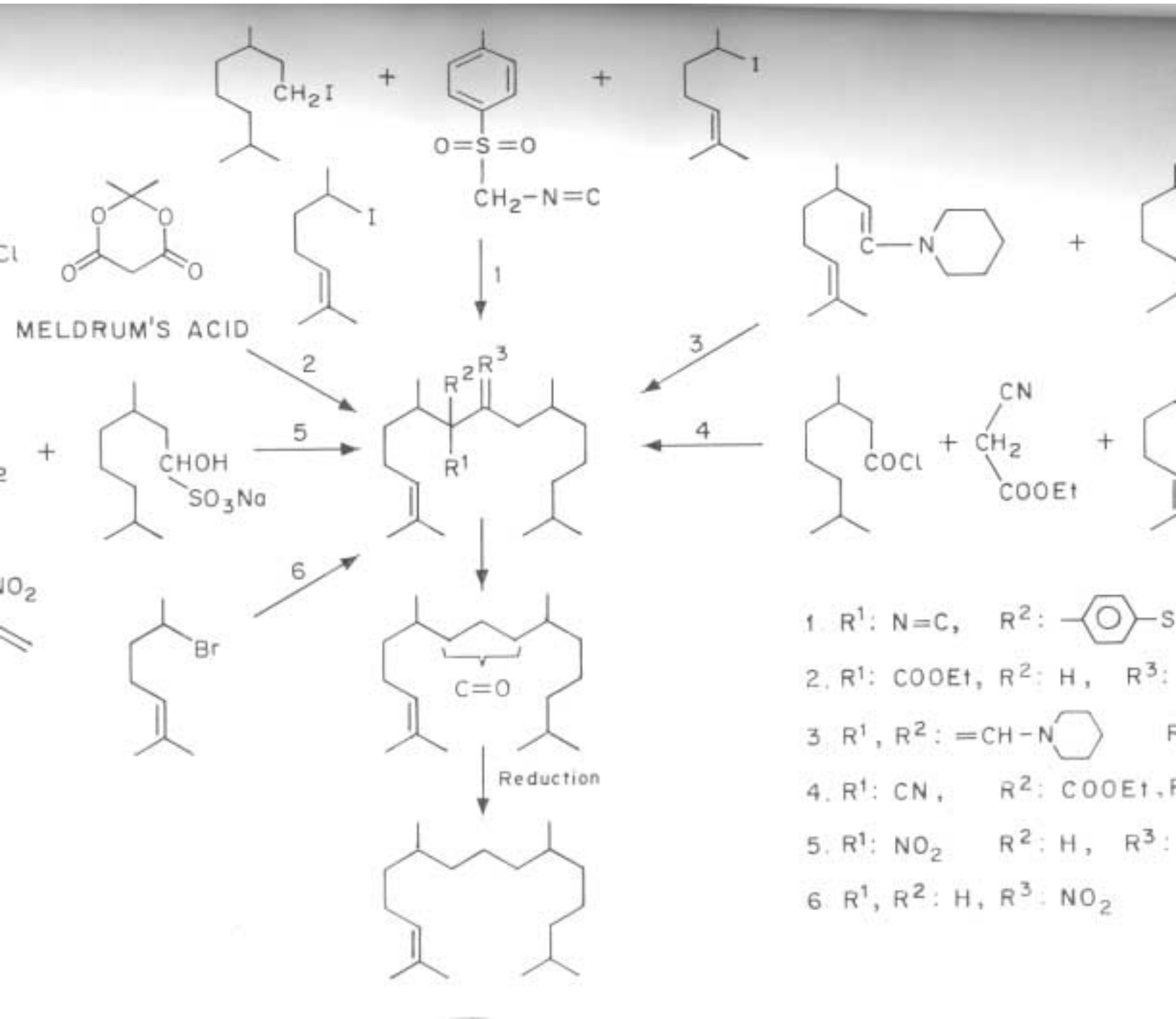
2,6,10,14-Tetramethylpentadec-2-ene is a naturally occuring C_{19}-mono-olefin obtained from mixed zooplankton in the gulf of main. Its structure was confirmed by ozonolysis and hydrogenation studies. Ozonolysis furnished the C_{16} aldehyde whereas hydrogenation gave

pristane[1].

Reported syntheses of 2,6,10,14-tetramethylpentadec-2-ene involves Grignard reaction on phytone (2), and the scheme is outlined below.

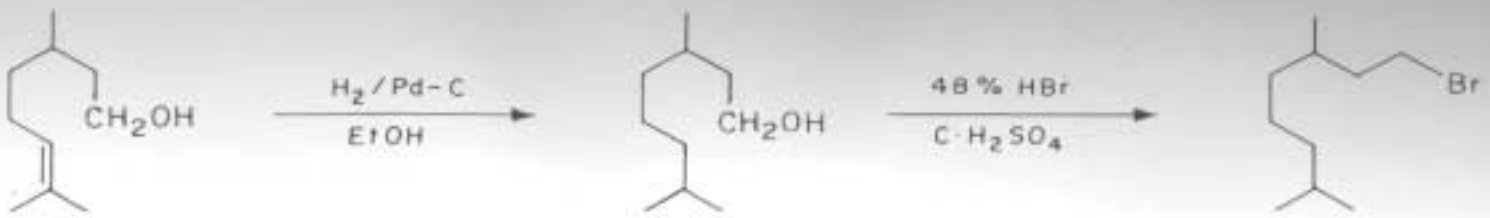


In the above syntheses the double bond is introduced at later stage, while in the syntheses developed in our laboratory, the starting materials like citronellal or methylheptenone were used; which already have this functionality. The methods developed in our laboratory using (i) TosMIC[3] , (ii) Enamines[3] , (iii) Meldrum acid[4] , (iv) Aliphatic nitro compounds[5] , (v) l,3,-dioxolane-2-methyl-[2-(3-chloropropyl)][6] and (vi) Ethyl cyanoacetate[7] are outlined in Scheme-1.


MELDRUM'S ACID
1
2
3
4
5
6
Reduction
C=O
1. R1: N=C, R2:
2. R1: COOEt, R2: H, R3:
3. R1, R2: =CH-N
4. R1: CN, R2: COOEt,
5. R1: NO2 R2: H, R3:
6. R1, R2: H, R3: NO2

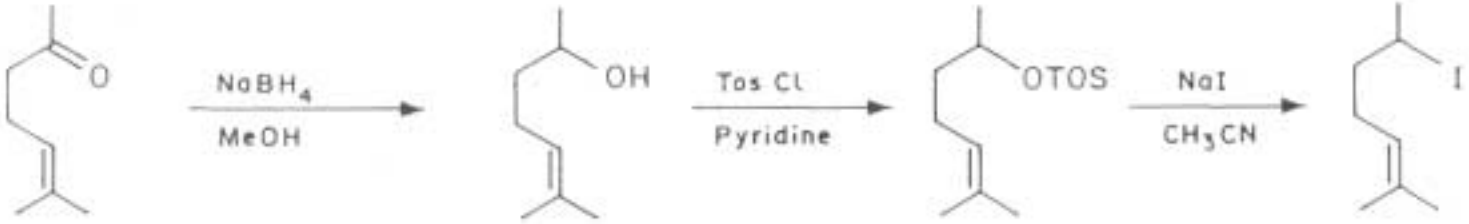
SCHEME - 2

PREPARATION OF 3, 7-DIMETHYLOCTYL BROMIDE (10, C-10 UNIT)



8 9 10

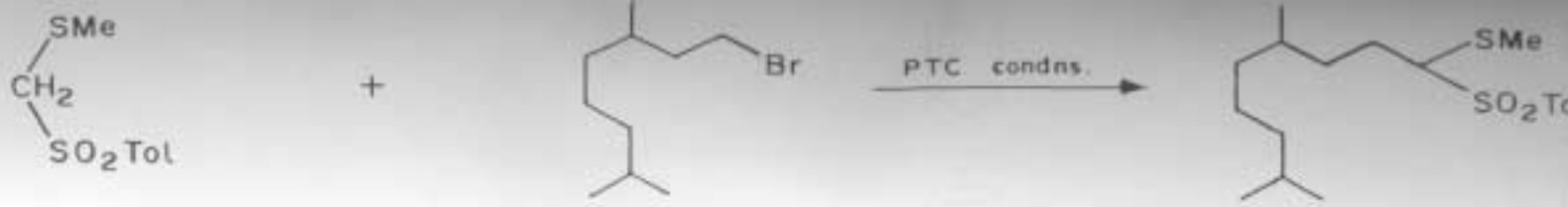
PREPARATION OF 2-IODO-6-METHYL-HEPT-5-ENE (14, C_8-UNIT)



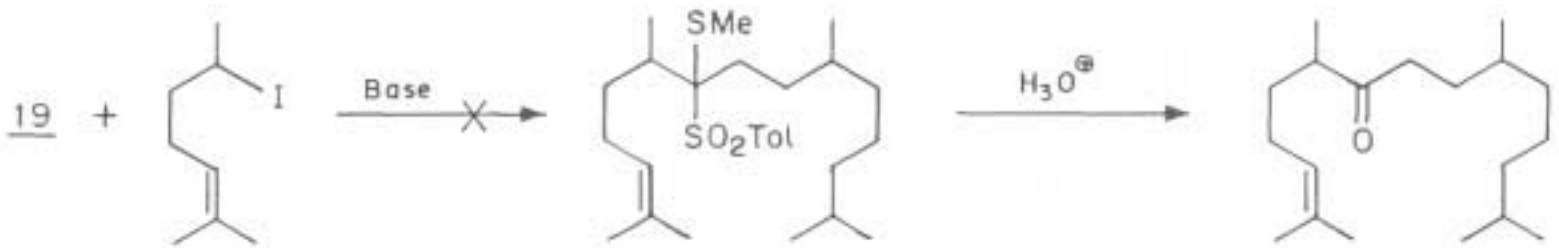
11 12 13 14

PREPARATION OF METHYLTHIOMETHYL-p-TOLYLSULFONE (18)

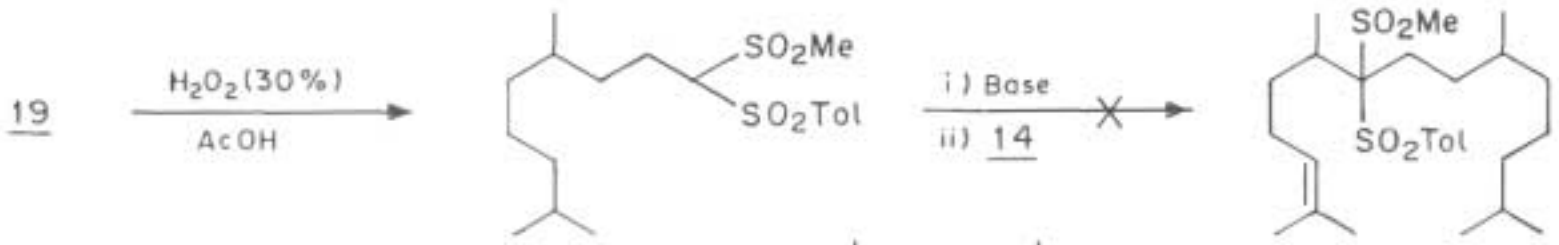
15 16 18



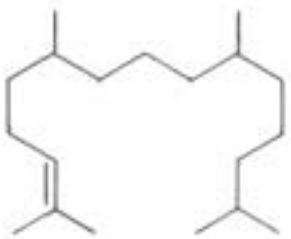
18 10 19



14 20 21



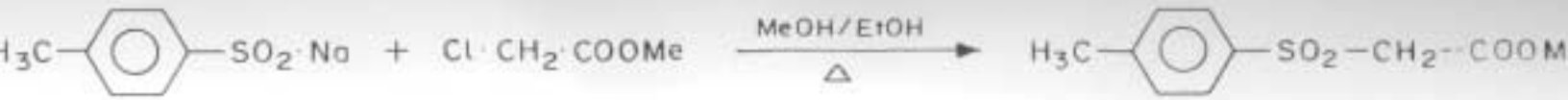
22 23



24 ≡ 37

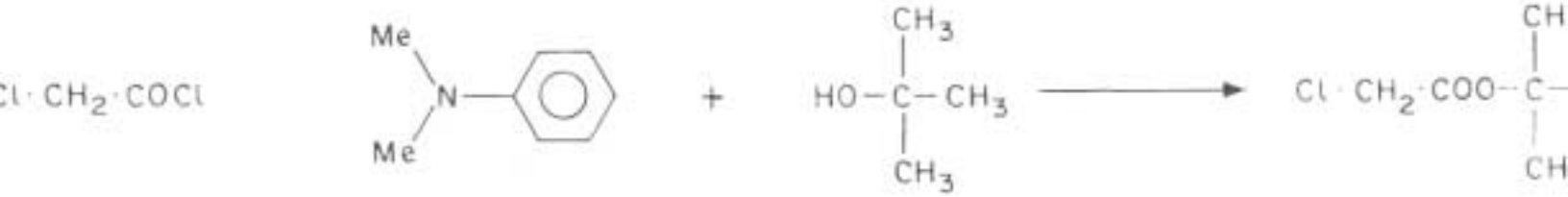
SCHEME – 4

PREPARATION OF p–TOLUENESULPHONYL ACETIC ACID METHYL ESTER.



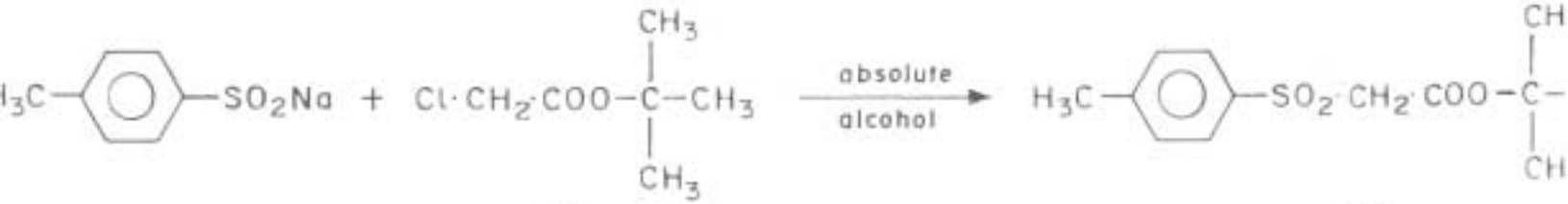
25 26

PREPARATION OF TERTIARY BUTYL CHLOROACETATE.



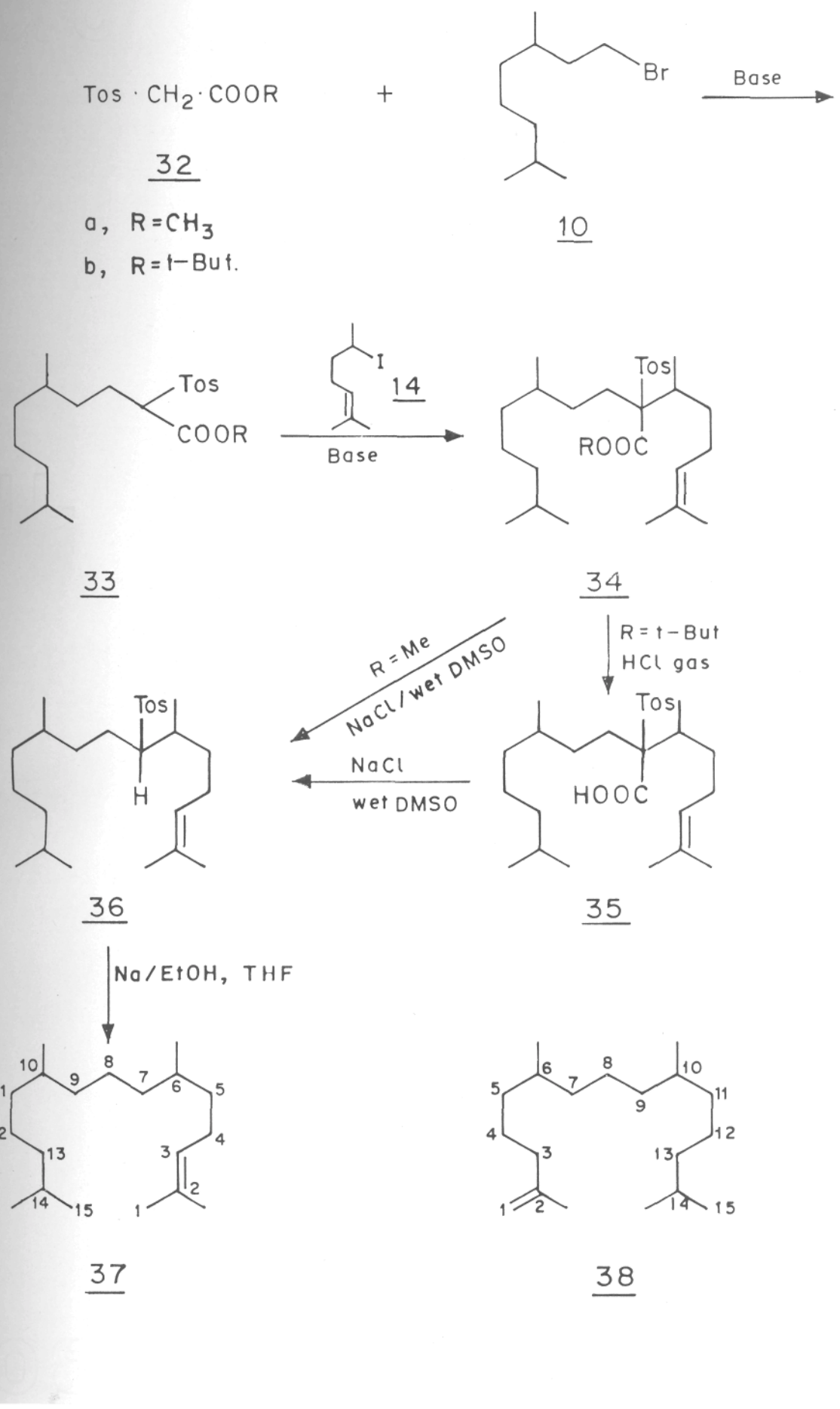
27 28 29 30

PREPARATION OF p–TOLUENESULPHONYL ACETIC ACID t–BUTYL ESTER.

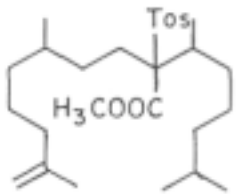


30 31

SCHEME – 5


Tos · CH2 · COOR
32
a, R=CH3
b, R=t-But.
+
Br
10
Base
Tos
COOR
33
I
14
Base
Tos
ROOC
34
R = Me
NaCl / wet DMSO
R = t-But
HCl gas
Tos
H
36
NaCl
wet DMSO
Tos
HOOC
35
Na/EtOH, THF
37
38

The compound (26) was used as a useful synthon which can readily form anions to which electrophilic centres can be attached and from which a C_1, unit can be derived.



The scheme can be visualised as shown below.

The compound (51) can then be transformed into norphytene (38), phytone (33), isophytol (54) and phytol (55).

PRESENT INVESTIGATION

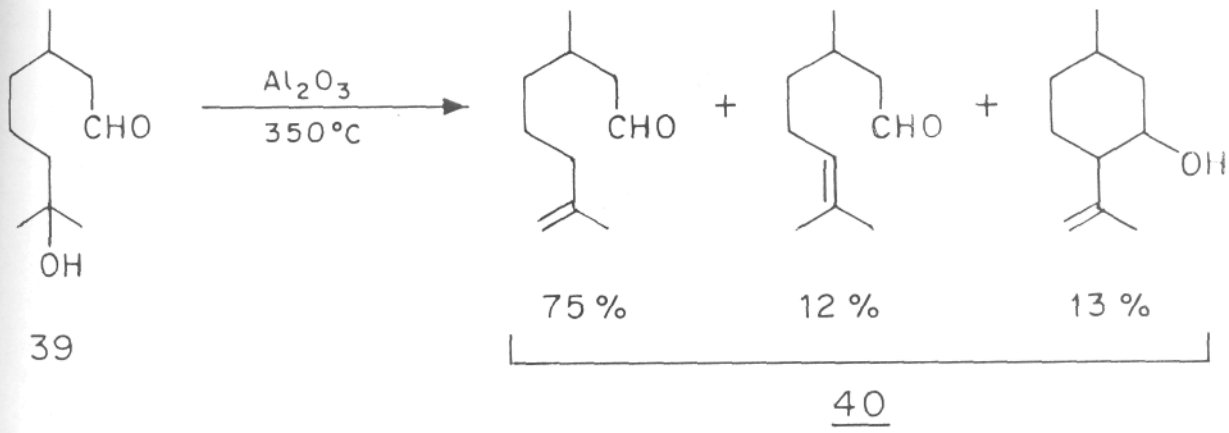
Norphytene (38) used in the synthesis of phytol isomers was prepared using p-toluenesulphonyl acetic acid methyl ester (26), 2-iodo-6-methyl heptane (49) and Rhodinyl iodide (44) (Scheme-7).

Rhodinyl iodide (44) was chosen to be an ideal C_{10} unit as it already possesses the required gem disubstituted double bond. Also, one of the steps towards the synthesis of phytol (55) comprises of Prins reaction. Phytol (55) and its isomers can only be prepared by Prins reaction on norphytene (38), hence preference was given to Rhodinyl iodide (44) over 3,7-dimethyloctyl bromide (10).

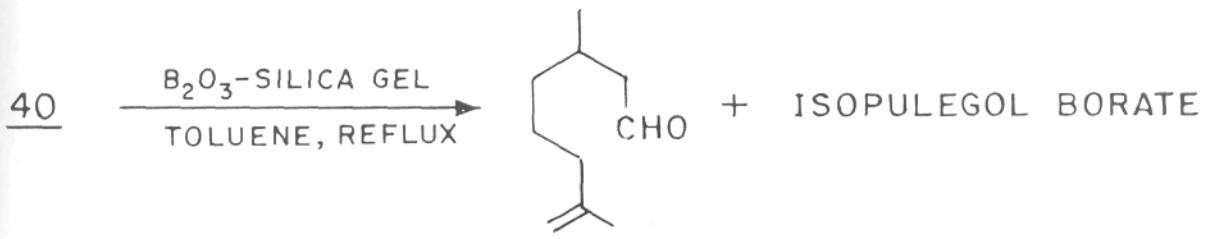
Rhodinal (41) was prepared by the pyrolysis of 7-hydroxycitronellal (39) over neutral alumina according to the literature procedure.[30] The pyroiysed product, which contained 75% Rhodinal (41) and 25% mixture of citronellal and isopulegol (40) was mixed with freshly activated boric anhydride and silica gel and was then refluxed in toluene, using Dean-Stark apparatus to remove water, (Scheme-6). In such acidic

SCHEME – 6

PREPARATION OF PURE RHODINAL 41

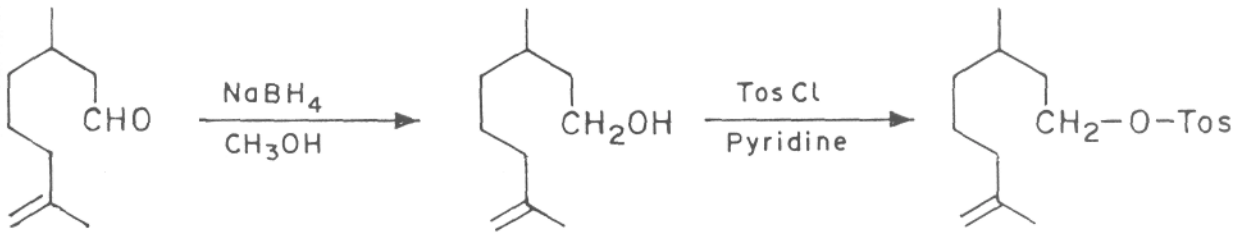


39 → 40

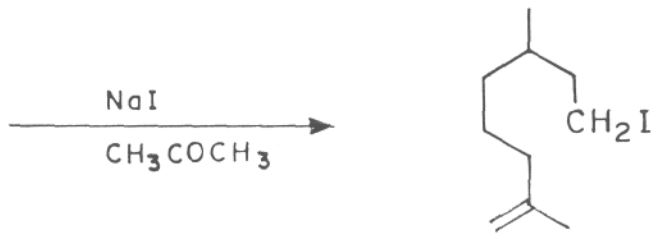


41

PREPARATION OF RHODINYL IODIDE (C_{10}-UNIT, 44)



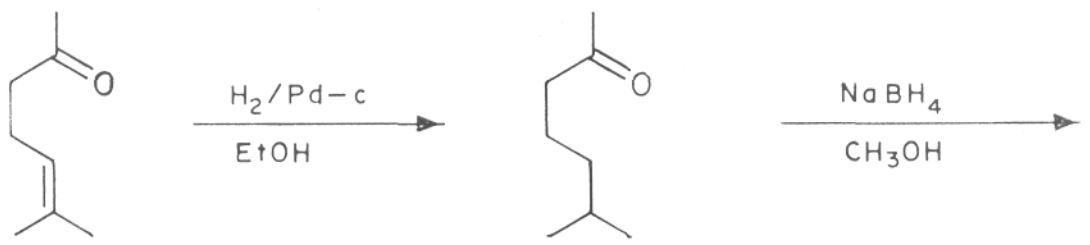
41 → 42 → 45



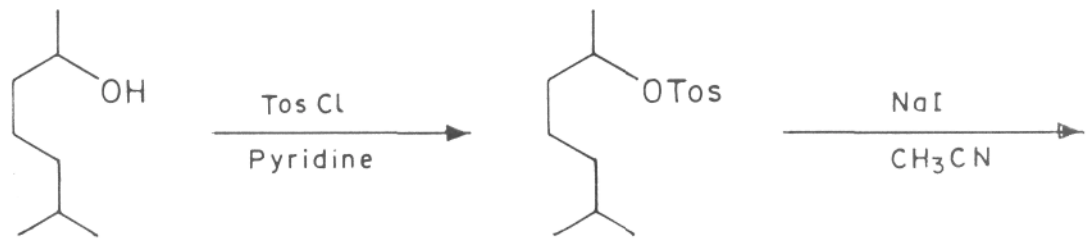
44

SCHEME-6 (contd.)

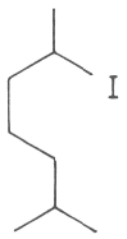
PREPARATION OF 2-IODO-6-METHYL HEPTANE (C_8 UNIT, 49)



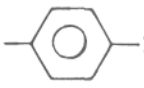
45 46



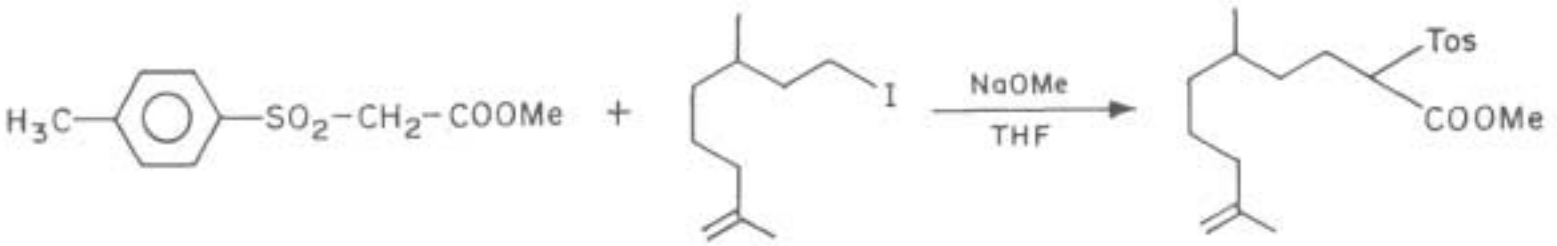
47 48



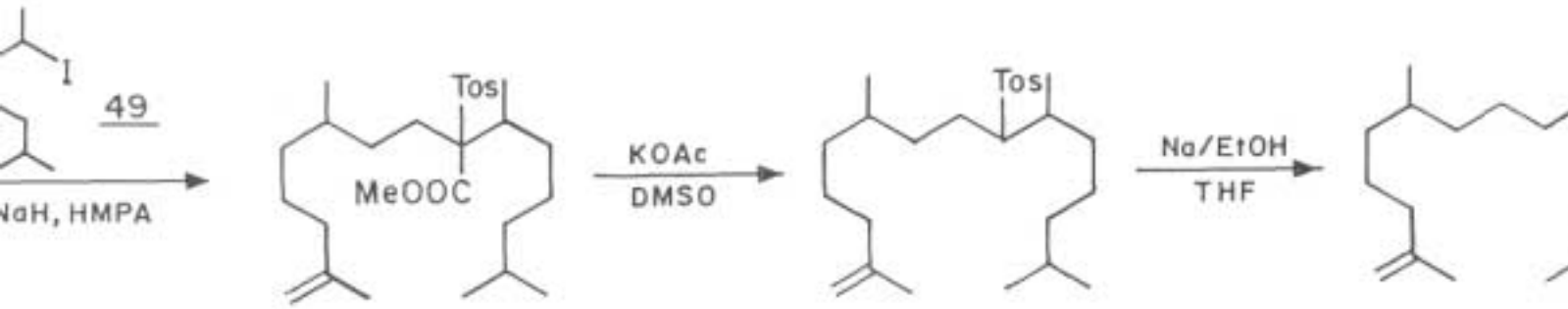
49

(Tos: p-TOLUENE SULPHONYL =  $-SO_2-$)

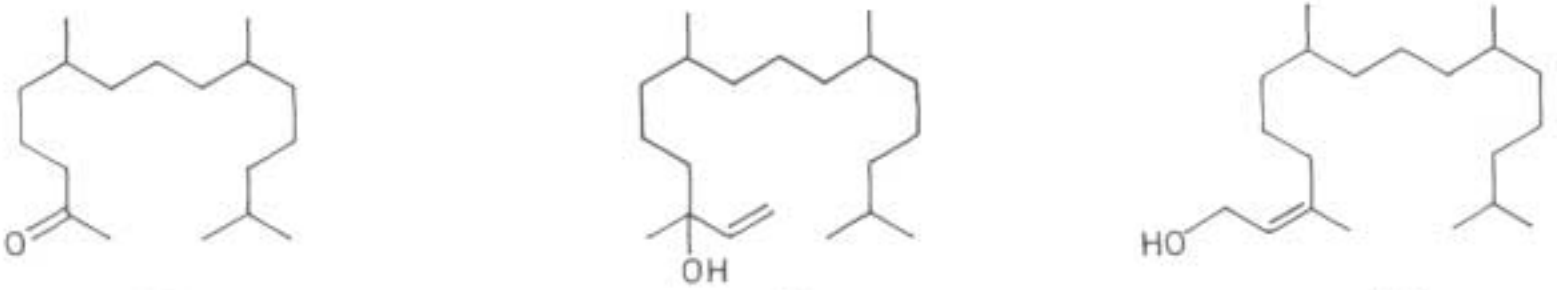
SYNTHESIS OF NORPHYLENE - 38



26 44 50



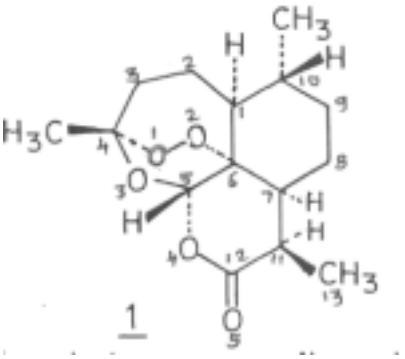
51 52 38



53 54 55

QHS with triphenylphosphine. The ^{1}H and ^{13}C spectra indicated the presence of three methyl groups, one tertiary and two secondary, an acetal function and several kinds of aliphatic carbon-atoms. From

'X' ray diffraction[8] structure and relative configuration of QHS is as shown in 1.



1

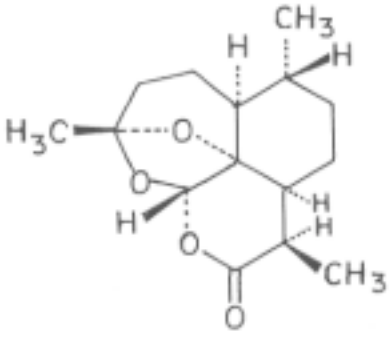
Its absolute configuration[8] and the trans-configuration of the lactone ring determined by comparison of its ORD spectrum with that of arteannuin B, a structurally related sesquiterpene isolated from A. annua in Yugoslavia. The compound is related to the cadinane/amorphane

class of sesquiterpenes which are defined by their cis-decalin skeleton. QHS is partially soluble in water[14]. In protic solvents it decomposes

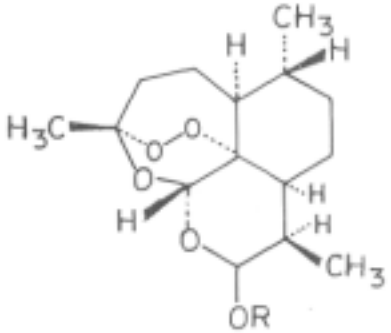
by opening of lactone ring. It is soluble in aprotic solvents and partially soluble in oil. It is thermally stable and remains unchanged for 3 min. at 50°C above its melting point and can be purified by sublimation.[15]

Chemical Reactions of QHS:

Hydrogenation of QHS with $Pd/CaCO_3$ gives desoxyartemisinin 2, while sodium borohydride reduction gives dihydroqinghaosu (3 R=H, dihydroartemisinin, DHQHS) having a lactol (hemiacetal) function[10,16].

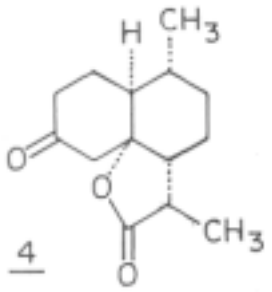


2



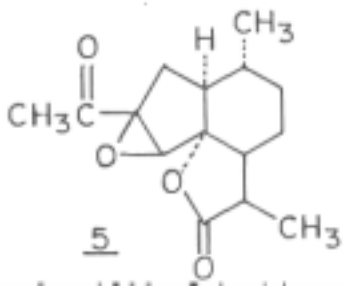
3

Treatment of QHS with 10% sulfuric acid in acetic acid at room temperature for 1 hr gave 4 a decalone with a γ -lactone ring fused cis to it. Its synthesis from (R)-(+)citronellal is reported.[17]



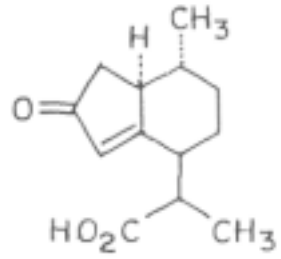
4

QHS on treatment with potassium carbonate in methanol at room temperature gave 5[18] and 6[19].

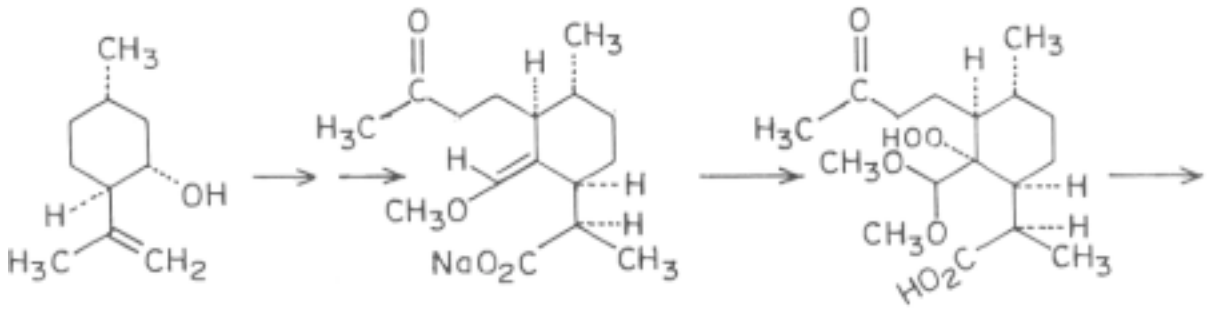


5

In 1983 Schmidt and Hofheinz[20] reported total synthesis of QHS starting from (-)-isopulegol 7. The key step is the irradiation of 8 with singlet oxygen at -78°C to give hydroperoxide intermediate 9. Treatment of 9 with formic acid in methylene chloride for 24 hrs at 0°C gave 30% QHS.



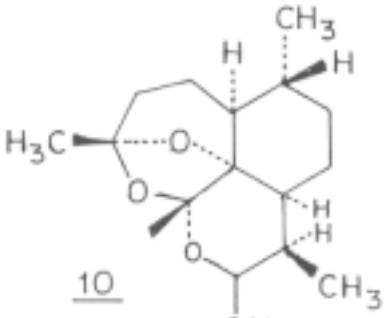
6


CH3
OH
H
H3C
CH2
O
C
H3C
H
CH3
H
CH3O
H
H
NaO2C
CH3
O
C
H3C
H
CH3
HOO
CH3O
H
CH3O
H
HO2C
CH3

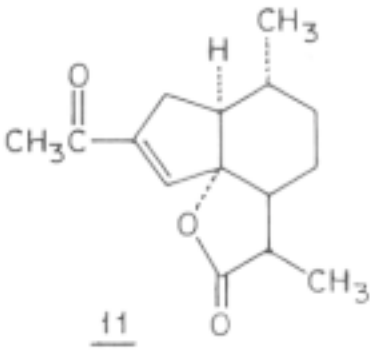
7 8 9

Metabolism of OHS:

Liver is the most probable site for the metabolism of QHS while kidney and lung are less active[24].Extraction with ethyl acetate of urine from patients given QHS orally yielded for metabolites - desoxy-artemisinin (2), dihydrodesoxyartemisinin (10), and crystal-7 (11), having no peroxide linkage, and 9,10-dihydroxyhydroartemisinin.[24,25,26]



10



11

Mechanism of Action:

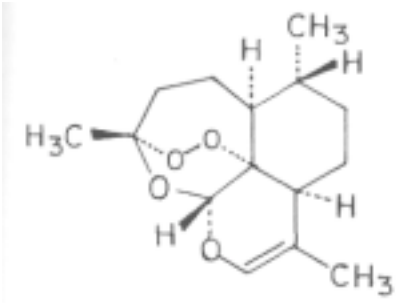
Mice infected with P. berghei were given QHS orally and blood samples were examined at regular intervals by electron microscopy. It was found that after 8 hrs, the trophozoites began to show morphologic changes such as swelling and spiral deformation of the membrane of the food vacuole. After 12 to 14 hr, it was observed that, most trophozaites showed whirls of the food vacuale and swelling of the outer mitochondrial and nuclear membranes. After 20 to 24 hr, the trophozoites showed extesnive degeneration of their inner structure[15,22].

The minimum concentration of QHS required to effect changes on the prarasite in vitro is $10^{-7'}$ M. QHS inhibits about 50% chloroquine-induced pigment clumping, suggesting a difference in mode and site of the action of the two drugs.[27,28] In mice infected with P. berghei, p-aminobenzoic acid (PABA) did not suppress the antimalarial activity of QHS, suggesting that QHS does not interfere with the folic acid metabolism of the parasites.[5,27]

Tremendous studies showed that activity of QMS is due to the presence of peroxy group. Other sesquiterpenes isolated from A. annua which lack peroxy group are inactive[29].

QHS on borohydride reduction gives DHQHS (3), retaining the peroxide function and is more potent than QMS[30].

Dehydrogenation of DHQHS (3) yielded two olefinic compounds, 12 and the DHQHS ether 13, formed on addition of DHQHS to 12,[31] Former compound 12 is inactive while 13 is active.



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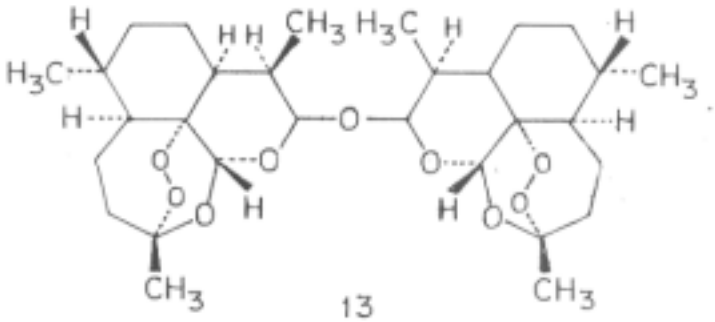
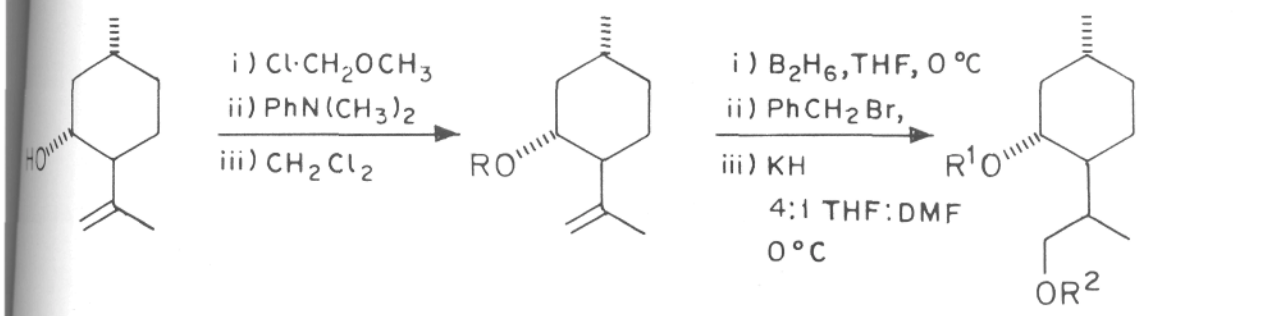


13

Three types of derivatives of DHQHS have been prepared and the activities in the order of QHS <ethers (3, R=alkyl) < esters [3, R=(C=O)-alkyl or aryl] < carbonates [3, R=C(=O)O-alkyl or aryl].[30] The ethers which are more oil soluble than QHS, are made by heating DHQHS with an alcohol in the presence of borontrifluoride etherate. Amongst 32 ethers prepared so far, the methyl ether (β -epimer), called artemther (3, R=CH_3) is more active but at the same time more toxic than QHS[32].

DHQHS can be esterified with an acid halide[31]or an acid anhydride in the presence of pyridine[33] or 4-dimethylaminopyridine[30,34]. Esters are in the α-epimeic form and are more active than QHS

SCHEME – 1



14

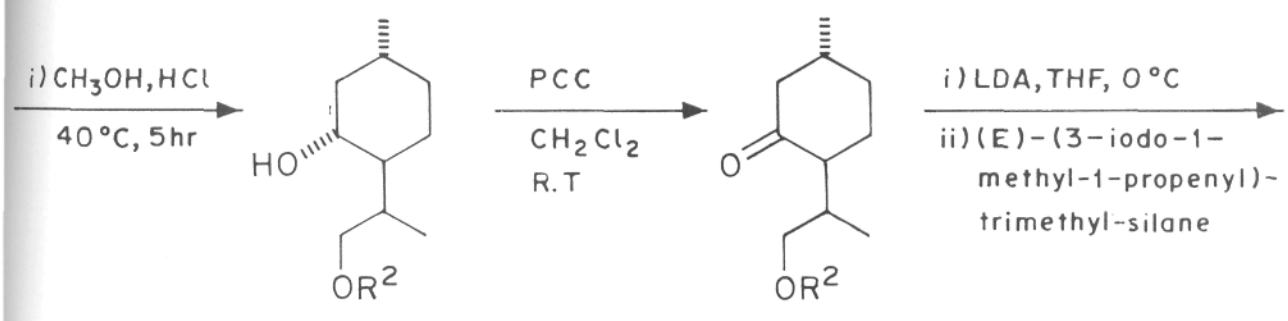
R = CH_2OCH_3

15

$R^1 = CH_2OCH_3$

$R^2 = CH_2Ph$

16



$R^2 = CH_2Ph$

17

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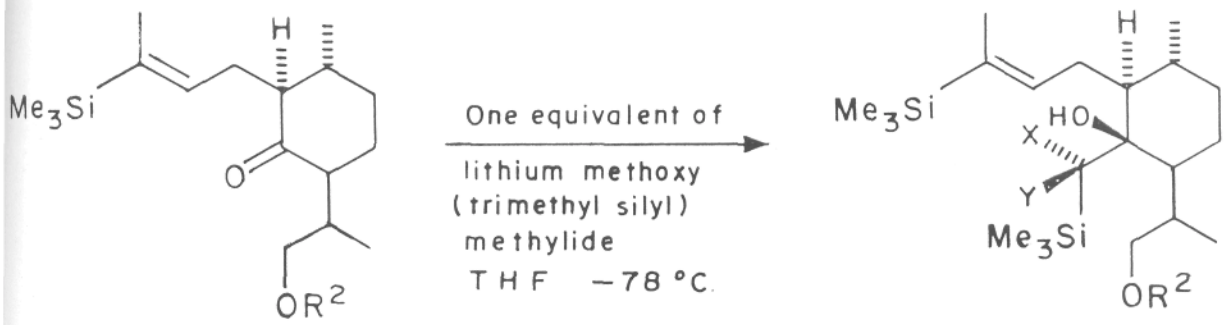

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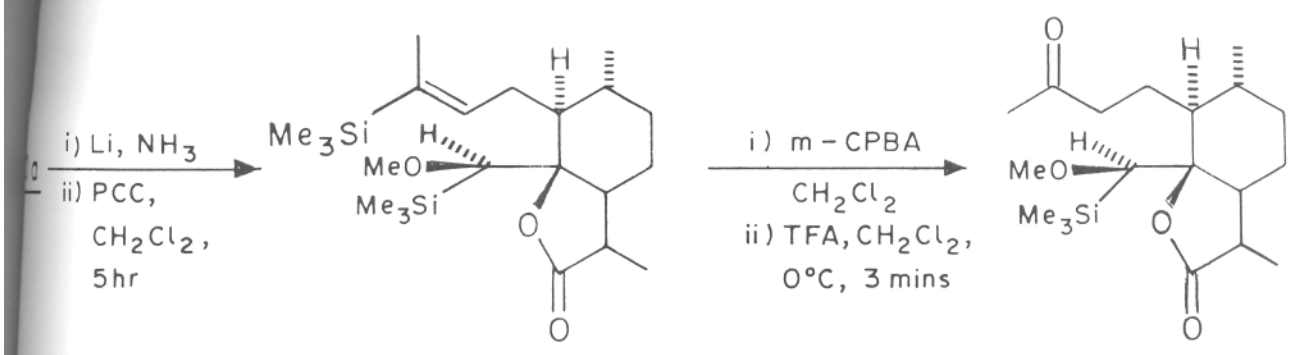
20a X = H, Y = OMe

20b X = OMe, Y = H

SCHEME – 1 (contd.)



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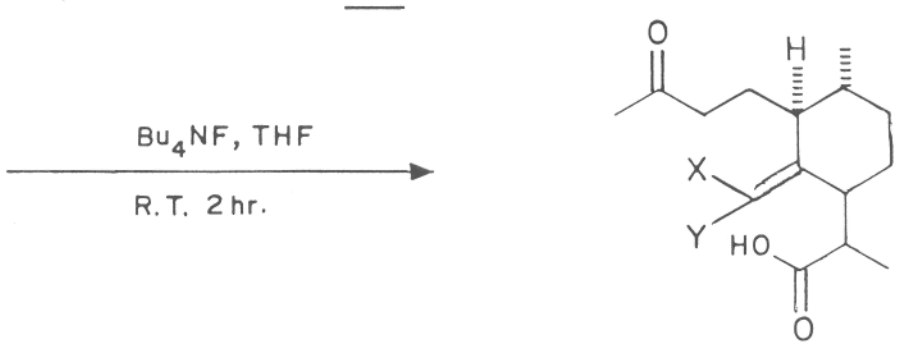
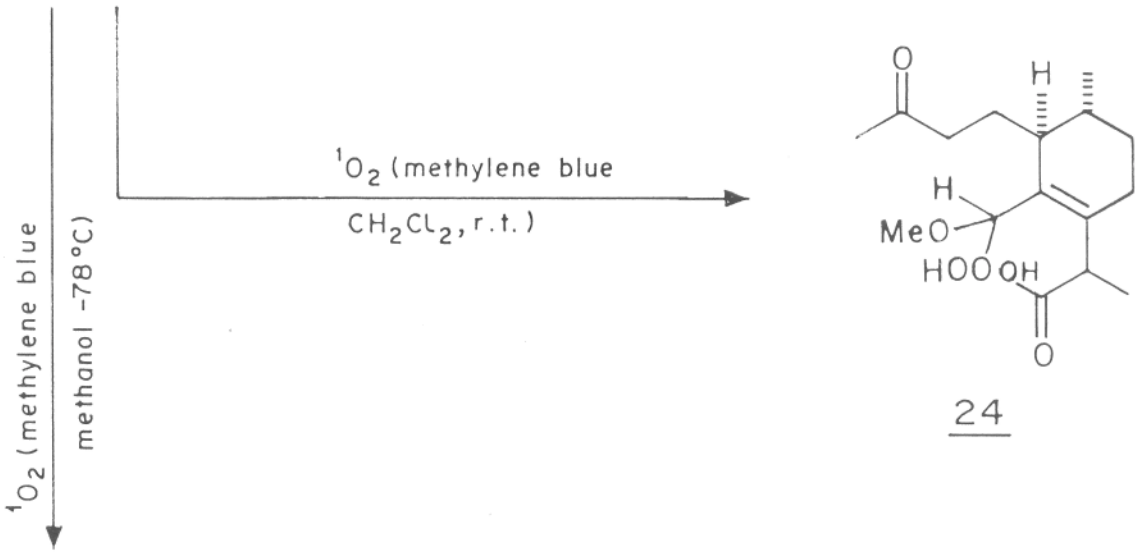
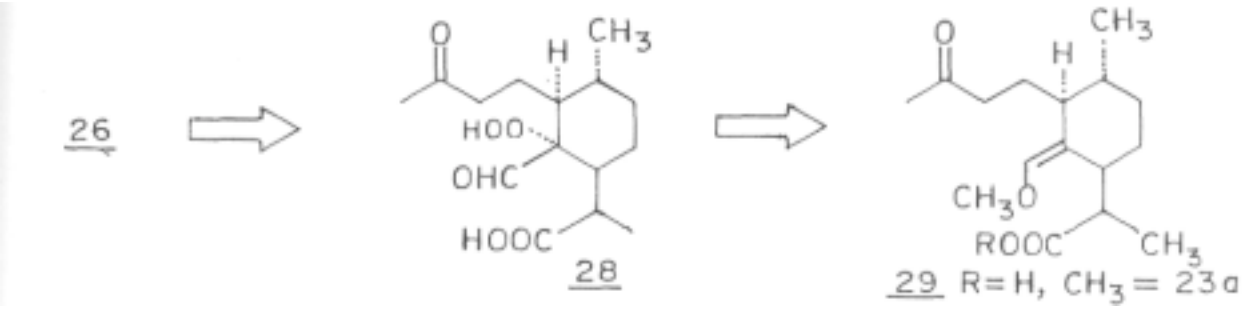


23a X = H, Y = OMe
23b X = OMe, Y = H



25 (MAJOR PRODUCT) QINGHAOSU 26

As the arteannuin molecule can be visualised as ketal-acetal-iactone system formed from the attack on the hydroperoxy group in the molecule (28), the enol methyl ether compound (29) might be used as a key intermediate for total synthesis (Scheme-2).

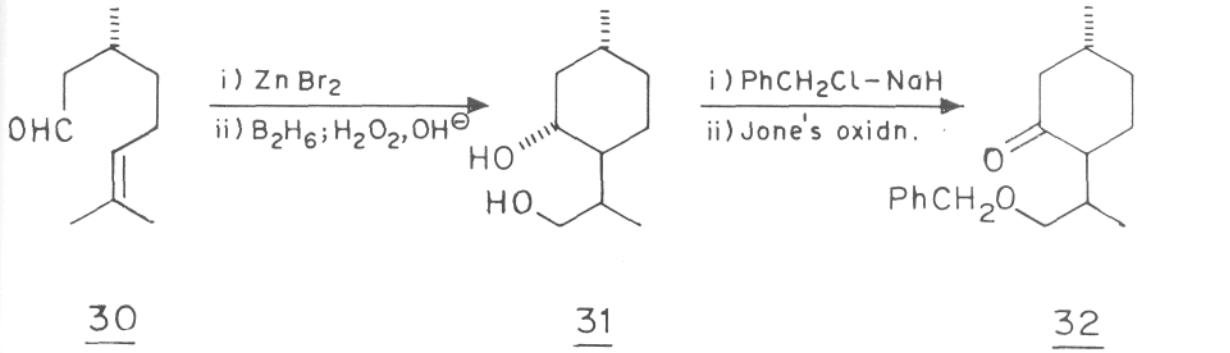


The conversion of (29) to (28) can be achieved through the hydro-peroxidation on the C_6, by photooxidation. The compound (29) was

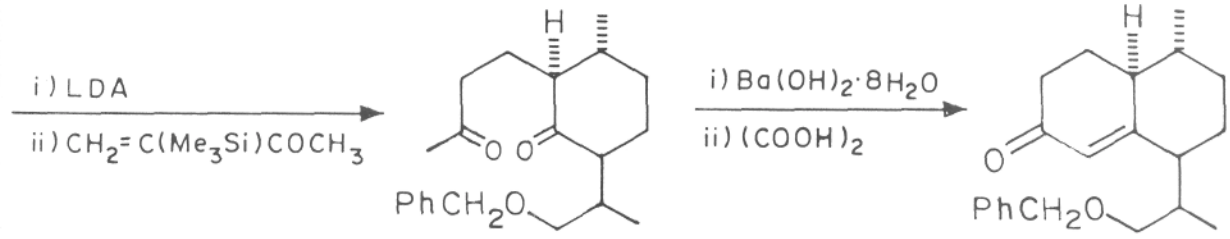
obtained from R(+)-citronellal (30) through the reaction sequence outlined in Scheme-3.

From 30 dihydroxy compound (31) was obtained, which on selective benzylation and oxidation gave the ketone (32). The 1,5-diketone (33) was obtained through kinetic deprotonation of 32 and reaction of the resulting enolate with silylated vinyl ketone, with simultaneous cleavage of trimethyl silyl group. Cyclisation of 33 with $Ba(OH)_2$ /2.5% ($COOH_2$) furnished mainly α,β-unsaturated ketone (34) which was purified through crystallisation. Reduction and oxidation of 34 afforded a ketone (35). This ketone 35 on treatment with MeMgl and dehydration gave a (1:1) mixture of (36) and its Δ^3-isomer, from which pure (36) was separated

SCHEME – 3



30 31 32



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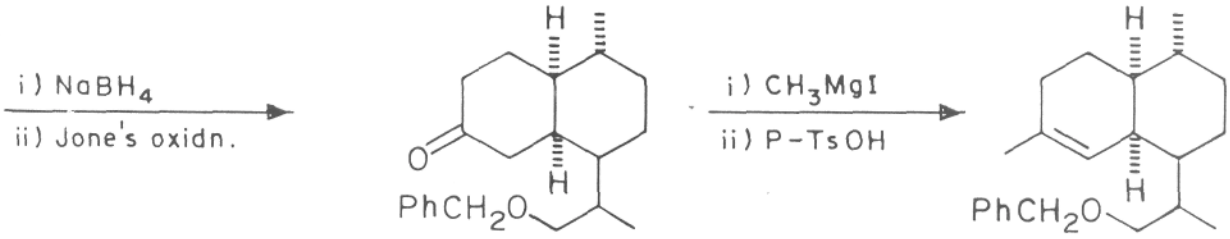

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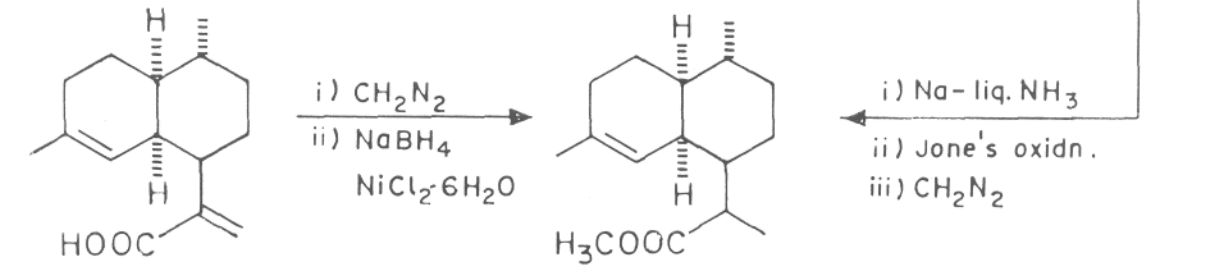

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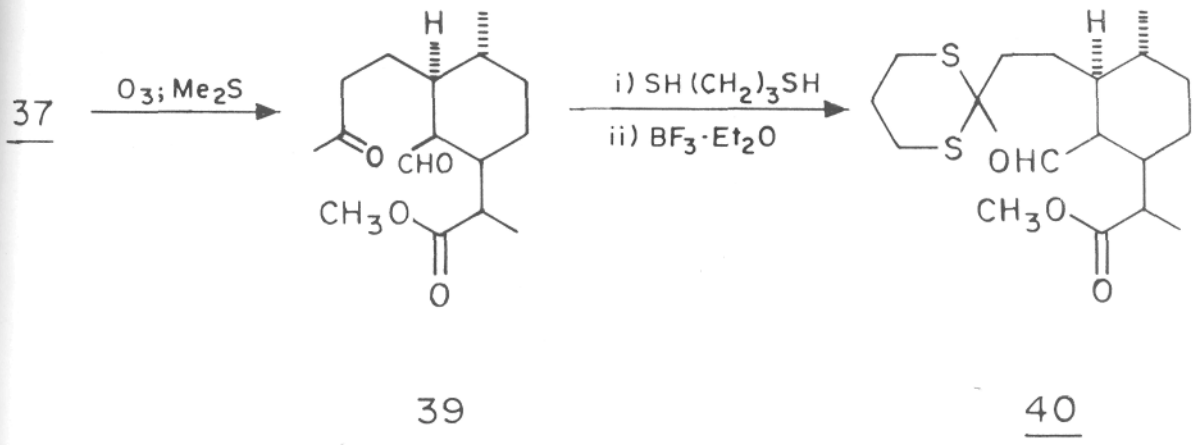
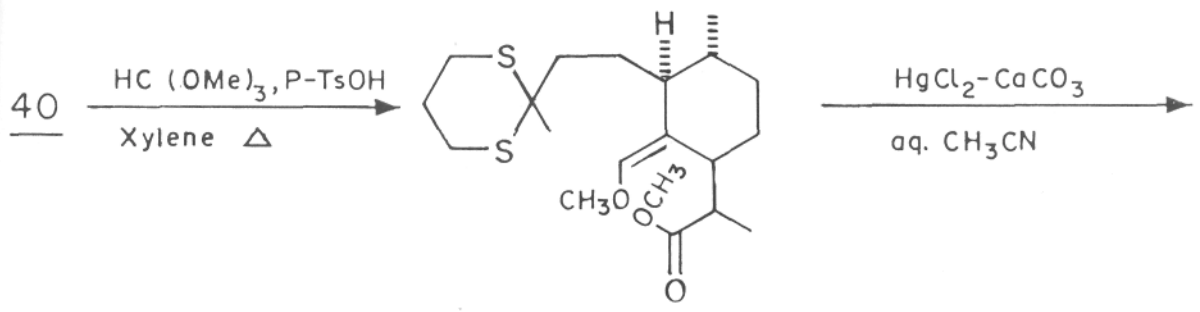
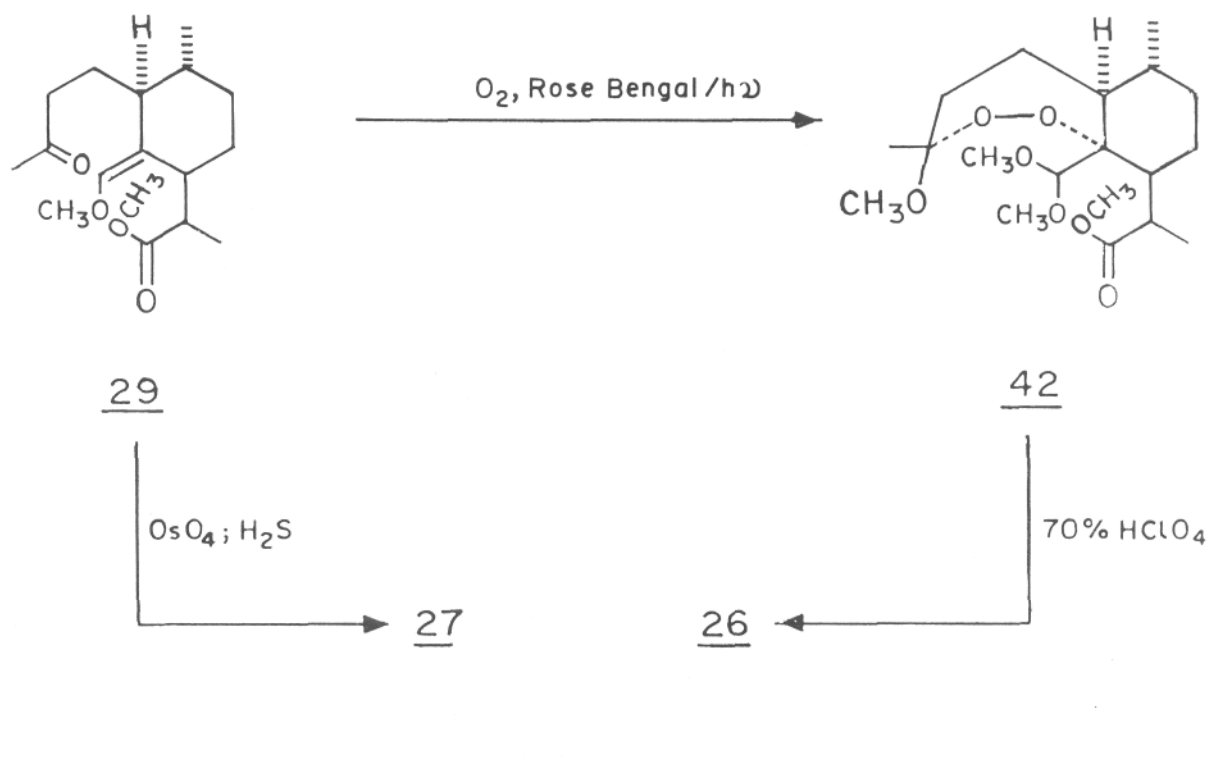
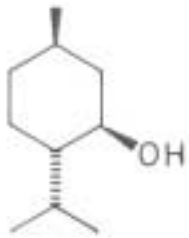
SCHEME-3 (contd.)









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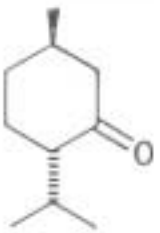
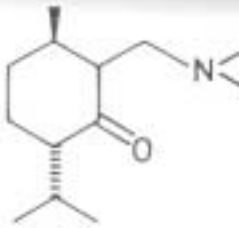
(O)



52

$(Me)_2NH_2^{\oplus}Cl^{\ominus}$

$(HCHO)_n / H^{\oplus}$



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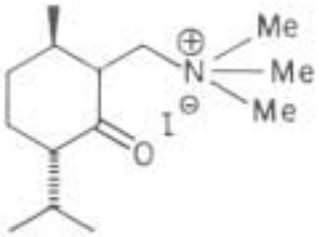
MeI



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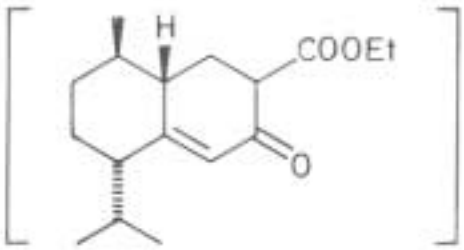
EAA

NaOEt



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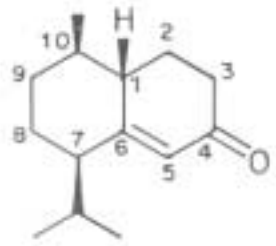

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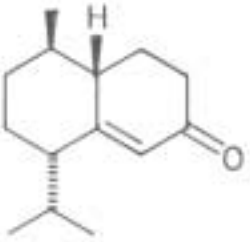

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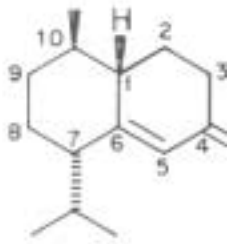

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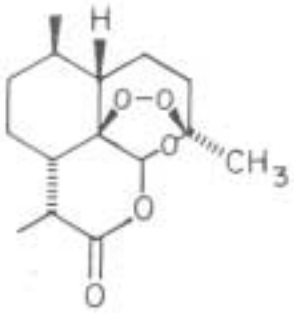

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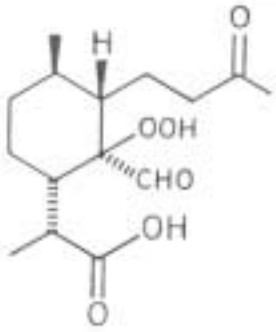

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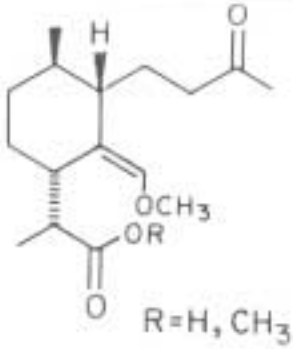

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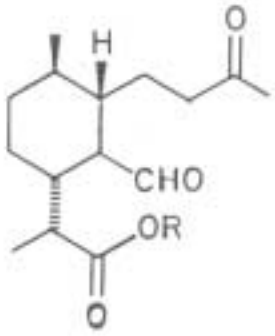

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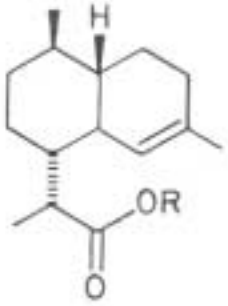

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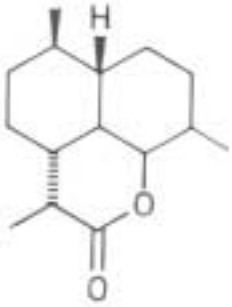

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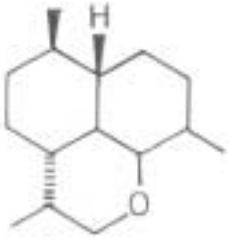

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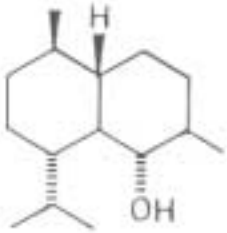

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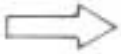

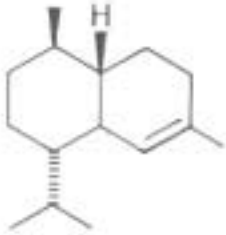

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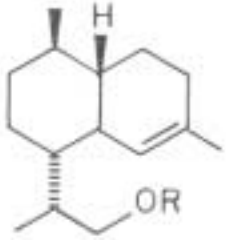
RETROSYNTHETIC SCHEME – 5



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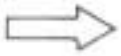

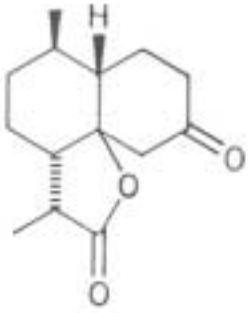

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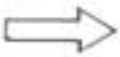

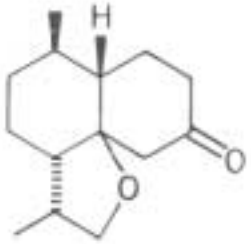

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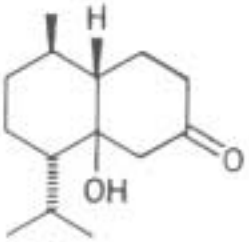

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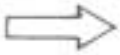

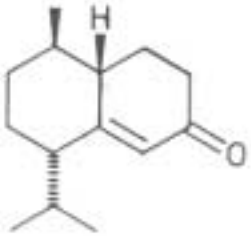

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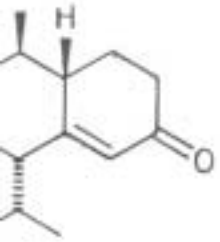

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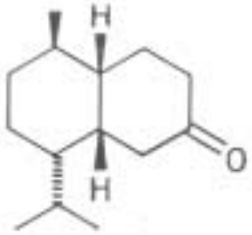

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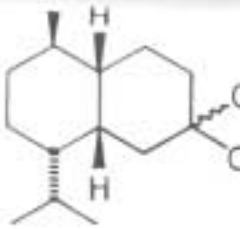

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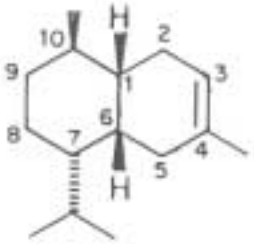

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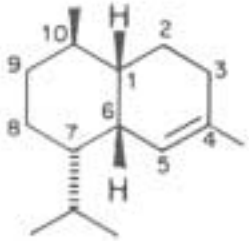

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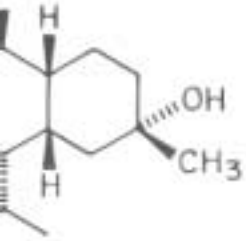
SCHEME – 7



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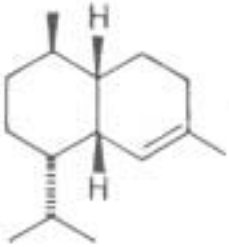

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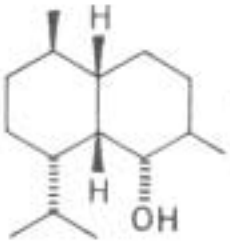

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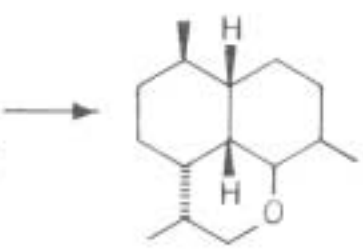

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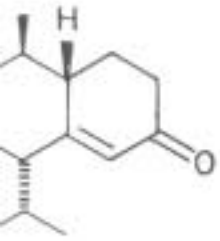

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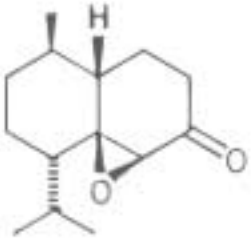
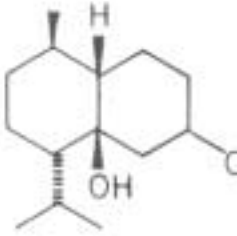
H_2O_2(30%)
6N NaOH



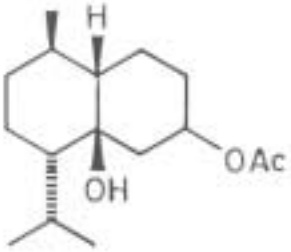
62

LAH
Et_2O



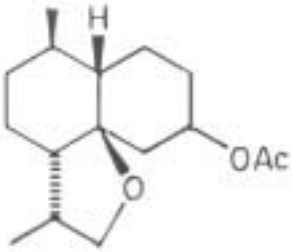
63

Ac_2O
Pyridine



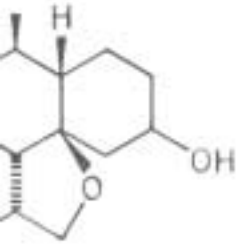
64

LTA / I_2



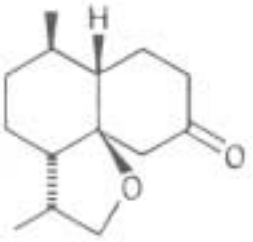
65

KOH / EtOH
H_2O



66

PCC/CH_2Cl_2



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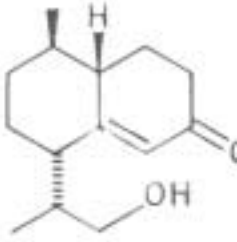
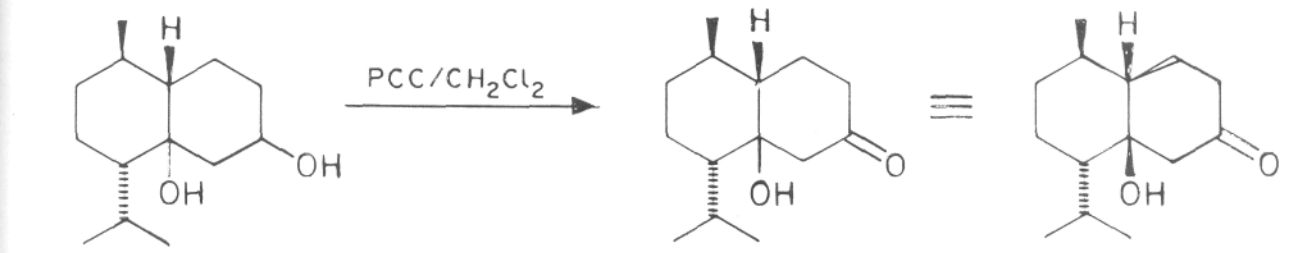
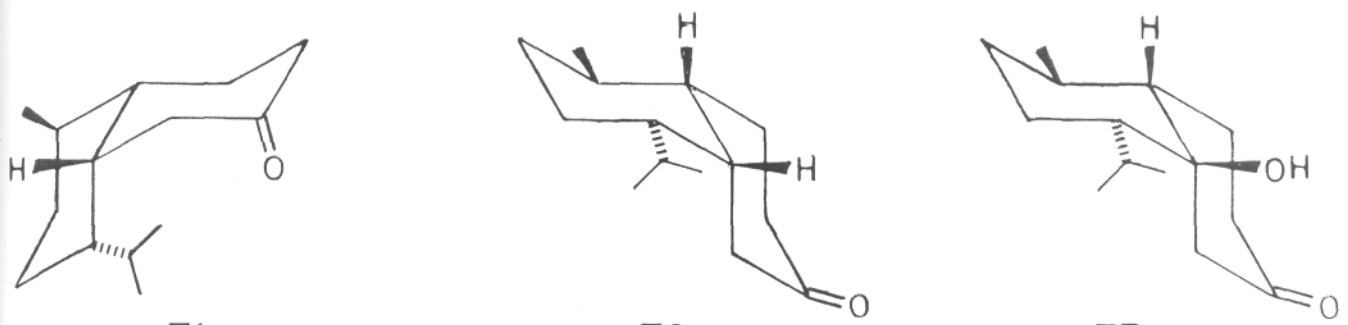


68

SCHEME-9



63 69 70

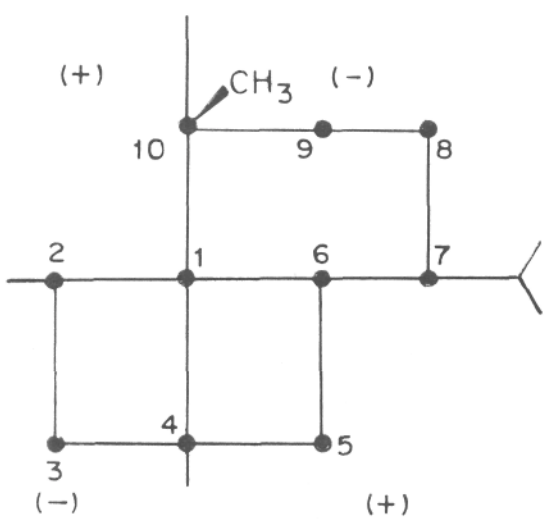


71 72 73

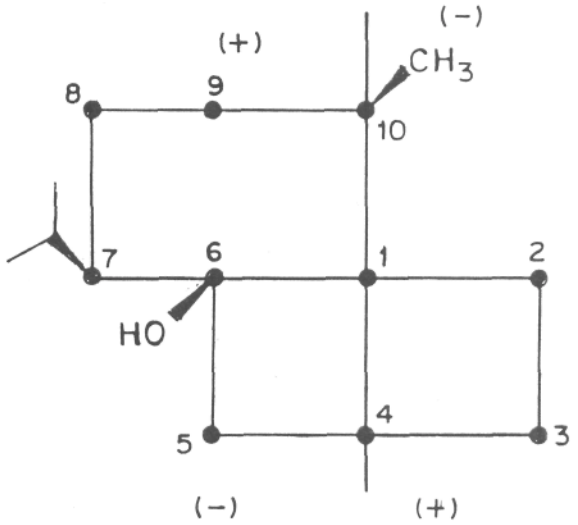
CIS-STEROIDAL (-ve CD)

CIS-NONSTEROIDAL (+ve CD)

CIS-NONSTEROIDAL (+ve CD)



OCTANT DIAGRAM FOR CIS-STEROIDAL DECALONE 71 (-ve CD)



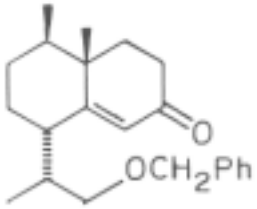
OCTANT DIAGRAM FOR CIS-NONSTEROIDAL DECALONE 73 (+ve CD)

and developed strongly in iodine chamber , was eluted with ethyl acetate The most polar spot showed IR (liquid film) bands at 3450 cm^{-1} assignable to primary hydroxyl group and 1681 cm assignable to α,β-unsaturated carbonyl stretching; but no bands at 1720 and 1770 cm^{-1} . Thus from IR spectrum it can be seen that this is not the expected lactone. PMR ($CDC1_3$) displayed signals at δ:0.88, 1.03 (2ds, J = 6Hz, 6H, 2XCH-CH_3), 1.66 (s, -CH_2-OH_, exchangeable with D_2O), 2.33 (m, 1H, C_{11}-H), 3.53 (d, J = 4Hz, 2H, -CH_2-OH), 5.88 (bs, 1H, $W_{1/2}$ = 4Hz, vinyl proton

CJ. This was analysed for $C_{44}H_{22}O_2$ $^{MS:}$ m/e = 222 (M+); b.p- 220° (bath temp.)/l mm, $[\alpha]^{26}_D$ = -44.15°.

Thus spectral data indicates that this is some rearranged product having hydroxyl function and showing conjugated ketone. This agrees with the structure (68) and can be explained as discussed below.

The following compound was reported by Zhou-Wei Shan52 ' in his total

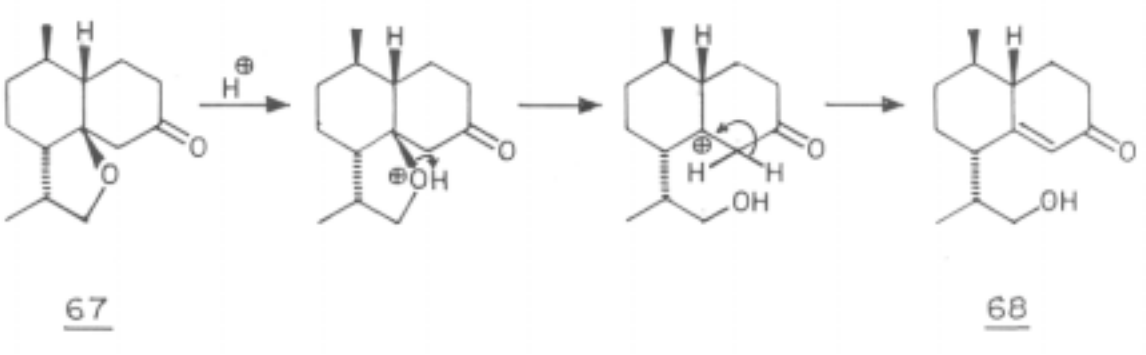


synthesis of qinghaosu.

The IR of this compound showed peaks at 1670, 1605 (α,β-unsaturated ketone), PMR displayed peaks at δ: 1.00-1.10 (6H, m, 10-CH_3, 2'-CH_3), 3.33 (2H, d, J = 4Hz, I'-CH_2), 4.38 (2H, s, PhCH_2), 5.61 (1H, s, C_5-H), 7.20 (5H, s, C_6H_5).

Thus except the benzyl proton signals, IR and PMR signals are in full agreement with that of our compound (68). So spectral data proved that the most polar compound isolated in chromic acid oxidation

rection followed by chromatography is (68) (Scheme-8). The possible mechanism for the formation of (68) is given below:



Thus in mild acidic conditions β -keto ether gets opened and gave the conjugated keto alcohol (68) in 35% yield. So we thought that this striking result was because of alumina having pH-4. To prove this keto ether (67) was directly chromatographed over acidic alumina (Gr.I) and eluted slowly with pet. ether, benzene and ethyl acetate. Benzene gave unreacted keto ether (65) while ethyl acetate fractions furnished the same unsaturated conjugated keto-alcohol was obtained from chromic acid oxidation reaction. IR, PMR, mass and optical rotation are same as above.

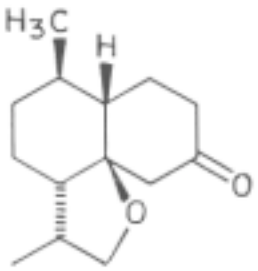
We have tried to make the benzyl derivative of compound (68) for the spectral comparison with that of reported by Zhou-Wet-Shan.[52] Benzylation was tried with K_2CO_3/$PhCH_2Cl$ in refluxing acetone, NaH/ $PhCH_2Br$ in dry DMF but unfortunately we could not get the required compound in our hand. In order to prove the primary hydroxyl group, the compound (68) was treated with dihydropyran in CH_2C1_2 and PTSA to get -O-THP derivative. This was purified by column chromatography over basic alumina using benzene as eluent. IR (liquid film) showed

bands at 1680 cm (αβ.-unsaturated ketone), 1620 cm^{-1} (>C = C<) while its PMR ($CDCl_3$) spectrum displayed signals at δ : 0.82,1.01, (2ds, J = 6Hz,6H,2XCH-CH_3,2.29 (bs, 1H, C_{11}-H), 3-4 (m, 10H),

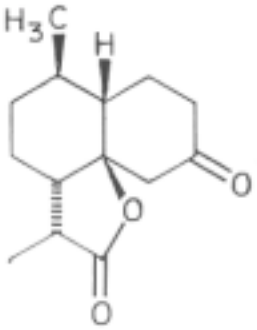
4.36 (bs, lH,),5.82 (s,1H, vinyl proton at C_5).

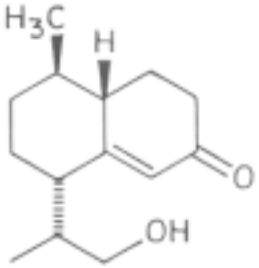
The reaction sequences. This is bourne out by comparison of the isopropyl methyl signals of solid conjugated ketone (50) at δ:O.9 and 0.99 and equilibrated conjugated ketone of (50) having β-configuration at C-7 showing isopropyl methyl signals atδ:O.77 and 0.98 and comparison of the signals of C_{11}-CH_2OH of (68) with that of (34) (C_{11}-CH_2OBz atδ:3.33).

Following are some important intermediates from which the crucial intermediate (37) or (39) can be obtained easily and which in turn can be converted to the total synthesis of QHS (26).



67





68

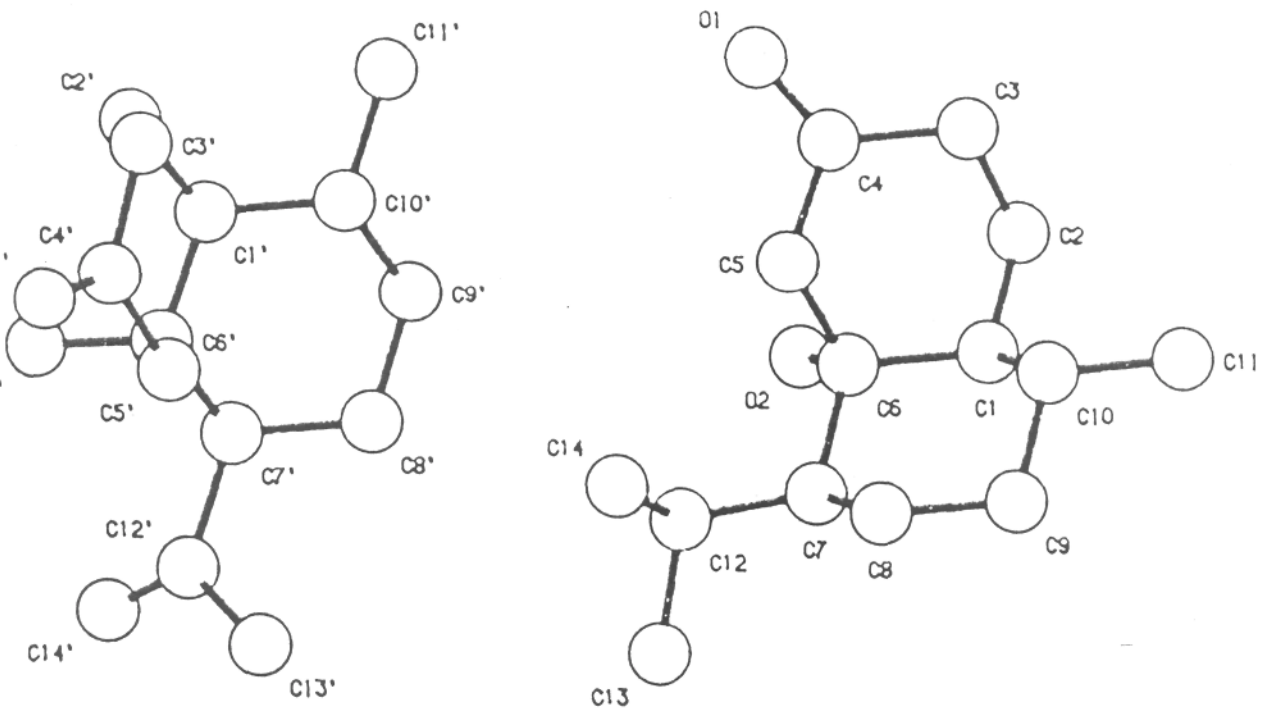
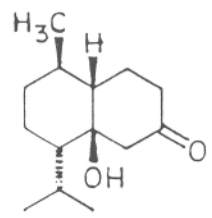


FIG. 3.13 a. X-RAY OF KETO-ALCOHOL 69 ≡ 70



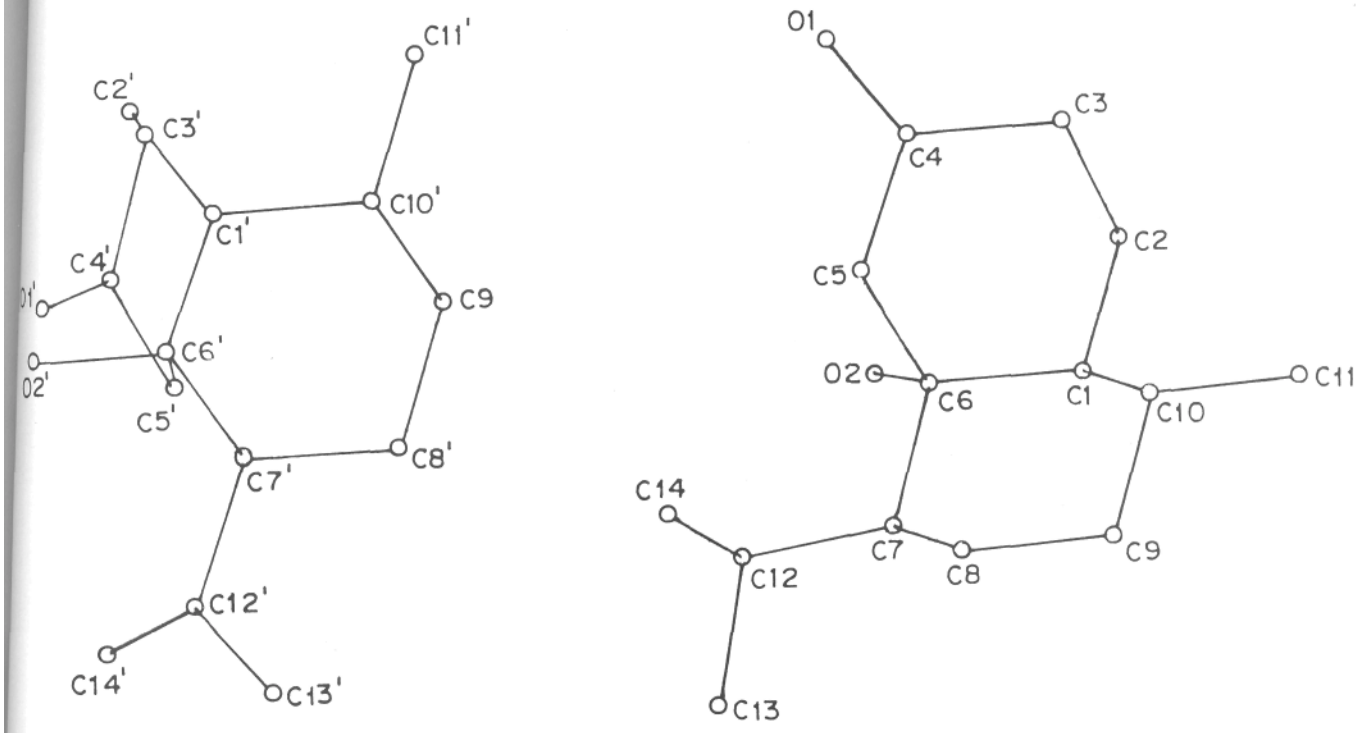
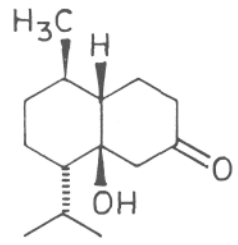


FIG.3.13b. X-RAY OF KETO-ALCOHOL 69 ≡ 70

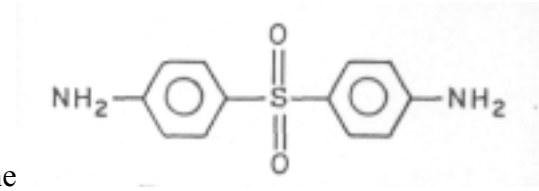


sufficiently long to allow the patients defences to eliminate them and should be free from undesirable side effects.

The older drugs used for tuberculosis were reviewed by Long.[3] Rich and Follis observed that large doses of sulphanilamide are effective

against tuberculosis in rabbit. Rist et al.[5] showed that 4,4'-diamino-diphenyl sulphone (DDS) was better than sulphonamides. DDS and its derivatives were also tested clinically but were too toxic.

(DOS or Dapsone)



The sulphones are at present the most effective drugs known for the treatment of leprosy and DDS may be alternative drug in tuberculosis.

Streptomycin discovered by Waksman and his colleagues[6], made a major advance in the chemotherapy of tuberculosis, since the drug is useful in a variety of tuberculosis conditions, including the miliary and meningeal types but at the same time producing serious toxic effects like chills, fever, nausea, vomitting and renal damage. Dihydrostrepto-mycin which at first appeared to be more satisfactory, ultimately proved to be even more toxic.

Bernheim[7] noted that salicylates and benzoates increase the oxygen

uptake of tubercle bacillus. This was confirmed by Lehmann[8] and prepared a series of compounds related to benzole acid and salicylic acid, with a view to obtain compounds which could compete with tubercle bacilli for cell receptors and by doing so, inhibit the growth of organism.

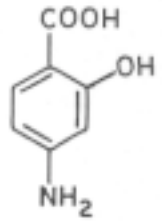
Amongst them para-amino salicylic acid commonly known as PAS was found to be more potent tuberculostat. It is widely used because of

its low toxicity and ability to retard the emergence of resistant strains

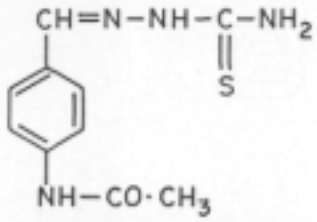
when given in combination with streptomycin[9,10] Disadvantage in

using PAS is that it is rapidly absorbed and excreted, so that to maintain adequate blood levels, it should be given in large doses, at frequent intervals.

Domagk[11] showed that thiosemicarbazones were active in experimental tuberculosis, out of which thioacetazone (T.B.I) was extensively investigated in Germany and U.S. but was found to be relatively toxic.

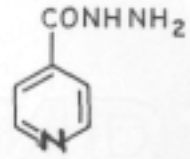


(PAS)



(THIOACETAZONE)

Lett and co-workers[12] , Fox from Hoffman La-Roche[13] and Domagk[11] in 1952 had published isonicotinic acid hydrazide (INH) simultaneously and independently, which have made spectacular advance in chemotherapy of tuberculosis. This was not only much more potent but also relatively



(INH or Isoniazide)

free from serious side effects.

Initially INH was used alone without combination with another drug but it soon became obvious that this was undesirable because of the development of resistant organism, so that at least two drugs

CH_3-, CH_3-, CH_3.,

I I I

CH_3-$(CH_2)_3$CH-$(CH_2)_5$-CH-$(CH_2)_9$-CH-CH_2-COOH

(Phthioic acid)

C_8H_{17}

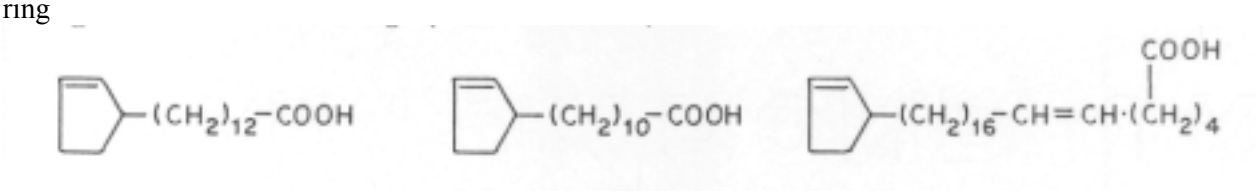
I

H-.C-C-CH_2--COOH I

C_8H_{17} (β-β-di-n-octyl-butyric acid)

Chaulmoogric acid, hydnocarpic acid and gorlic acid are presented in major quantities in chaulmoogra oil.[47] These acids have cyclopentene

ring



situated at the omega position in fatty acid chain.

(Chauimoogric acid) (Hydnocarpic acid) (Gorlic acid)

Physiological activity of these acids was supposed to be because of ring structure in the omega position. Hence Adams and co-workers introduced cyclic structure like cyclopentane, cyclohexane and cyclo-heptane in the omega position of various fatty acids and tested them for antibacterial activity. Fatty acids with cyclohexane ring exhibited maximum activity Adams and coworkers[48] have studied numbers of dialkylated

acids of the type R-CH(R')-COOH where R = straight chain or cyclic group and R' = straight chain alkyl group with two or four carbon atoms and they have observed that for the maximum activity, the branched

chain acids should have a totai number of 12-19 carbon atoms and the carboxylic group should be near the centre of the molecule. Asano and Yamakawa[49] synthesised the following type of compounds:

$R_2CH.COOH$, R_2CHCH_2COOH and $R_2CH(CH_2)_2.COOH$ in which R varies from hexyl to octyl groups. They found that acids containing total carbon atoms of $C_{16}C_{17}$ were highly effective irrespective of the nature of the side chain.

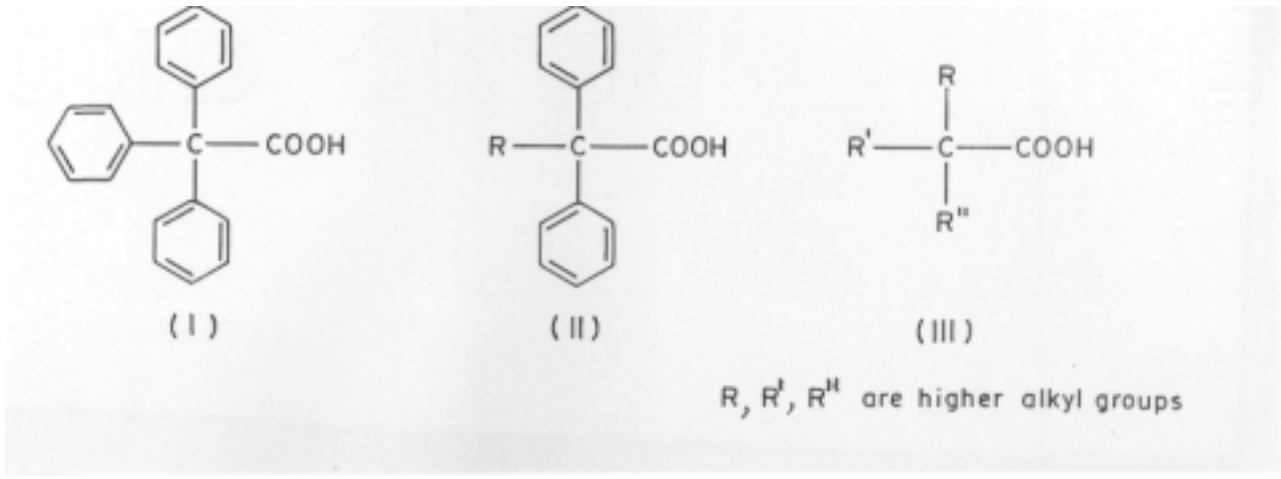
Rocellic acid,[50] (α-methyl-α'-n-dodecyl succinic acid) isolated from Lichen was found to inhibit the growth of mycobacterium tuberculosis completely in vitro at the dilution of about 1/50,0000.

$C_{12}H_{25}$-CH-COOH

(Rocellic acid) H_3C -CH- COOH

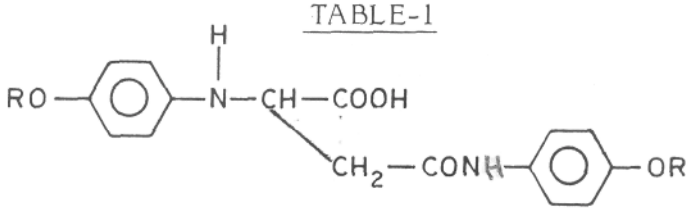
Barry and Twomey[51] showed that alkyl substituted succinic acids, their sodium salts, esters, amides and anilides having 17-19 carbon atom exhibit maximum activity. Similarly Barry[52] observed maximum activity for monoalkylated succinic acids having 13-15 carbon atoms.

Prigg, Prigg and Kicksh[53] have shown that the introduction of phenyl nucleus into the aliphatic acids invariably increased the antibacterial property of the acids. They prepared the following three types of the acids.



(I) (II) (III)

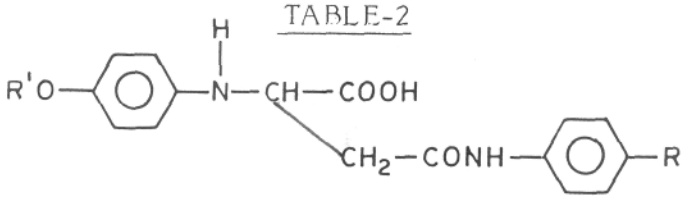
TABLE-1



Symmetrically substituted arylamino succinmonoanilides

Serial No.	R	Minimum inhibitory concentration (meg/mi)
1	C_2H_5	0.2
2	n-C_4H_9	0.2
3	(iso)C_5H_{11}	2.0
4	C_6H_5	0.04
5	P-ClC_6H_4	0.3
6	P-$CH_3C_6H_4$	0.3

TABLE-2



Differently substituted arylamino succinmonoanilides

Serial No.	R'	R	Minimum inhibitory concentration (meg/mi)
J	C_2H_5	OCH_3	0.2
8	C_2H_5	Cl	0.5
9	n-C_4H_9	H	0.1
10	n-C_4,H_9	OCH_3	0.1
11	n-C_4H_9	Cl	0.04
12	n-C_4H_9	CH_3	0.1
13	iso-C_5-H_{11}	H	2.0
14	iso-C_5H_{11} .	Cl	10.0
15	C_6H_5	H	0.04
16	C_6H_5	OCH_3	0.04
17	C_6H_5	Cl	0.04
18	C_6H_5	CH_3	0.04
19	p-CH_3-C_6H_4	H	1.0
20	P-CH_3-C_6H_4	OCH_3	5.0
21	p-Cl-C_6H_4	H	0.5
22	P-C1-C_6H_4	OCH_3	0.5
23	p-Cl-C_6H_4	Cl	0.04

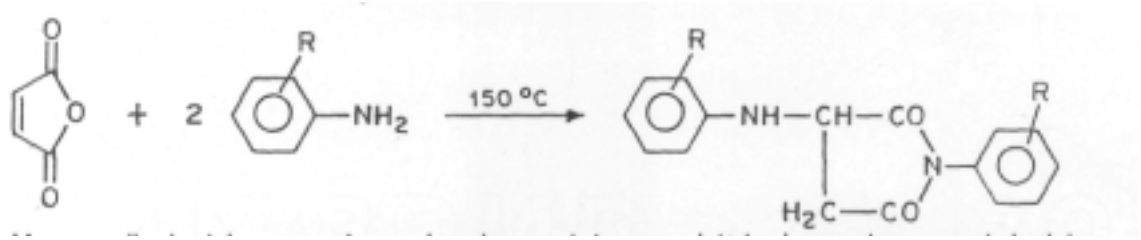
24	p-Cl-C_6H_4	CH_3	1.0
25	p-CH_3-C_6H_4	CH_3	1.0

PRESENT INVESTIGATION

As described in the introduction, preparation of N-aryJ aspartic acids and their corresponding β-monoamides (N-aryl asparagines), as possible antituberculosis compounds was of interest. Our aim was to search for new class of antituberculosis compounds.

A literture survey showed that only few N-aryl aspartic acids have been tested against Mycobascterium tuberculosis[40] and none of the N-aryl asparagines have been tested as antituberculosis compounds. Many of these compounds are unknown and are not reported in literature. Padsalgikar in Parle College, Bombay, prepared arylamino succini-mides, with the same substituents on both the nitrogen atoms, by heating a mixture of maleic anhydride and aniline at 140-60°C.

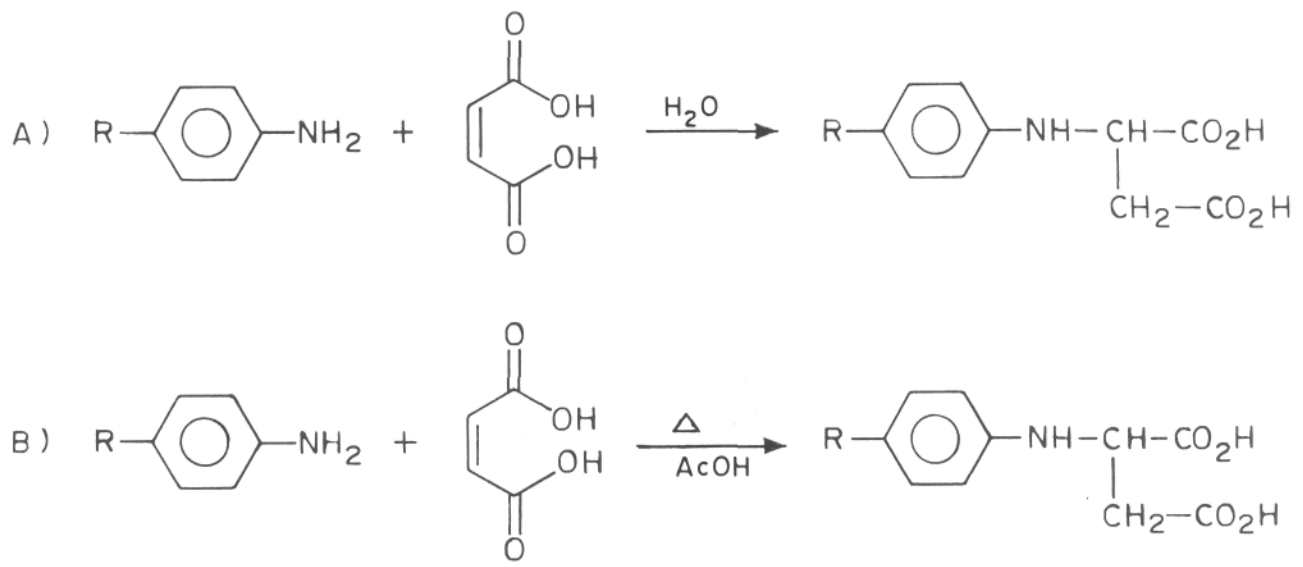
He



studied this reaction closely and he could isolate the succinimide even using 0.1 mole of aniline per mole of maleic anhydride. This indicates that the addition of aniline across the double bond of the maleimide first formed, is a fast reaction at 150°C. The symmetrically substituted succinimides so obtained on hydrolysis gave arylamino succin-monoanilides with the same substituents in both the phenyl rings.

Dabholkar[40] et al. have used these succinimides for the prepara-tion of N-aryl aspartic acids. The succinimides and its monoamides are further hydrolysed with the excess of alkali. Every time the liberated aniline was removed by extraction with ether and subsequent acidification.

SCHEME – 1



SCHEME – 2