CHAPTER-IV

STUDIES ON BIOMIMETIC MEDIUM-RING FORMATION

ABSTRACT

This chapter consists of two parts :

Part-A describes the preparation of 2(Z)-, and 2(E)-6,7-dihydrofarnesyl diethyl phosphates and their reaction with active alumina, as an attempted synthetic route to 10/11 membered rings.

Part-B describes the preparation of 2(E)-6,7-dihydroxy (protected by phenylboronic acid) farnesyl diethyl phosphate and its reaction with active alumina as an attempted synthetic route to 10/11 membered rings.

PART-A

PREPARATION AND HETEROLYSIS OF 2(Z)- AND 2(E)-6,7-DIHYDROFARNESYL DIETHYL PHOSPHATES

A. Introduction

The most fundamental and important biogenetic pathway in sesquiterpenoids is the cyclization of acyclic carbonium ions (eg. farnesyl cation) to form the monocyclic ions, with 10 or 11 membered rings[1]. It was observed in solvolytic reactions of farnesyl derivatives (eg. halides, phosphates, dinitrobenzoates, etc.) the formation of six membered rings are more facile and could not be obtained any detectable amounts of 10 or 11 membered rings. That alumina induced cyclization of allylic diethyl phosphate esters is a potential tool for the biogenetic-type synthesis of variety of terpene skeletons has amply been demonstrated in the chapter-II. In our earlier experiments of farnesyl diethyl phosphate esters (both 2(cis)- and 2(trans)-) with active alumina, we could not get any detectable amounts of 10 or 11 membered rings, though this mode is quite freqent for enzymic reactions occuring in nature[2]. It was observed that cyclic products from allylic diethyl phosphate esters result from the carbocations, generated by ionization of the C-O bond, thereby concommittant attack by double bonds leading to a new carbocation reactive species, which after proton loss, gives products. By considering our earlier investigations of alumina induced cyclizations of farnesyl diethyl phosphate esters (2(cis)- and 2(trans)-),

we thought that in the presence of 6,7-double bond the 10,11-double bond is not pacticipating in the ionization step of allylic phosphate ester, thereby leading to entropically more favourable six membered rings. Under these circumstances, it was thought to make farnesyl moiety, void of 6,7-double bond, in order to simulate the interaction between C_1 and C_{10}, thereby forming 10 or 11-membered rings. Thus, it arose the need to synthesise 2(cis)- and 2(trans)- 6,7-dihydro-farnesyl diethyl phosphates, with an expectation that these phosphate esters on active alumina would give allylic carbocation, followed by anchimeric assistance of 10,11-double bond, leading to the formation of 10 or 11-membered rings (Scheme-I).

In connection with the preparation of 2(cis)- and 2(trans)- dihydro-farnesyl diethyl phsphate esters, for the cyclization studies, we required the corresponding alcohols of the said stereochemistry with maximum purity possible. A survey of literature was therefore made for the methods already reported for the synthesis of these compounds. The information gathered is summarised below. The methods, finally chosen, and the reasons which prompted the choice of both these syntheses are also discussed.

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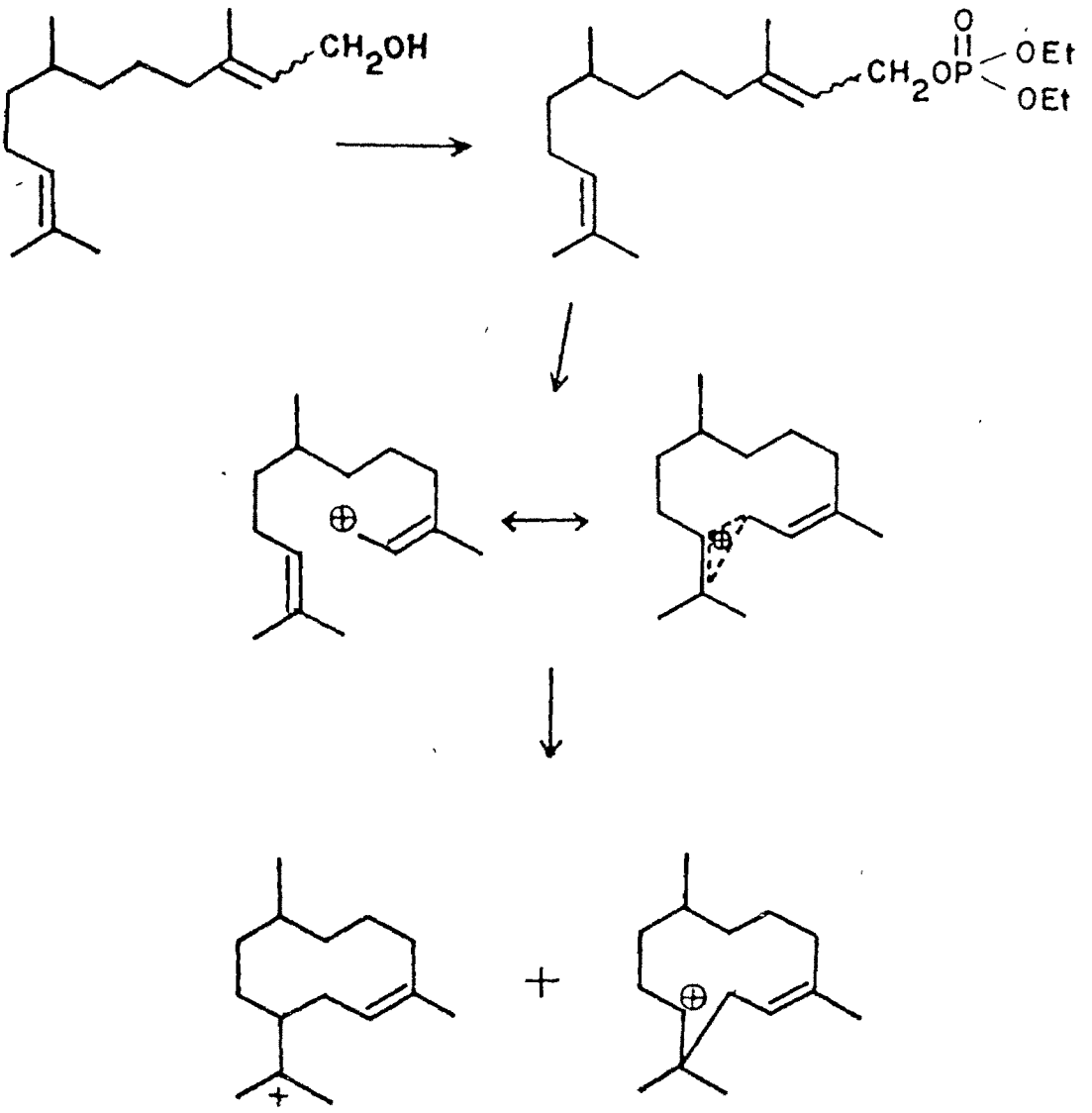


SCHEME – I

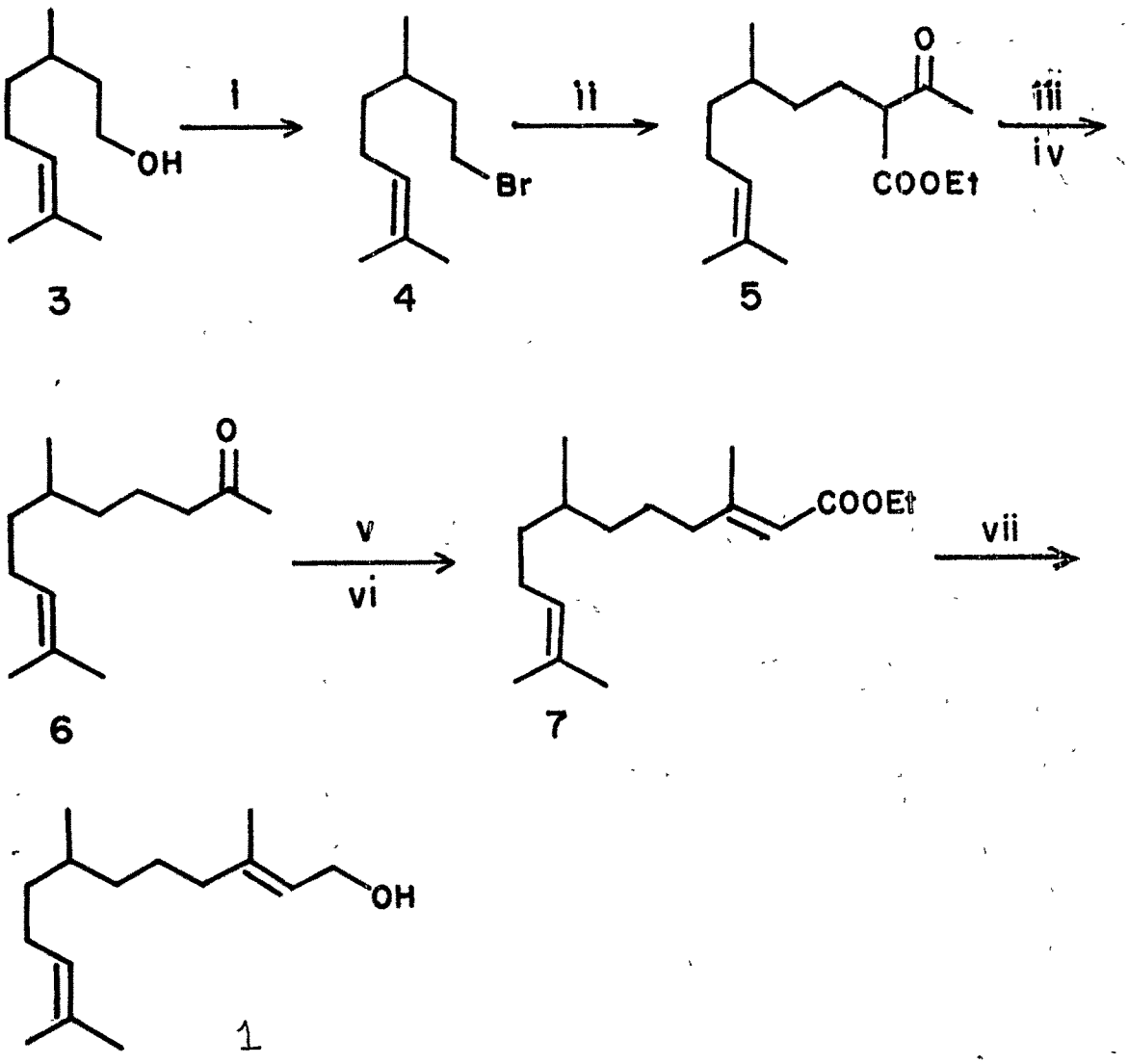
B. Synthesis of 2(cis)- and 2(trans)- 6,7-dihydro-farnesols (1)

(a) Known routes

The Known synthetic routes to 2(cis)- and 2(trans)-6,7-dihydro-farnesols are as follows :

(i) A synthesis of 6,7-dihydro-farnesols by partial hydrogenation ($N_2H_4.H_2O$; $CuSO_4$) of (E,E) and (Z,E) farnesols was reported by Bergstrom et al.[3] in 1967. Besides the required compound, DL-2,3-dihydro-6(E)-farnesol, other dihydro derivatives such as 10,11-dihydro-2(E), 6(E)-farnesol and 10,11-dihydro-2-(Z), 6(E)-farnesol are also present in the reaction product, making the purification difficult.

(ii) In 1965, Robert Azerad et al.[4] reported the synthesis of 6,7-dihydrofarnesol starting from citronellol by a sequence of reactions which involves bromination of alcohol (3), condensation of citronellyl bromide (4) with ethyl acetoacetate to afford (5). It was subjected to Wittig--Horner reaction with $(EtO)_2P(O)CH_2CO_2Et$ to afford a mixture of (cis)- and (trans)-α,β-unsaturated ethyl esters which were separated, followed by LAH reduction gives the desired alcohols. (Scheme-II)



(i) PBr_3/Py (ii) $CH_3-\overset{\overset{O}{\|}}{C}-CH_2-COOEt$ (iii) KOH/MeOH (iv) HCl (v) $(EtO)_2-\overset{\overset{O}{\|}}{P}-CH_2CO_2Et$/NaH (vi) E- and Z-separation (vii) LAH/ether

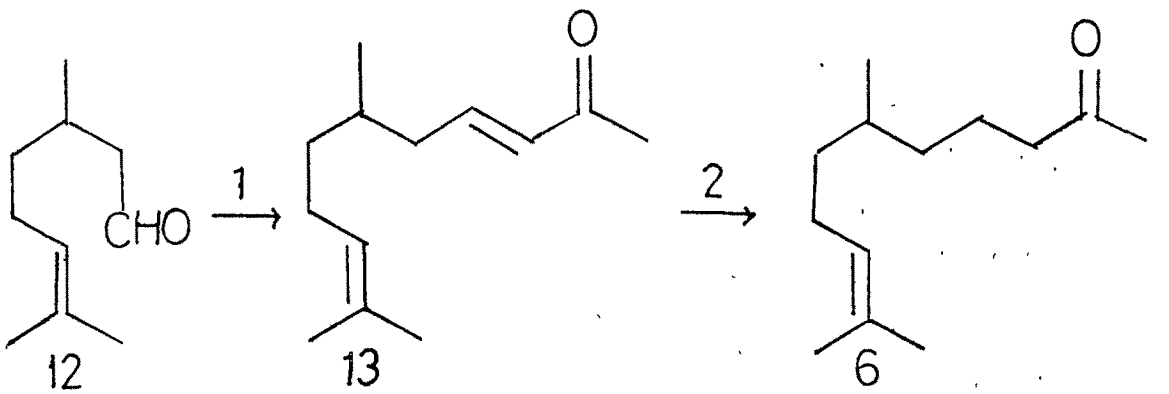
SCHEME-II

(iii) In an earlier study[5] from this laboratory for the synthesis of dihydro-farnesols, hydrogenation of farnesol over $Pd/CaCO_3$ (15 percent) in ethanol was investigated. But, the product was found to be a mixture of all the three dihydro derivatives (2,3; 6,7; 10,11-dihydro-farnesols).

(iv) Recently William N. Washburn and his group[6] have developed a method for the synthesis of (1) from 6 methyl hept-5en-2-one (8) by a sequence of reactions which are depicted in Scheme-III.

(b) The present approach

The starting compound chosen was 5,6-dihydro-geranyl acetone (6), which was obtained by, acetone condensation of citronellal[7] (12), followed by selective hydrogenation of α,β-unsaturated ketone (13) using 5 % $Rh-Al_2O_3$ as a catalyst in ethanol.

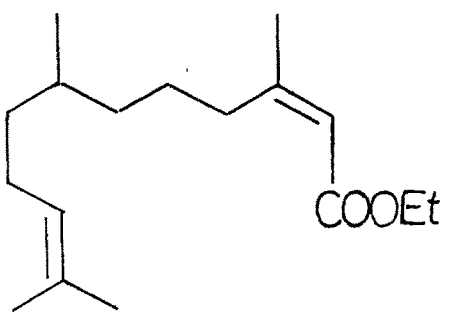


(1) $CH_3\overset{O}{\overset{\|}{C}}CH_3$, NaOH ; (2) $H_2/5\%\ Rh/Al_2O_3$.

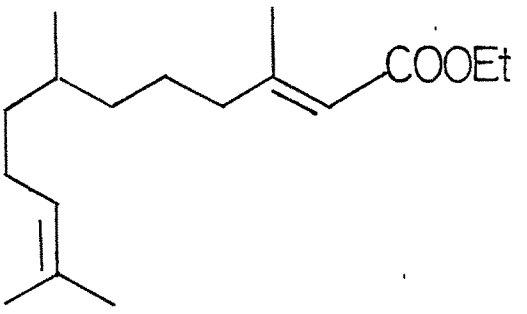
With this starting material (6) two different routes were attempted.

(i) The Wittig-Horner reaction route[4]:

The first step involves the Wittig-Horner reaction between 5,6-dihydro-geranyl acetone (6) and the ylide, generated from $(EtO)_2P(O)CH_2COOEt$ using sodium hydride as base. Dry dioxan was used as solvent and the reaction temperature was reported to be 100°C. In our hands, however, the reaction didn't proceed smoothly under the prescribed reaction conditions (temp. 100°C). We found that the reaction proceeds very smoothly at 50°C in THF solvent, giving almost quantitative yields of the α,β-unsaturated esters. Furthermore, the product ratio obtained was 41.28 percent of the (cis)-ester (7a) and 48.2 percent of the (trans)-ester (7b) and 10 percent of the unwanted isomers. Studies also showed that the product ratio obtained is sensitive to the reaction conditions used. The required Z- and E-esters [(7a) and (7b)] were separated by column chromatography (SiO_2-gel, grade IIB) and characterized by their PMR spectra.



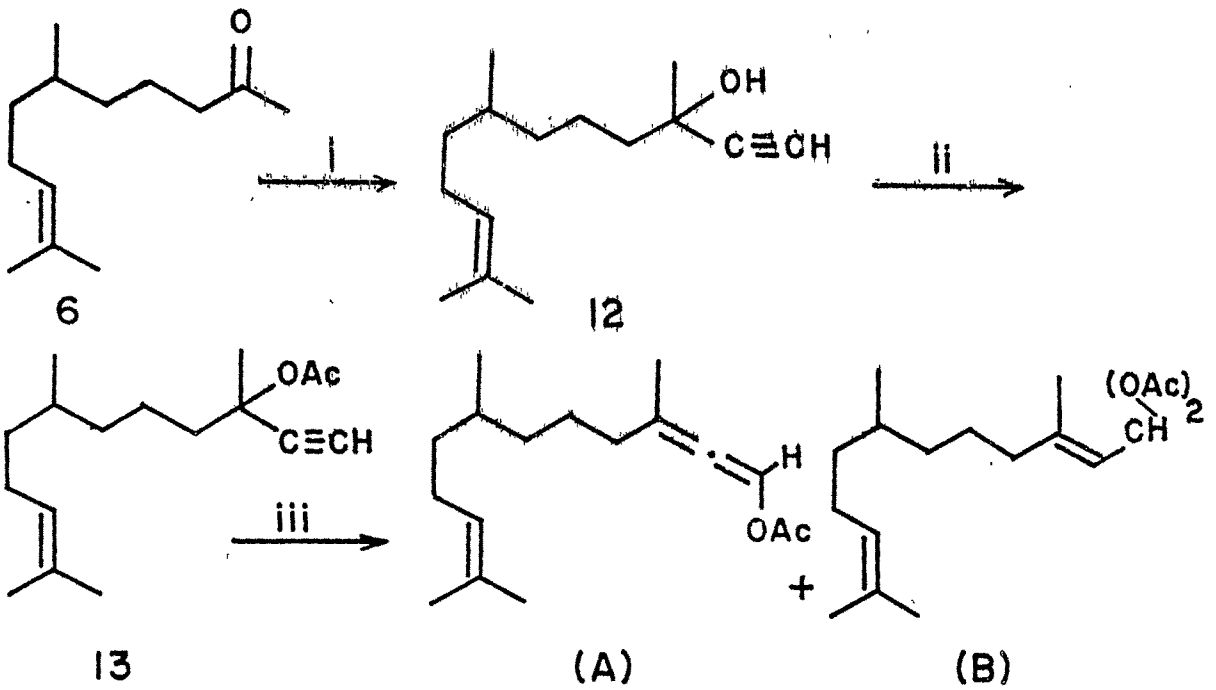
7a

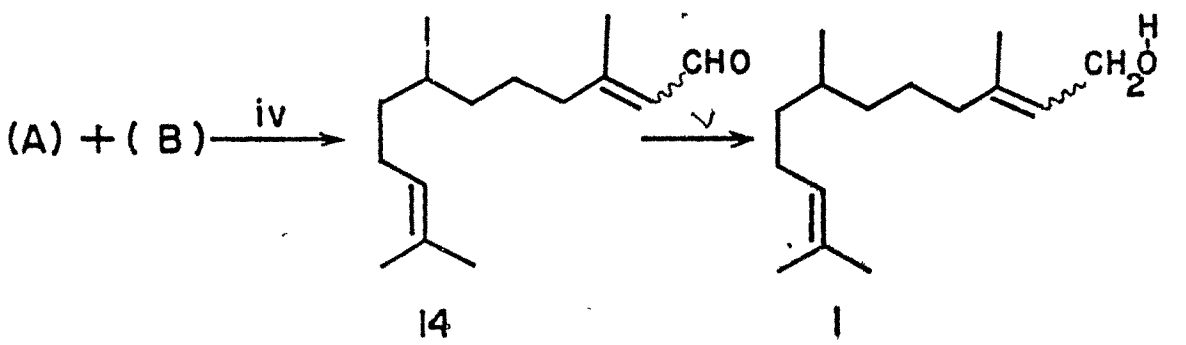


7b

The LAH reduction of the esters 7(a) and 7(b) was reported at room temperature and supposedly gave 95 percent yield of the alcohol (1) after a two hour reaction period. Our observation was that this reduction was not so facile, longer reaction times were necessary. There were also signs of the formation of a side-product which probably is the α,β-saturated alcohol (a broad peak at 3.61 in the PMR spectrum possibly for the α- to hydroxyl protons). This impediment was overcome by first stirring at $-5^{\circ}C$ for 2 hrs, then allowing the reaction mixture stirring at $0^{\circ}C$ for 6 hrs and further stirring for 2 hrs at room temperature ($30^{\circ}C$).

(ii) The second approach attempted consists of the sequence of reactions shown in Scheme-IV.





(i) $HC{\equiv}CH$, $K^+ \; ^-O-C(Me)_2-Et$ (ii) Ac_2O/H_3PO_4 (iii) AcOH, Ag_2CO_3

(iv) NaOMe/MeOH (v) $LiAlH_4$

SCHEME-IV

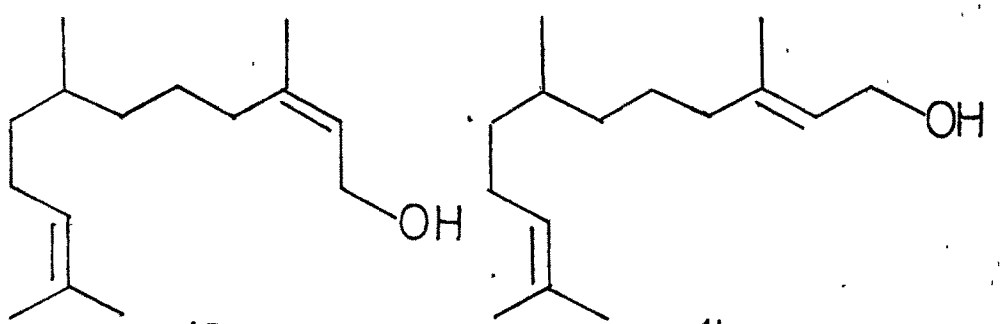
This scheme parallels that reported by Isler and coworkers[8] which was later subjected to some modifications[9] in the conversion of geranyl acetone to farnesol. This sequence has not been reported on 5,6-dihydro-geranyl acetone so far, thus presenting a new approach to the synthesis of (1).

The pure 5,6-dihydro-geranyl acetone (6) was subjected to acetylene addition in presence of tert-AmOK, utilising the method of Gould and Thompson[10] to furnish finally pure tertiary alcohol (12) in 94 % yield, which was characterised by its IR and PMR spectra.

The pure tertiary alcohol (12) was converted into its corresponding acetate (13) by Ac_2O/H_3PO_4. An analytical sample of this acetate was prepared for spectral and physical data.

The acetate (13) was transformed by treatment with AcOH, Na_2CO_3 and Ag_2CO_3 into a mixture of allenic acetate and diacetate, which was then hydrolysed by an exchange reaction with sodium methoxide in methanol to afford a mixture of (Z)- and (E)- 6,7-dihydro-farnesals (14).

This mixture of 2(Z)- and 2(E)-6,7-dihydro-farnesals was easily reduced by $LiAlH_4$ to furnish a mixture of 2(Z)- and 2(E)- 6,7-dihydro-farnesols. The alcohol thus obtained was a mixture of 60 percent E- and 40 percent Z- isomers (as per PMR). No 1,2-dihydro-alcohol could be detected in the LAH reduction product. The 2(Z)- and 2(E)- isomers were separated by column chromatography (10 percent $AgNO_3$ on SiO_2-gel) and characterised by their spectral data.



1a 1b

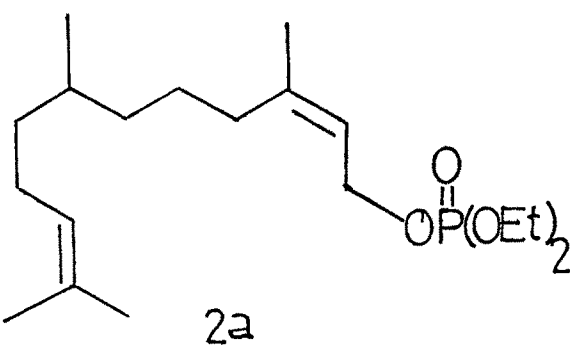
(C) Preparation of 2(cis)-6,7-dihydro farnesyl diethyl phosphate:

2(cis)-6,7-dihydro farnesol (1a) was converted into its diethyl phosphate ester, using diethylchlorophosphate, pyridine in dry dichloromethane under the same experimental conditions that was employed for the preparation of geranyl diethyl phosphate. After usual aqueous work up, it afforded 2(cis)-6,7-dihydro farnesyl diethylphosphate ester (2a), pure by TLC analysis (15 % EtOAc/Pet.ether

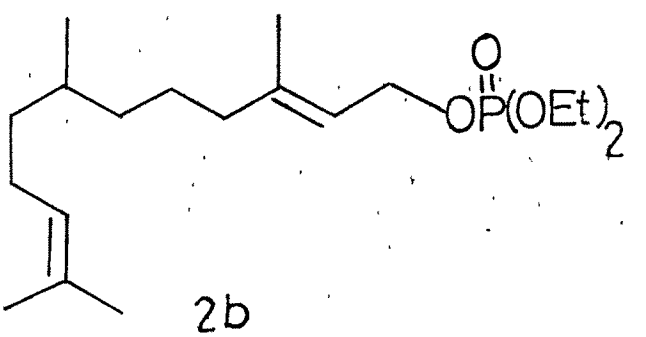
60-80°C) and spectroscopically consistent. It was not further purified due to its lability towards heat and adsorbents.

Preparation of 2(trans)-6,7-dihydro-farnesyl diethyl phosphate:

2(trans)-6,7-dihydro-farnesol (1b) was converted into its diethyl phosphate ester, using the above experimental conditions. After usual aqueous work up it afforded 2(trans)-6,7-dihydro-farnesyl diethyl phosphate ester (2b), pure by TLC analysis (15 % EtOAc/Pet. ether 60-80°C) and spectroscopically consistent. It was also not further purified due to its lability towards heat and adsorbents.



2a



2b

(D) Reaction of 2(cis)-6,7-dihydro-farnesyl diethyl phosphate with active alumina:

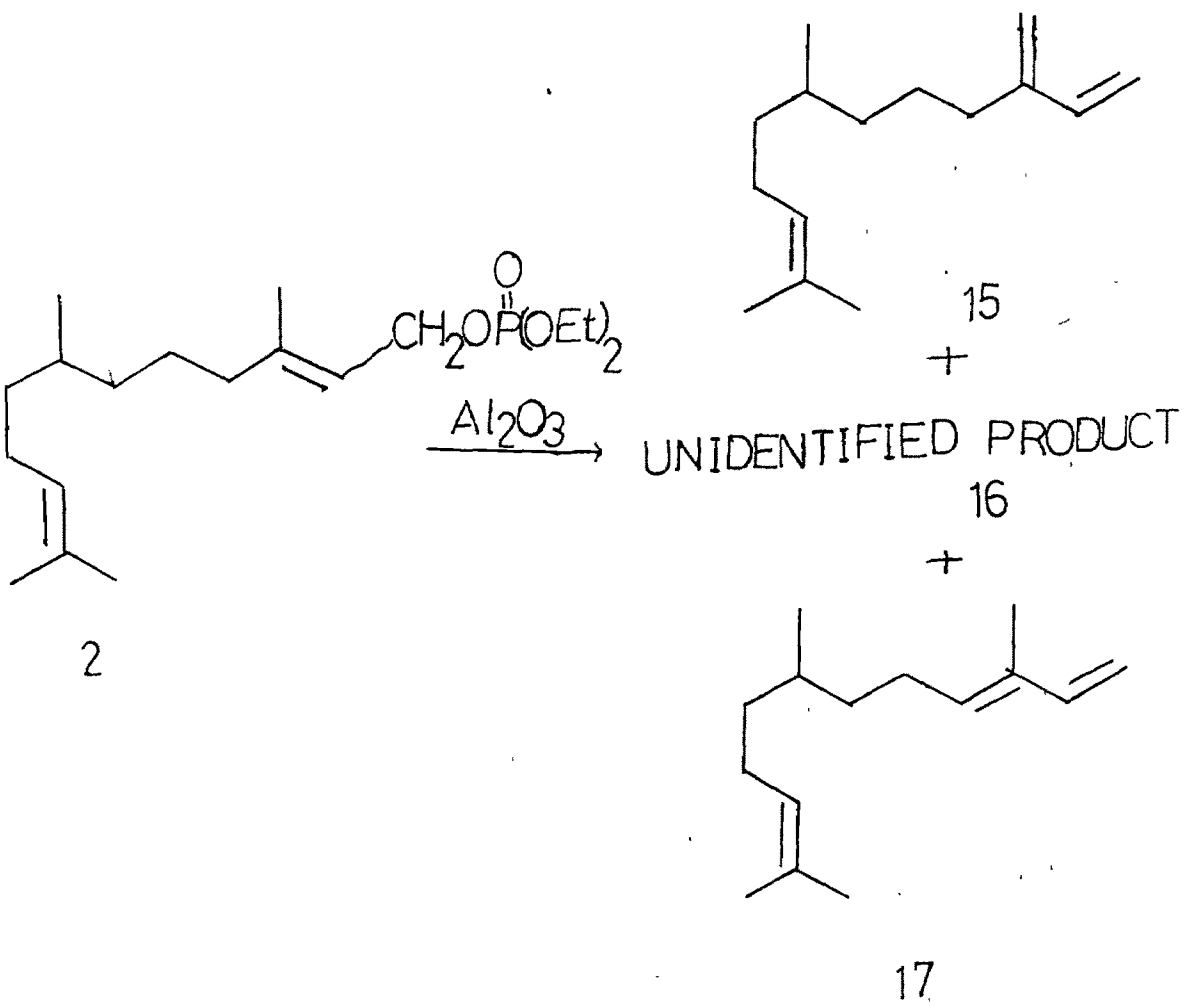
2(cis)-6,7-dihydro-farnesyl diethyl phosphate (2a) (0.5 gm, 0.0011 mol) in dry dichloromethane was added to a

slurry of active alumina (prepared from aluminium isopropoxide, grade I, pH = 7, 15 gm) in dry dichloromethane under manual shaking in 2minutes. The reaction mixture was flushed with dry N_2 gas and stoppered the r.b.flask. It was shaken using mechanical shaker for 4 hrs at room temperature (~ 30°C) and kept at room temperature (25°C) for 12 hours. After usual filtration work up, and distillation of the solvent, it afforded a crude compound which was distilled under reduced pressure. GLC of the distillate showed the formation of three compounds. The PMR of the distillate shows, that it is a mixture of only elimination products. No trace of cyclised products was obtained. (Scheme-V). However, these compounds were tried to separate on 15 % $AgNO_3$-Silica gel G - column chromatography and could get two pure compounds. These were identified as 1,3(15),10-dodecatriene 7,11 dimethyl (15); 1,3(7)(trans),10-dodecatriene 3,7,11 trimethyl(17) by their spectral characterstics (IR, PMR, Mass). The mass spectra were taken on computerised GC-MS spectrophotometer. GLC of the mixture is shown in Fig. 1.

Reaction of 2(trans)-6,7-dihydro-farnesyl diethyl phosphate with active alumina:

Reaction of 2(trans)-6,7-dihydro farnesyl diethyl phosphate (0.5 gm, 0.0011 mol) with active alumina (activity; grade I, pH = 7, 15 gm) in dry dichloromethane

was carried out under the similar experimental conditions described above. After usual filtration work up and distillation of the solvent afforded a crude material. It was distilled under reduce pressure. The GLC of the distillate shows the formation of the three compounds, found to be elimination products only, as in the case of 2(cis)-isomer, but in different proportions. The GLC of the mixture is shown in Fig. 2.



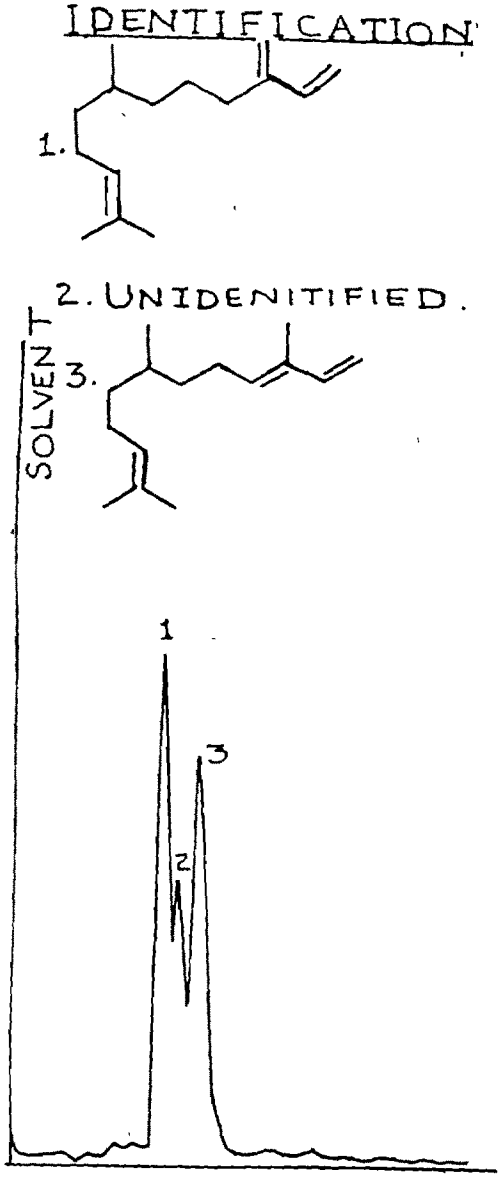


Fig.1 : GLC of reaction products from the reaction of 2(Z)-6,7-dihydro farnesyl diethyl phosphate with active alumina

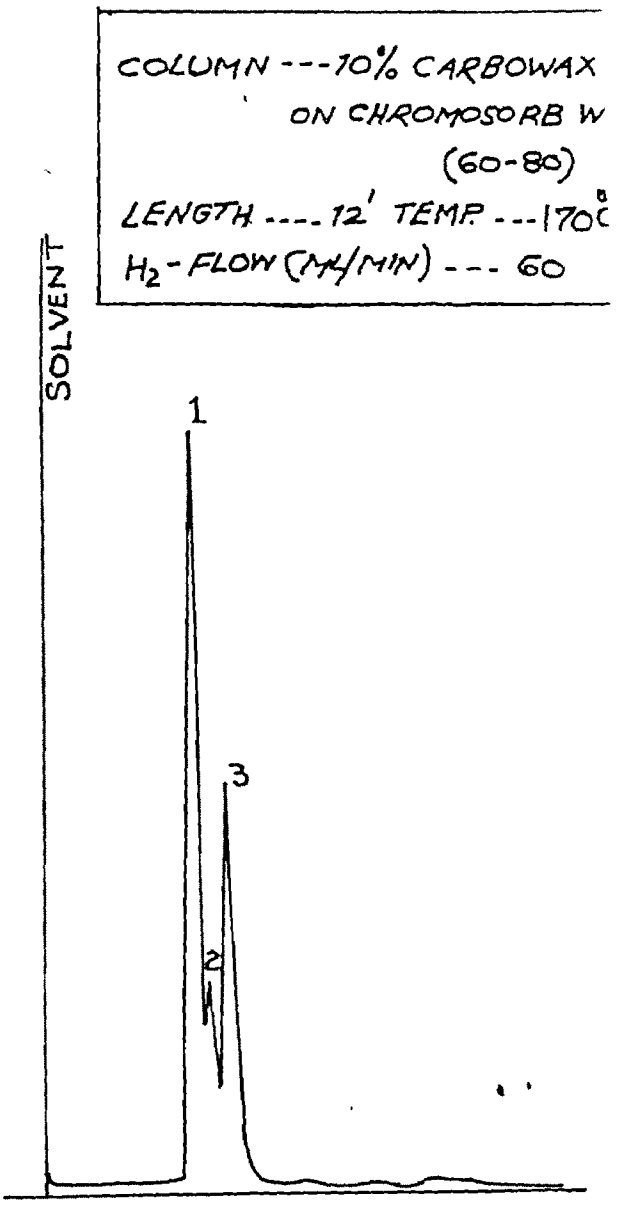
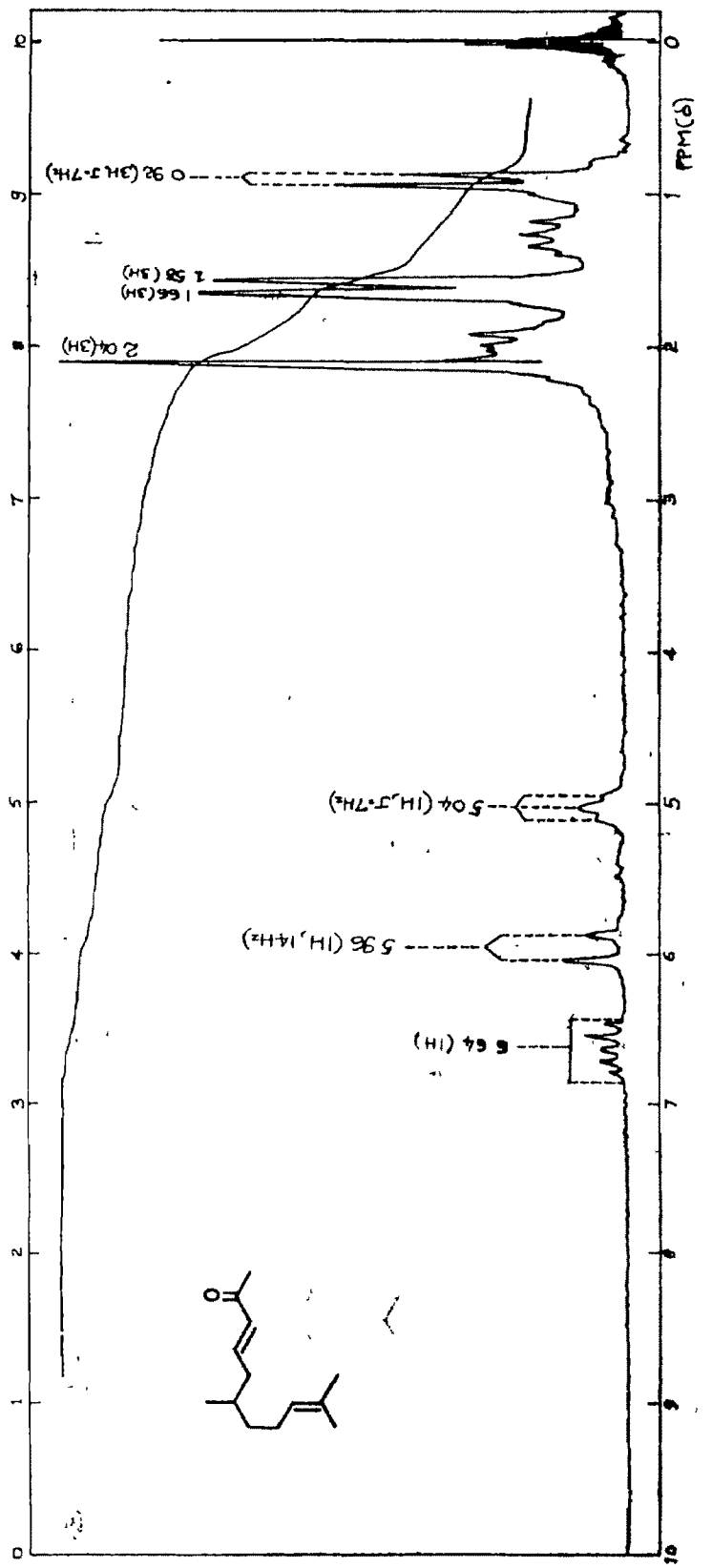
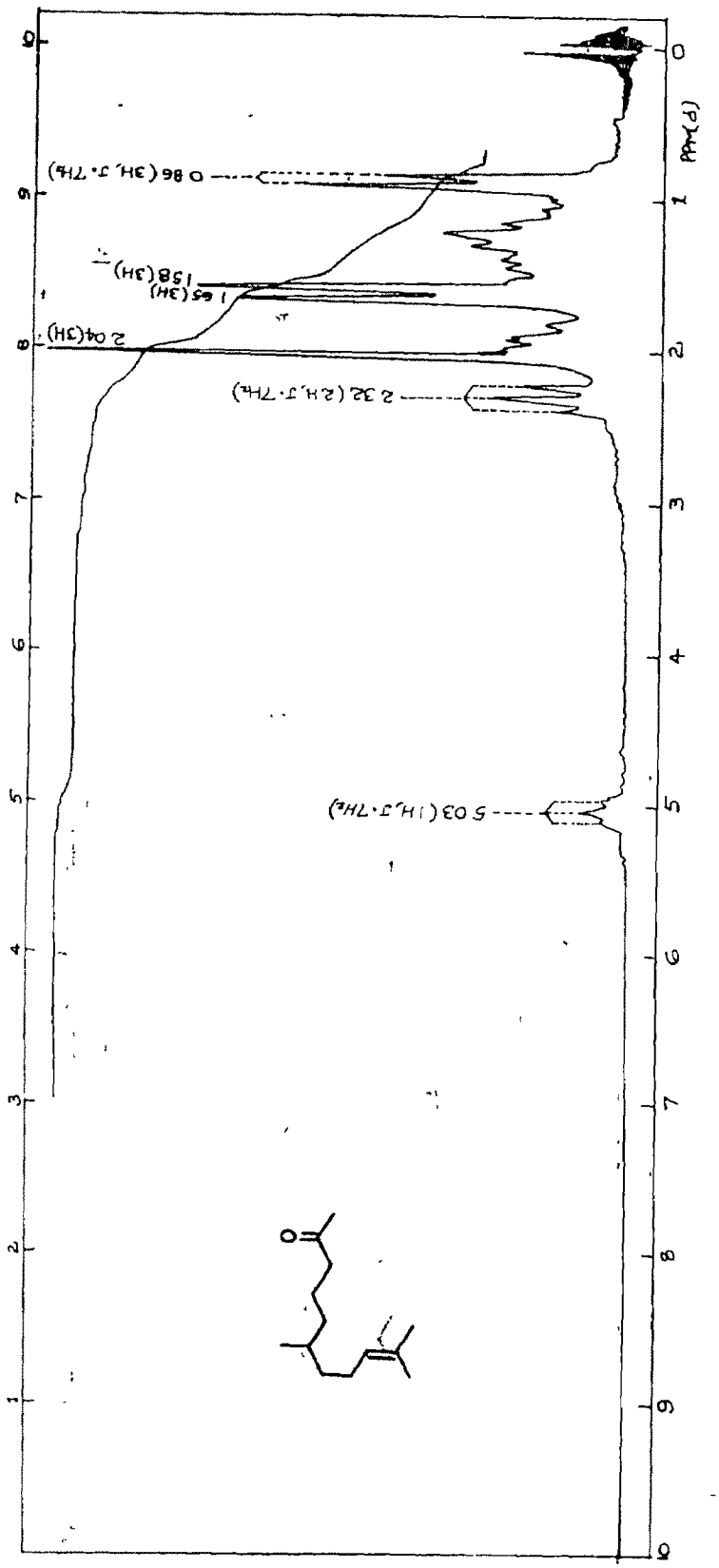


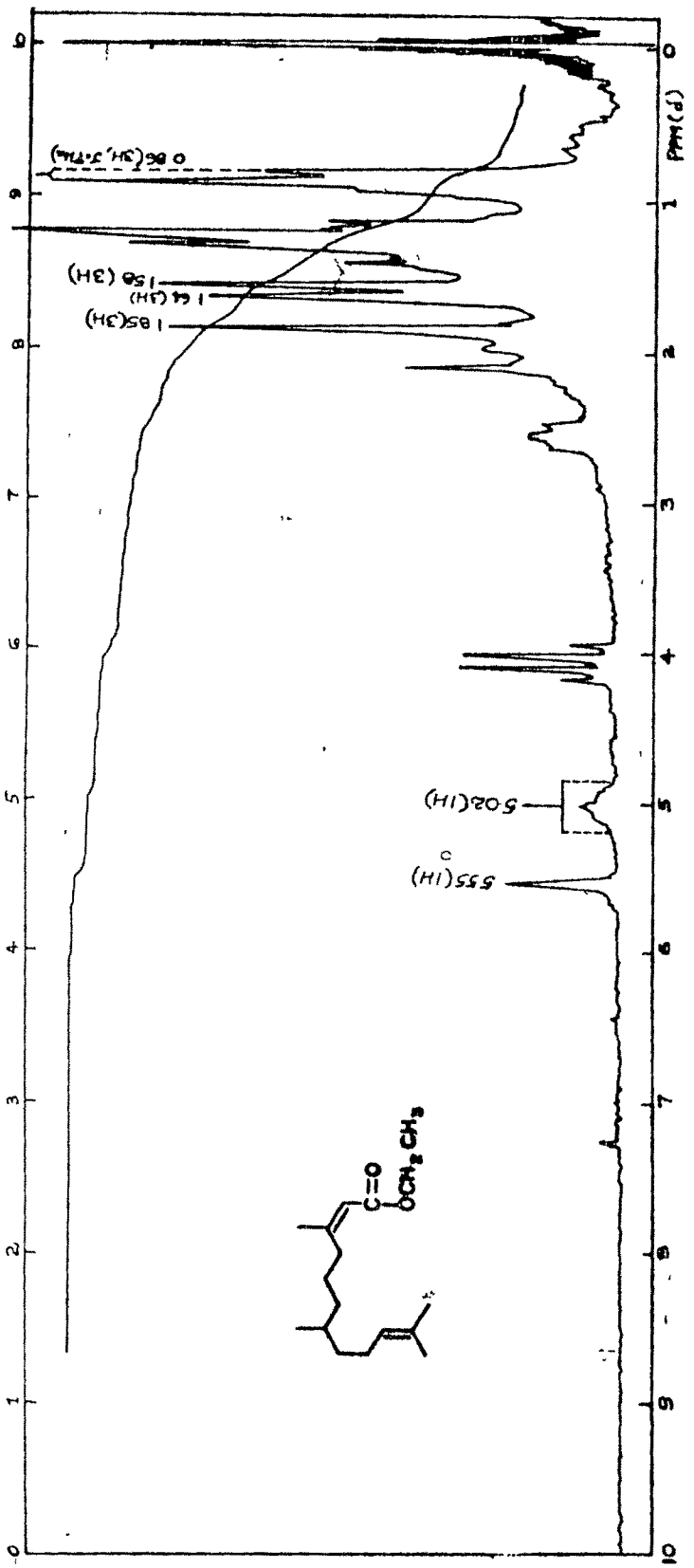
Fig.2 : GLC of reaction products from the reaction of 2(E)-6,7-dihydro farnesyl diethyl phosphate with active alumina



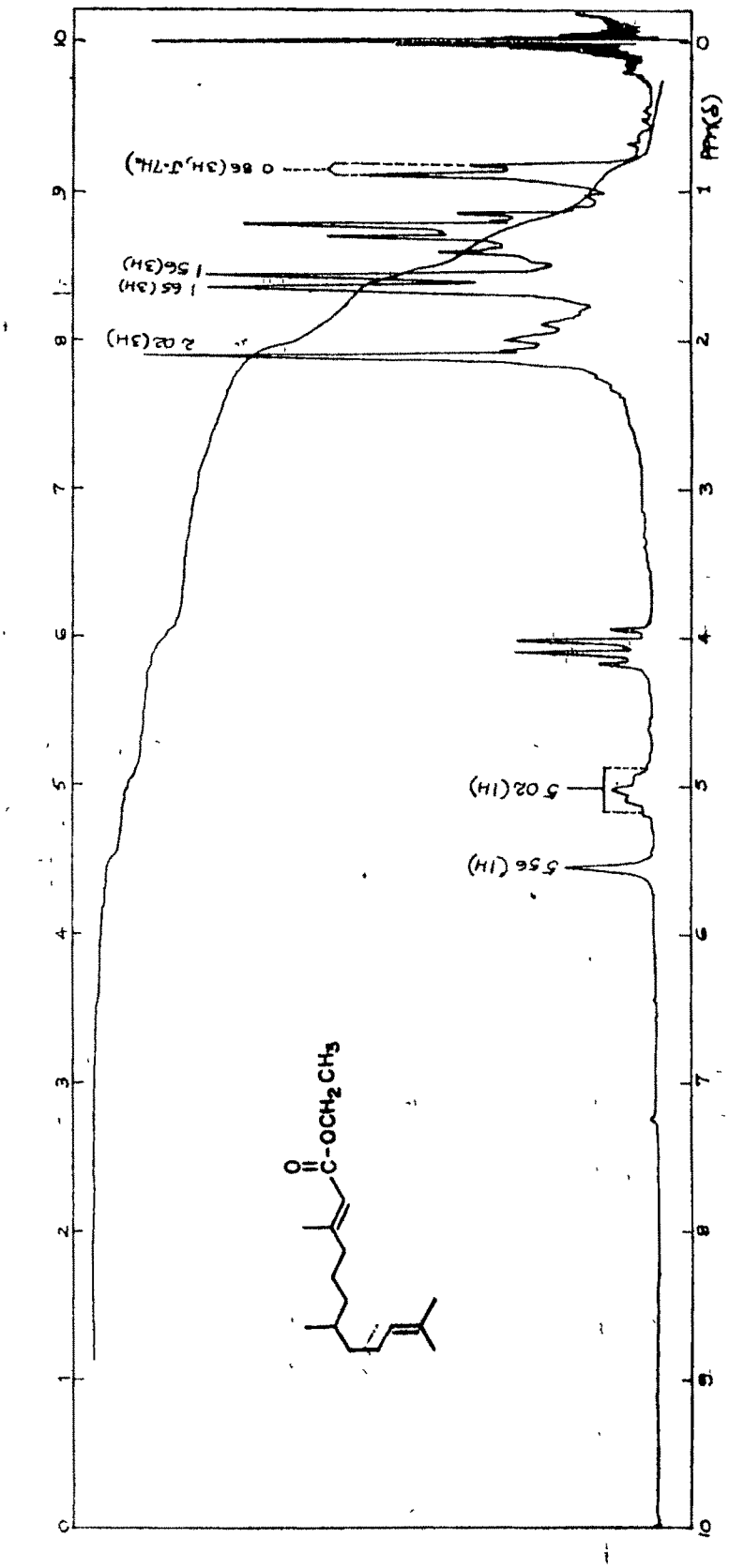
Sp.A.1 : PMR spectrum of 3,9-undecadien-2-one-6,10-dimethyl (13)



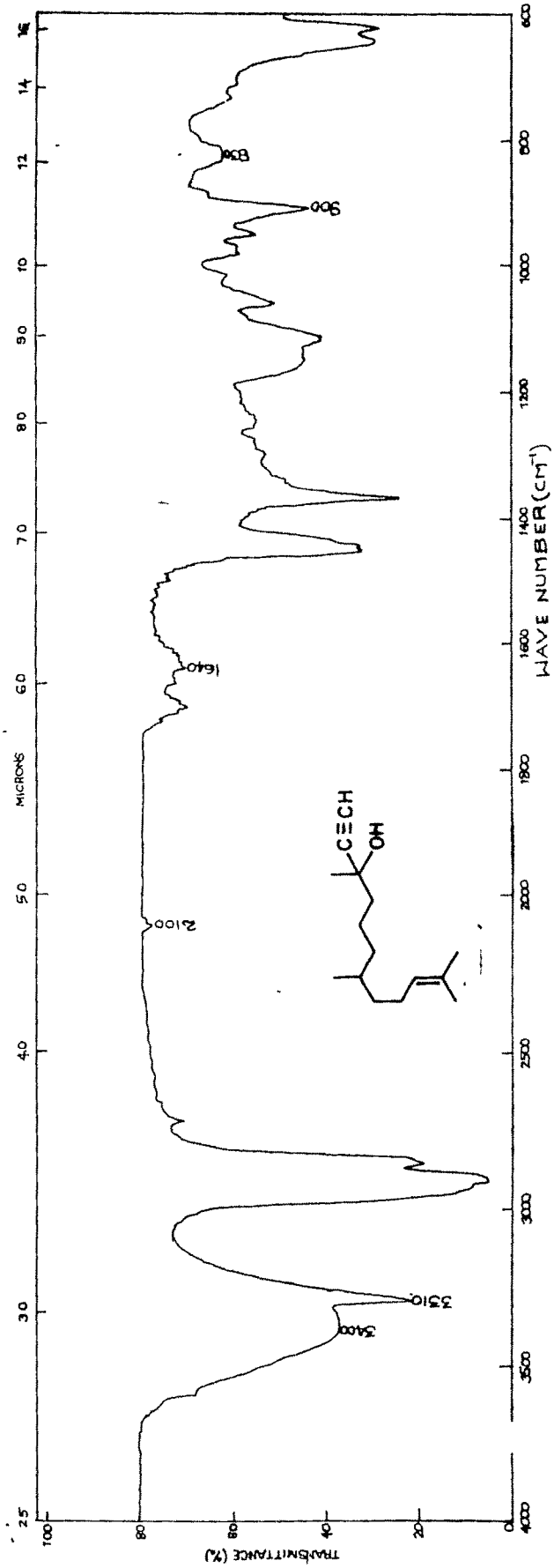
Sp. A. 2 : PMR spectrum of 5,6-dihydrogeranyl acetone (6)



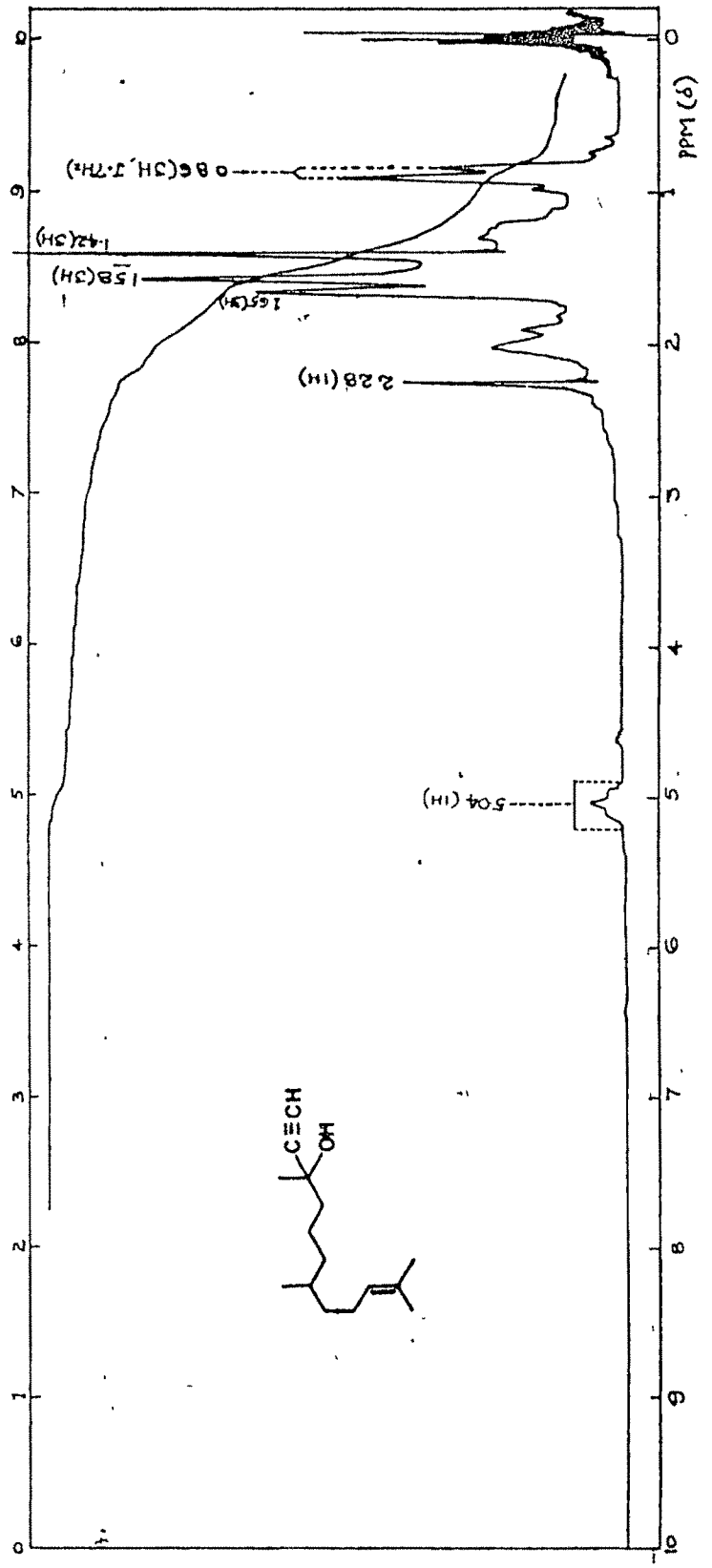
Sp.A.3 : PMR spectrum of 2(Z)-6,7-dihydro-ethyl farnesate (7a)



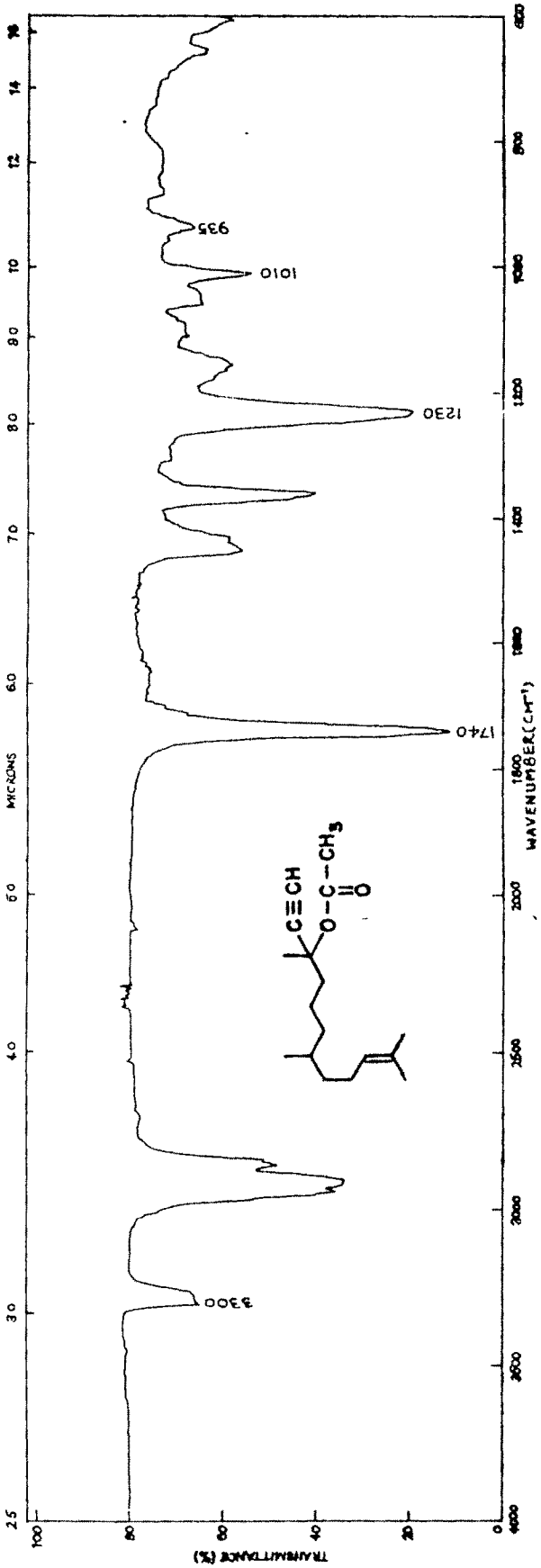
Sp.A.4 : PMR spectrum of 2(E)-6,7-dihydro-ethyl farnesate (7b)



Sp.A.5a : IR spectrum of acetylene addition product (12)



Sp.A.5b : PMR spectrum of acetylene addition product (12)



Sp.A.6a : IR spectrum of tertiary acetate (13)

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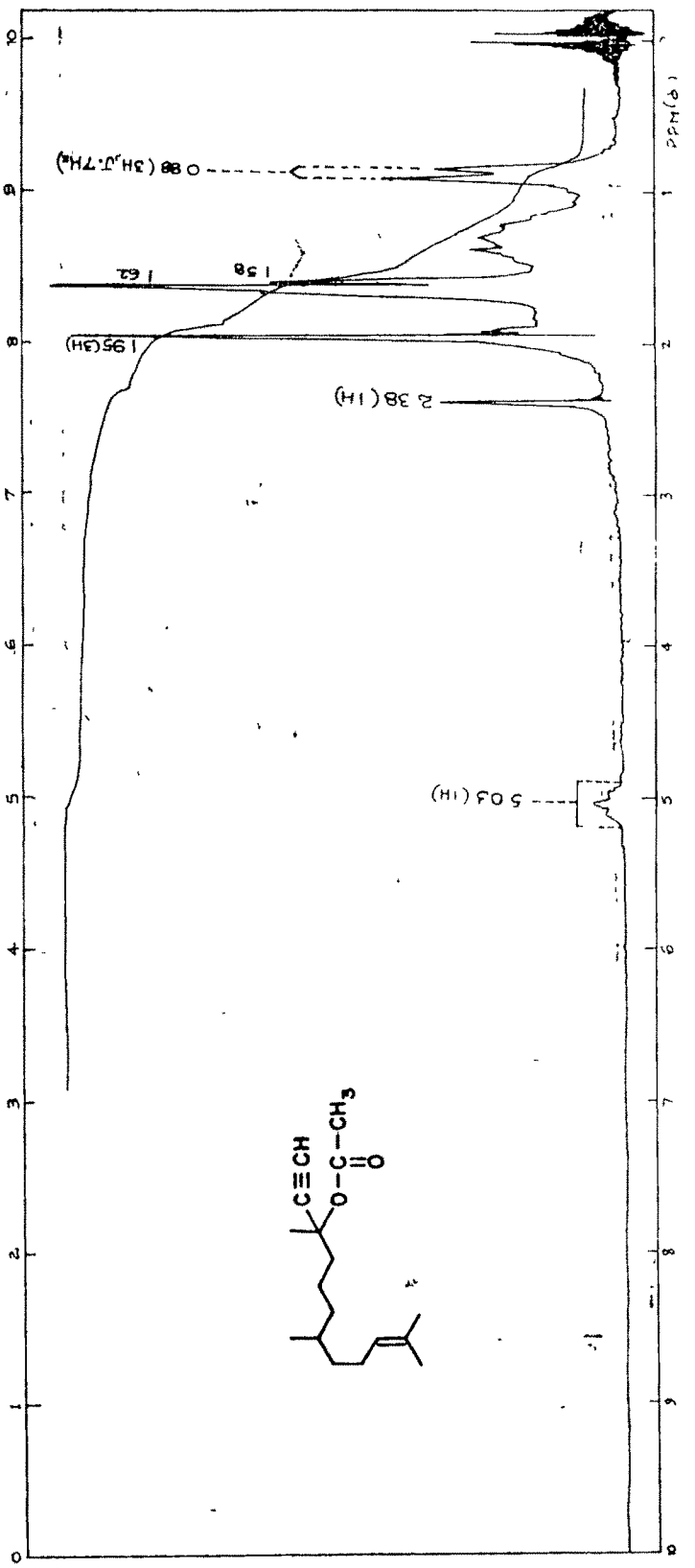
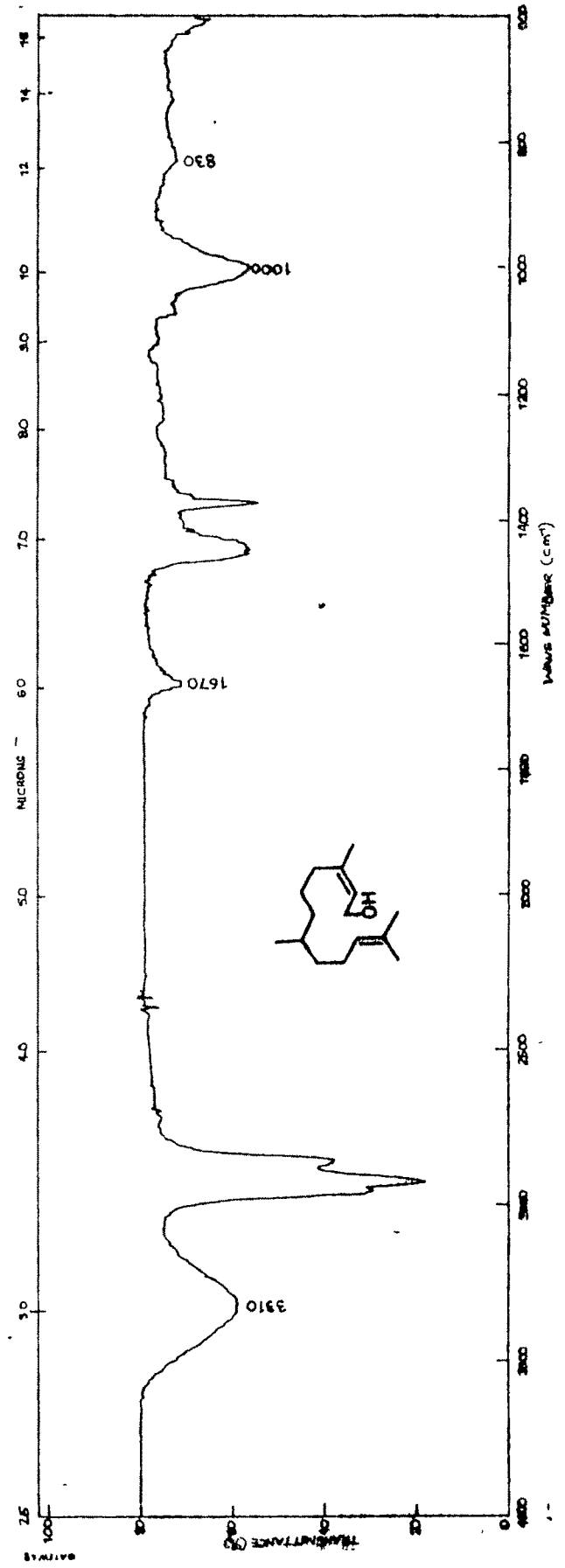
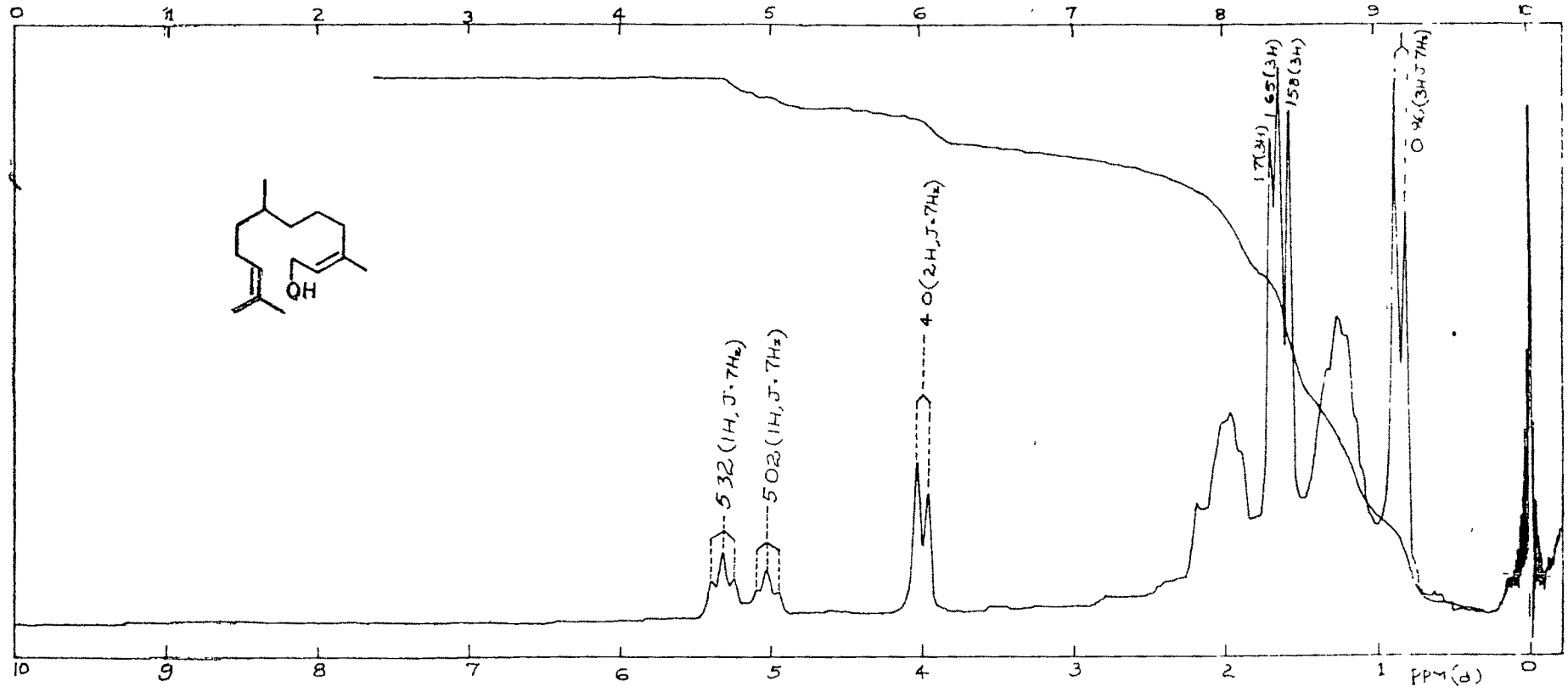


Sp.A.6b : PMR spectrum of tertiary acetate (13)



Sp.A.7a : IR spectrum of 2(Z)-6,7-dihydrofarnesol (1a)



Sp.A.7b : PMR spectrum of 2(Z)-6,7-dihydrofarnesol (1a)

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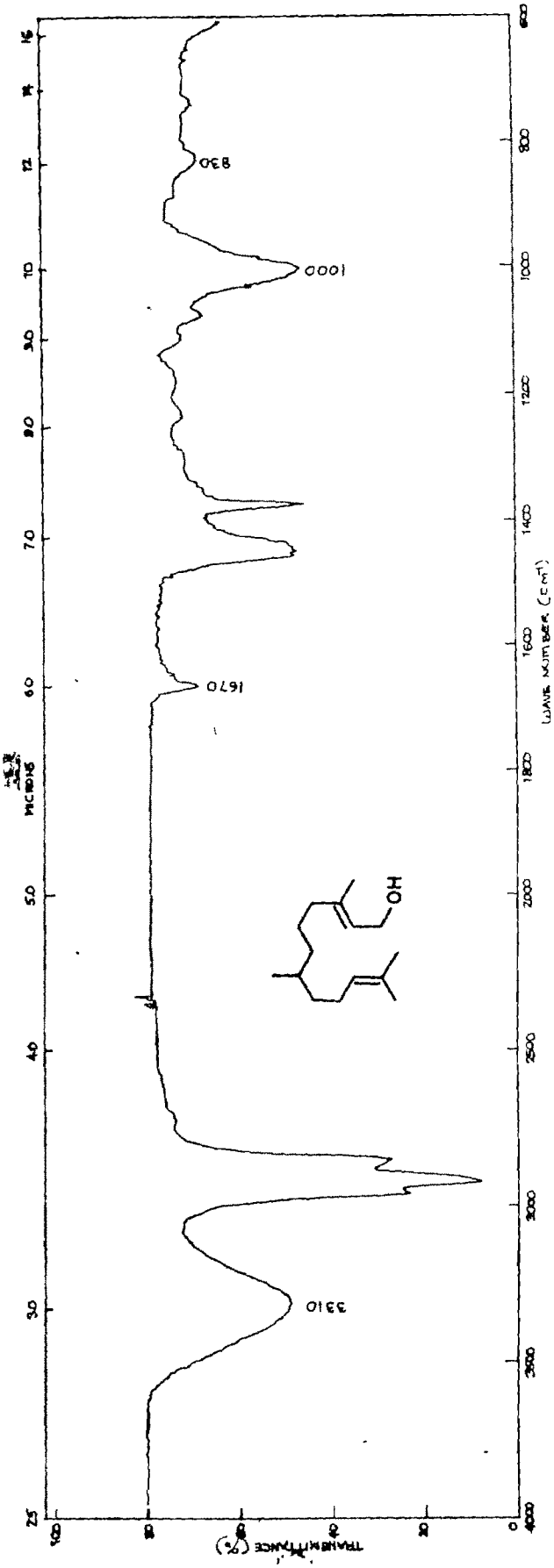
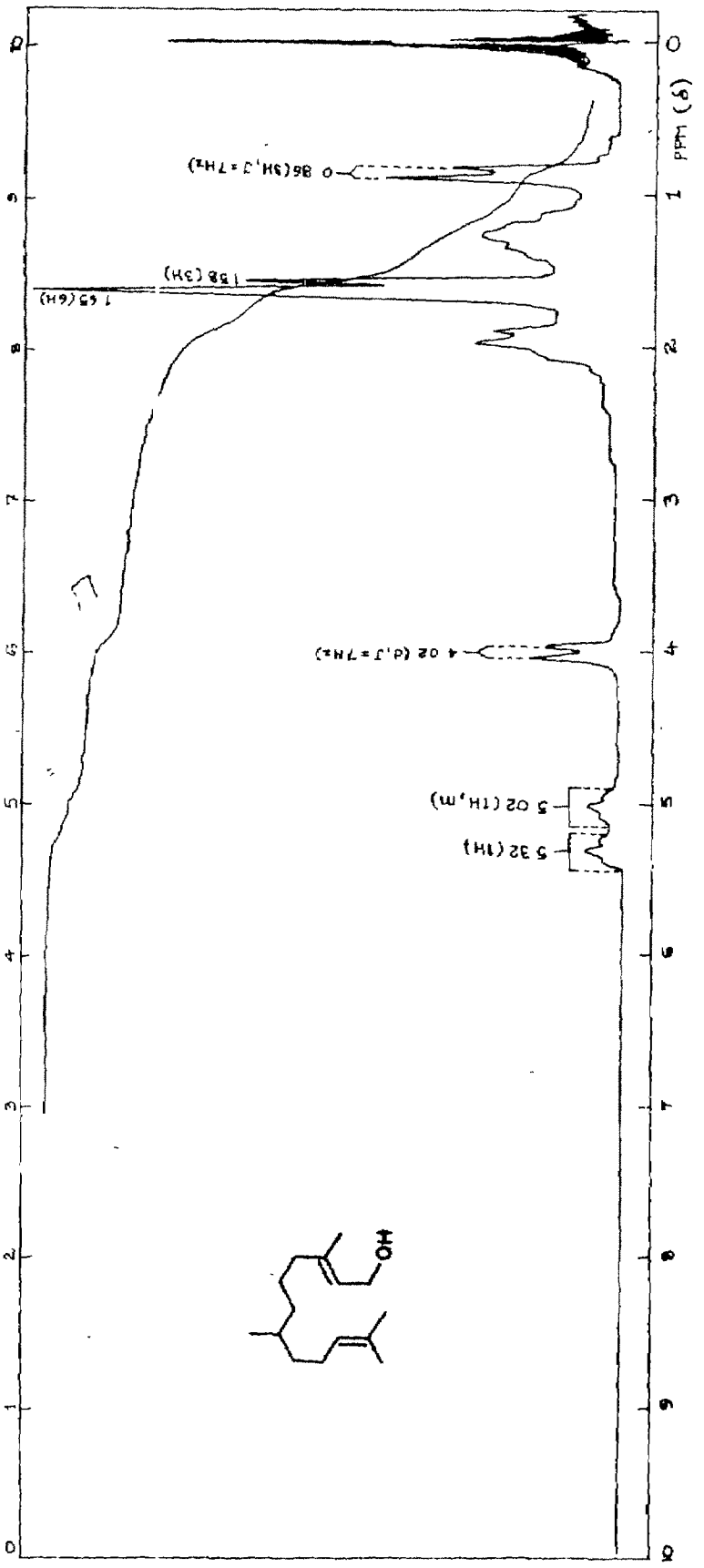
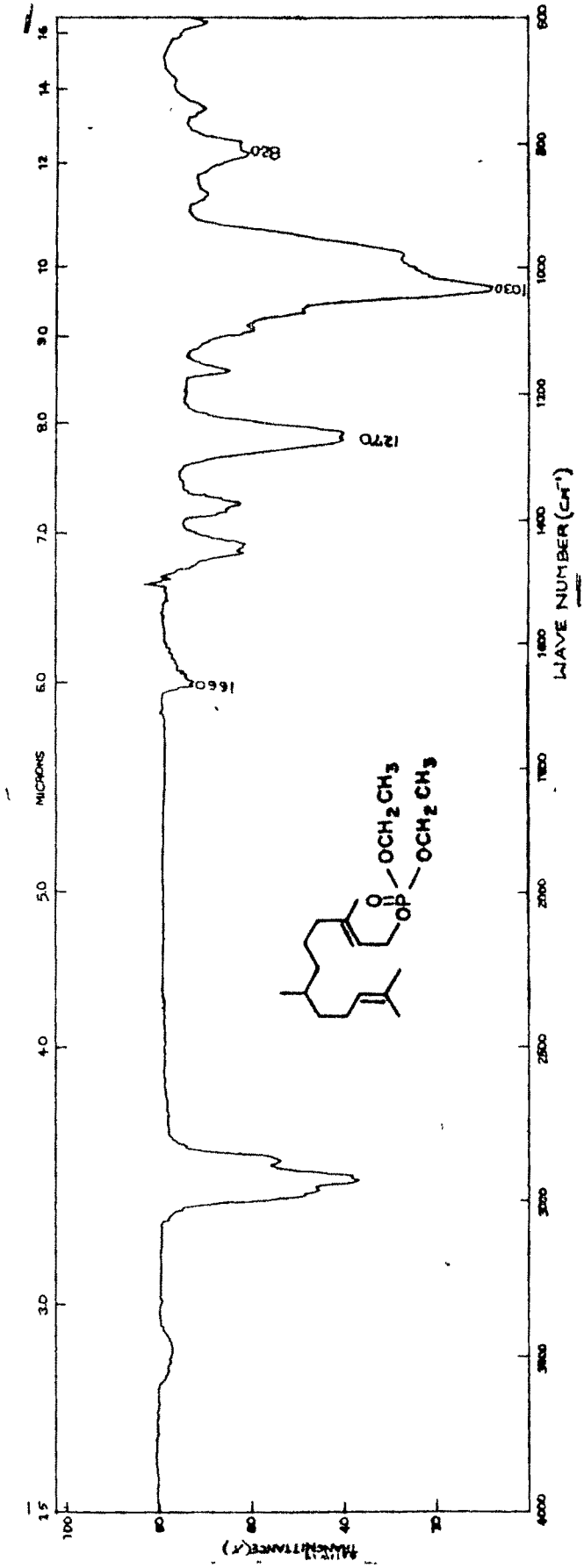


Sp.A.8a : IR spectrum of 2(E)-6,7-dihydrofarnesol (1b)

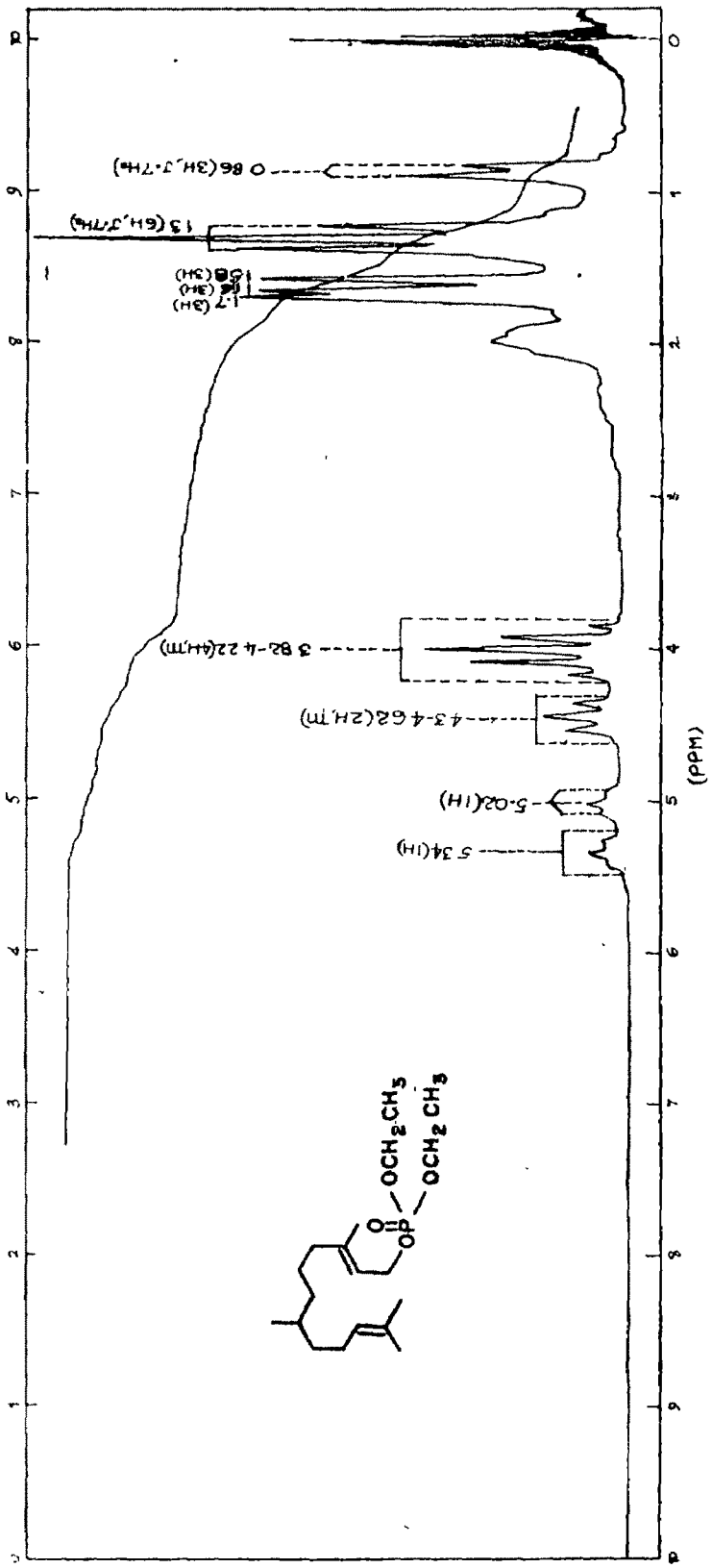
261



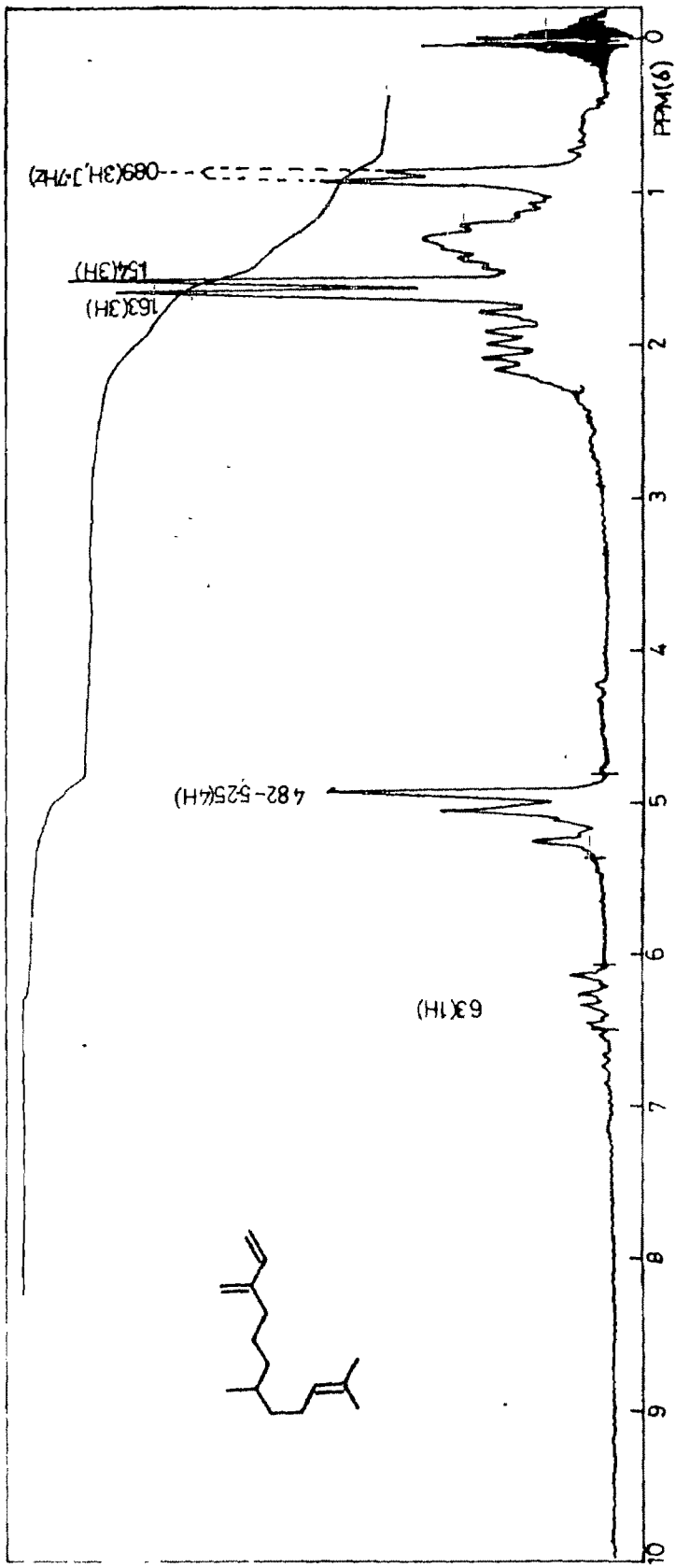
Sp.A.8b : PMR spectrum of 2(E)-6,7-dihydrofarnesol (1b)



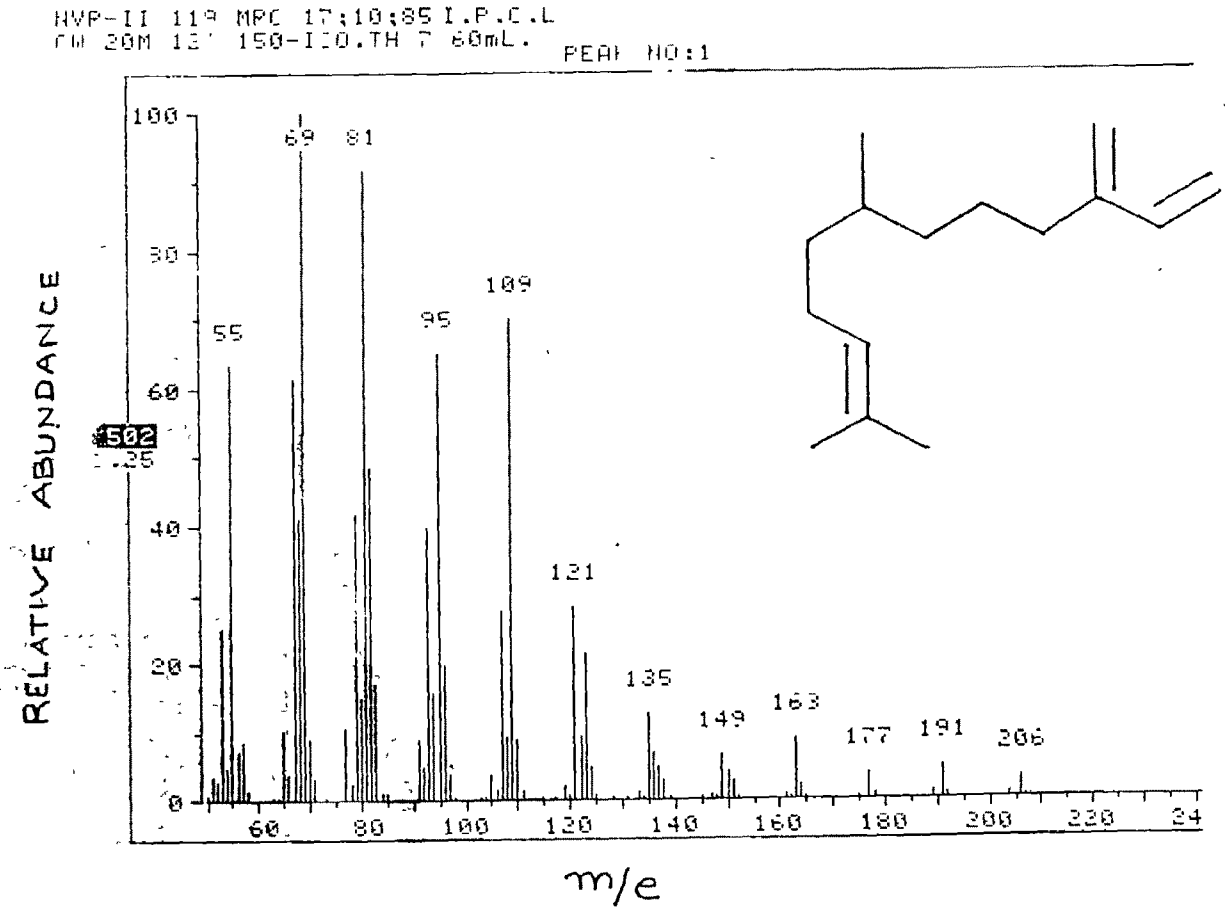
Sp. A.9a : IR spectrum of 2(E)-6,7-dihydrofarnesyl diethyl phosphate (2b)



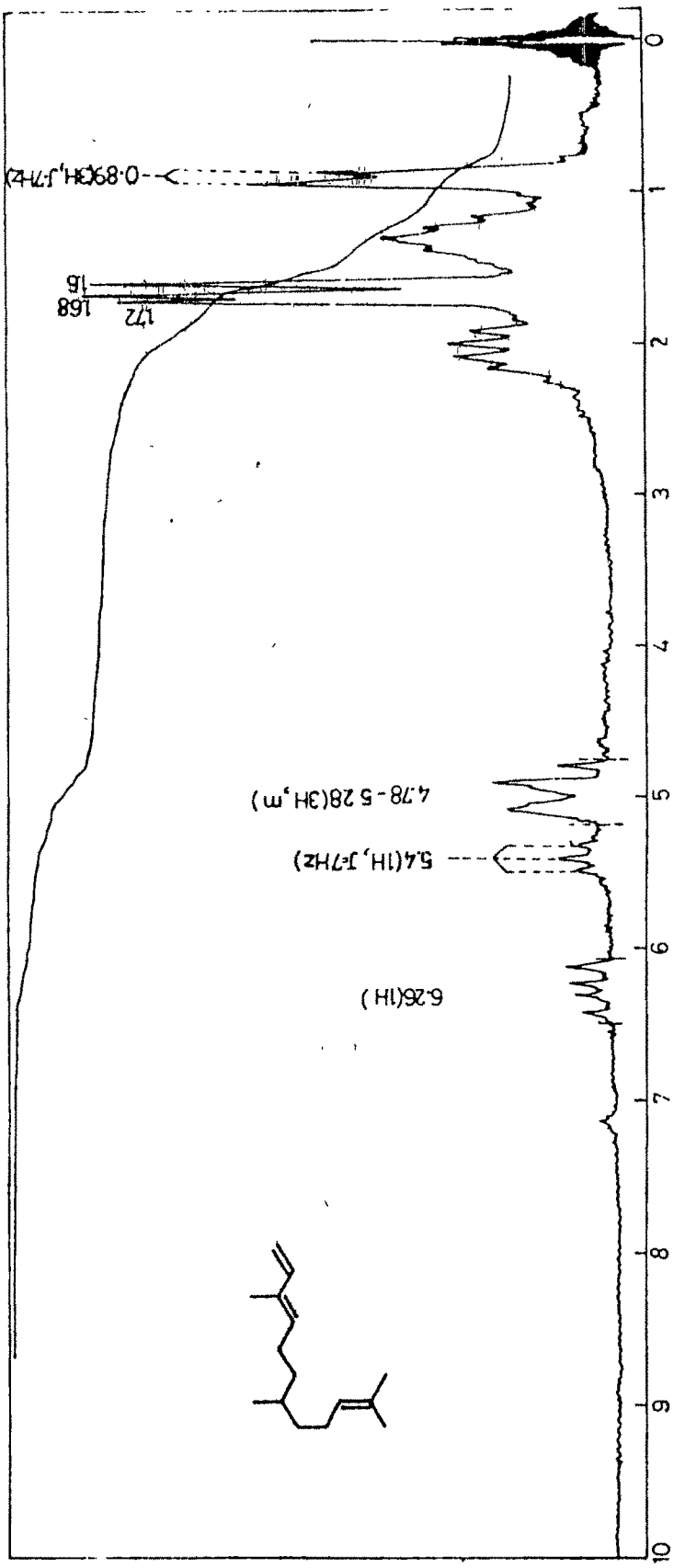
Sp.A.9b : PMR spectrum of 2(E)-6,7-dihydrofarnesyl diethyl phosphate (2b)



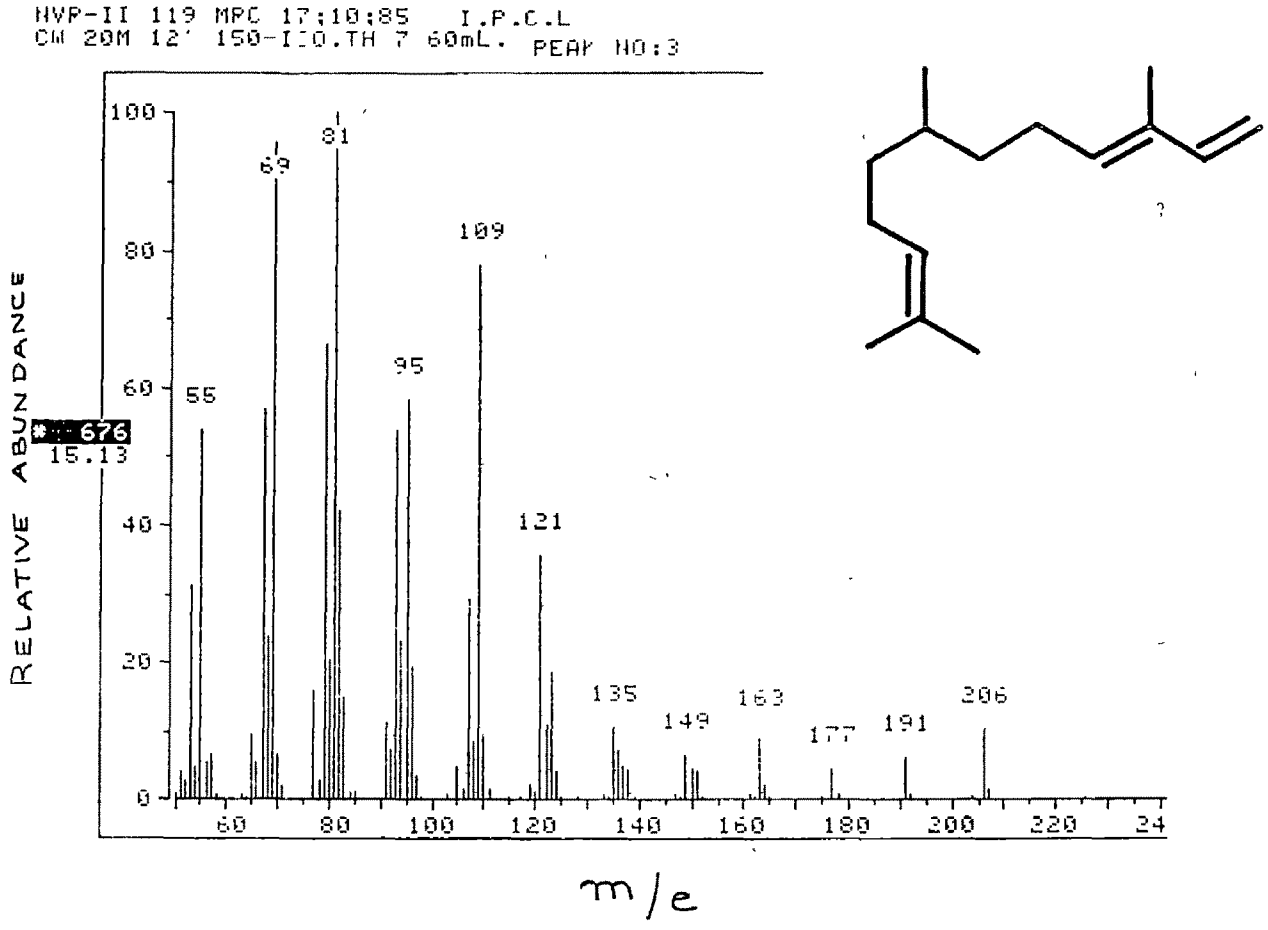
Sp.A.10a : PMR spectrum of 1,3(15),10-dodecatriene-7,11-dimethyl (15)



Sp.A.10b : Mass spectrum of 1,3(15),10-dodecatriene-7,11-dimethyl (15)



Sp.A.11a : PMR spectrum of 1,3(7)(trans)-10-dodecatriene 3,7,11 trimethyl (17)



Sp.A.11b : Mass spectrum of 1,3(7)(trans),10-dodecatriene 3,7,11 trimethyl (17)

Discussion :

The reaction of 2(Z) and 2(E)-6,7-dihydro-farnesyl diethyl phosphates with active alumina resulted in the formation of only elimination products and not even a trace of cyclization product could be detected. This observation supports Ruzicka et al.[11] postulates of alicyclic rings formation. Ruzicka et al. have discussed the formation of alicylic rings in terms of two factors. The first of these, the probability factor, is a measure of ability of the ends of the carbon chain to approach each other. The frequency with which this occurs will decrease with increasing chain length and thus reflects itself in an unfavourable activation entropy for the formation of medium and large rings. The deterioration of probability factor in case of medium and large rings is because the acyclic carbon chain will tend to adopt the most stable zig-zag conformation where the ends of the chains are further apart (ie.) where it contains the greatest number of anti-butane segments.

The activation energy for ring closure will depend on the stability of the ring formed. This gives rise to the second of the factors, the strain factors. The strain factor becomes more favourable to closure as the ring size increases from 3 to 6-membered, less favourable for the formation of 7,9 and 10-membered rings and then more favourable for larger rings.

By combining all these factors, we were able to relate the ease of formation of a ring to the number of carbon atoms it contained and were thus able to explain, satisfactorily, the observed formation of only elimination products in our experiments.

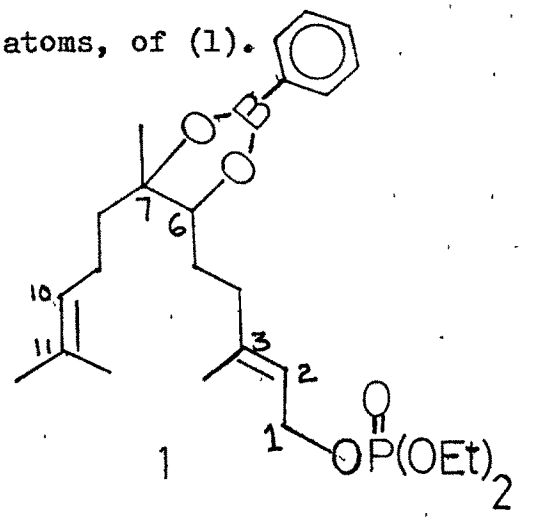
PART-B

PREPARATION AND HETEROLYSIS OF 2(E)-6,7-DIHYDROXY (PROTECTED BY PHENYLBORONIC ACID) FARNESYL DIETHYL PHOSPHATE

In part A, it is observed that our objective in the formation of 10 or 11-membered rings from the 6,7-dihydro-farnesyl derivatives was not realised, due to the probability and ring strain factors. It was obvious from the observations that in the acyclic farnesyl chain, the probability and ring strain effects are such that it allows the formation of 6-membered rings more favourably. So, it was thought, under the imposition of certain constraints to the acyclic farnesyl chain, the probability factors of the system can be brought favourable in simulating the interactions between C_1 and C_{10} atoms, thereby leading to the formation of 10 or 11-membered rings.

Under these circumstances, it was decided to protect the 6,7-double bond of acyclic farnesyl chain as diol. It serves the exclusion of the 6-membered ring formation, thereby allowing the terminal double bond ($\Delta^{10,11}$) to interact with more electrophilic centre of C_1 atom. And also, it was thought that the diol protection with phenyl boronic acid, can bend the acyclic farnesyl chain, sufficiently enough, to bring the terminal double bond ($\Delta^{10,11}$) into the proximity of C_1 atom, due to the repulsive interactions between the π-electron cloud of phenyl group and that of the 2,3 and 10,11-double bonds

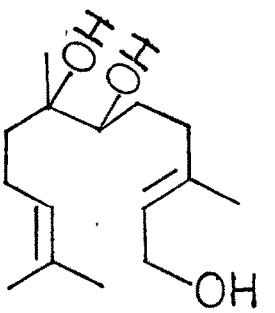
of farnesyl chain, thereby simulating the interaction between C_1 and C_{10} atoms, of (1).



1

SYNTHESIS OF 2(E)-6,7-DIHYDROXYFARNESOL

In connection with the preparation of (1), for the cyclization study, we required the corresponding alcohol [2(trans)-6,7-dihydroxyfarnesol (2)] of the said stereochemistry with maximum purity possible. A survey of the literature was therefore made for the methods already reported for the synthesis of (2).



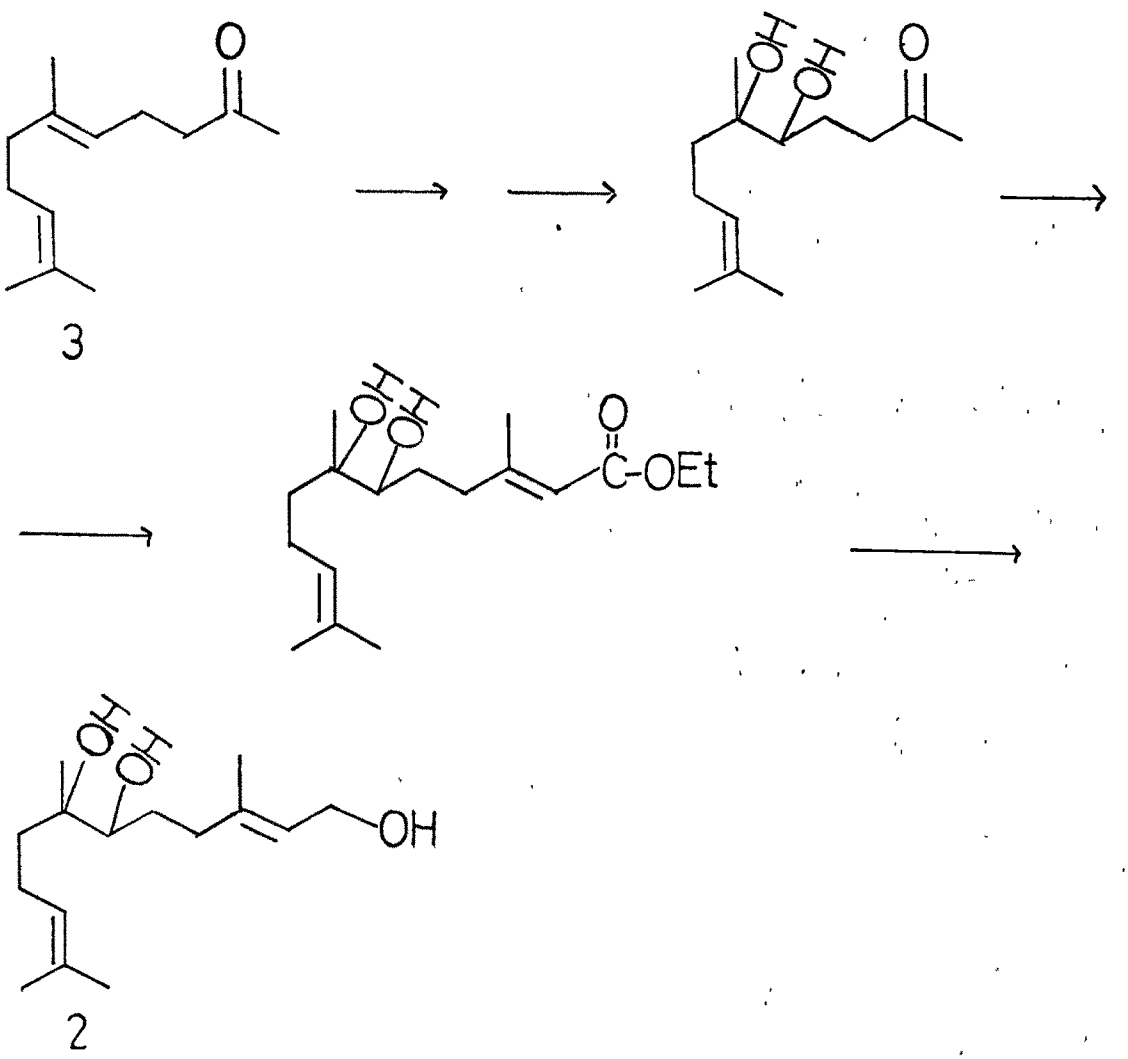
2

It was found that synthesis of (2) was not reported until now. So, various methods to synthesize this triol

were tried, which are briefly summarised below with appropriate comments.

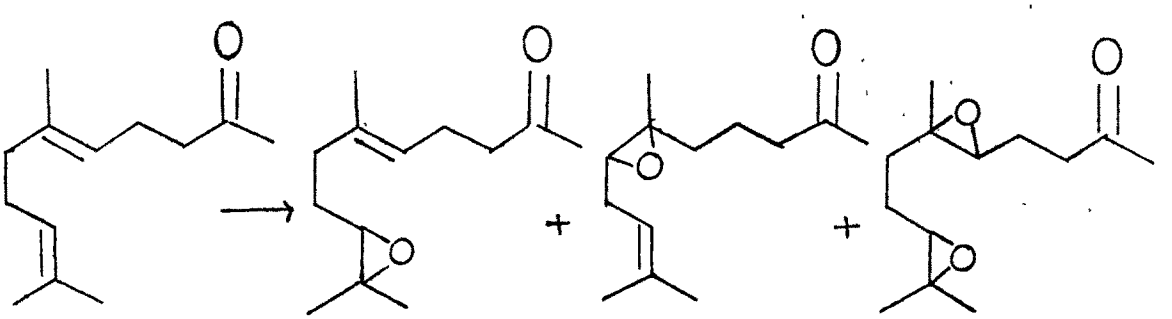
(1) Proposed scheme for the synthesis of (2)

(trans)-Geranyl acetone was chosen as starting material for the synthesis of triol (2), for which a scheme was proposed. (Scheme-I).



SCHEME-I

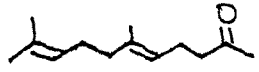
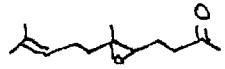
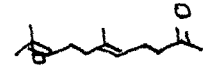
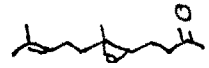
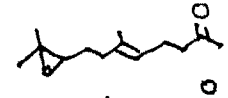
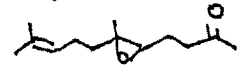
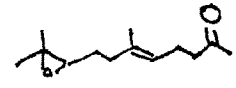
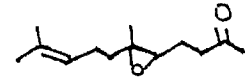
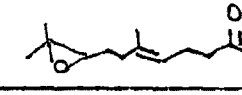
cis-Hydroxylation of (trans)-geranyl acetone was attempted with potassium permangnate, but it could not yield the diol. Starting material was recovered. An alternative approach was thought, to epoxidise 5,6-double bond of (3) and then cleavage of epoxide to 5,6-diol. To achieve 5,6-epoxy geranyl acetone, various epoxidation reactions were carried out on (3) using different peracids and hydroperoxides. The details of these reactions were summarised in the Table-1. In all these reactions, three different epoxides were formed, though in different ratios in various reactions.



3 3a 3b 3c

None of these reactions gave selective 5,6-epoxy geranyl acetone. Various methods were attempted to separate the monoepoxides (5,6 and 10,11-). from the

TABLE-1

Sr. No.	Substrate (mol)	Epoxidation reagent[a] (mol)	Solvent	Reaction conditions	Product after separation from column chromatography[b]	% of epoxide[c]	% yield of mix. of mono-epoxides
1.	 970 mg (0.005 mol)	C_6H_5-COOOH 720 mg (0.0052 mol)	$CHCl_3$	Peracid in $CHCl_3$ was added to stirred substrate at 5-10°. After addition, stirring continued for 2 hrs.	 	22 78	19
2.	-do-	C-$(CH_3)_3$- OOH 455 mg (0.005 mol)	C_6H_6	Molybdenum stearate as a catalyst. At refluxing temp. addition of peracid to substrate in benzene. Further refluxed for 4 hrs	 	25 75	33
3.	-do-	monoperphthallic acid 910 mg (0.005 mol)	$(C_2H_5)_2O$	Addition of peracid/ether to substrate at 5-10° while stirring. Further stirred for 1 hr.	 	73 27	30
4.	-do-	m-Chloroperbenzene acid	CH_2Cl_2	Addition of peracid in CH_2Cl_2 to substrate at 5-10°C. Stirred further 30 minutes.	 	55 45	34

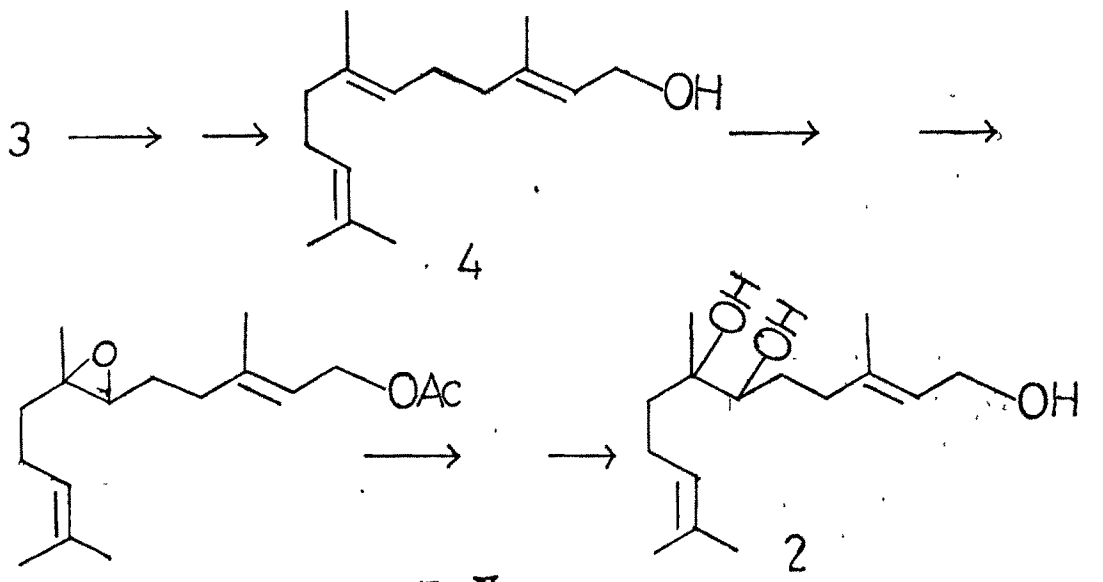
(a) All the peracids/Hydroperoxides are prepared and estimated (iodometrically) before use.

(b) Chromatography of crude reaction product was carried out on grade IV alumina.

(c) The ratios are based on PMR study.

mixture. [(Silica gel-G TLC, 15 % $AgNO_3$ - Silica gel G, GLC using 10 % SE 30, 10 % CW, 5 % CW, 5 % p, 5 % $CuBr_2$ treated 10 % CW)]. None of these methods could separate the monoepoxides (5,6 and 10,11) in pure form. So, this route had to be abondoned.

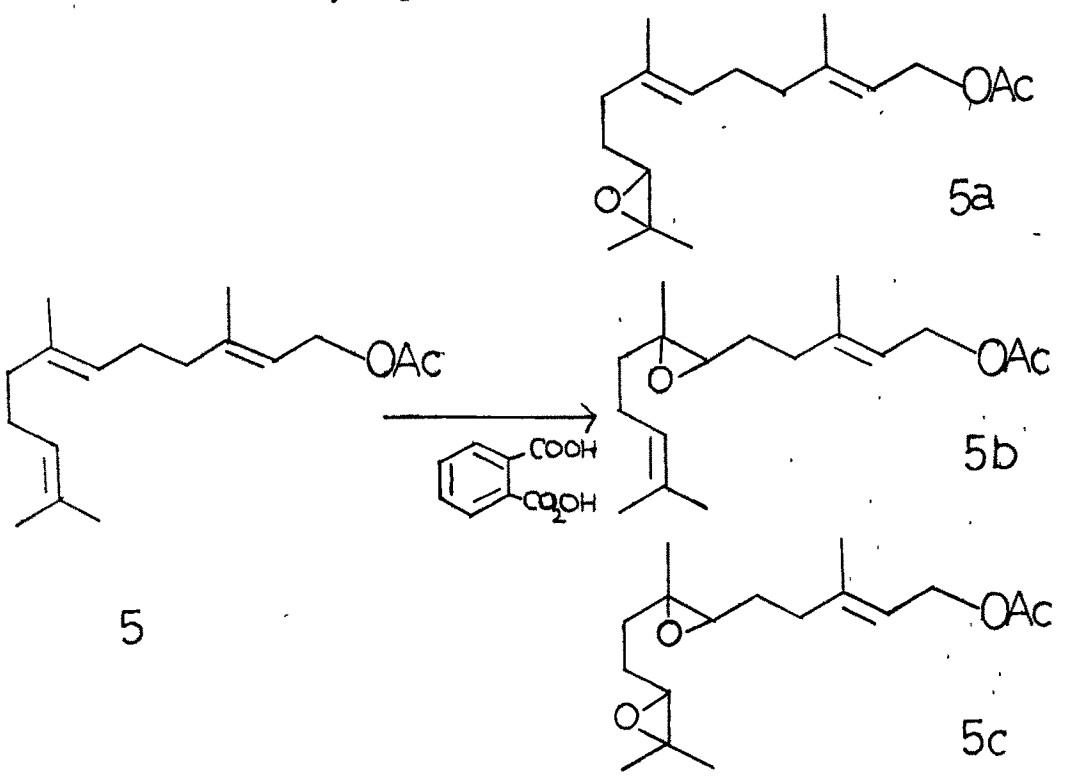
(2) So, in an alternative approach, it was thought to synthesise, pure (E),(E)-farnesyl derivative and then study epoxidation reactions on it. (Scheme-II)



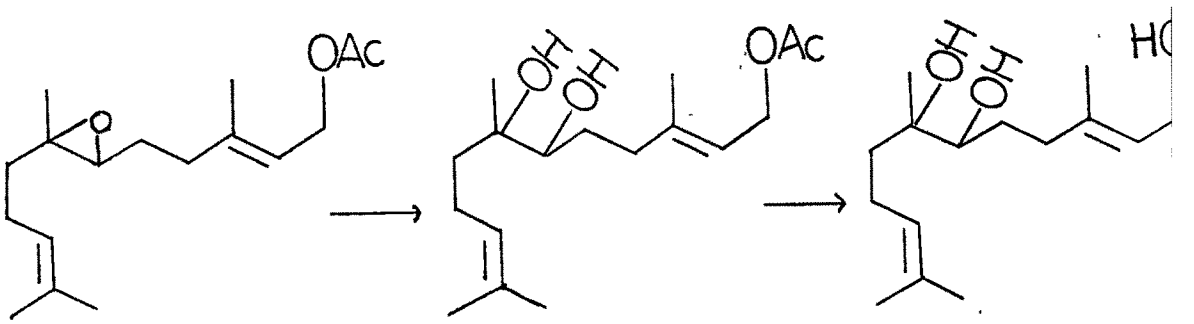
SCHEME-II

For the synthesis of (E),(E)-farnesol, the method had to be so chosen that the starting material was readily available to us. Thus, the choice fell on (E)-geranyl acetone (3), as it would fix the geometry of 6,7-double bond in the final product as (E)- and thereby reduce the complexity of farnesol(s) into a mixture of 2 instead of 4 isomers.

Out of all available routes to prepare (E),(E)-farnesol from (E)-geranyl acetone, we followed the route consists of the Wittig-Horner olefination of (3) and separation of the resultant (cis)- and (trans)-esters by precise fractionation on an annular teflon spinning band column of 80 theoretical plates and converting the (E)-ester into allylic alcohol by LAH reduction. (For details see Chapter-II, synthesis of (E),(Z)-farnesols). (trans) , (trans)-Farnesol, prepared in the described way, was converted into its acetate by the action of acetic anhydride and pyridine. (E),(E)-Farnesyl acetate (5) was subjected to epoxidation reaction with monoperphthallic acid[12] in diethyl ether solution, which afforded mixture of 6,7- and 10,11-monoepoxides and 6,7; 10,11-diepoxide but no trace of 2,3-epoxide was observed. These were



separated by column chromotography (Silica-gel-G, grade III, 8 % EtOAc in benzene) in pure form and characterised the monoepoxides by their spectral characteristics. 6,7-epoxy farnesyl acetate 5(b) was converted into 6,7-dihydroxy-farnesyl acetate by the action of 1 % H_3PO_4/aq. dioxan. It was purified by column chromatography (Silica gel-G, grade II-B) and distilled the diol under reduced pressure. It was characterised by its spectral properties. 2(trans)-6,7-dihydroxy-farnesyl acetate (6) was hydrolysed using KOH/aq. ethanol to afford 2(trans)-6,7-dihydroxy-farnes-1-ol (2). It was distilled under reduced pressure and characterised by its spectral properties.

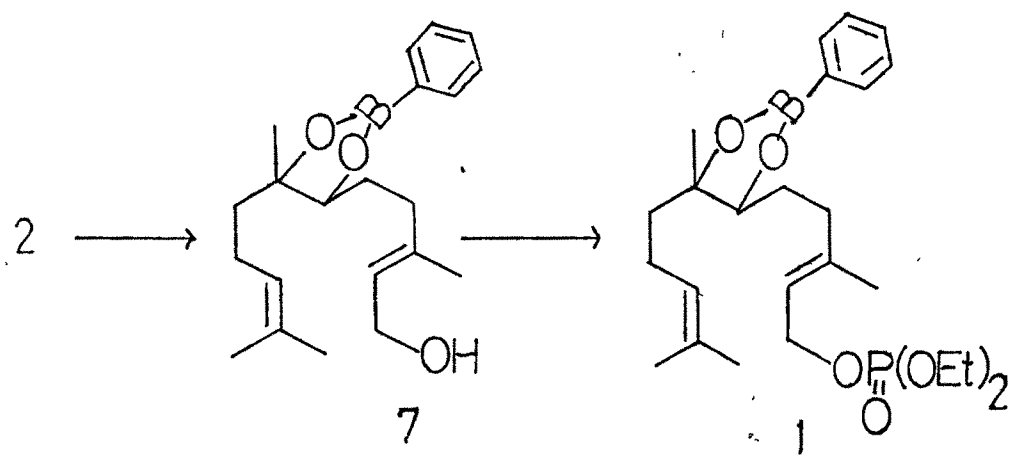


5b 6 2

(3) Protection of diol (2) was carried out with phenyl boronic acid[13] by refluxing in pyridine. The protected diol (7) was purified by column chromatography (Silica gel-G, grade II-B) and characterised by its spectral properties.

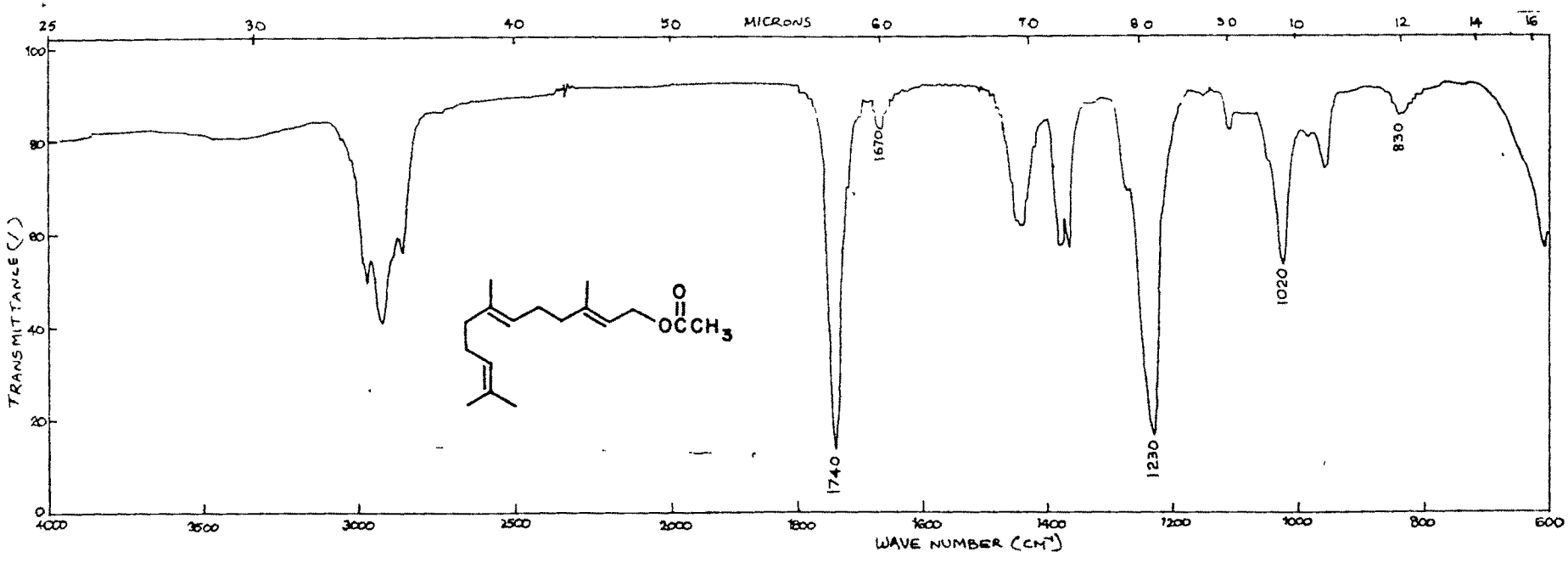
Preparation of 2(trans)-6,7-dihydroxy (protected by phenyl boronic acid) farnesyl diethyl phosphate (1):

2(trans)-6,7-dihydroxy (protected by phenyl boronic acid) farnes-1-ol (7) was converted into its diethyl phosphate ester by using diethyl chlorophosphoridate and pyridine in dry dichloromethane, under the similar experimental conditions described for geranyl diethyl phosphate.

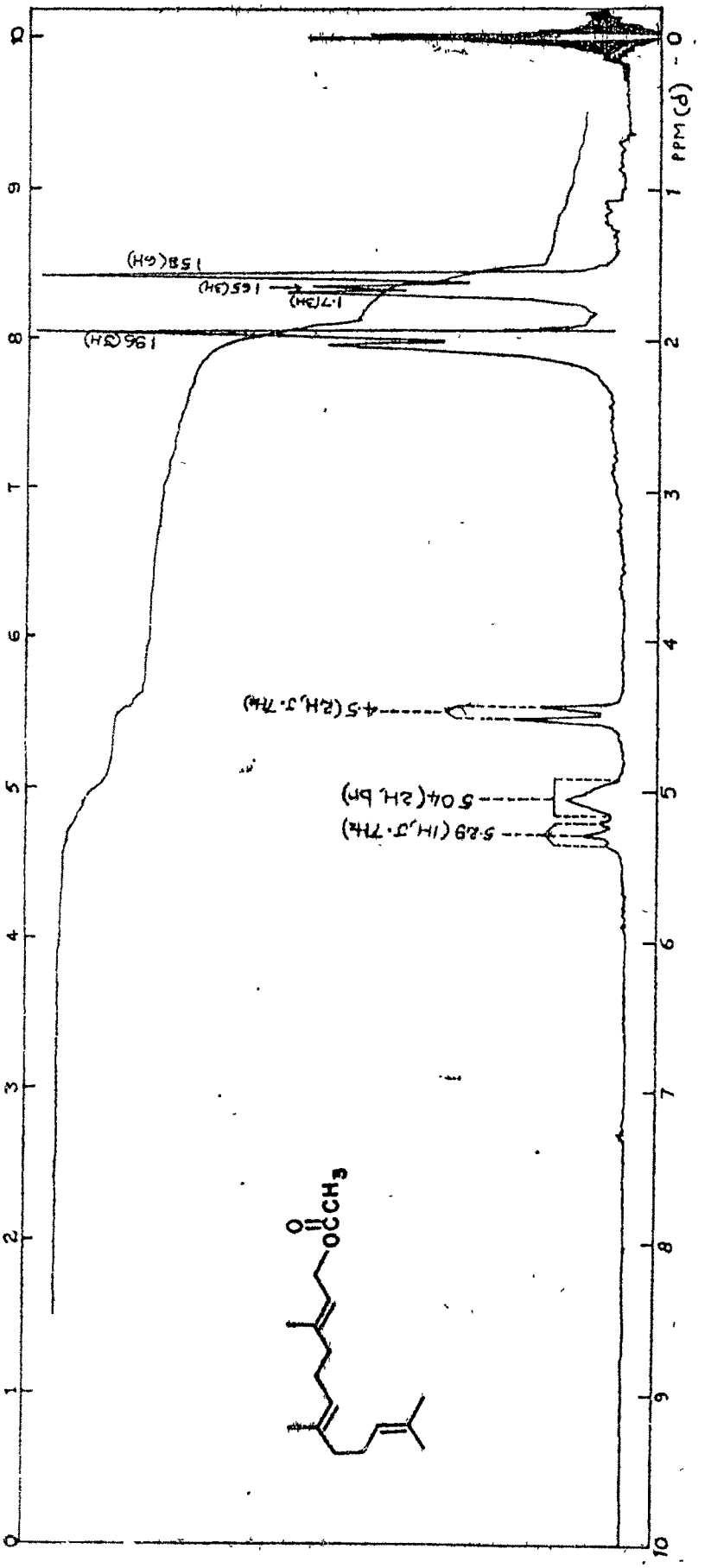


Reaction of (1) with active alumina:

A reaction of (1), (0.5 gm, 0.001 mol) with active alumina (15 gm, grade I) in dry dichloromethane was carried out by shaking the reaction flask, using mechanical shaker for 4 hours at room temperature (~30°C) and kept the reaction flask for 12 hours at room temp. (~30°C). After work up, it afforded a crude light yellow oil, 0.120 gm. PMR of this revealed, it is a mixture of many compounds, mainly elimination products. It was not further studied.

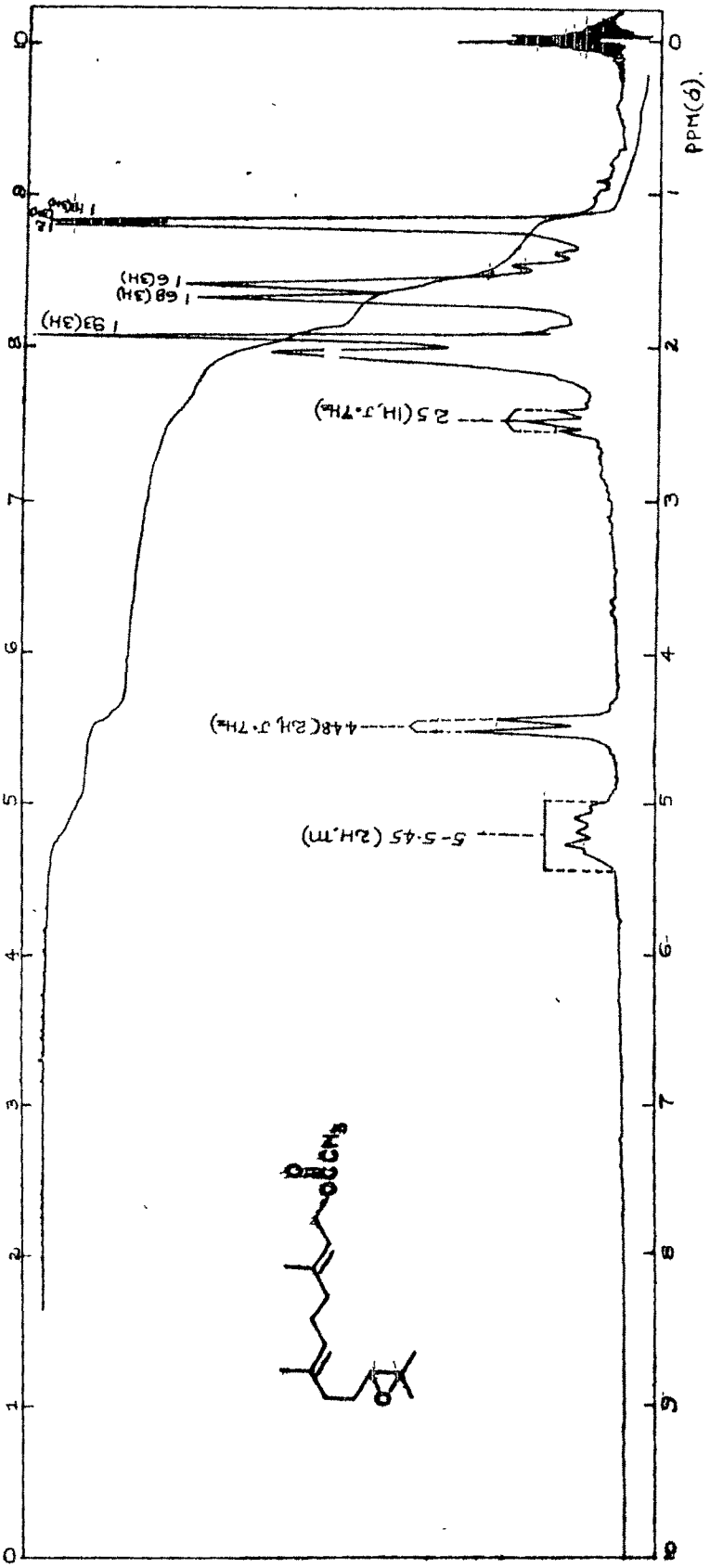


Sp.B.1a. : IR spectrum of 2(E), 6(E)-farnesyl acetate (5)

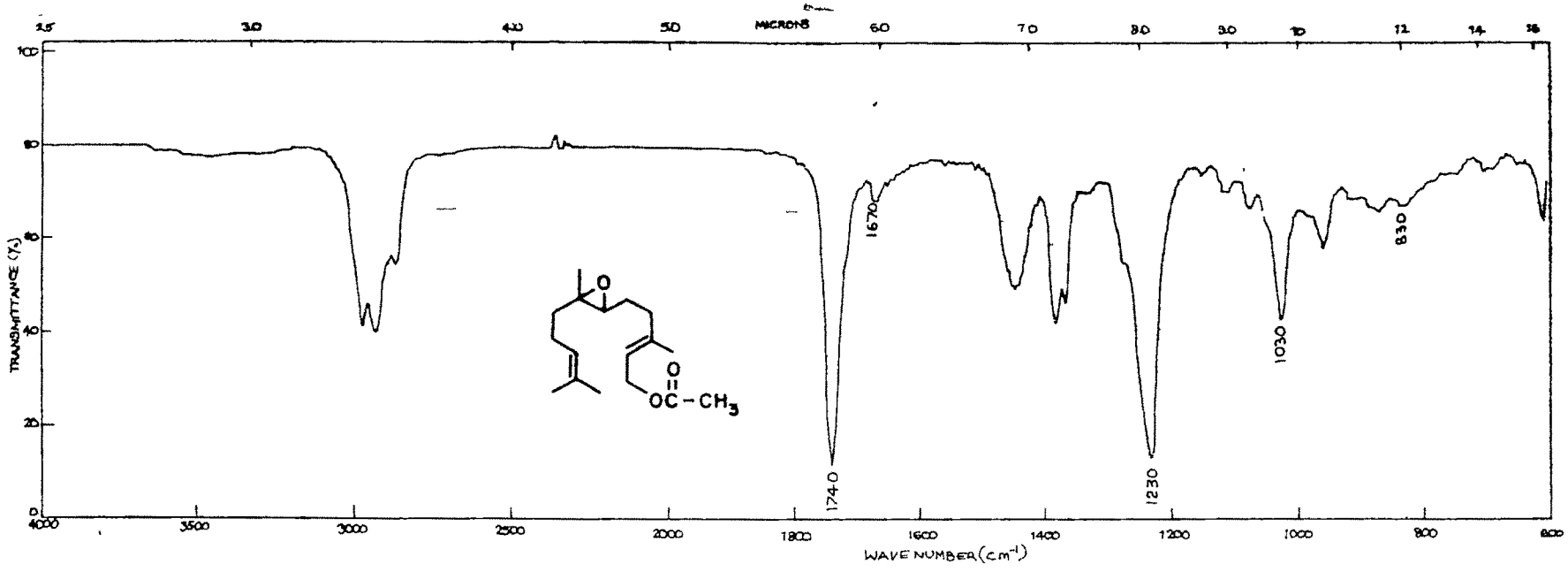


Sp.B.1b : PMR spectrum of 2(E), 6(E)-farnesyl acetate (5)

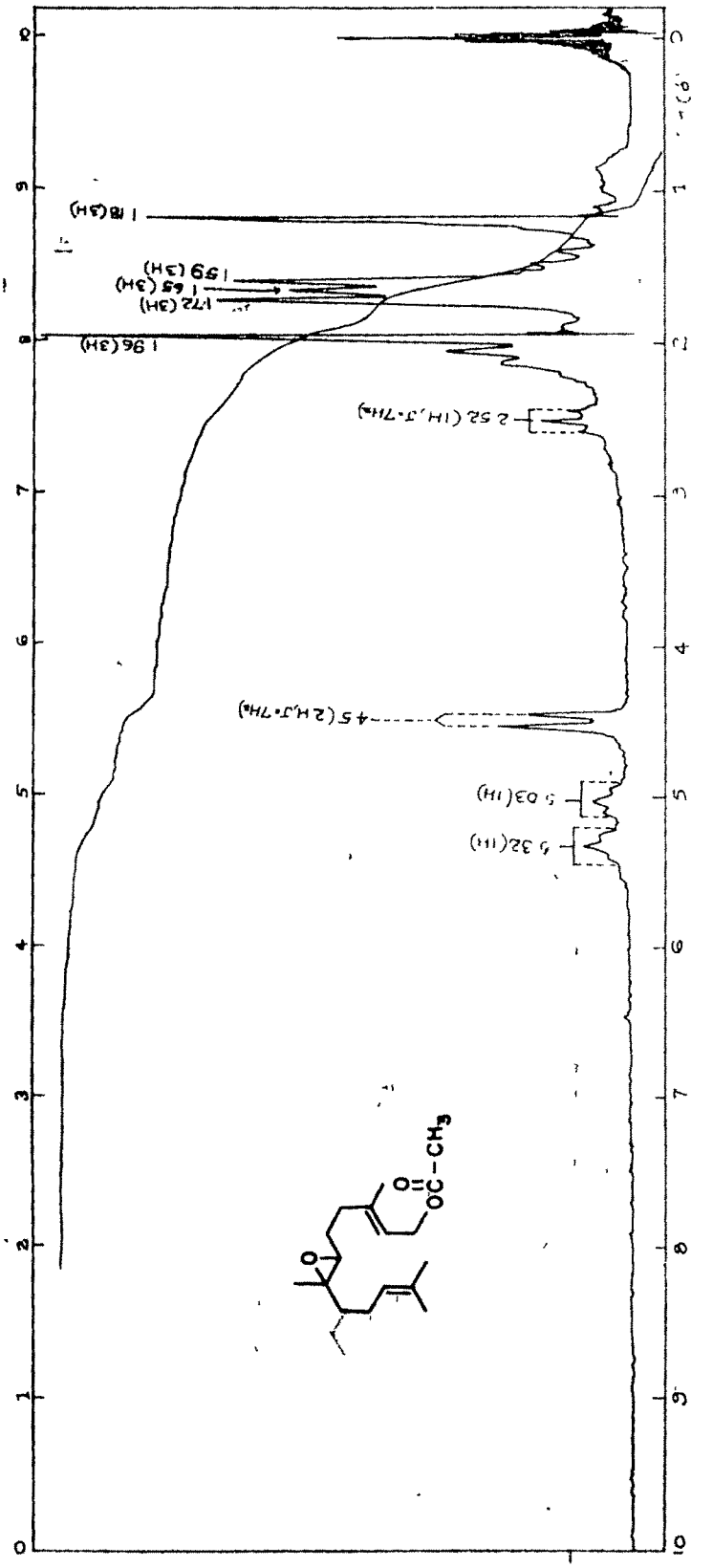
281



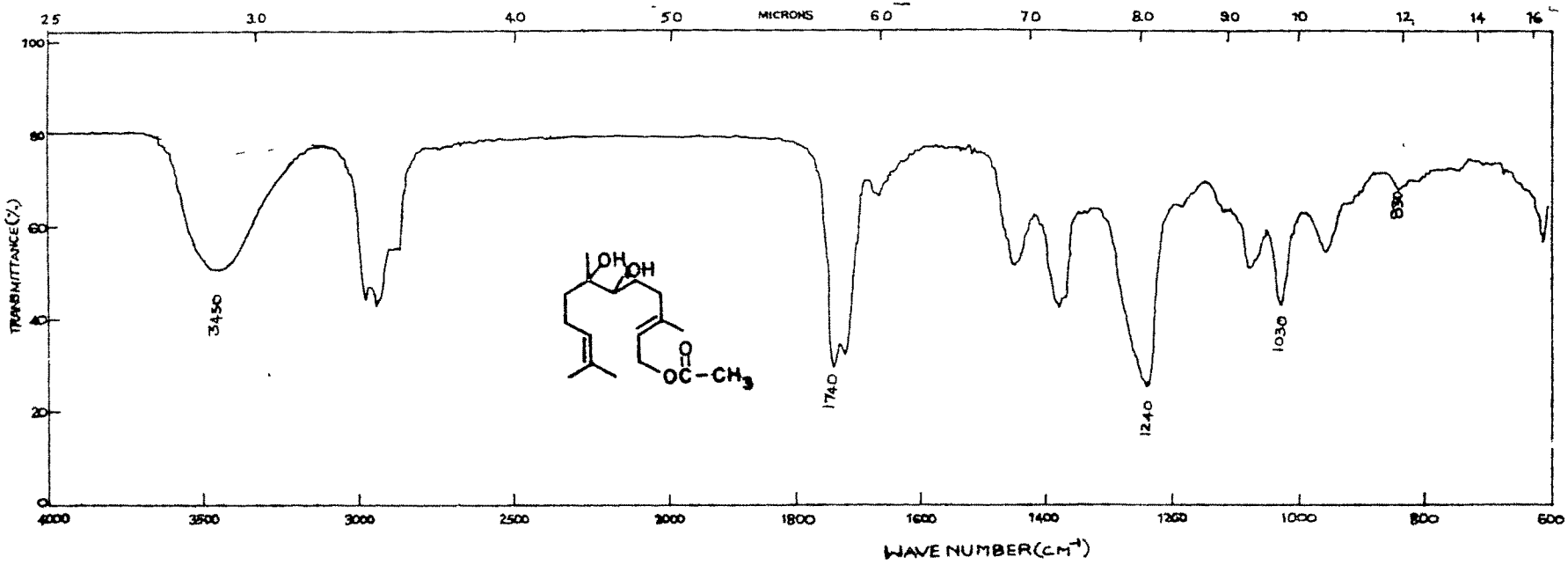
Sp.B.2 : PMR spectrum of 2(E), 6(E)-10,11-epoxy farnesyl acetate (5a)



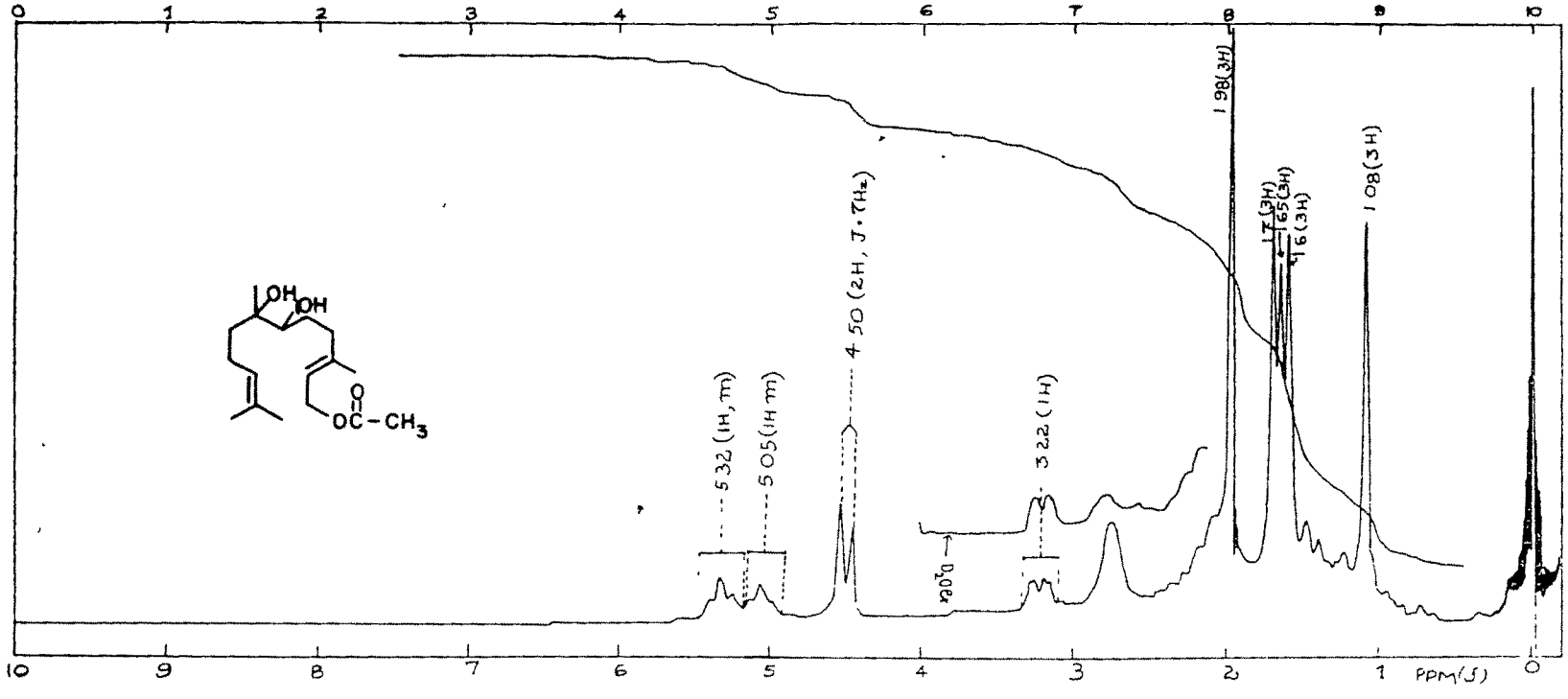
Sp.B.3a : IR spectrum of 2(E)-6,7-epoxyfarnesyl acetate (5b)



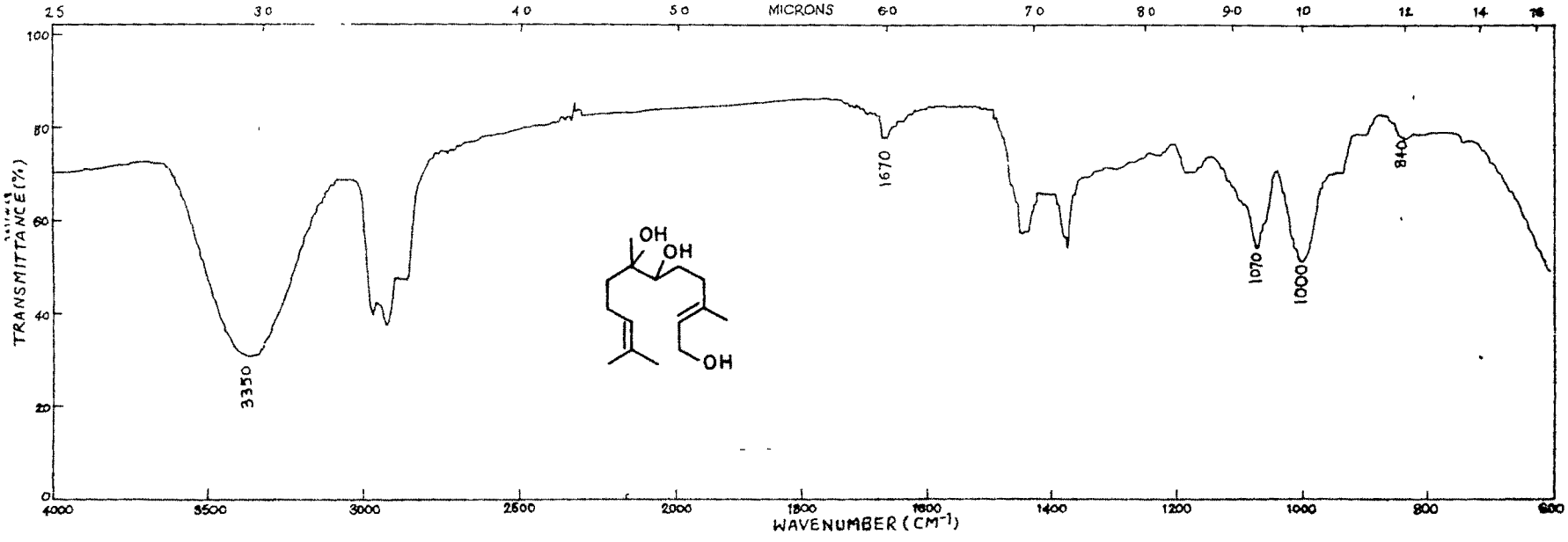
Sp.B.2b : PMR spectrum of 2(E)-6,7-epoxyfarnesyl acetate (5b)



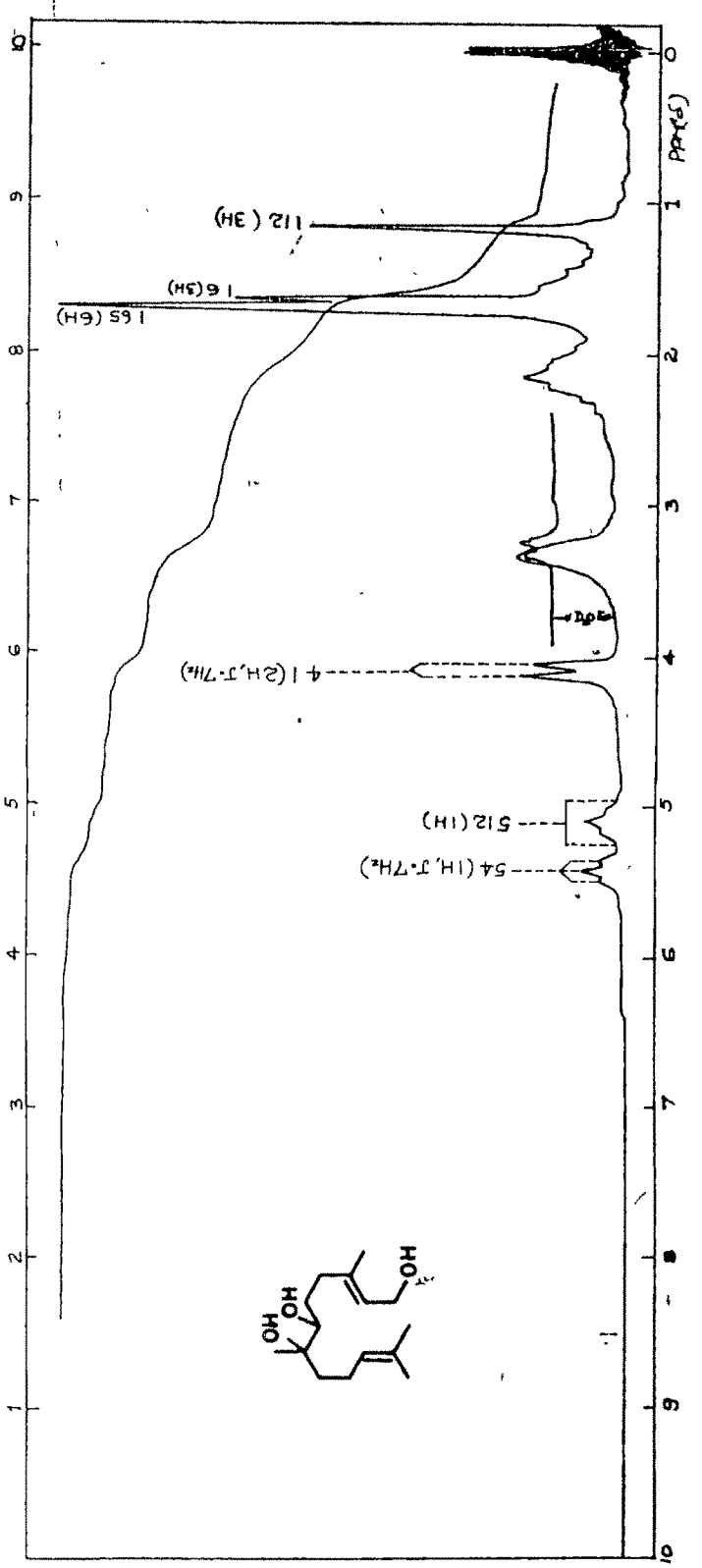
Sp.B.4a : IR spectrum of 2(E)-6,7-dihydroxy farnesyl acetate (6)



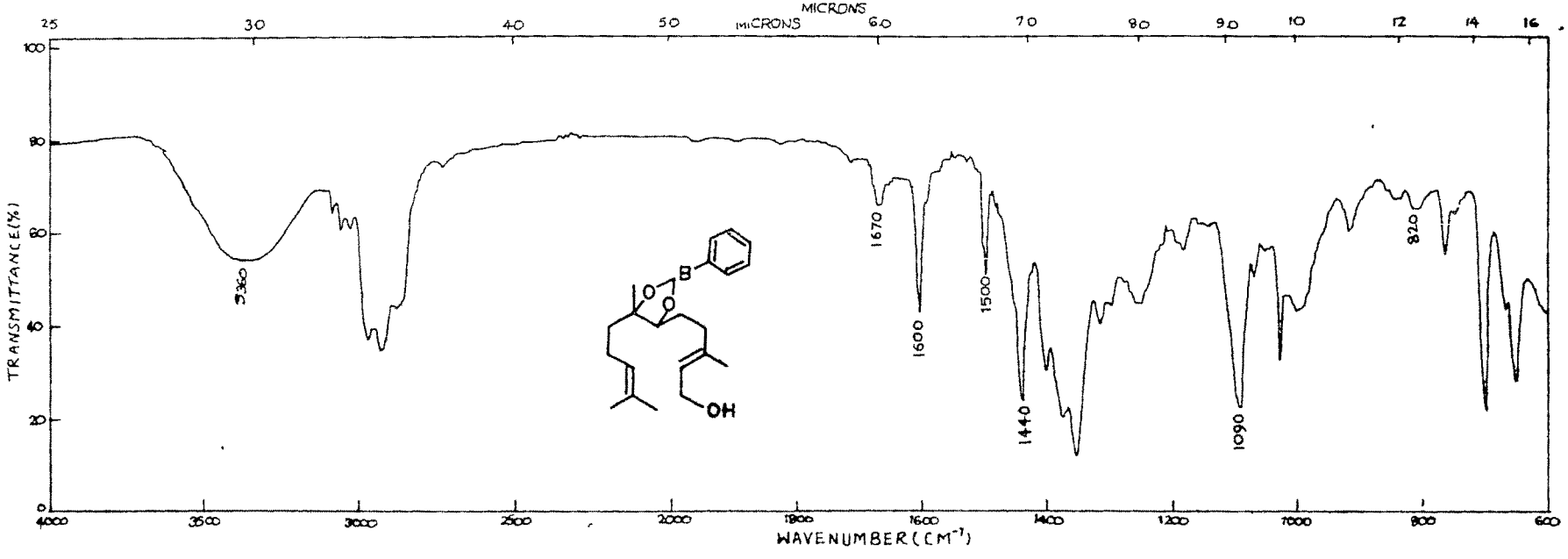
Sp.B.4b : PMR spectrum of 2(E)-6,7-dihydroxyfarnesyl acetate (6)



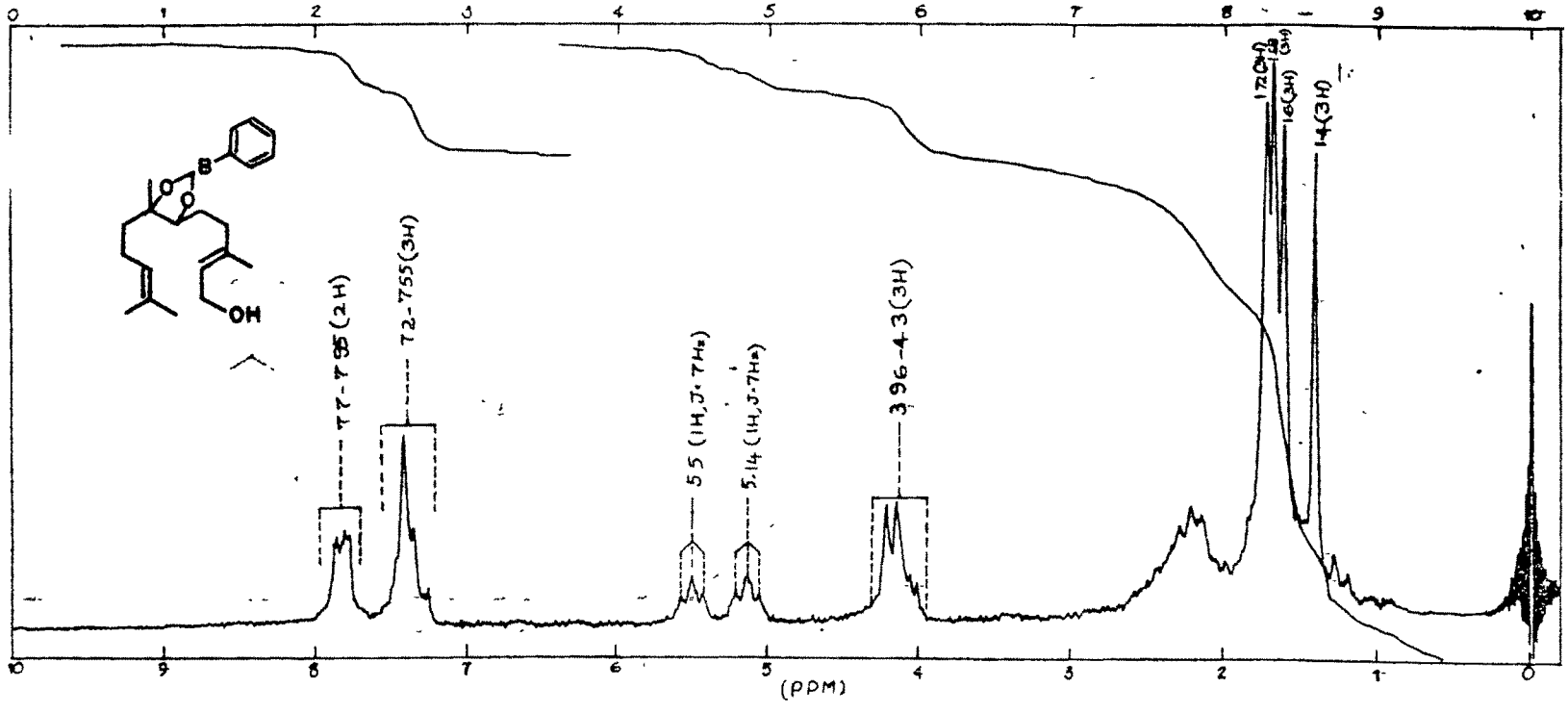
Sp.B.5a : IR spectrum of 2(E)-6,7-dihydroxyfarnesol (2)



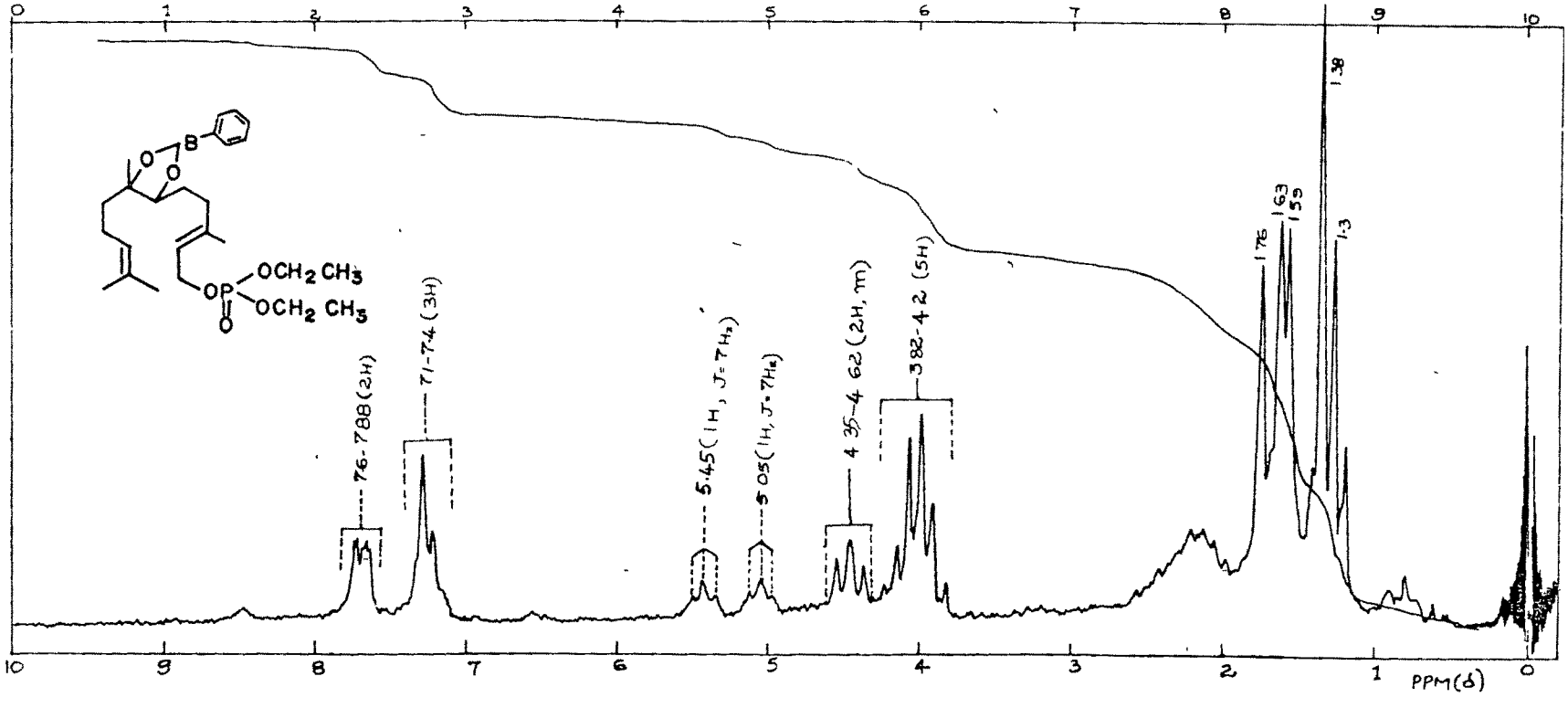
Sp.B.5b : PMR spectrum of 2(E)-6,7-dihydroxyfarnesol (2)



Sp.B.6a : IR spectrum of 2(E)-6,7-dihydroxy (protected by phenyl boronic acid) farnesol (7)



Sp.B.6b : PMR spectrum of 2(E)-6,7-dihydroxy (protected by phenyl boronic acid) farnesol (7)



Sp.B.7 : PMR spectrum of 2(E)-6,7-dihydroxy (protected by phenyl boronic acid) farnesyl diethyl phosphate (1)

Discussion :

Obviously our initial objective of achieving a synthesis of 10 or 11-membered ring compounds via biogenetic pathway, by intramolecular cyclization of 2(E)-6,7-dihydroxy (protected by phenyl boronic acid) farnesyl diethyl phosphate, has not been realized. Though, our mode of detection does not preclude the presence of trace amounts of 10/11-membered ring compounds, this approach can have no synthetic utility.

EXPERIMENTAL

All m.p.'s and b.p.'s are uncorrected. For general remarks see Chapter-II (Experimental)

PART-A

Aldol condensation of citronellal (7) with acetone

To the mechanically stirred solution of 1 % KOH solution (450 ml) and acetone (distilled, 90 gm, 1.85 mol), pure citronellal (freshly distilled, 60 gm, 0.39 mol) was added dropwise over a period of 15 minutes at room temperature (35°C) and further stirred vigorously for 50 hrs at 30°C. Organic layer was separated. The aqueous layer was extracted with solvent ether (50 ml x 4). The combined organic layers were washed with cold water, till the washings are neutral to pH. Finally, it was washed with brine solution (40 ml). It was dried over anhy. Na_2SO_4. Solvent was removed by distillation, which afforded 68 gm of the crude yellow oil. It was fractionated and three fractions were collected.

Frn No.	Wt. (gm)	Temperature	Vacuum
1	14.59	60-95°C	3.5 mm
2	48.16	100-150°C	3.5 mm
3	3	130-138°C	3.5 mm

Fraction No.2 contains α,β-unsaturated ketone and hydroxy ketone. This fraction was refluxed with acetic anhydride (60 ml) for 3 hrs and distilled off the acetic anhydride, which afforded a crude mixture. It was again fractionated.

Frn No.	Wt. (gm)	Temperature	Vacuum
1	10.22	80°C	0.06 mm
2	6.8	80-85°C	0.06 mm
3	28	85-88°C	0.06 mm
residue	2	-	-

Fraction No.3 was redistilled, b.p. 86-87°C/0.06 mm, to get 26 gm (34 % yield) of α,β-unsaturated ketone (95 % pure), (GLC column: 360 cm X 0.318 cm, stainless steel

column, packed with 10 % carbowax on 60-80 mesh Chromosorb W; temperature: 170°C; Carrier gas: 60 ml H_2/min).

3,9 Undecadien-2-one 6,10 dimethyl (13)

B.P. : (86-87°C)/0.06 mm

IR (Film) : 1680, 1630, 830 cm^{-1}

PMR : $\underline{H_3C}$-CH (3H, d, J=7Hz, 0.92 ppm); 2 $\underline{CH_3}$-C=C (6H; 3H, S, 1.58 ppm, 3H, S, 1.66 ppm); $\underline{CH}$=C< (1H, ill resolved triplet 5.04 ppm); $\underline{HC}$=C-C (1H, d, J=14Hz, 5.96 ppm); CH_2-$\underline{CH}$=C-C (1H, sextet, J=7Hz, 5.64 ppm).

Hydrogenation of α,β-unsaturated ketone (13)

α,β-Unsaturated ketone (1 gm, 0.005 mol) was hydrogenated (162 ml of H_2) over 5 % Rh/Al_2O_3 catalyst in ethanol (10 ml) by stirring the heterogenous mixture. Solvent was filtered and was distilled, which afforded 1 gm of (~100 % yield) 5,6-dihydro geranyl acetone (6) (95 % pure). It was distilled under reduced pressure (81-82°C/0.35 mm).

5,6-dihydro geranyl acetone (6)

B.P. : 81-82°C/0.35 mm

I.R. (Film) : 1715, 830 cm^{-1}

PMR : $\underline{H_3C}$-CH (3H, d, J=7Hz, 0.86 ppm); 2 $\underline{CH_3}$-C=C (6H; 3H, S, 1.57 ppm, 3H, S, 1.65 ppm); $\underline{CH_3}$-$\underset{\underset{O}{\|}}{C}$- (3H, t, J=7Hz, 2.32 ppm); $\underline{HC}$=C-C (1H, ill resolved triplet 5. ppm).

Wittig-Horner reaction on 5,6-dihydro-geranyl acetone (6)

Sodium hydride (1 gm, 50 % , 0.021 mol) was placed in dry THF and the slurry was cooled to 10°C. Triethyl phosphonoacetate (freshly prepared and distilled, 3.51 gm, 0.015 mol) was added dropwise under stirring in 30 minutes. After completion of the addition stirring was continued at room temp. for 1 hr. At the end of this period 5,6-dihydro-geranyl acetone (6) (2.0 gm, 0.01 mol) in THF (3 ml) was added dropwise during which some evolution of heat was observed. The solution was stirred at 50°C for 3 hrs and kept at room temperature (~30°C) for 12 hrs. The reaction mixture was taken up in a large excess of water (30 ml) and extracted with ether (10 ml x 3). The combined ethereal extract was dried (Na_2SO_4) and evaporated to give the crude mixture of esters (2.72 gm, ~100 percent yield).

Separation of 2(Z)- and 2(E)-esters (7a and 7b)

GLC of the mixture showed a composition of 41.28 percent of (cis)-ester (7a), 48.2 percent of the (trans)-ester (7b) and 10 percent of the unwanted isomers. The required isomers (7a) and (7b) were separated by column chromatography (grade: II-B).

CHROMOTOGRAM-I

Column dimensions : 80 cm x 2.1 cm

Amt of silicagel : 100 gm

Wt.of compd loaded : 5 gm

Frn No.	Solvent	Vol of eluate	Wt. (gm)	Remarks
1-5	Pet.ether (60-80°)	50 ml x 5	-	-
6-9	,,	50 ml x 4	0.6	Unwanted isomers
10-15	,,	50 ml x 6	0.7	(7a)
16-20	,,	50 ml x 5	0.8	(7a)
21-25	,,	50 ml x 5	0.4	(7a)
26-30	,,	50 ml x 5	0.2	(7a)
31-35	,,	50 ml x 5	0.4	(7a) + (7b)
36-40	,,	50 ml x 5	0.6	(7b)
41-60	1 % EtOA/PE	50 ml x 20	0.9	(7b)

The Z-isomer (7a) and E-isomer (7b) were obtained in 96 percent (GLC). Their PMR spectra agreed with the reported values.

PMR : 7(a)

H_3C-CH (3H, d, J=7Hz, 0.86 ppm); H_3C-C=C (6H; 3H, s, 1.5 ppm, 3H, s, 1.64 ppm); H_3C-C=C-COOEt (3H, s, 1.85 ppm); CH_2-C=C-COOEt (2H, ill resolved triplet 2.52 ppm); O-CH_2-CH_3 (2H, qr; J=7Hz, 4.08 ppm), CH-C=C< (1H, ill resolved triplet 5.02); -C(=O)-CH-C=C (1H, S, 5.55 ppm).

PMR : 7(b)

H_3C-CH (3H, d, J=7Hz, 0.86 ppm); H_3C-C=C (6H; 3H, s, 1.56 ppm, 3H, s, 1.65 ppm); H_3C-C=C=COOEt (cis- to ester group, 3H, s, 2.02 ppm); -O-CH_2-CH_3 (2H, qr, J=7Hz, 4.08 ppm); HC-C=C< (1H, ill resolved triplet 5.02 ppm); -C(=O)-CH-C=C (1H, s, 5.5 ppm).

Reduction of the ester to the alcohol (1)

A suspension of 500 mg lithium aluminium hydride in dry ether (5 ml) was cooled to -5°C and to it was added a solution of the ester (cis + trans) (3 gm, 0.01127 mol) in dry ether (5 ml) in a dropwise manner, under stirring, over a period of about 15 minutes. After completion of addition the stirring was continued for 2 hrs at -5°C, then the reaction mixture was allowed to get 0°C and the stirring continued for a further period of 6 hrs. It was allowed to come to room temperature (~25°C) and stirred at this temp. for 2 hrs. The reaction mixture was then decomposed with cold water, 5 percent HCl and extracted with ether (20 ml x 3). The combined extract was washed with water, dried (Na_2SO_4) and evaporated to yield 2.3 gm of the alcohol (92 percent yield). Purification was done by column chromatography.

Acetylene addition route (Scheme-IV)

Anhydrous ether (18 ml) was cooled to -18°C and saturated with dry purified acetylene gas for 1 hr under mechanical stirring with the acetylene flow at a rate of 15 lit/hr. A solution of 5,6-dihydro geranyl acetone (6) (9 gm, 0.045 mol) in dry ether (17 ml) and a solution of potassium (2.6 gm), dissolved in anhydrous (refluxed and distilled over Na) t-amyl alcohol (46 ml), were added

separately to the ether solution of acetylene under vigorous mechanical stirring over a period of 2 hours. The acetylene flow rate was raised to 32-35 lit/hr during this addition and the reaction mixture kept at -10°C to -15°C. After complete addition, the reaction mixture was further stirred for 4 hrs at 0° with the acetylene gas flow rate reduced to 15 lit/hr. when by TLC (12 percent ethyl acetate in pet.ether 60-80°C) it was revealed that the reaction was complete. The reaction mixture was decomposed by cold water, the product taken up in ether (40 ml x 3), washed with 5 percent NH_4Cl (20 ml x 2) followed by water till the aqueous layer was neutral. Drying (Na_2SO_4) of the ether extract followed by removal of solvent furnishes the crude tertiary alcohol (12). Distillation yields the pure material (b.p. 120-130°C/1.8 mm) in good yield (9.38 gm, 93 percent yield).

I.R. (Neat) : 3400, 3310, 1640, 1115 cm^{-1}.

PMR : $\underline{H_3C}$-CH (3H, d, J=7Hz, 0.86 ppm); $\underline{H_3C}$-$\overset{OH}{\overset{|}{C}}$-C≡C (3H, s, 1.42 ppm); two $\underline{CH_3}$-C=C< (6H; 3H, s, 1.58 ppm, 3H, s, 1.65 ppm); $\underline{HC}$≡C- (1H, s, 2.28 ppm); $\underline{HC}$=C (1H, ill resolved triplet 5.04 ppm).

MS : m/e 222 (M^+, 0.96 %), 207 (2.24 %), 204 (3.2 %), 189 (30.12 %), 176 (3.8 %), 161 (22.4 %), 109 (54.48 %), 69 (100 %), 55 (69.23 %), 41 (98.7 %).

Anal : Found C, 80.45; H, 11.89. $C_{15}H_{26}O$ requires C, 81.08; H, 11.7.

Tertiary alcohol to acetate (13)

In a 100 ml 3-necked flask equipped with a thermometer, reflux condenser and dropping funnel was taken 5 gm (0.023 mol) of (12). A mixture of acetic anhydride (4.014 gm, 0.039 mol) and H_3PO_4 (0.057 gm) was added during one hour with stirring whereby the temp. rises to ~50°C. After complete addition it was kept overnight at room temperature when it shows complete conversion (tlc). The reaction mixture was poured over cold water and extracted with ether (70 ml x 3). The combined extract washed with cold water and dried (Na_2SO_4). Evaporation of solvent gives (6 gm, quantitative). A small portion of the acetate (13) was distilled for its spectral data (b.p. 120-140° (bath)/ 1.5 mm).

IR (Neat) : C≡C-H 3280; C=O 1730, C-O 1230 cm^{-1}.

PMR : $\underline{CH_3}$-C-H (3H, d, J=7Hz, 0.88 ppm); $\underline{CH_3}$-C(OAc)-C≡C (3H, s, 1.58 ppm); gem di Me's (6H, br, 1.62 ppm); $\underline{CH_3}$-CO-O (3H, s, 1.95 ppm); $\underline{H}$-C≡C (1H, s, 2.40 ppm); $\underline{HC}$=C (1H, ill resolved triplet 5.03 ppm).

MS : m/e 249 (M^+, 1.28 %), 222 (12.82 %), 204 (9.61 %), 189 (51.28 %), 161 (44.83 %), 133 (60.25 %), 109 (98.7 %), 93 (81.4 %), 69 (100 %), 55 (96.15 %).

Anal : Found C, 77.03; H, 10.56, $C_{17}H_{28}O_2$ requires C, 77.27; H, 10.60.

Acetate to allenic acetate + diacetate (A + B)

The above acetate (5 gm, 0.019 mol) was rearranged by treatment with glacial acetic acid (10 gm, 0.176 mol) and silver carbonate (0.03 gm) and warming to 90°C under a nitrogen atmosphere for 1.5 hr. whereby due to heat of reaction the inner temp. after 1 hr reached 110°C. The reaction mixture was then cooled, poured into water and extracted with Et_2O (30 ml x 3). The combined ether extracts was washed with water and dried (Na_2SO_4). Evaporation of ether gives the allenic acetate + diacetate mixture as a pale yellow oil (6 gm) which without further purification was put for hydrolysis.

Hydrolysis with sodium methoxide

1 gm of the above mixture was added to a solution of sodium methoxide (0.1 gm Na dissolved in 30 ml methanol) and the mixture kept at room temperature for 4 hrs. The reaction mixture was poured into water (20 ml), saturated with brine and extracted with ether (30 ml x 3). Drying (Na_2SO_4) followed by solvent removal from the combined extract gave a residue (1.0 gm).

6,7-dihydro-farnesal(s) (14)

In IR and PMR only characteristic bands or signals due to aldehyde group are mentioned.

IR : C=O, 1675 cm^{-1}

PMR : =CH CHO (1H, d, 5.78 ppm); =CH CHO (1H, m, 9.9 ppm due to the (cis)- and (trans)-isomers).

Aldehyde to alcohol (1)

To a cooled ($0^{\circ}C$), well dispersed suspension of LAH (0.6 gm, 80 percent active) in dry ether is added under stirring a solution 3 gr (14) in dry ether (3 ml) over a period of 15 min. After completion of addition, stirring is continued at $0^{\circ}C$ for 1 hr at the end of which the reaction mixture was decomposed with cold water and extracted with ether (5 ml x 3). The ether extract was dried (Na_2SO_4) and then evaporated to give the crude mixture of Z- and E-6,7-dihydrofarnesol (1) (3.0 gm).

Separation of 2(Z)- and 2(E)-6,7-dihydrofarnesols

On the basis of PMR the mixture appeared to contain the isomers in the proportion [cis] : [trans], 40:60. Separation was affected by column chromatography over 5 percent $AgNO_3$-SiO_2-gel (grade: II B).

CHROMATOGRAM-II

Column dimensions : 105 cm X 1.7 cm

Amt. of Silica gel : 120 gm

Wt. of compd loaded : 3.5 gm

Frn No.	Solvent	Vol.of eluate	Wt. (gm)	Remarks
1-10	Pet.ether	5 ml x 10	-	-
11-20	Pet.ether+ 1 % EtOAc	5 ml x 10	-	-
21-25	Pet.ether+ 5 % EtOAc	5 ml x 5	-	-
26-30	- do -	5 ml x 5	0.02	impurities
31-34	- do -	5 ml x 4	-	-
35-41	- do -	5 ml x 7	0.9	cis- (1a)
42-49	- do -	5 ml x 8	1.0	cis+trans (1)
50-60	- do -	5 ml x 11	1.1	trans- (1b)

Pure (Z)- and (E)-6,7-dihydrofarnesols were obtained by this procedure and they were characterised from their PMR and IR spectra. The PMR values coincide with those reported for these compounds.

(i) Z- (1a)

B.P. : 111-114°C/0.2 mm

IR (Neat) : 3325, 1660, 1000 cm^{-1}

PMR : $\underline{H_3C}$-CH (3H, d, J-7Hz, 0.86 ppm); 3 $\underline{H_3C}$-C=C (9H; 3H, s, 1.58 ppm; 3H, s, 1.65 ppm; 3H, s, 1.7 ppm); HO-$\underline{CH_2}$- (2H, d, J=7Hz, 4.0 ppm); $\underline{HC}$=C< (1H, ill resolved triplet 5.02 ppm); $\underline{HC}$=C-CH_2OH (1H, ill resolved triplet 5.32 ppm).

(ii) E- (1b)

B.P.:111-116°C/0.2 mm

I.R. (Neat): 3325, 1670, 1000 cm^{-1}

PMR : $\underline{CH_3}$-CH (3H, d, J=7Hz, 0.86 ppm); 3 $\underline{CH_3}$-C=C (9H; 3H, s, 1.58 ppm; 6H, s, 1.65 ppm); -$\underline{CH_2}$-OH (2H, d, J=7Hz, 4.02 ppm). $\underline{HC}$=C< (1H, ill resolved triplet 5.02 ppm) $\underline{HC}$=C-CH_2OH (1H, ill resolved triplet 5.32 ppm).

Preparation of 2(cis)-6,7-dihydrofarnesyl diethyl phosphate

Diethyl chlorophosphoridate (freshly distilled, 0.952 gm, 0.0055 mol) in dry dichloromethane (2 ml) was added dropwise during one hour to a stirred mixture of 2(cis)-6,7-dihydrofarnesol (freshly distilled, 0.9 gm, 0.004 mol), pyridine (0.784 gm, 0.0099 mol) and dichloromethane (2 ml) under the exclusion of moisture (anhy. $CaCl_2$ guard tube) at -5°C. Stirring was continued for a period of 3 hours at 0°C. The reaction mixture was poured over ice-water and extracted with solvent ether (10 ml x 3). The combined organic extract was washed with dil H_2SO_4 (5 % aq.; 5 ml x 2), water, dil. $NaHCO_3$ (5 % aq., 5 ml x 2) and thoroughly with water till the washings are neutral and dried over Na_2SO_4 (anhy.). The solvent was filtered and evacuated in vacuo to give a colourless oil, 1.56 gm (97.5 % yield). This diethyl phosphate ester was pure to TLC analysis (18 % EtOAc/Pet. ether 60-80°C) and spectroscopically consistent.

IR (Neat) : 1660, 1370, 1040, 830 cm^{-1}

PMR : $\underline{H_3C}$-CH (3H, d, J=7Hz, 0.86 ppm), $\underline{CH_3}$-CH_2-O$\overset{O}{\overset{\|}{P}}$ (6H, t, J=7Hz, 1.3 ppm); three $\underline{H_3C}$-C=C (9H; 3H, s, 1.58, 3H, s, 1.66, 3H, s, 1.7 ppm); P-O-$\underline{CH_2}$-CH_3 (4H, m, 3.82-4.22 ppm). -$\underline{CH_2}$-O$\overset{O}{\overset{\|}{P}}$- (2H, m, 4.3-4.62 ppm); HC=C< (1H, ill resolved triplet, 5.02 ppm); C=$\underline{CH}$-CH_2-OP (1H, ill resolved triplet, 5.34 ppm).

Preparation of 2(trans)-6,7-dihydrofarnesyl diethyl phosphate

2(trans)-6,7-dihydrofarnesol was converted into its diethyl phosphate ester by the same procedure as described for 2(cis)-isomer. 2(trans)-6,7-dihydrofarnesol (0.9 gm, 0.004 mol), diethyl chloro phosphate (0.952 gm, 0.0055 mol), pyridine (0.784 gm, 0.0099 mol). After the usual work up, it afforded 2(trans)-6,7-dihydrofarnesyl diethyl phosphate ester (1.4 gm, 87.5 % yield).

IR (Film) : 1660, 1270, 1030, 820 cm^{-1}

PMR : $\underline{H_3C}$-CH (3H, d, J=7Hz, 0.86 ppm); $\underline{H_3C}$-CH_2-O$\overset{O}{\overset{\|}{P}}$ (6H, t, J=7Hz, 1.3 ppm); 3 $\underline{H_3C}$-C=C (9H; 3H, s, 1.58, 3H, s, 1.7 ppm); P-O-$\underline{CH_2}$-CH_3 (4H, m, 3.82-4.22 ppm); -CH_2-OP- (2H, m, 4.34.62 ppm); $\underline{HC}$=C< (1H, ill resolved triplet, 5.34 ppm); C=$\underline{HC}$-CH_2-OP (1H, ill resolved triplet, 5.02 ppm).

Reaction of 2(cis)-6,7-dihydrofarnesyl diethyl phosphate with active alumina

Active alumina (pH:7, activity: grade I, 15 gm) was made as slurry with dry dichloromethane (15 ml) in a single necked flask and to this slurry, 2(cis)-6,7-dihydrofarnesyl diethyl phosphate (0.5 gm, 0.0013 mol) in dry dichloromethane (5 ml) was added dropwise by manually shaking

the flask. The reaction flask was flushed with dry nitrogen and stoppered. It was shaken for 4 hours by mechanical shaker at room temperature (~30°C) and kept overnight for 14 hrs at room temperature (~25°C). The reaction contents were transferred to a vertical chromatographic column and eluted with dichloromethane (15 ml x 10). The combined solvent eluants were distilled off very carefully using perkin triangle, which afforded crude colourless oil, 0.1 gm. It was distilled using micro bulb distillation unit, 110-130° (bath)/2 mm to furnish 0.085 gm of distillate and 0.010 gm of residue.

Reaction of 2(trans)-6,7-dihydrofarnesyl diethyl phosphate with active alumina

A reaction of 2(trans)-6,7-dihydrofarnesyl diethyl phosphate (0.5 gm, 0.0015 mol) with active alumina was carried out using the similar experimental conditions, described for 2(cis)-isomer. After work up, it afforded the colourless crude oil (0.160 gm). It was distilled to afford 0.110 gm of distillate and 0.015 gm of the residue.

Separation of pure isomers

Separation of pure isomers from the hydrocarbon mixture was attempted by column chromatography over 10 % $AgNO_3$-Silica gel G (100-200 mesh).

CHROMATOGRAM-III

Column dimensions - 33 cm X 0.8 cm

Amt.of Silica gel - 8 gm

Wt.of compd.loaded - 0.15 gm

Frn No.	Solvent	Vol.of eluate	Wt. (gm)	Remarks
1-5	Pet.ether (60-80°)	10 ml x 5	-	-
6-10	-do-	10 ml x 5	0.015	compd. (15)
11-20	-do-	10 ml x 10	0.020	mix.(15)+(16)
21-25	-do-	10 ml x 5	-	-
26-30	0.5 % EtOAc/Pet. ether	10 ml x 5	0.058	mix.(16)+(17)
31-35	-do-	10 ml x 5	0.0281	compd. (17)
36-50	-do-	10 ml x 15	-	-
51-60	4 % EtOAc/Pet. ether	10 ml x 10	0.010	impurities

Compound No.15 : 1,3(15),10-Dodecatriene,7,11-dimethyl

B.P. : 110-120 (bath)/2 mm

IR : 1620, 1580, 970, 870, 810 cm^{-1}

PMR : $\underline{H_3C}$-CH (3H, d, J=7Hz, 0.89 ppm); 2 $\underline{CH_3}$-C=C (6H; 3H, s, 1.54; 3H, 1.63 ppm); $\underline{CH_2}$=C and $\underline{CH}$=C (5H, m, 4.82-5.25 ppm); =C-$\underline{CH}$=CH_2 (1H, d,d, J=11Hz, 16Hz, 6.3 ppm).

Mass : m/e 206 (M^+, 2.8 %), 69 (100 %), 81 (87.8 %), 95 (60.7 %), 109 (64.2 %), 121 (25.3 %), 163 (7.8 %), 177 (3.6 %), 191 (4.3 %).

Compound No.17 : 1,3(7)(trans)-10-Dodecatriene,3,7,11-trimethyl

B.P. : 110-120 (bath)/2 mm

IR : 1640, 1610, 990, 895 cm^{-1}

PMR : $\underline{H_3C}$-CH (3H, d, J=7Hz, 0.89 ppm); 3 $\underline{CH_3}$-C=C- (9H; 3H, s, 1.6 ppm; 3H, s, 1.68 ppm; 3H, s, 1.72 ppm); $\underline{CH_2}$-C=C and $\underline{CH}$=C< (3H, m, 4.78-5.28 ppm); $\underline{HC}$=C (1H, t, J=7Hz, 5.4 ppm); =C-$\underline{CH}$=C (1H, d, d, J=11Hz, 16Hz, 6.26 ppm).

Mass : m/e 206 (M^+, 9.5 %), 191 (6.4 %), 177 (4.5 %), 163 (10.2 %), 121 (38.1 %), 109 (74.6 %), 95 (57.5 %), 81 (100 %), 69 (97.8 %), 55 (55.7 %).

PART-B

Attempted cis-hydroxylation of (E)-geranyl acetone

To a stirred solution of $KMnO_4$ (2.37 gm, 0.015 mol) in water, (E)-geranyl acetone (0.98 gm, 0.005 mol) in THF (4 ml) was added dropwise at room temperature (~30°C). It was further stirred vigorously for 12 hrs at room temp. (~30°C). TLC showed no change in the starting material. It was poured into cold water and extracted the compound in solvent ether (10 ml x 3). The combined organic extract was washed with water till neutral to pH and dried over sodium sulphate (anhy.). Solvent was removed by distillation, which afforded starting compound, (E)-geranyl acetone (0.9 gm).

Epoxidation of (E)-geranyl acetone

To a stirred solution of (trans)-geranyl acetone (0.98 gm, 0.005 mol) in CH_2Cl_2 solvent, meta-chloro perbenzoic acid (m-CPBA) in dry CH_2Cl_2 (0.86 gm, 0.005 mol) was added dropwise over period of 15 minutes at (5-10°C). It was further stirred for 30 minutes at 10°C. The reaction mixture was poured in water and extracted with solvent ether (10 ml x 3). The combined organic extract was washed successively with 10 % aq. sodium hydroxide (10 ml x 2) and then thoroughly with water till the water washings are

neutral and finally with the brine solution (10 ml). It was dried over anhy. sodium sulphate and evaporated the solvent by distillation. It afforded a crude product 1.29 gm. Mixture of monoepoxides was separated by column chromatography (on grade IV alumina) and PMR of this compound showed it is a mixture of 5,6- and 10,11-epoxy geranyl acetones. These monoepoxides could not be separated either by TLC or GLC techniques.

For the synthesis of (E),(E)-farnesol (see Chapter II, experimental)

Acetylation of (E),(E)-farnesol (4)

To the stirred solution of (E),(E)-farnesol (0.9 gm, 0.004 mol), in pyridine (0.5 gm, 0.0063 mol), acetic anhydride (1.63 gm, 0.0208 mol) was added slowly at 10°C and the flask was stoppered. It was kept at 5°C (refrigerator) for 14 hrs. It was poured into ice-water and extracted with ether (10 ml x 3). The combined solvent extract was washed successively with 10 % aq. sodium carbonate (10 ml x 4) and thoroughly with water till the washings are neutral to pH and finally washed with brine solution (10 ml). It was dried over anhy. sodium sulphate and removed the solvent by distillation. It afforded a crude product 0.95 gm which was distilled (140-150°(bath)/ 5 mm) to afford 0.90 gm of pure (E),(E)-farnesyl acetate.

IR (Neat) : 1740, 1670, 1230, 1020, 830 cm^{-1}

PMR : four $\underline{H_3C}$-C=C (9H; 6H, s, 1.58 ppm, 3H, s, 1.65 ppm, 3H, s, 1.7 ppm); $\underline{H_3C}$-C(=O)-O (3H, s, 1.96 ppm); $\underline{CH_2}$-OAc (2H, d, J=7Hz, 4.5 ppm); $\underline{HC}$=C (2H, br, 5.04 ppm); C=$\underline{CH}$-CH_2OAc (1H, t, J=7Hz, 5.29 ppm).

Epoxidation of (E), (E)-farnesyl acetate (5)

To a stirred solution of (E),(E)-farnesyl acetate (1.1 gm, 0.0041 mol) in solvent ether (10 ml), monoperphthallic acid (0.82 gm, 0.0044 mol) in solvent ether (19 ml) was added slowly, over a period of 30 minutes by maintaining the reaction temperature at 5°C. The reaction flask was stoppered and kept in refrigerator (5°C) for 14 hours. The ether layer was separated from the solid (phthallic acid). The solid was rinsed with solvent ether (10 ml x 3) and the combined ether layer was washed, successively with 10 % aq. sodium sulphate (10 ml x 2), 10 % aq. sodium hydroxide (10 ml x 2), then thoroughly with water till the water washings are neutral, and finally with brine solution (25 ml). The ether extract was dried over anhy. Na_2SO_4 and evaporated the solvent by distillation, which afforded a crude product 1.055 gm.

Separation of epoxides

Separation of 6,7- and 10,11-monoepoxy and 6,7; 10,11-diepoxy farnesyl acetates, was carried out by column chromatography (Silica gel-G; grade II-B).

CHROMATOGRAM-IV

Amt.of Silica-gel G (grade II-B) : 40 gm

Column dimensions : 52 cm X 1.8 cm

Wt.of compd loaded : 1 gm

Frn No.	Solvent	Vol. of eluate	Wt. (gm)	Remarks
1-5	Pet.ether	50 ml x 5	-	-
6-9	-do-	50 ml x 4	-	-
10-15	5 % EtOAc/Pet.ether	50 ml x 6	0.165	compd(5)
16-20	-do-	50 ml x 5	0.121	-do-
21-25	-do-	50 ml x 5	0.0836	-do-
26-28	-do-	50 ml x 3	0.0627	impurities
29-30	6 % EtOAc/Pet.ether	50 ml x 2	-	-
31-32	-do-	50 ml x 2	0.101	compd 5(b)
33-38	-do-	50 ml x 6	0.1432	compd 5(b)+ 5(a)
39-45	-do-	50 ml x 7	0.0812	compd 5(a)
46-50	-do-	50 ml x 5	0.160	compd 5(c)

The pure 6,7- and 10,11-monoepoxy farnesyl acetates were obtained by this procedure and they were characterised from their PMR and IR spectra.

(i) 2(trans)-6,7-epoxyfarnesyl acetate 5(b)

IR (Neat) : 1730, 1665, 1230, 830 cm^{-1}

PMR : $\underline{H_3C}$-$\overset{O}{\overset{/\backslash}{C}}$-C- (3H, s, 1.18 ppm); 3 $\underline{CH_3}$-C=C- (9H; 3H, s, 1.59, 3H, s, 1.65, 3H, s, 1.72 ppm); $\underline{CH_3}$-$\overset{O}{\overset{\|}{C}}$-C (3H, s, 1.96 ppm); $\overset{O}{\overset{/\backslash}{HC}}$-C- (1H, t, J=7Hz, 2.52 ppm); $\underline{CH_2}$-O-$\overset{O}{\overset{\|}{C}}$ (2H, d, J=7Hz, 4.5 ppm); 1 $\underline{HC}$=C (1H, ill resolved triplet, 5.03 ppm); 1 C=$\underline{HC}$-CH_2OAc (1H, ill resolved triplet, 5.32 ppm).

(ii) 2(trans)-, 6(trans)-10,11-epoxyfarnesyl acetate 5(a)

IR (Neat) : 1730, 1675, 1235 cm^{-1}

PMR (CCl_4): 2 $\underline{CH_3}$-$\overset{O}{\overset{/\backslash}{C}}$-C- (6H; 3H, s, 1.18; 3H, s, 1.2 ppm); 2 $\underline{CH_3}$-C=C- (6H; 3H, s, 1.6; 3H, s, , 1.68 ppm); CH_3-$\overset{O}{\overset{\|}{C}}$-O (3H, s, 1.93 ppm); $\underline{HC}$$\overset{O}{\diagup\!\diagdown}$C< (1H, t, J=7Hz, 2.5 ppm); $\underline{CH_2}$-O-$\overset{O}{\overset{\|}{C}}$- (2H, d, J=7Hz, 4.48 ppm); 2$\underline{HC}$=C- (2H, m, 4.95-5.4 ppm).

Cleavage of 2(E)-6,7-epoxyfarnesyl acetate (5b) to diol

To a stirred solution of 5(b) (0.38 gm, 0.00135 mol) in THF (6 ml), 1 ml of 2 % aq. $HClO_4$ was added at room temperature (~30°C). It was further stirred at this room temperature for 8 hrs. The reaction mixture was poured into cold water (10 ml) and extracted with solvent ether (10 ml x 2). The aqueous layer was saturated with sodium chloride and extracted with ether (10 ml x 2). The combined ether layer was washed successively with 5 % aq. sodium carbonate solution (5 ml x 2), with water till washings are neutral and finally with brine solution (10 ml). It was dried over sodium sulphate (anhy.) and evaporated the solvent by distillation, which afforded a crude product 0.380 gm (~100 % recovery). It was purified by passing through a short column of silica gel (40 cm X 1.5 cm, IIA) which afforded 0.22 gm of pure diol (6). It was distilled (160-180°(bath)/1 mm) to afford 0.20 gm, which was characterised by its spectral properties.

IR (Neat) : 3450, 1740, 1240, 1030, 830 cm^{-1}

PMR : $\underline{H_3C}$-C- (3H, s, 1.08 ppm); three $\underline{CH_3}$-C=C- (9H; 3H, s, 1.6 ppm; 3H, s, 1.65 ppm; 3H, s, 1.7 ppm); O=C-$\underline{CH_3}$ (3H, s, 1.98 ppm); $\underline{HC}$-OH (1H, d, d, 3.22 ppm); $\underline{CH_2}$-OAc (2H, d, J=7Hz, 4.50 ppm); $\underline{HC}$=C- (1H, ill resolved triplet, 5.05 ppm); C=$\underline{HC}$-CH_2OAc (1H, ill resolved triplet, 5.32 ppm).

Anal.: Found C, 68.22; H, 9.99. $C_{17}H_{30}O_4$ requires C, 68.42; H, 10.132.

Hydrolysis of 2(E)-6,7-dihydroxyfarnesyl acetate (6)

To a stirred solution of (6) [1.2 gm, 0.004 mol] in ethanol (2 ml), ethanolic KOH (0.2 gm/10 ml ethanol) was added at room temperature (~30°C). It was further stirred at this temperature for 2 hrs. The reaction mixture was poured into ice-water and extracted with ethyl acetate (15 ml x 3). The combined organic extract was washed with water till the washings are neutral to pH and dried over anhy. sodium sulphate. The solvent was removed by distillation, which afforded 1.0 gm of triol (~100 % recovery). It was purified by passing through a small column of silica gel G [(40 cm X 1.5), II A] and obtained the pure triol. It was distilled (180-190°(bath)/0.1 mm) which afforded 0.85 gm of the triol(2), which was characterised by its spectral properties.

IR (Neat) : 3350, 1670, 1000, 840 cm^{-1}

PMR : $\underline{H_3}C$-COH (3H, s, 1.12 ppm); 3 $\underline{CH_3}$-C=C (9H, s, 1.6; s, 1.65 ppm); HO-$\underline{HC}$-C-OH (1H, m, 3.3 ppm); $\underline{CH_2}$-OH (2H, d, J=7Hz, 4.1 ppm); $\underline{HC}$=C- (1H, ill resolved triplet, 5.12 ppm); $\underline{HC}$=C- (1H, ill resolved triplet, 5.4 ppm).

Mass : m/e 256 (M^+)

Anal.: Found C, 70.04; H, 10.59. $C_{15}H_{28}O_3$ requires C, 70.27; H, 11.

Protection of diol (2) with phenylboronic acid

The triol (2), (0.051 gm, 0.000199 mol), phenylboronic acid (0.024 gm, 0.000199 mol) and dry pyridine were taken in a small r.b.f. (15 ml), which was fitted with a vigreux column, contained of molecular sieves ($4A^{\circ}$), which in turn reflux condenser was attached to it. The reaction mixture was refluxed for 2 hrs under stirring. Excess pyridine was distilled off, which afforded a crude product (0.072 gm). It was purified by passing through a small column of silica gel (grade: II B, 20 cm X 0.5 cm). It was characterised by its IR and PMR data.

IR (Neat) : 3350, 1670, 1600, 1500, 1440, 820 cm^{-1}

PMR : $\underline{H_3}C-C-C-$ (3H, s, 1.4 ppm); 3 $\underline{CH_3}-C=C$ (9H, s, 1.66; s, 1.68; s, 1.72 ppm); $\underline{CH_2}-OH$ and $\underline{CH}(OH)-C(OH)-C$ (3H, m, 3.95-4.3 ppm); $\underline{HC}=C$ (1H, ill resolved triplet, 5.14 ppm); $\underline{HC}=C$ (1H, ill resolved triplet, 5.5 ppm); Aromatic $\underline{CH}$ (3H, m, 7.2-7.6 ppm); Aromatic $\underline{CH}$ (2H, m, 7.7-8.0 ppm).

Phosphorylation of (7)

Diethyl chlorophosphoridate (freshly distilled, 0.206 gm 0.00125 mol) in dry dichloromethane (2 ml) was added dropwise during one hour to a stirred mixture of 2(trans)-6,7-dihydroxy (protected by phenylboronic acid) farnesol (0.342 gm, 0.001 mol), pyridine (0.2 gm, 0.0025 mol) and dichloromethane (2 ml) under exclusion of moisture (anhy. $CaCl_2$ guard tube) at -5°C. Stirring was continued for a period of 3 hrs at 0°C. The reaction mixture was poured over ice-water and extracted with solvent ether (10 ml x 3). The combined organic extract was washed successively with dil. H_2SO_4 (5 % aq., 5 ml x 2), water, dil $NaHCO_3$ (5 % aq., 5 ml x 2) and thoroughly with water till the washings are neutral to pH and dried over anhy. sodium sulphate. The solvent was filtered and evacuated in vacuo to give a colourless oil, 0.45 gm (~95 % yield). This ester was pure to TLC analysis (40 % EtOAc/pet. ether 60-80°) and spectroscopically consistent.

PMR : two $\underline{H_3C}-CH_2-O$ and $\underline{H_3C}-C(O)-C(O)-B$ (9H, m, 1.1 to 1.5 ppm); three $\underline{CH_3}-C=C-$ (9H; 3H, s, 1.59; 3H, s, 1.63; 3H, s, 1.76 ppm). $O-\underline{CH_2}-CH_3$ and $\underline{HC}-C(O)-C(O)-B$ (5H, m, 3.83-4.28 ppm). $\underline{CH_2}-O-P(=O)$ (2H, m, 4.35-4.62 ppm); $\underline{HC}=C-$ (1H, ill resolved triplet, 5.05 ppm); $\underline{HC}=C-$ (1H, ill resolved triplet, 5.45 ppm); Aromatic $\underline{CH}$ (3H, m, 7.1-7.4 ppm, and 2H, m, 7.6-7.88 ppm).

Reaction of 2(trans)-6,7-dihydroxy-(protected by phenylboronic acid) farnesyl diethyl phosphate (1) with active alumina

Active alumina (pH=7, activity: grade I, 15 gm) was made as slurry with dry dichloromethane (15 ml) in a single necked flask and to this slurry, 2(trans)-6,7-dihydroxy (protected by phenylboronic acid) farnesyl diethyl phosphate (0.478 gm, 0.001 mol) in dry dichloromethane (5 ml) was added dropwise by manually shaking the flask. The reaction flask was flushed with dry nitrogen and stoppered. It was shaken for 4 hrs by mechanical shaker at room temperature (~30°C) and kept overnight for 14 hrs at 25°C. The reaction contents were transferred to a vertical chromatographic column and eluted with 20 % EtOAc/pet.ether (15 ml x 10). The combined solvent eluants were distilled off, which afforded a crude colourless oil 0.12 gm.

REFERENCES

1. J.B. Hendrikson, Tetrahedron, 7, 82 (1952); L. Ruzika and H. Heusser, Experientia, 9, 357 (1953).

2. D.V. Banthrope and B.V. Charlwood, Secondary plant products (Edited by E.A. Bell and B.V. Charlwood), p. 190. Springer-Verlag, Berlin (1980).

3. G. Bergstrom, B. Kullenberg, S. Stallberg-Stenhagen and E. Stenhagen, Arkiv.Kemi., 28, 453 (1967).

4. R. Azerad and M.O. Cyrot, Bull.Soc.Chim., (France), 12, 3740 (1965).

5. R. Sahani, Ph.D. Thesis, Poona University (1976).

6. William N. Washburn and Ronald Kow, Tetrahedron Lett., 18, 1555 (1977).

7. C.H. Eugster, E. Linner, A.H. Trivedi and P. Karrer, Helv.Chim.Acta., 39, 690 (1956).

8. G. Saucy, R. Marbet, H. Lindler and O. Isler, Helv.Chim.Acta., 42, 1945 (1959).

9. K.M. Saplay, Ph.D. Thesis, Maharaja Sayajirao University (1980).

10. R.G. Gould, Jr., and A.F. Thompson, J.Am.Chem.Soc., 57, 340 (135).

11. L. Ruzicka et. al., Helv.Chim.Acta., 9, 499 (1926).

12. P.J. Dunphy, Chemistry and Industry, 34, 1112 (1970).

13. J.M.T. Frechet, L.J. Nuyens and E. Seymour, J.Am.Chem.Soc., 101, 432 (1979).