CHAPTER II

MECHANISM OF REARRANGEMENT OF LONGIFOLENE TO ISOLONGIFOLENE

MECHANISM OF REARRANGEMENT OF LONGIFOLENE TO ISOLONGIFOLENE

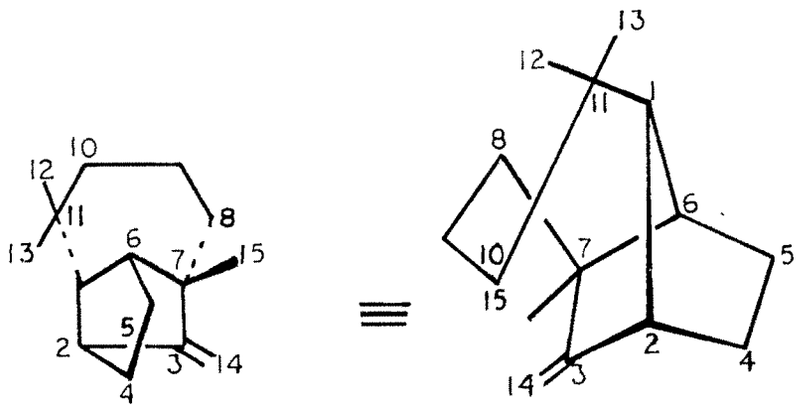
Abstract

The mechanism of rearrangement of longifolene to isolongifolene has been established by using site-specifically labelled longifolene-4,4,5,5-d_4 and shown to follow the Berson's proposed route which involves 3,2-exo-methyl shift in preference to 3,2-endo methyl migration proposed earlier. A novel synthetic route to longifolene-4,4,5,5-d_4 from isolongifolol is described. The results of rearrangement of longifolene with BF_3Et_2O-AcOD show that longicyclene is not an intermediate in the formation of isolongifolene as proposed by McMurry.

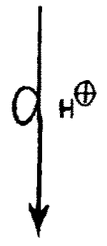
MECHANISM OF REARRANGEMENT OF LONGIFOLENE TO ISOLONGIFOLENE

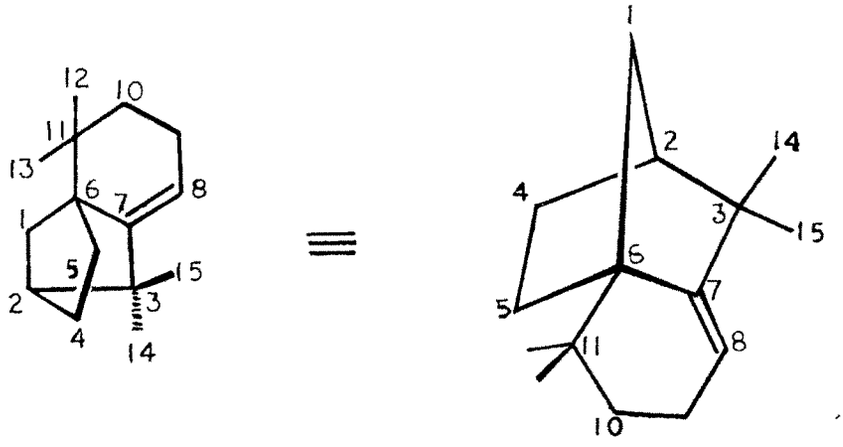
1. INTRODUCTION

LONGIFOLENE (1), a sesquiterpene hydrocarbon of compact tricyclic skeleton, on treatment with strong acids undergoes a deep seated molecular rearrangement to isolongifolene[1]. Isolongifolene has been shown to possess the structure 2 by its degradation and synthesis by Sukh Dev and his coworkers[2-6]. Three mechanisms have so far been proposed for this complex rearrangement. Sukh Dev[2] and Ourisson[7] have postulated a mechanism *via* classical carbonium ion as formulated in Chart I, which involves protonation of longifolene to produce tertiary ion 3 followed by *endo*-*endo*-3,2-methyl migration resulting in a carbonium ion at the bridge-head as in 4. This bridge-head carbonium ion undergoes a number of Wagner-Meerwein rearrangements to produce isolongifolene. The carbonium ion 3 is quite amenable for racemization by 1,2-shift of large bridge, a process similar to one of the mechanisms of racemization of camphene[8]. In fact, the degree of racemization of isolongifolene depends upon the reaction conditions used. During the course of his study of the chemistry of methyl norbornyl cations, Berson *et al.*[9] established that *endo*-3,2-methyl shifts occur with great difficulty and while examining a number of vicinal shifts reported in literature, he proposed an alternate mechanism for the rearrangement of longifolene as shown in Chart II which envisages an *exo*-3,2-methyl



(+) LONGIFOLENE (I)





(±) AND (-) ISOLONGIFOLENE (2)

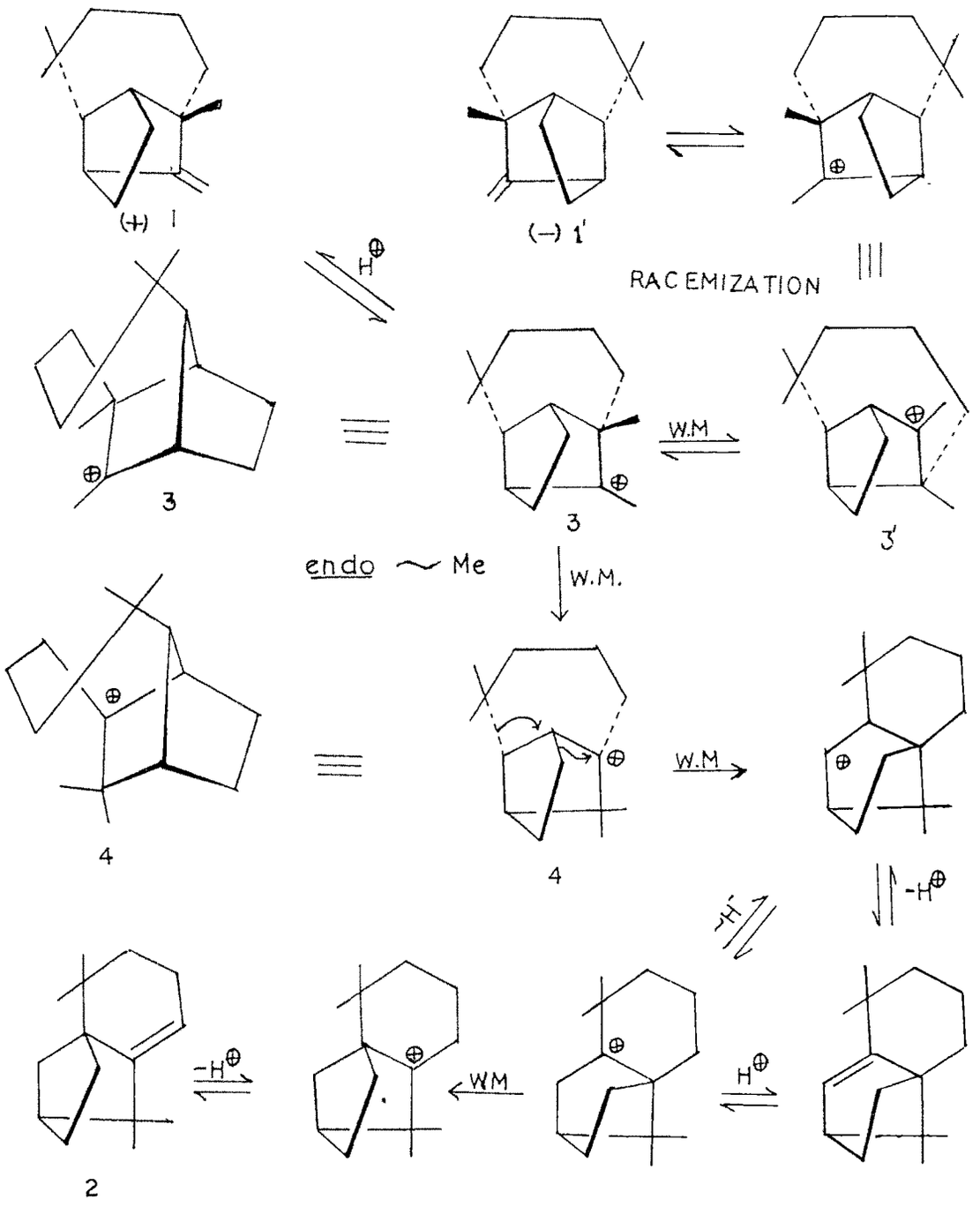


CHART I: RACEMIZATION AND ISOMERIZATION OF LONGIFOLENE (OURISSON AND SUKH DEV)

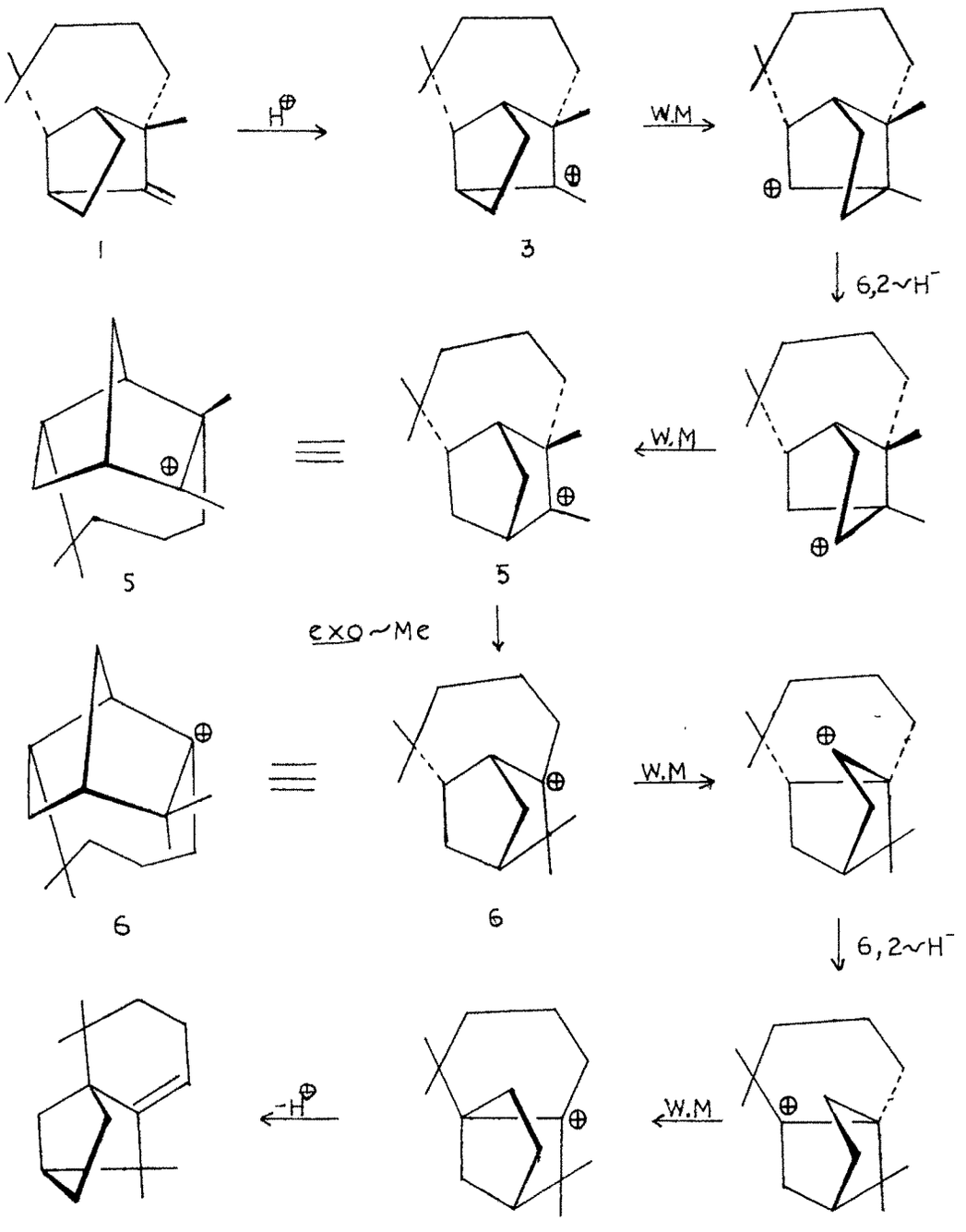


CHART II ISOMERIZATION OF LONGIFOLENE (BERSON *et al*)

shift in the genesis of isolongifolene. The mechanism proposed by Berson *et al.*[9] involves circuitous but more precedented sequences to implicate an *exo*-3,2-methyl shift, similar to those of norbornyl cations *via* a number of Wagner-Meerwein and 6,2-hydride shifts. The rearrangement of longifolene has been proposed to proceed through ion **5** which undergoes an *exo*-3,2-methyl shift to give a bridge-head ion **6** and then isolongifolene. McMurry[10] later postulated another less complex route for ion **5**, arising simply from protonation of longicyclene **7** (Chart III). This ion **5** is an important intermediate for *exo*-methyl shift in Berson's formulated mechanism.

These mechanisms are not easily distinguishable by ordinary methods of configurational correlation because all three mechanisms produce same enantiomer of isolongifolene for a given enantiomer of longifolene. In order to unequivocally resolve the above controversy, we have investigated this rearrangement using deuterium labels. Two different approaches have been followed (a) effecting the rearrangement of longifolene with deuterated acetic acid *viz* BF_3Et_2O-AcOD followed by location of the deuteriums incorporated in isolongifolene and (b) using site-specifically labelled longifolene.

2. ISOMERISATION OF LONGIFOLENE WITH BF_3Et_2O-AcOD

McMurry's proposed mechanism* for this transformation

* Chronologically, the work with deuterated acetic acid was initiated to check the intermediacy of hydrocarbons **7**, **18** and **19**[10] in this rearrangement. During the course of our study, McMurry proposed longicyclene **7** as an intermediate. The results of our study were equally valid to scrutinize McMurry's proposal.

involves longicyclene (7) as an intermediate, which on protonation opens to a tertiary carbonium ion 5, which in turn is an important intermediate for exo-3,2-methyl shift in Berson's hypothetical route. D^+-catalysed rearrangement of longifolene to isolongifolene will require incorporation of a deuterium at C-1 in the latter, if the transformation is mediated through longicyclene. Simultaneously, it will incorporate deuteriums at positions C-5 and C-1, if this isomerisation is proceeding through intermediate hydrocarbons 18 and 19 respectively, as it is shown in Chart IV. This is the rationale for carrying out the rearrangement of longifolene with BF_3Et_2O-AcOD. When longifolene was treated with BF_3Et_2O-AcOD, it produced isolongifolene with deuterium contents as shown in Table 1 (Expt. 1) by mass spectral analysis. The PMR spectrum (Fig 8B) showed a significant loss of absorption at the vinyl proton and at two of the four methyl groups. To see whether deuteriums have been incorporated in isolongifolene during transformation from longifolene or it was a result of an interaction between isolongifolene with deuterated reagent under the reaction conditions, a time study was carried out, the results of which are recorded in Table 1. It shows that isolongifolene under the condition of the rearrangement (in 20 min), incorporates negligible amount of deuteriums and that too only at vinylic proton at C-8 (PMR). Deutereoisolongifolene was treated with BF_3Et_2O-AcOH for 20 min to wash off extra deuteriums which isolongifolene itself incorporated under the reaction conditions. Similarly, longicyclene (7) and cycloisolongifolene (18) on treatment with BF_3Et_2O-AcOD, passed over to

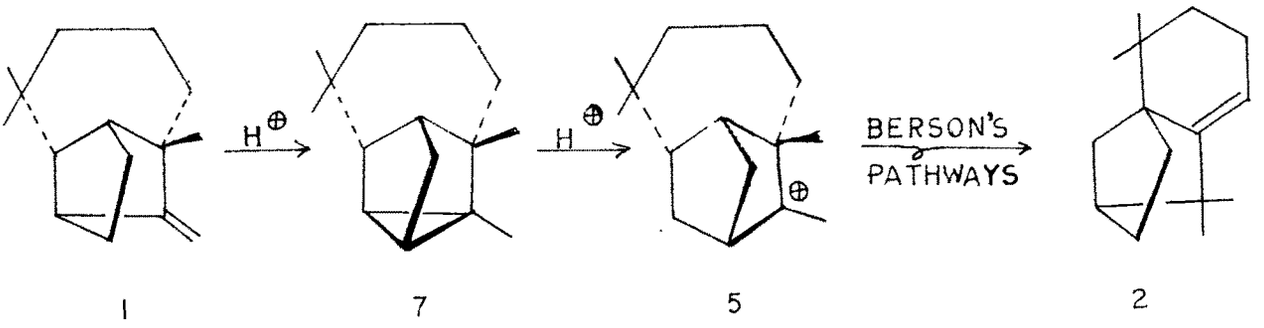


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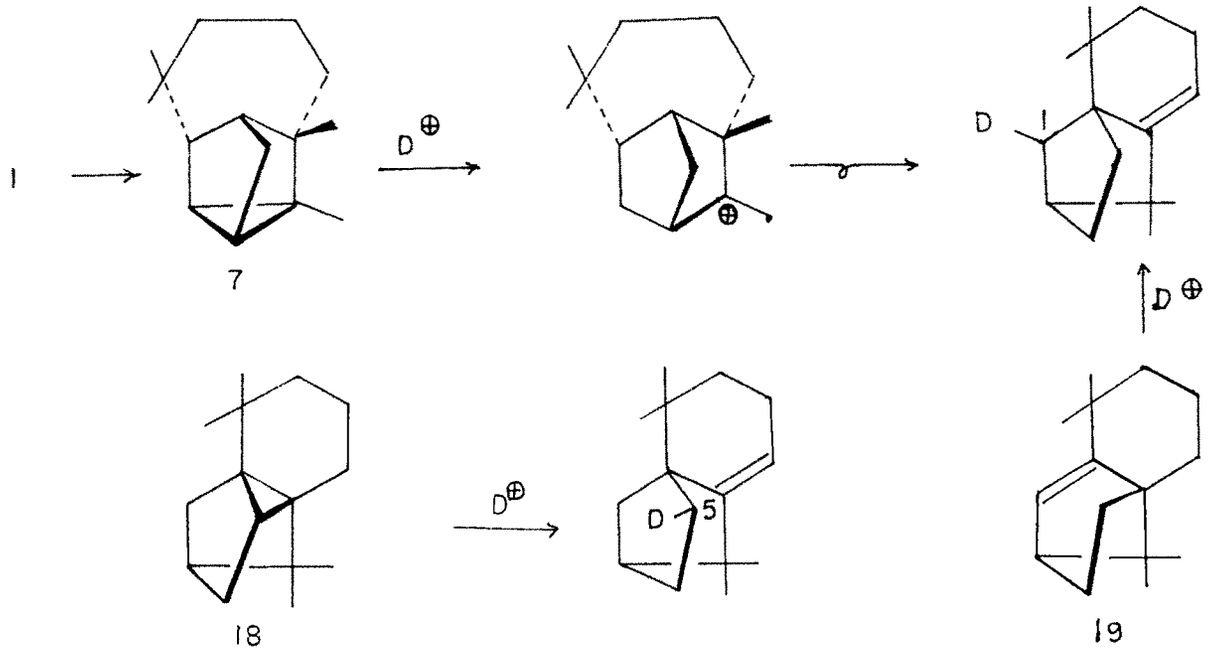
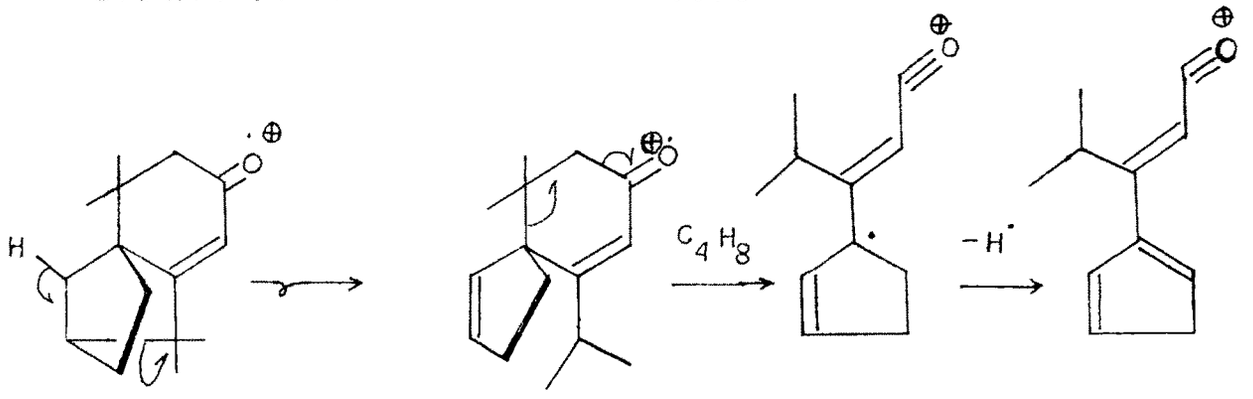
CHART III ISOMERIZATION OF LONGIFOLENE (McMURRY)



18 19

CHART IV: ACTION OF $D^{\oplus}$ ON POSTULATED INTERMEDIATES



8 m/e 218 m/e 163 m/e 161

CHART V: MASS FRAGMENTATION OF 9-OXOISOLONGIFOLENE

Table 1: DEUTERIUM CONTENTS IN M^+ OF ISOLONGIFOLENE DERIVED FROM VARIOUS SUBSTRATES

Expt. No.	Substrates	Acid media BF_3Et_2O	Reaction time	Relative percentage of deuterated species								Total d/mol.
				0D	1D	2D	3D	4D	5D	6D	7D	
1.	Longifolene	AcOD	20 min	2.29	6.52	14.89	23.82	21.64	16.15	11.34	3.32	3.66
2.	Product of 1	AcOH	20 min x 2	6.43	9.91	20.86	25.91	15.47	14.43	6.95	-	3.06
3.	Product of 1	AcOH	24 hrs	10.97	12.67	22.25	31.23	12.47	6.48	2.99	0.89	2.57
4.	Isolongifolene	AcOD	20 min	65.89	32.55	1.55	-	-	-	-	-	0.35
5.	Product of 4	AcOH	20 min x 2	97.61	1.42	0.95	-	-	-	-	-	0.04
6.	Isolongifolene	AcOD	27 hrs	8.00	12.25	23.82	22.00	14.05	10.41	5.67	2.48	2.96
7.	Product of 6	AcOH	20 min x 2	12.10	26.14	25.43	14.73	10.70	7.01	2.63	1.22	2.23
8.	Product of 6	AcOH	24 hrs	41.95	26.13	13.06	9.90	8.11	0.82	-	-	1.18
9.	Longicyclene (7)	AcOD	20 min + 45 min	1.10	5.70	9.20	13.70	18.50	16.70	16.10	13.10	4.59
10.	Cycloisolongifolene	AcOD	20 min + 2 hrs	2.50	6.93	26.90	39.81	18.73	3.75	1.40	-	2.82

isolongifolene with deuterium contents as given in Table 1.

Our next problem was to locate the deuteriums in isolongifolene derived from longifolene (BF_3·Et_2O-AcOD) and to see which of these three routes is operative.

2.1. Location of Deuteriums in Isolongifolene

Deuterated isolongifolene (2a) from longifolene(BF_3·Et_2O-AcOD) was oxidized[2,11] to α,β-unsaturated ketone (8a) with oxygen over cobalt naphthenate; the ketone obtained contained deuteriums as shown in Table 2, and is comparable with deuterio-isolongifolene in its deuterium content. Further, even after treatment with NaOH/EtOH, 8a did not show any loss of deuteriums (Table 2) by mass spectral analysis (Fig. 15, A.B.C). Mass fragment ion at m/e 162, which is a result of the loss of C_4H_8 (M-56) from ketone 8a carries all of its deuteriums intact. C-10, C-11 along with its gem-dimethyl groups can account for the loss of C_4H_8 unit in the above fragmentation, by a mechanism depicted in Chart V. These results clearly indicate that there are no deuterium atoms at C-9, C-10 and two methyls at C-11.

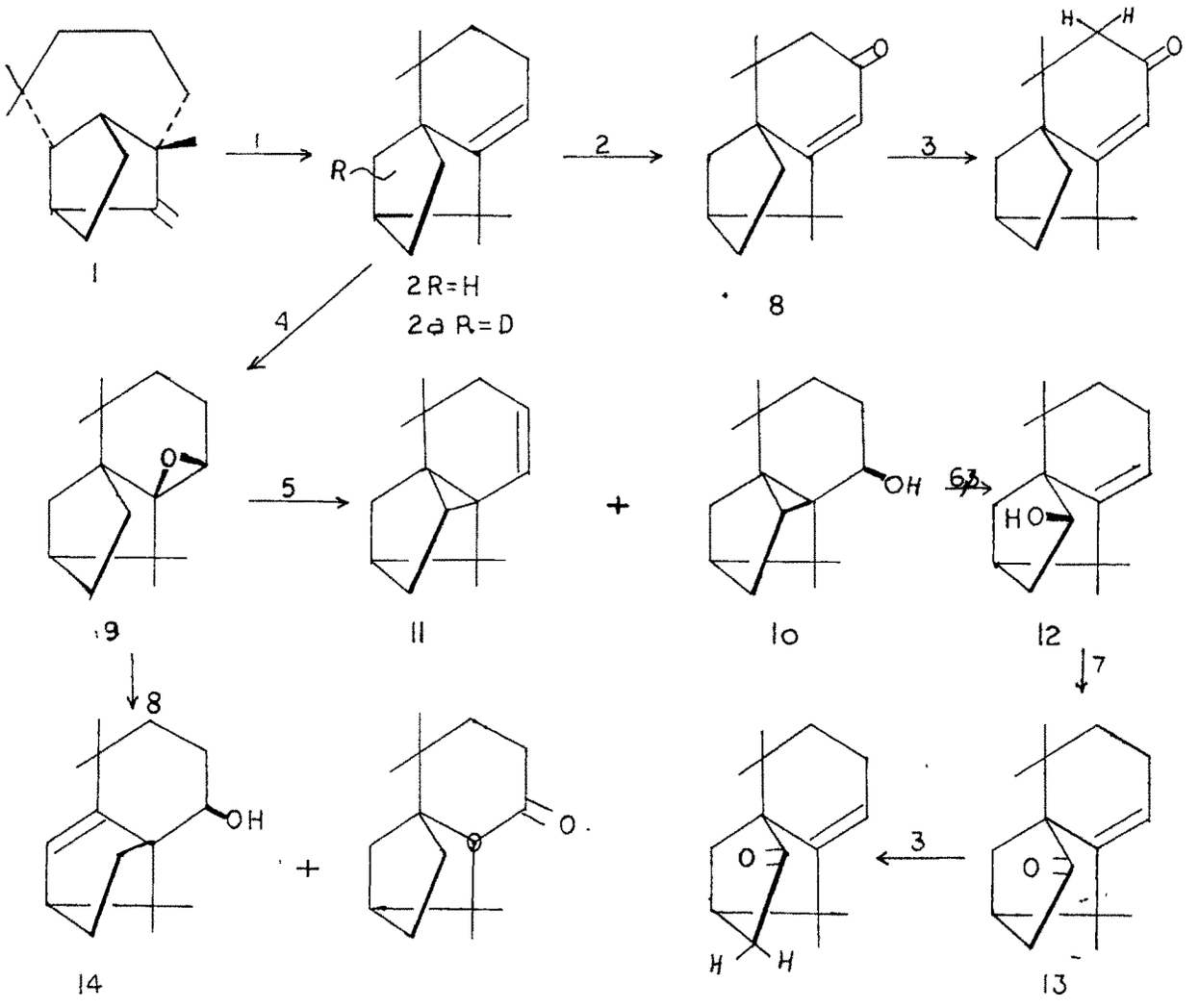
To ascertain the location of deuterium at other positions in isolongifolene-d_7, it was planned to functionalize the relevant positions in the molecule. In order to achieve this, isolongifolene-d_7 was exposed to perbenzoic acid to give isolongifolene oxide (9a) which was isomerized over alumina

Table 2: DEUTERIUM CONTENTS IN M^+ OF THE DERIVATIVES OF ISOLONGIFOLENE 2a DERIVED FROM LONGIFOLENE AFTER TREATMENT WITH BF_3Et_2O-AcOD

S.No.	Products.	Relative percentage of deuterium species in products.								Total D/mol.
		0D	1D	2D	3D	4D	5D	6D	7D	
1.	Isolongifolene(2a)	2.29	6.52	14.89	23.82	21.64	16.15	11.34	3.34	3.66
2.	α,β-Unsaturated ketone 8a	5.65	5.75	12.33	21.47	20.45	16.34	12.94	3.80	3.73
3.	α,β-Unsaturated ketone after treatment with OH^-	3.98	6.36	15.43	22.78	21.06	15.73	10.83	3.79	3.61
4.	Cycloisolongifolol (10a)	1.10	4.60	12.80	21.20	22.2	19.5	13.7	4.9	3.96
5.	Homoallylic alcohol 12a	2.00	5.2	12.6	21.6	21.8	18.3	14.0	4.8	3.82
6.	Ketone 13a	1.7	4.5	12.2	20.4	22.9	19.7	14.3	5.1	3.86
7.	Ketone 13a after washing with OH^-	2.1	5.6	14.6	20.4	21.3	16.6	15.3	4.3	3.91
8.	Unsaturated alcohol 14a	1.8	9.4	13.6	24.4	20.7	16.8	13.1	4.2	3.80

to cycloisolongifolol (10a) and dehydrocycloisolongifolene (11a) (Chart VI). It has been reported[12] in literature that cycloisolongifolol (10), when refluxed with aqueous phosphoric acid gets converted to a homoallylic alcohol 12. However, we could not get this alcohol (12) under the conditions reported. Through personal communication from Prof. Shaffer, we understood that it was obtained in a very poor yield (ca 10-15%)[12,13]. ~~The~~ Better yields (54%) of homoallylic alcohol 12 were obtained by exposing 10 to 1% aq H_2SO_4 (50% v/v) in acetic acid at 5-10° for 12 hours. PMR spectrum (Fig 10B) of alcohol 12a clearly indicates the absence of deuterium at position α to OH i.e. at C-5, since the proton α to OH appears as a double doublet, with the same coupling constants (J_1= 3Hz, J_2= 6Hz) as in non-deuterated alcohol 12 (Fig. 10A); it further demonstrates the absence of deuteriums at vicinal carbon C-4. To confirm this result further alcohol 12a was oxidized to ketone 13a which was refluxed with NaOH/EtOH to exchange any deuterium, if at all present, at active methylene carbon C-4. Mass spectra of ketone 13a before and after treatment with alkali did not show any loss of deuteriums (Table 2, Fig 17D). These results firmly establish the absence of deuteriums at C-4 and C-5.

Similarly, epoxide 9a was treated with 1% HCl in chloroform for 12 hrs at -3± 2° to get an unsaturated alcohol 14a to trace deuteriums at C-1 and C-2[6]. In the PMR spectrum (Fig 12B) of this alcohol 14a , the signal due to the olefinic proton at 5.47 ppm was intact and further it appeared as a doublet with



a: DERIVED FROM ISOLONGIFOLENE (2a)

1. $BF_3 Et_2O$-AcOH (D)
2. COBALT NAPHTHENATE-O_2
3. NaOH-EtOH
4. PhCOOOH-C_6H_6
5. Al_2O_3
6. $H^{\oplus}$-AcOH
7. Jone's Reagent
8. HCl-$CHCl_3$, 0°

CHART VI: LOCATION OF DEUTERIUMS

the same coupling constant as in non-deuterated alcohol 14 (see Fig 12A). These results rule out the presence of deuterium at C-2 also. Mass spectrum (Fig 18C) of 14a did not show any loss of mass (Table 2) indicating that only a proton and not a deuteron had been lost from C-1 during the elimination, to form an olefinic alcohol 14a.

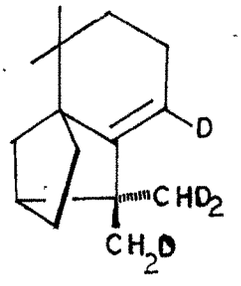
Thus, the above experiment clearly demonstrates the absence of deuteriums at C-1, C-2, C-4, C-5, C-9 and C-10. The only possible positions left out for locating deuteriums in isolongifolene 2a are at the methyl groups and also ofcourse partially at the olefinic proton at C-8. Four methyl groups resolve nicely in the PMR spectra of compounds 11, 13 and 14. The PMR spectra (Fig 9B, 10B, 11B, 12B) of these compounds show a significant loss of absorption (66%) for one of the methyl groups and the loss of ~34% of the intensity of another methyl group. The remaining two methyl groups do not show any diminution in intensity of absorption in PMR. Any mechanism for isomerization of longifolene to isolongifolene, therefore, involves protonation (deuteronation) of olefinic bond to give tertiary carbonium ion 3 which may undergo racemization by migration of seven-membered rings to give enantiomeric tertiary carbonium ion 3' (c_f Chart I). This equilibrium between two enantiomeric carbonium ions coupled with deprotonation-protonation would ultimately lead to the deuteration of both methyl groups C-14 and C-15.

As indicated earlier, the intermediacy of longicyclene (7)

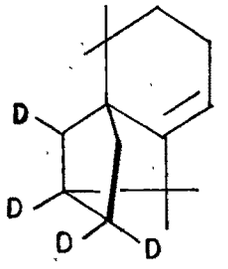
in the isomerization of longifolene to isolongifolene with BF_3Et_2O-AcOD demands the incorporation of deuterium at C-1 in isolongifolene (2a). The absence of deuterium at C-1 precludes such a proposition. Simultaneously, it also eliminates the possibility of hydrocarbons 18 and 19 as intermediates for the formation of 2 from 1.

2.2 Evidence based on Mass spectral Analysis

The mass spectra of isolongifolene 1 and some of its deuterated derivatives 2a and 2b are reproduced in Fig No. 14A-F. Deuterioisolongifolene 2b was obtained by the rearrangement of site-specifically labelled longifolene-4,4,5,5-d_4 (vide infra). The location of deuteriums in both 2a and 2b is well-secured by chemical transformations. The mass fragmentation pattern for



2a



2b

isolongifolene has been deduced by comparing the spectra of deuterated derivatives 2a and 2b with that of non-deuterated isolongifolene and is delineated in Chart VII. The principal mass spectral fragmentation peaks are recorded in Table 3. It is clear from Table 3 (Expt. No. 1) that the fragment at m/e 175

Table 3: MASS SPECTRAL DEUTERIUM DISTRIBUTION IN THE M, M-29 AND M-43 IONS FROM ISOLONGIFOLENE DERIVATIVES FROM DIFFERENT SUBSTRATES ON TREATMENT WITH BF_3Et_2O-AcOD

Expt.No.	Substrate (Reaction time)	Fragment ion m/e	Relative percentage of deuterium species[37]								Total D/mol
			0	1	2	3	4	5	6	7	
1.	Longifolene (20 min)	204(M)	02.3	06.5	14.9	23.8	21.6	16.2	11.3	03.3	3.67
		175(M-29)	02.2	07.2	15.4	24.9	22.2	15.5	11.1	03.3	2.66
		161(M-43)	47.2	47.2	02.8	02.8	-	-	-	-	0.61
2.	Cycloisolongifolene (20 min+ 2 hrs)	204(M)	02.5	06.9	26.9	39.8	18.7	1.40	-	-	2.82
		175(M-29)	00.5	13.3	49.0	29.7	07.1	-	-	-	2.28
		161(M-43)	02.5	05.3	23.4	54.5	13.0	-	-	-	2.67
3.	Longifolene-4,4,5,5-d_4	204(M)	00.0 ~~02.6~~	02.6 ~~13.9~~	13.9 ~~29.1~~	29.1 ~~42.6~~	42.6 ~~11.8~~	11.8	-	-	3.47
		175(M-29)	12.0	52.2	30.9	3.5	-	-	-	-	1.24
		161(M-43)	2.5	5.3	23.38	54.45	13.0	-	-	-	2.67
4.	Isolongifolene (27 hrs)	204(M)	08.0	12.3	23.8	22.0	14.10	10.4	5.7	02.5	2.96
		175(M-29)	05.2	19.1	28.9	20.0	11.8	8.9	3.9	3.9	2.52
		161(M-43)	07.3	22.5	37.6	22.6	6.0	0.8	-	-	2.02
5.	Longicyclene (20 min+ 45 min)	204(M)	01.1	05.7	09.2	13.7	18.5	16.7	16.1	13.1	4.59
		175(M-29)	01.6	08.6	08.9	16.4	21.8	16.2	16.3	9.7	4.14
		161(M-43)	12.6	48.7	28.6	6.8	03.4	-	-	-	1.4

(M-29) from 2a retains all the deuteriums, whereas, 2.23 D/mole or 64% of total deuterium is lost in the corresponding fragment from 2b. It is reasonable to assume, therefore, that the fragment at m/e 175 involves a loss of C-4 and C-5 according to the sequence 2→17 shown in Chart VII.

The base peak in the mass spectrum of isolongifolene appears at m/e 161 (M-43). The corresponding peak from 2a appears at m/e 162 (47.23%), 163 (2.77%) and 164 (2.77%) and contains only 0.61 D/mole compared to 3.67 D/mole in the parent ion peak. The same peak from 2b contains 2.67 D/mole and retains approximately 77% of the total deuterium present. These results are rationalized by the loss of C-14 and C-15 as an isopropyl radical via the route 2→16a→16b→16 as depicted in Chart VII. In the fragment at m/e 148 (M-56) both 2a and 2b retain their deuteriums. This fragment thus involves a cleavage of C_4H_8 unit by retro-Diels-Alder mechanism. It is indeed gratifying that the principal mass spectral peaks at m/e 175, 161 and 148 arise from different parts of isolongifolene molecule. These data proved to be of immense value in locating deuterium in isolongifolene derived from different substrates. This in turn resolved a number of speculations regarding the genesis of isolongifolene from longifolene, longicyclene etc.

2.3 Is Longifolene to Isolongifolene Rearrangement Reversible?

Treatment of isolongifolene 2 with BF_3Et_2O-AcOD for

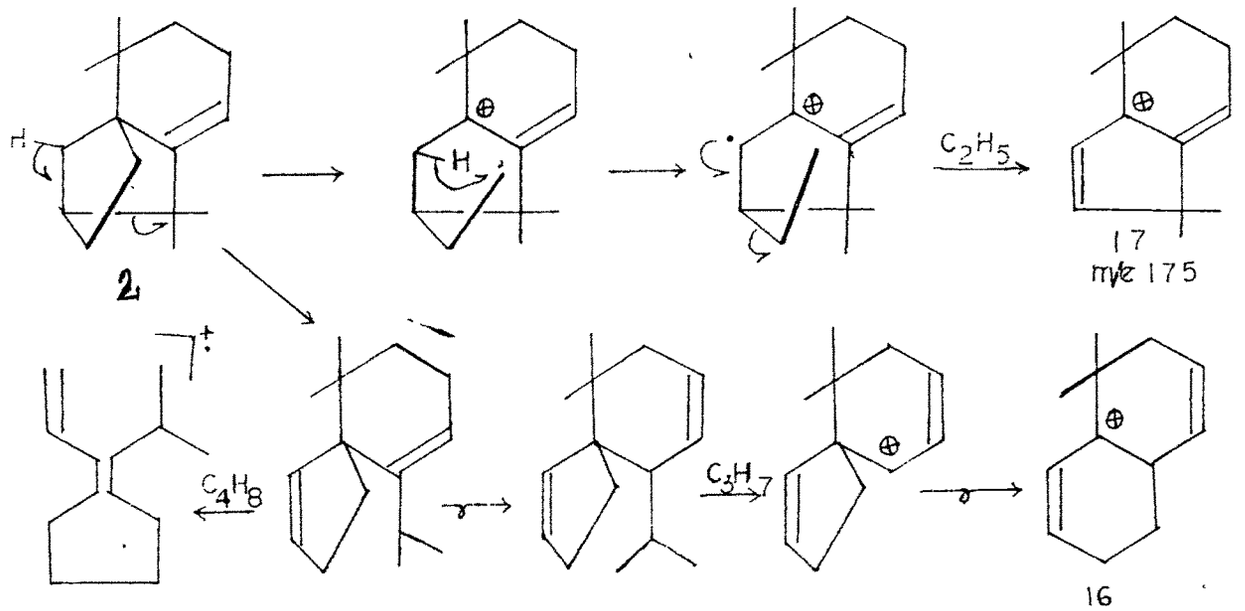
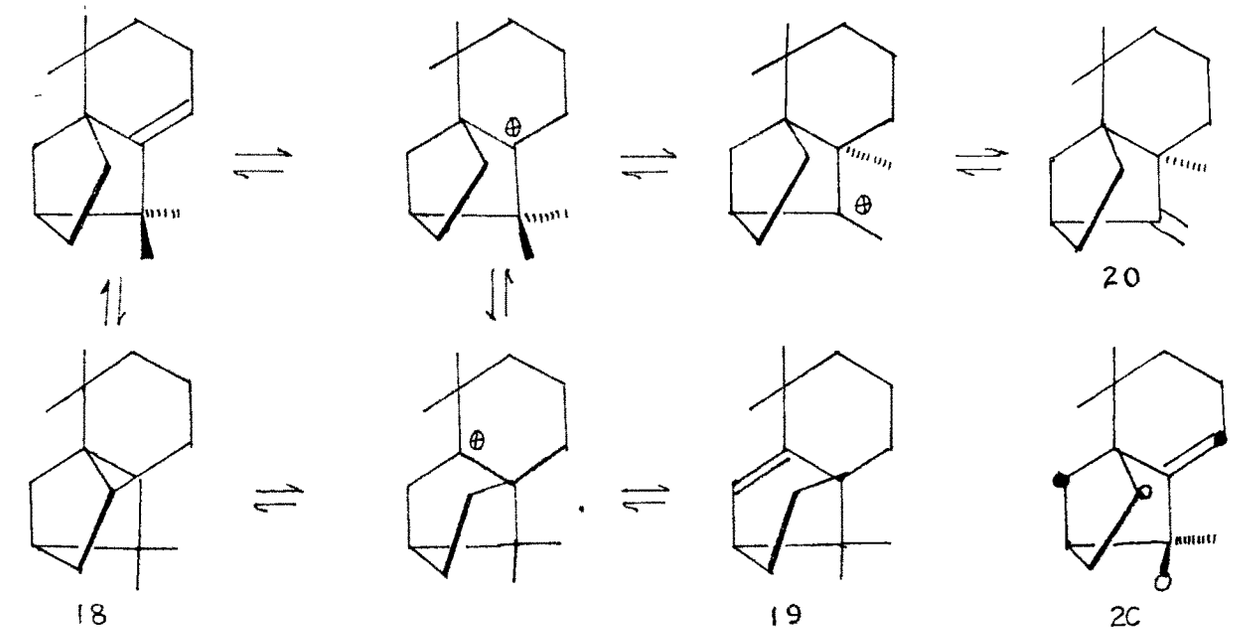


CHART VII. MASS FRAGMENTS OF ISOLONGIFOLENE



● major D-atoms
○ minor D-atoms

CHART VIII DEUTERATION OF ISOLONGIFOLENE WITH AcOD - BF_3 Et_2O

27 hours resulted in deuterium incorporation to the extent of 2.96 D/mole which could mostly be washed off with BF_3Et_2O-AcOH (Table 1, Expt. No. 6 and 8). At the first glance it was speculated that longifolene to isolongifolene may be reversible and an equilibrium may exist. However, the following analysis clearly rules out such a proposition.

The distribution of deuteriums in mass spectral peaks of the product from a typical experiment are recorded in Table 3 (Expt. No. 4). It can be seen that peaks at m/e 175 and 161 retain about 85% and 66% of the total deuteriums in the parent ion peak. Clearly, the product contains substantial deuterium at carbons other than C-4, C-5, C-14 and C-15. There is no loss of deuterium in the peak at m/e 148, indicating the absence of deuteriums at C-10, C-11, C-12 and C-13.

A number of other hydrocarbons derivable from isolongifolene can be postulated which will cause the deuterium incorporation at C-1, C-5, C-8 and C-15 (2c) as shown in Chart VIII. The PMR spectrum of deuterioisolongifolene (2c) resulting from the above reaction shows a significant decrease (33%) in intensity for one of the methyl groups appearing at 1.05 ppm (Fig.8c). This methyl is less deuterated in isolongifolene 2a derived from longifolene, while the methyl group at 0.99 ppm is more deuterated in 2a. This observation is significant in resolving the question of reversibility of longifolene to isolongifolene.

The initial step in the transformation of longifolene to isolongifolene 2a, in presence of deuterated acid, is the deuteronation of exomethylene double bond (ie. at C-14) to give the tertiary carbonium ion 3. The methyl group generated from the exomethylene group is likely to be highly deuterated. By any of the proposed mechanisms this methyl group should appear as exo-methyl group (C-14) in the products. By contrast, deuterioisolongifolene (2c, derived from isolongifolene) carries the methyl group at endo C-15 position; 2c conceivably arises by the deuteronation of hydrocarbon 20 (Chart VIII) followed by exo-methyl migration from C-7.

It is thus abundantly clear that the rearrangement of longifolene to isolongifolene is not reversible.

2.4. Rearrangement of Longicyclene to Isolongifolene

Transformation of longicyclene (7) to isolongifolene 2 can proceed either through the formation of longifolene or as proposed by McMurry, by direct protonation of cyclopropane ring to give the ion 5 which can rearrange according to Berson's mechanism to isolongifolene. The question has been resolved by analysing the PMR and Mass spectra of the deuterioisolongifolene obtained from the treatment of longicyclene with BF_3Ft_2O-AcOD. In the mass spectrum , the base peak at m/e 161 contains only about 31% of the total deuterium present in the molecular ion peak at m/e 204 (Table 3, Expt. No. 5). This implies that

significant amounts of deuterium are present at C-14 and/or C-15. If longicyclene were to directly open to ion 5, only one of the methyl groups can be conveniently deuterated as shown in Chart X. The deuteration of both methyl groups requires equilibration of ion 5 to ion 21, which being highly strained, is less probable. On the other hand, it is more likely that protonation of longicyclene takes place at the less hindered carbon C-4 to give cation 3 in preference to protonation at more hindered carbon (C-2) leading to cation 5. Thus, conversion of longicyclene to isolongifolene proceeding through longifolene is a distinct possibility. It may further be emphasized that longicyclene 7 to isolongifolene isomerization is slower than the rate of isomerization of longifolene to isolongifolene. Longicyclene may not be the intermediate in this isomerization.

Based on the above conclusion, the rearrangement of longicyclene (7) to isolongifolene with deuterated reagent could, in principle, distinguish between the two proposed mechanisms. D^+-Catalysed opening of longicyclene 7 would produce 4-deuteriolongifolene; isomerization of the latter according to Ourisson's and Sukh Dev's mechanism should give deuterioisolongifolene carrying deuterium at C-4. On the other hand, Berson's mechanism will produce deuterioisolongifolene with deuterium at C-1 (Chart IX). Unfortunately, deuterium at C-1 could also

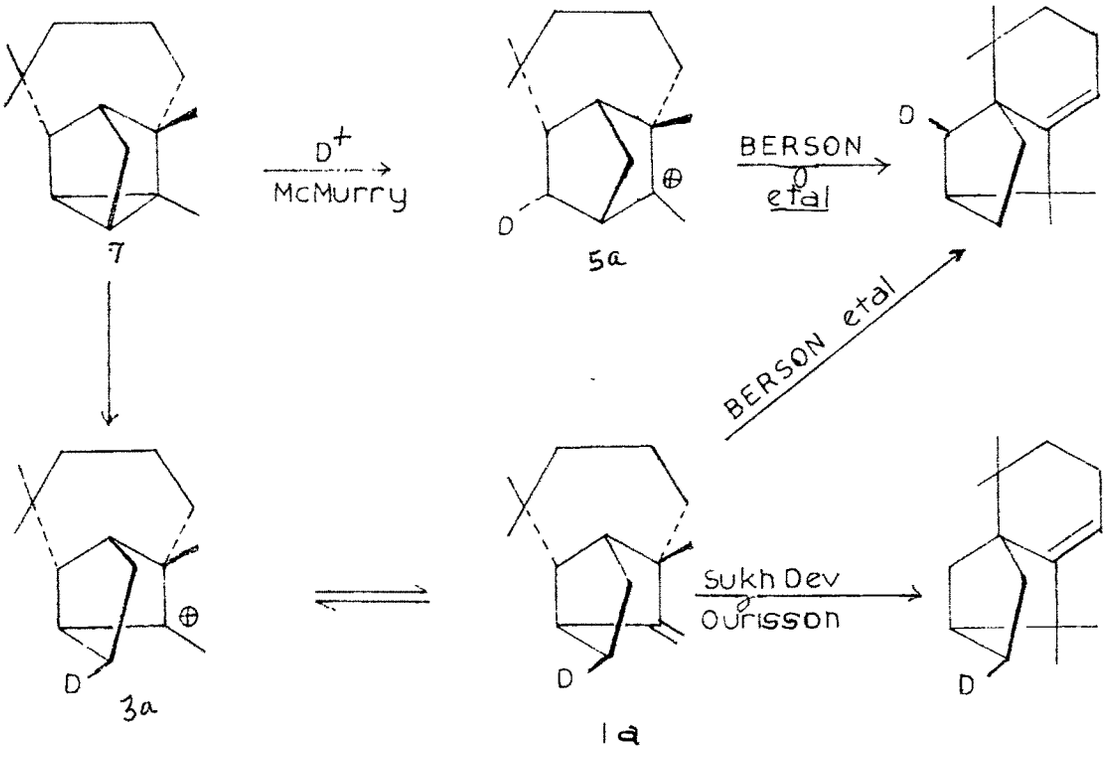


CHART IX. ISOMERIZATION OF LONGICYCLENE

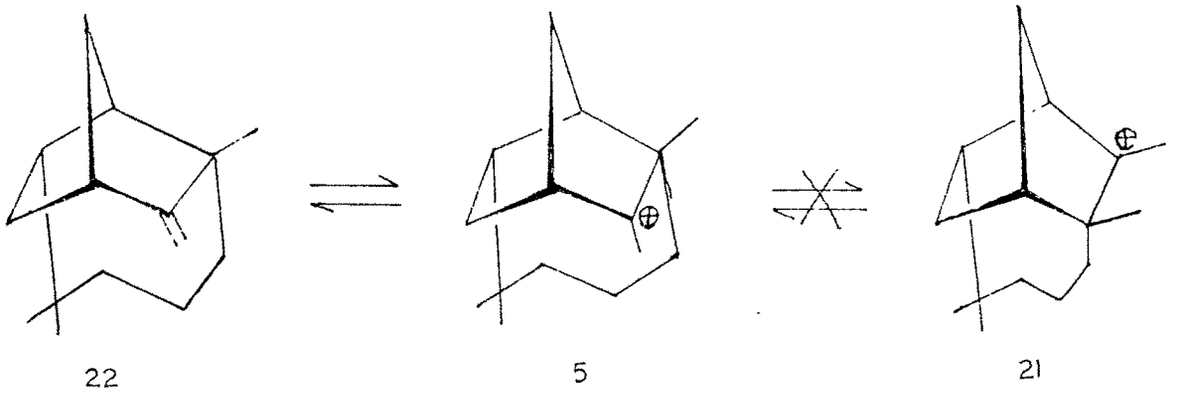


CHART X. DEUTERATION OF METHYLS

appear by deuteration of isolongifolene *via* the olefinic hydrocarbons 19 (Chart VIII). Also, mass spectral analysis of deuterioisolongifolene (derived from longicyclene, Table 3, Expt. No. 5) does not permit a clear location of deuterium at C-1 or C-4. Hence, recourse was taken to the synthesis and rearrangement of site-specifically labelled longifolene, which is described in the next section.

3. USING SITE-SPECIFICALLY LABELLED LONGIFOLENE-4,4,5,5-D_4

We have already established that the mechanism proposed by McMurry is not valid for the isomerization of longifolene to isolongifolene. However, the above data is inadequate to decide which of the two mechanisms proposed by Berson on one hand and Ourisson and Sukh Dev on the other, is operative. These mechanisms differ from each other in two respects:

(i) The two carbon atoms indicated by heavy dots in longifolene 1b will acquire different relationship depending on whether one or the other of the mechanisms being followed. In Sukh Dev's and Ourisson's mechanism these assume a 1,3-relationship, whereas in Berson's mechanism these are vicinally located (Chart XI & XII).

(ii) Similarly, tetradeuterated longifolene 1b would produce isolongifolene-4,4,5,5-d_4 2d or isolongifolene-1,2,4,4-d_4 (2b) depending upon the former or latter mechanisms as given below, (Chart XIII).

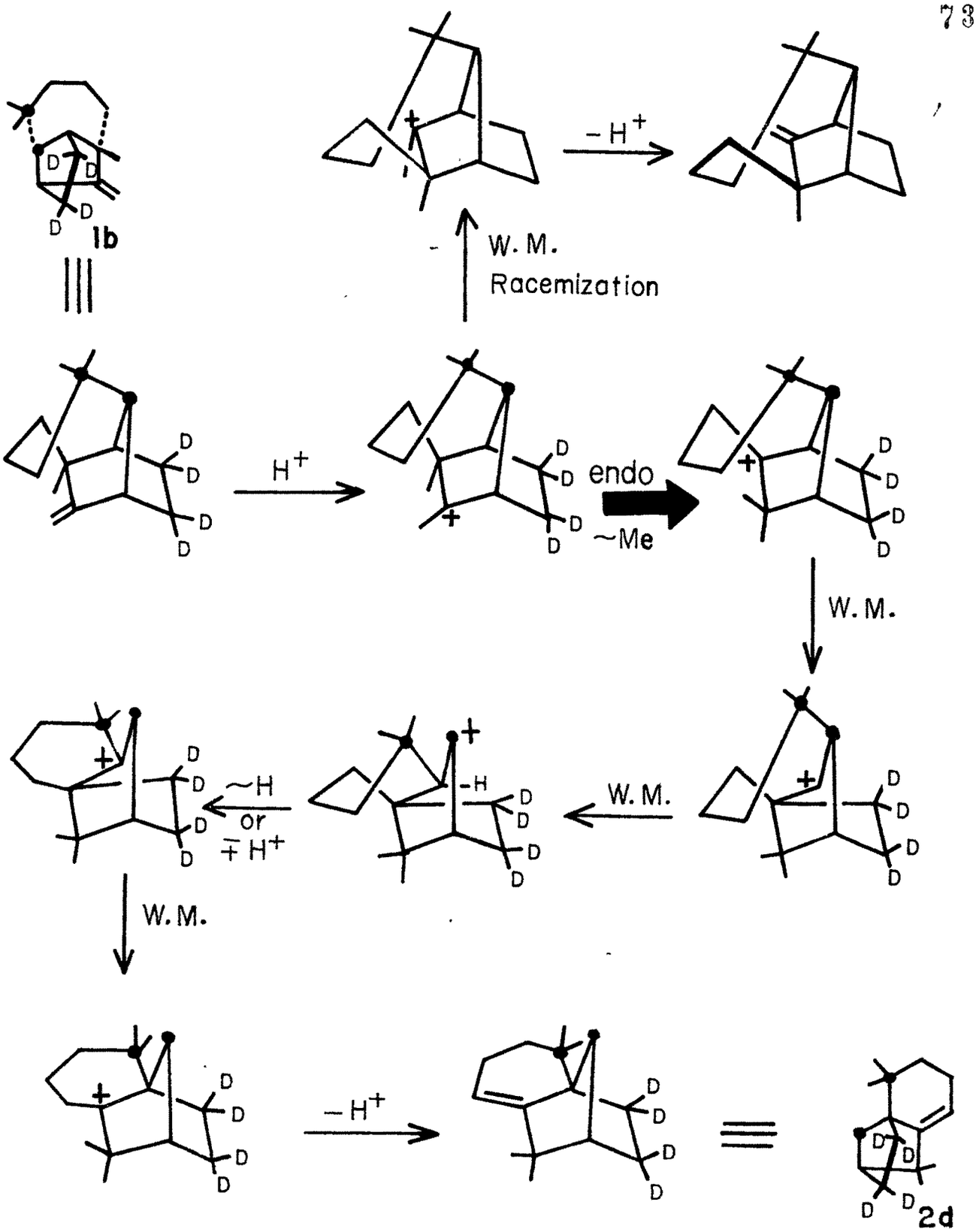


CHART XI: ISOMERIZATION OF LONGIFOLENE-4,4,5,5-d_4
(SUKH DEV AND OURISSON)

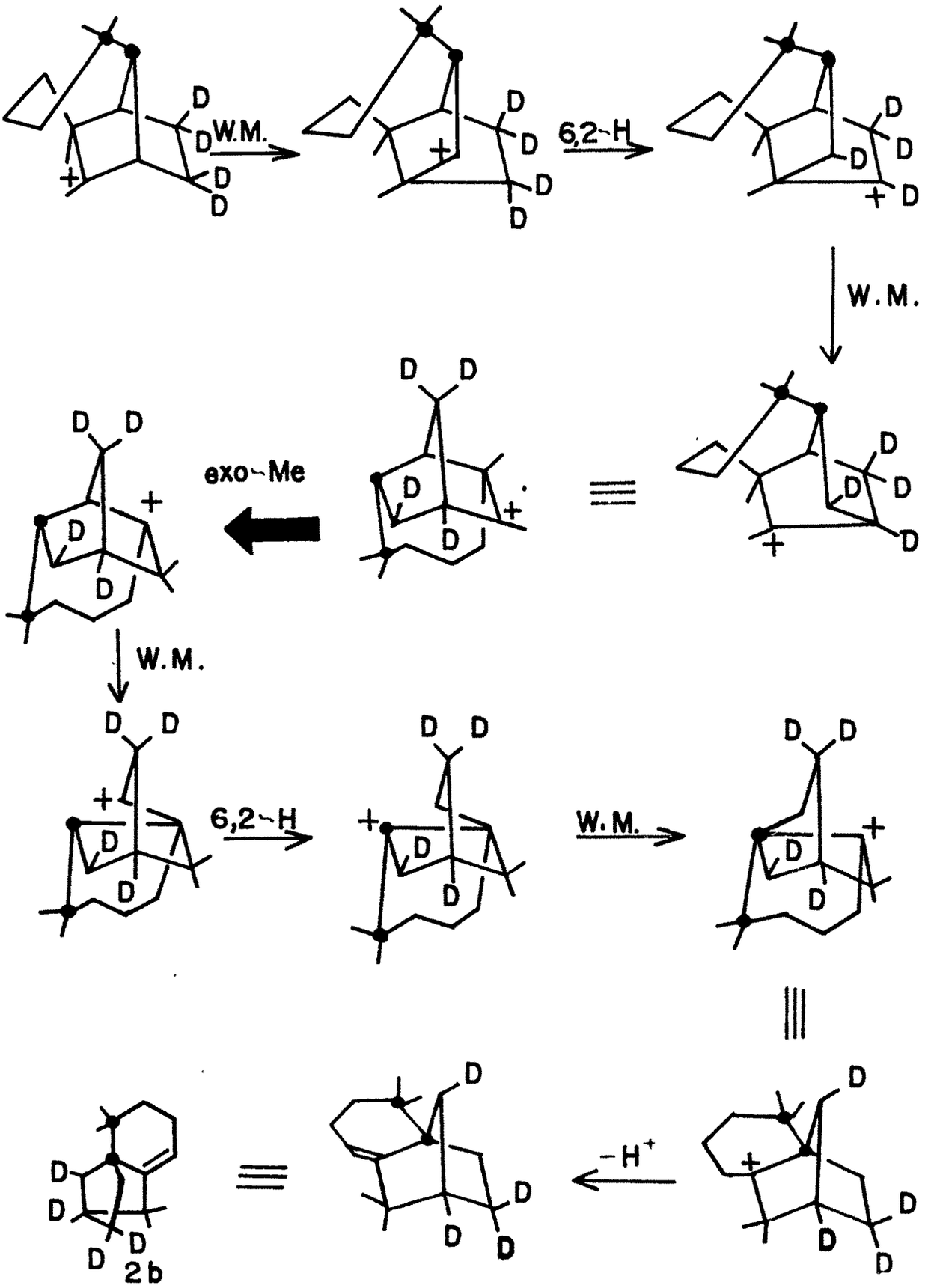


CHART XII: ISOMERIZATION OF LONGIFOLENE-4,4,5,5-d_4 (BERSON *etal*)

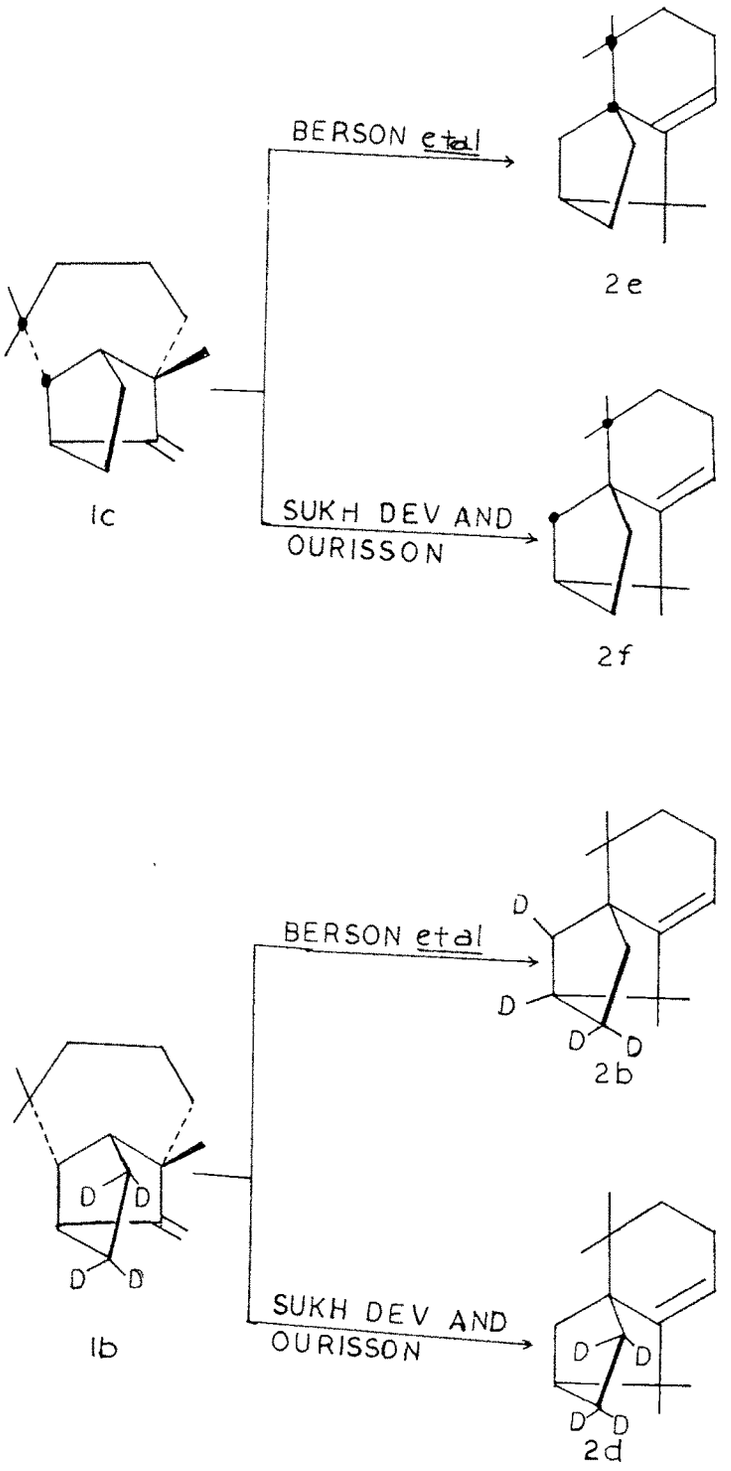


CHART XIII: DISTINCTION OF MECHANISMS

Longifolene with ^{13}C at positions indicated by heavy dots in 1c would produce 2e or 2f which can be easily distinguished, as 2e should show large ^{13}C-^{13}C coupling, whereas, there will be very small coupling between ^{13}C-C-^{13}C for 2f. Since it is rather difficult to synthesise a complex molecule like longifolene with ^{13}C at C-1 and C-11, it was considered more practical to synthesise tetradeuteriolongifolene 1b in order to make the distinction between these two mechanisms.

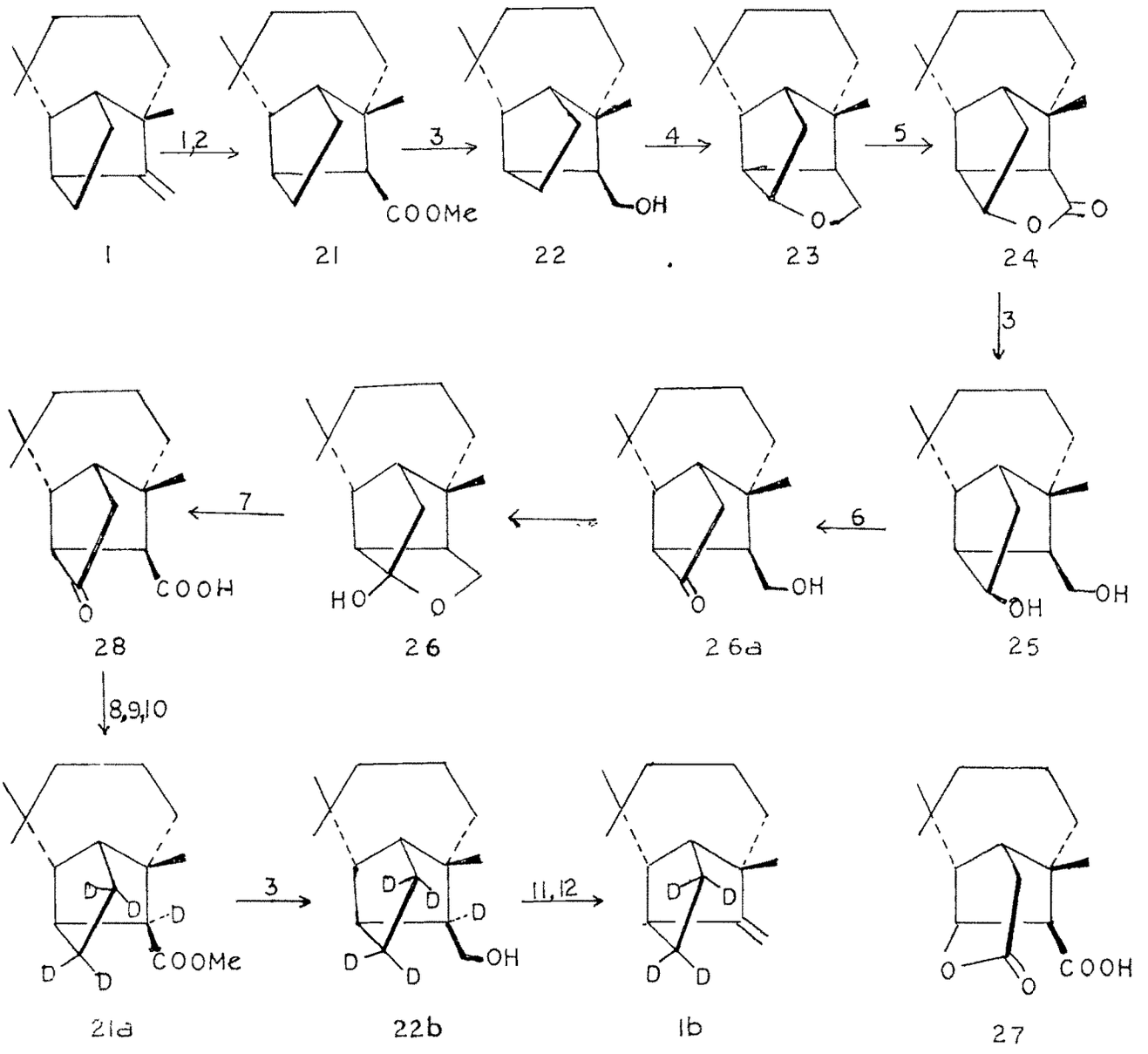
3.1. Synthesis of Longifolene-4,4,5,5-d_4 1b

Any method for introducing deuteriums in longifolene at C-4 and C-5 would require functionalization of atleast one of these carbon atoms. A search of literature[14,15] reveals that isolongifolol (22) on oxidative cyclization, gives ether 23, thus providing an entry for the functionalization of C-4 carbon in 1 and ultimately to the synthesis of deuteriolongifolene. Isolongifolol (22) was prepared in the following way: Oxidation of longifolene with chromic acid in acetic acid gave isolongifolic acid together with other acids; methyl esters of mixture of acids were fractionally crystallized to obtain pure methyl isolongifolate[16,17] (m.p. 55-56°). The latter compound on reduction with lithium aluminium hydride gave isolongifolol[18] 22.

The earlier method for the preparation of this ether 23 from alcohol 22 was by oxidative cyclization with lead tetra-acetate in refluxing benzene, which is reported[14,15] to give a very poor yield (10-15%), the major product being corresponding acetate of alcohol 22 and the reaction rate is very slow. However, an excellent yield (98%) of this ether 23 was obtained by irradiation of isolongifolol with 250 watt tungosten lamp in presence of lead tetraacetate and iodine in cyclohexane - by a general procedure reported by Heusler et al.[19]. When lead tetraacetate is used alone, isolongifolol, being consumed as isolongifolyl acetate, gives very poor yield of ether 23, whereas, it does not happen when lead tetraacetate-iodine combination is used. The reported work up procedure for LTA-I_2 reaction is tedious and gives poor yield of the product. We have modified the work up procedure to give much better yield and it is given below.

After completion of the reaction, the violet coloured reaction mixture is brought to room temperature (28-30^0) and silica gel impregnated with KI (15% w/w) is introduced portion-wise till the colour is discharged. By this the lead oxide becomes grannular so that it can be filtered and washed easily. The filtrate is directly fractionated without any further treatment.

The sequence of reactions used to synthesize longifolene-4,4,5,5-d_4 1b from ether 23 is outlined in Chart XIV. Ether 23



1. CrO_3-AcOH-H_2SO_4
2. MeOH-H_2SO_4
3. LAH
4. LTA-I_2
5. CrO_3-AcOH
6. NBS, t-BUOH-C_5H_5N
7. Jone's reagent
8. tBUOK-D_2O-$(CH_2CH_2OD)_2O$
9. $ND_2ND_2D_2O$-KOD
10. CH_2N_2
11. p-TsCl-C_5H_5N
12. Al_2O_3

CHART XIV: SYNTHESIS OF LONGIFOLENE-4,4,5,5-d_4 (1b)

was oxidized to lactone 24 which on reduction with lithium aluminium hydride gave diol[14] 25. Oxidation of diol 25 with Jone's reagent[20] gave a poor yield of ketoacid 28 and a lactone acid was also isolated whose spectral data (vide experimental) were in agreement with structure 27. However, we achieved a quantitative conversion (95%) to ketoacid 28 by selective oxidation[21,22] of the secondary alcohol function in 25 with N-bromosuccinimide to hemiacetal 26, followed by treatment with Jone's reagent. Ketoacid 28 was dissolved in diethylene glycol-O-d_2 containing KOD (prepared by adding D_2O in t-BuOK) and refluxed to exchange active methylene protons at C-5 for deuteriums. To this solution was added $ND_2ND_2D_2O$ to carry out Wolf-Kishner reduction to deuterio-isolongifolic acid, which was esterified to methylisolongifolate-3,4,4,5,5-d_5 (21a). This was reduced with lithium aluminium hydride to isolongifolol-3,4,4,5,5-d_5 22a. Isolongifolyl tosylate[24] on passing through dry packed column of alumina produced longifolene-4,4,5,5-d_4 1b in 95% yield. This method of dehydration of isolongifolol 22 via. the tosylate is more convenient than the one previously reported[23]. Longifolene-4,4,5,5-d_4 was isomerized with BF_3Et_2O in benzene to get isolongifolene.

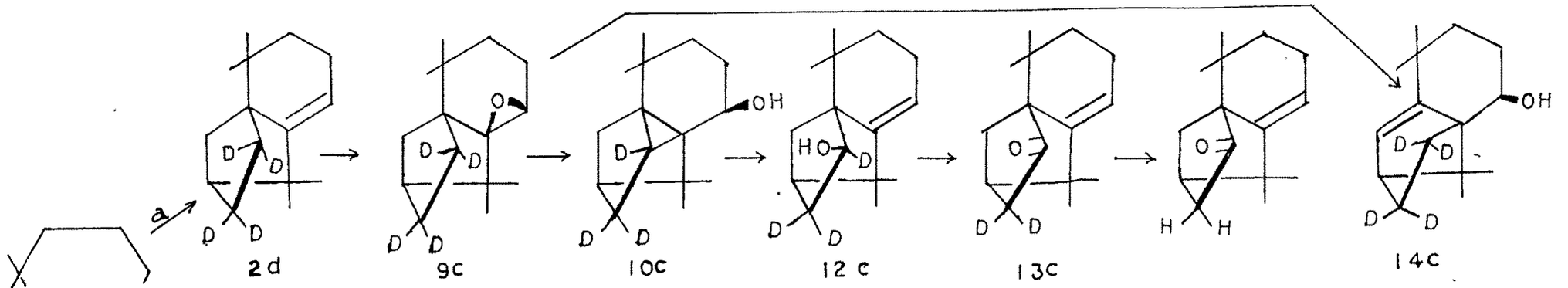
3.2. Location of Deuteriums in Isolongifolene-d_4

To determine the positions of deuteriums in isolongifolene-d_4, it was converted to its epoxide, whose conversion to other related

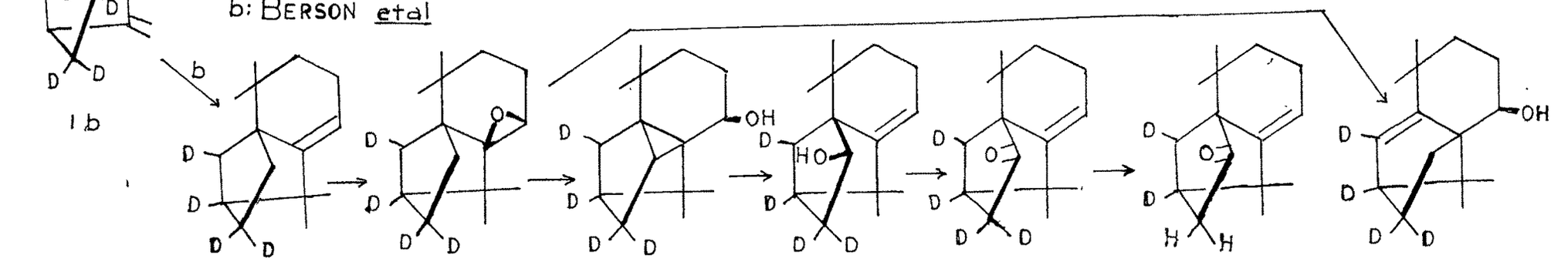
derivatives has already been discussed in the previous section (depicted in Chart XV).

Derivatives 12, 13 and 14 are eminently suited for spectroscopic distinction between the two possible structures of isolongifolene-d_4; 2b is derivable from Berson's mechanism and 2d will arise according to Ourisson's and Sukh Dev's proposed pathways (Chart XV). The appearance of 1H singlet at 4.07 ppm (CHOH) in the PMR spectrum of deuterioalcohol 12 (Fig 10C) is consistent with structure 12b derived from isolongifolene 2b. The singlet nature of the resonance signifies the presence of deuterium at C-4, while in nondeuterated 12 the proton on the hydroxyl bearing carbon (CHOH) appears as a double doublet (J_1= 3Hz, J_2= 6Hz) (Fig. 10A). On the other hand 12c dictates absence of any signal in this region (cf. Table 4). The mass spectrum (Fig. 17A,B) of deuterioketone 13 (obtained by oxidation of deuterioalcohol 12) shows M^+ at m/e 222 which is four mass units more than the M^+ at m/e 218 for the unlabelled ketone 13. These results clearly support the absence of any deuterium at C-5 in isolongifolene-d_4. Furthermore, deuterioketone 13 on treatment with alkali loses two mass units (M^+ at m/e 220) which lends support to the presence of two deuteriums at C-4, α to carbonyl function. This pattern of deuterium distribution can arise only from 2b. In contrast 2d would have given a parent peak at m/e 220 for 13c and after base treatment would have shown a peak at m/e 218 for the ketone 13c (cf. Fig 17B, 17C).

a: SUKH DEV AND OURISSON



b: BERSON *etal*



REL. % OF D-SPECIES	2b	9b	10b	12b	13b		14b
2D	13.89		09.11	08.50	09.29	47.69	09.88
3D	29.09		23.65	22.93	26.21	30.52	25.93
4D	42.62		51.75	53.60	58.02	04.85	50.13
D/MOL.	3.47		3.59	3.66	3.46	2.25	3.56

CHART X-V: LOCATION OF DEUTERIUMS IN ISOLONGIFOLENE

Table 4: PMR SPECTRA OF LONGIFOLENE-d_4, ISOLONGIFOLENE-d_4 AND THEIR DERIVATIVES

S.No.	Compounds	ring protons ∝ to OH protons							olefinic protons					Total No. of protons in non-deuterated	Total No. of protons in deuterated.	No. of D/mole
		non-deuterated	deuterated		non-deuterated		Deuterated			non-deuterated		Deuterated				
				δ-ppm	splitting	protons	splitting	protons	δ-ppm	splitting	protons	splitting	protons			
1.	Methyl isolongifolate 21	14	11	-	-	-	-	-		-	-	-	-	26	23	3.0
2.	Longifolene 4b	13	10	-	-	-	-	-	4.44	s	1	s	1			
									4.70	s	1	s	1	24	21	3.0
3.	Isolongifolene 2b	11	8.1	-	-	-	-	-	5.1	t	1	t	1	24	21.1	2.9
4.	Cycloisolongifolol 10b	11	7.9	4.17	t	1	t	1	-	-	-	-	-	24	20.9	3.1
5.	Alcohol 12b	9	6	4.07	dd	1	s	1	5.20	t	1	t	1	24	21	3.0
6.	Ketone 13b	9	6	-	-	-	-	-	5.52	t	1	t	1	22	19	3.0
7.	Ketone 13b after alkali treatment	9	7	-	-	-	-	-	5.52	t	1	t	1	22	20	2.0
8.	Alcohol 14b	9	6.7	3.83	t	1	t	1	5.67	t	1	s	0.25	24	21.43	2.5

The location of other two deuteriums in isolongifolene-d_4 was revealed from the spectral characteristics of derivative 14 (prepared from the opening of deuterated epoxide with HCl-$CHCl_3$). The PMR spectrum (Fig 12C) of this compound was characterized by the presence of an olefinic proton (1/4H,S) at 5.67 ppm. It can be inferred that due to predominantly trans-elimination 3/4H is lost from C-1 during rearrangement of epoxide 9 to 14. It is also noteworthy that the resonance appears as a singlet, thus indicating a D-atom at C-2 as in 14b (in unlabelled 14 the olefinic proton appears as doublet J= 3H_z, Fig. 12A). Consistent with the PMR data, the mass spectrum (Fig. 18C) of 14b reveals two strong peaks at m/e 223 (26%) and at m/e 224 (50%) corresponding to 14b arising from either the loss of D or H respectively during elimination step.

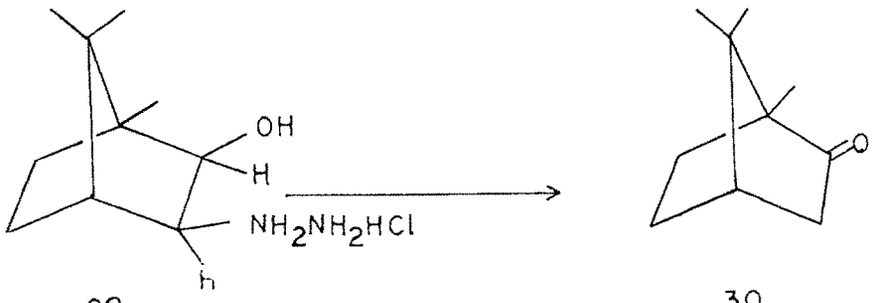
The location of D-atoms in isolongifolene-d_4 has been unequivocally established at C-1, C-2 and C-4 corresponding to structure 2b. This, in turn, provides experimental proof for the mechanism proposed by Berson et al.[9] involving exo-3,2-methyl shift in preference to endo-3,2-methyl migration implicated in Durisson's and Sukh Dev's proposal[2,7].

4. DISCUSSION

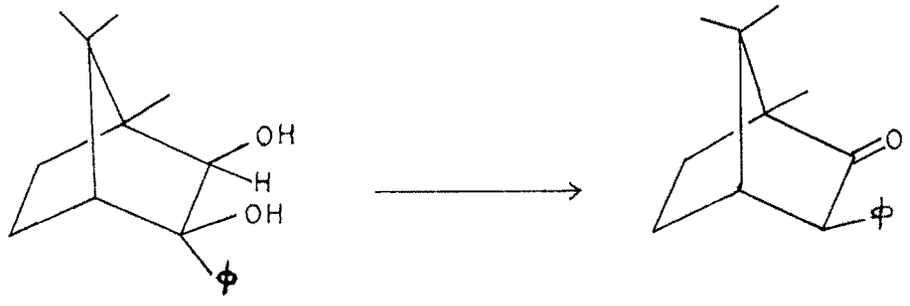
Berson's original contention for an exo-3,2-methyl

migration in the rearrangement of longifolene to isolongifolene was based on the analogy with norbornane derivative, where methyl migration almost always takes place from an exo-side[25-28]. However, subsequent to his proposal a number of cases where endo-endo migrations are involved, have been brought to light. For instance, the deamination of 3-hydroxybornyl-2-amine hydrochloride 29 to give camphor 30 or the pinacol rearrangement of diol 31 to produce corresponding ketone 32 involve endo-endo-3,2-hydride shift[29,30], since such a process relieves the interaction between C-7 methyls and 3-exo-hydroxyl group by generating a planar carbonium ion at C-3. Similarly, the decomposition of phosphorylated triazoline 33 to diethyl endo-3-methyl-2-norbornylidene phosphoramidate 34 involves an endo-endo-3,2-methyl migration[31] (see Chart XVI). Recently it has been shown that racemization of camphene also involves, upto some extent, endo-endo methyl migration[32]. Thus, under compelling steric or electronic reasons, endo-endo migrations do sometimes take precedence over the competing Wagner-Meerwein shifts.

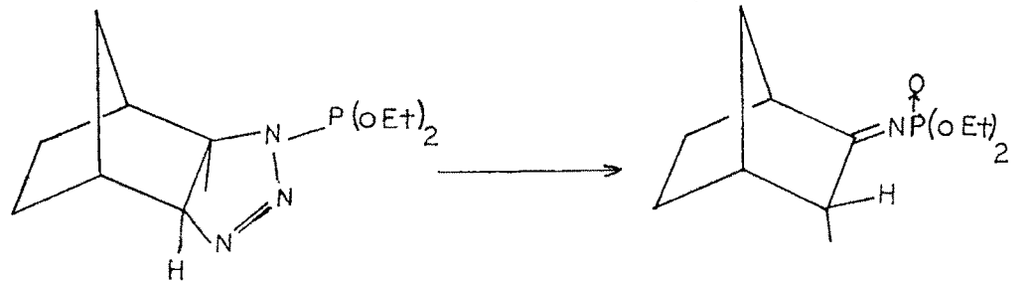
In longifolene molecule, the exo-side is crowded by the seven membered ring. This is reflected in the addition of hydrogen halides to longifolene, which gives exclusively endo-longibornyl halides 35[33]. Longifolene molecule, after protonation undergoes a Wagner-Meerwein shift and the resulting carbonium ion traps the nucleophile only from the endo side[36],



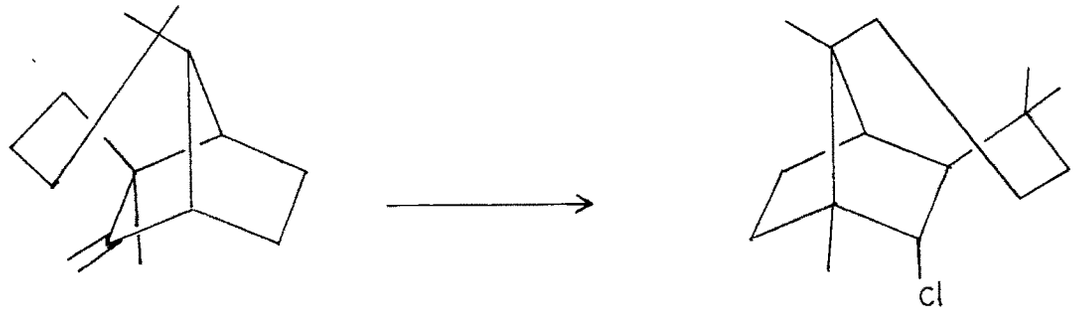
29 30



31 32



33 34

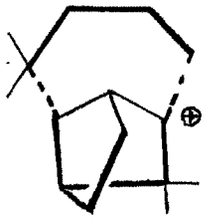


1 35

CHART XVI SOME EXAMPLES OF endo, endo- MIGRATIONS

partly because the exo-side is blocked by transannular hydride participation. Hydration and hydroboration also proceed this way, where the approach of the reagent is from the endo-face[34,35]. But, still, the steric crowding on exo-side of longifolene molecule does not force an endo-endo-3,2-methyl migration to give carbonium ion 4, which is an important intermediate in Ourisson's and Sukh Dev's proposal. It is worthwhile to rationalize why the reaction takes a circuitous route involving an exo-3,2-methyl shift as outlined in Berson's scheme (Chart II). A close scrutiny of the two mechanisms reveals that two distinct bridgehead carbonium ions 4 and 6 are implicated in the two mechanisms.

Bridgehead carbonium ion 6 is situated at the bridge of a bicyclo[4,3,1] decane system, whereas ion 4 is located at the



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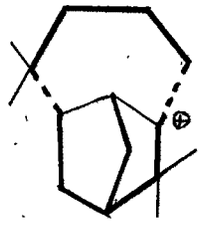

6

bridge of bicyclo[4,2,1] nonane system. The ion 6 is therefore situated in a larger ring and can take up more planar structure than ion 4 and is hence more stable and may be preferred to ion 4. The energy difference or stability of

ion 6 may be responsible for the transformation to follow the route depicted in Chart II.

5. CONCLUSION

Thus, the rearrangement of longifolene to isolongifolene proceeds according to Berson's mechanism plausibly because the bridgehead carbonium ion formed in this process is more stable.

6. EXPERIMENTAL

All m.ps and b.ps are uncorrected. Light petroleum ether and petroleum ether refer to the fractions b.p. 40-60° and 60-80° respectively. All solvent extracts were finally washed with brine and dried over anhydrous sodium sulphate.

IR spectra were recorded as smears (liquid) or nujol mulls (solid), unless stated to the contrary, on Perkin-Elmer Infra cord model 137E. PMR spectra were taken in 10-20% carbon tetrachloride solution (unless stated to the contrary) with TMS as an internal standard, on Varian A-60 or T-60 spectrometer; signals are indicated in δ ppm relative to TMS. Mass spectra were obtained with a consolidated Electrodynamics corporation spectrometer type 21-110B (mass 70 eV direct inlet system). Natural abundance spectra were recorded for comparison with spectra of deuterated samples.

Analytical GLC was run on 'Aerograph' model A-350B, using a 150 mm x 5 mm column packed with 20% stationary phase on chromosorb W (60-80 mesh) and 20% silicone SE-30 celite (60-100 mesh) with H_2 as carrier gas.

Alumina used for detosylation and rearrangement was neutral to phenol~~ate~~phthalein test and was activated at 450° for 6 hrs.

Isolongifolene oxide used for the present work was the solid (±) epoxide m.p. 39-40°.

Heavy water (minimum isotopic purity 99.5 atom % deuterium) was purchased from Isotope Division of Bhabha Atomic Research Centre, Bombay, India and used for preparing deuterated reagents such as AcOD, $ND_2ND_2D_2O$ and $(CH_2CH_2OD)_2O$ and the isotopic purity of reagents was ascertained by PMR and Mass spectrometer.

6.1. SYNTHESIS OF LONGIFOLENE-4,4,5,5-D_4 (1b)

6.1.1. Methyl isolongifolate (21)

Longifolene (505 gm) in gl AcOH (2 ltr) was mechanically stirred in a three necked flask, equipped with a stirrer, thermometer and a dropping funnel. To this, a solution of CrO_3 (1 kg) in water (600 ml) and conc H_2SO_4 (25 ml) was added at such a rate that the inside temperature was maintained at 45-50° (addition time, 3 hrs). The oxidation was completed by warming the resulting green reaction mixture on a water bath for 2 hours. The green material was cooled to room temperature, diluted with water (6 ltr) and separated into acidic (210 gm) and neutral (110 gm) portions with 10% aq. KOH.

The mixture of crude acids (210 gm), MeOH (250 ml), conc H_2SO_4 (70 ml) and benzene (500 ml) was refluxed on a water-bath for 70 hours. The benzene layer was separated and the aqueous layer was diluted with water (1 ltr) and extracted with benzene (500 ml x 3). The combined organic extracts were mixed and separated into acidic (80 gm) and neutral (126 gm) fractions with 10% aq KOH. The neutral fraction was diluted with pet. ether (20 ml) and chilled to -10^{o}C (ice salt bath) to give methyl isolongifolate (60 gm, m.p. 48-53^{o}) which was recrystallized from petroleum ether to furnish white crystals of m.p. 54.5^{o}-55.5^{o} (52 gm).

6.1.2 Isolongifolol (22)

To a stirred slurry of lithium aluminium hydride (LAH, 7.8 gm, 92%) in ether (150 ml) was added dropwise, methyl isolongifolate (52 gm) in ether (175 ml). After the addition was over, the mixture was stirred for an additional six hours and then cooled to 10^{o}, water (8 ml) was added dropwise cautiously and then 15% aq NaOH (8 ml) followed by more water (24 ml). The white grannular solid was filtered off and washed with ether (25 ml x 4). The residue (50 gm, m.p. 110-112^{o}C) was crystallized from petroleum ether to furnish white glass-wool-like crystals of isolongifolol 22 (m.p. 112.5-113^{o}, 48 gm). IR: OH 3170, 1038, 1015 cm^{-1}. PMR: $-\overset{|}{\underset{|}{C}}-Me$ (3H, s, 0.85 ppm, 6H, s, 1.03 ppm), CHOH (1H, d, 3.67 ppm; J_1= 7Hz).

6.1.3. 4,14-Isolongifolanoxide (23)

Isolongifolol 22 (20.0 gm, 0.09 mol), commercial lead tetraacetate (44.4 gm, 0.1 mol) and iodine (11.47 gm, 0.045 mol) were placed in a one litre three necked flask and cyclohexane (250 ml, purified, benzene free) was added.* This reaction mixture was heated with stirring to reflux by irradiating with a 250 Watt tungsten lamp from underneath (N_2 atmosphere). After the reaction was over (in 1/2 hr, monitered by TLC), excess lead tetraacetate was destroyed by adding ethanediol (10 ml). To remove excess iodine, silica gel (35 gm) coated with 15% KI, was added portionwise and stirred for 15 minutes. The dark violet colour of the reaction mixture turned into light pink and lead tetraacetate had become grannular and so it was filtered off and washed easily. The lead salt and silica gel were filtered through alumina (gr. III, mixed with 10% (w/w) sodium thiosulphate, 5 cm x 4 cm) and washed with ether-cyclohexane (1:3, 25 ml x 5). The colourless residue (21 gm), after removal of solvent, was distilled, b.p. 128-130°/ 2.5 mm. (19 gm, 95%; GLC and TLC pure). IR: C-O-C 1062, 1042, 1038, 990, 935 cm^{-1}. PMR: $-\overset{|}{\underset{|}{C}}-$ Me (3H, s, 0.93 ppm; 6H, s, 0.98 ppm), CH_2OC (1H, q, 3.42 ppm, J_{gem} = 8.5Hz, J_{vic} = 3.5Hz; 1H, d, 3.67 ppm, J_{gem} = 8.5Hz, J_{vic} = 0) CHOC (1H, br.t 4.18 ppm, $J_1 = J_2$ =6Hz).

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*Without iodine, lead tetraacetate oxidation gives the ether 3 in very poor yield (15% only)[14,15].

6.1.4. 4,14-Isolongifolanolide (24)

Chromium trioxide (21 gm) in water (40 ml) and glacial acetic acid (360 ml) was added to isolongifolanoxide 23 (19 gm) in gl. AcOH (400 ml). The reaction mixture was kept at 50° for 6 hours. The reaction product was cooled to room temp (30°), diluted with water (2 ltr) and extracted with petroleum ether (500 ml x 4). Organic layer was washed with aqueous sodium carbonate (400 ml x 3) and water (300 ml x 3). The residue (20.0 gm, m.p. 40-50°), after removal of solvent, was saponified by refluxing with KOH (15 gm) in water (10 ml) and methanol (40 ml) for 3 hours. The product was cooled to room temperature, diluted with water and extracted with petroleum ether (50 ml x 3) to remove unreacted ether 23 (1.9 gm). The aqueous portion, after acidification with dil HCl, was extracted with petroleum ether (50 ml x 6). The organic extract was washed with aqueous sodium carbonate (50 ml x 3) and water (50 ml x 3) and dried. Solvent was flashed off, residue (17 gm, m.p. 52-59°) on crystallization from petroleum ether gave white crystals of lactone 24 (m.p. 60.5-61.5°, 15 gm). IR: CO 1775, C-O-C 1182, 1072, 1038, 1028 cm^{-1}. PMR: $-\overset{|}{\underset{|}{C}}-$ Me (6H, s, 1.02 ppm; 3H, s, 1.10 ppm), CHCO (1H, t, 3.07 ppm, J= 5Hz) CHOCO (1H, t, 4.60 ppm, J = 6Hz).

6.1.5. 4-endo-Hydroxyisolongifolol (25)

Lactone 24 (16 gm) in dry ether (150 ml) was added dropwise to a slurry of LAH (3.2 gm) in ether (100 ml) with stirring. Excess LAH was destroyed by adding water (3.5 ml) and 15% aq. NaOH (3.5 ml) followed by water (10 ml). The grannular precipitate was filtered off and washed with ether. Diol 25 (m.p. 72-78°, 16.2 gm) was crystallized from petroleum ether to furnish white crystals (m.p. 94.5-95.5°, 14.8 gm; lit.[14] m.p. 88-89°). IR: OH 3250, 1098, 1065, 1040, 1018, 1005 cm^{-1}. PMR: $-\overset{|}{\underset{|}{C}}-Me$ (9H, s, 0.93 ppm); CHOH (3H, m, spanned between 3.40 and 4.38 ppm).

6.1.6. 4-Oxoisolongifolic acid (28)

6.1.6.1. Oxidation of diol 25 with CrO_3: Jone's reagent was added to a cooled (5°C) and stirred solution of diol 25 (12.07 gm) in acetone (250 ml) till the orange colour persisted. The reaction mixture was left at 25° for 1 hr, then diluted with water (1 ltr) and extracted with ethyl acetate (300 ml x4). The organic layer was washed with 10% aq KOH (200 ml x 4) to separate into neutral (4.1 gm) and acid portions. The aqueous portion after acidification and extraction with ethyl acetate (150 ml x 4) gave a mixture of two acids 27 and 28 (8.0 gm). The crude acid after crystallization from acetonitrile gave ketoacid 28 (5.0 gm, m.p. 184.5-185.5°). The mother liquor

on chromatography (silica gel gr. III, 150 gm, 7 cm x 35 cm) gave some more ketoacid 28 (1.8 gm) with ethyl acetate-benzene (1:1, 200 ml x 4). The lactone acid 27 (0.6 gm, m.p. 221-222°) was eluted out with ethyl acetate (500 ml). Small amounts of both acids were esterified with diazomethane, crystallized from petroleum ether and characterized. 4-oxo-Methylisolongifolate (28a, m.p. 77.5-78.5°). IR: CO 1748, 1185, 1100 cm^{-1}. PMR: $-\overset{t}{\underset{t}{C}}-$ Me (3H, s, 0.97 ppm; 3H, s, 1.01 ppm; 3H, s, 1.08 ppm), CHCOOMe (1H, d, 3.13 ppm, J= 5Hz), COOMe (3H, s, 3.63 ppm). Methyl ester of lactone acid (27); m.p. 107-108°C. IR (Fig.4): CO 1740, 1200, 1167, 1052 cm^{-1}. PMR (Fig. 3): $-\overset{t}{\underset{t}{C}}-$Me (3H, s, 1.07 ppm; 3H, s, 1.10 ppm; 3H, s, 1.18 ppm), CHCOOMe (1H, d, 3.0 ppm J = 4Hz), COOMe (3H, s, 3.67 ppm), CHOCO (1H, bd 4.77 ppm, J = 4Hz). $C_{16}H_{24}O_4$ requires C, 68.54; H, 8.63%; found C, 68.77; H, 8.69%. Mass: Ten most intense peaks, M^+ 280 (33.5%), 237 (44.5%), 205 (25%), 137 (95%), 136 (100%), 135 (31%), 121 (55%), 109 (73.5%), 107 (51%), 105 (50%).

6.1.6.2. Oxidation of diol 25 with N-bromosuccinimide to 4-oxo-isolongifolol-hemiacetel 26 and further oxidation to ketoacid 28: Diol 25 (5.8 gm) was dissolved in t-BuOH (135 ml), pyridine (4.5 ml) and water (15 ml) and to this, N-bromosuccinimide (8.8 gm, 2 mole equivalent) was added in one lot at room temperature 28-29° and stirred for half an hour. The product was diluted with saturated aq Na_2CO_3 (150 ml) and extracted with ether (50 ml x 5). Ether extract

was washed with water and dried. Removal of solvent gave hemiacetal 26 (5.8 gm, m.p. 122-128°).

The above crude hemiacetal (5.6 gm) was dissolved in acetone (150 ml), cooled to 0°C and treated with Jone's reagent (10 ml) dropwise addition with stirring) and left at room temperature 25° for one hour. The product was diluted with water (400 ml) and extracted with ethyl acetate-benzene (1:1, 150 ml x 4). The organic extract was washed with water. Ketoacid 28 (5.3 gm, m.p. 170-178°, 90% yield based on diol), obtained was crystallized from acetonitrile to furnish white crystals (5.0 gm m.p. 184-185.5°, mixed m.p. was not depressed with authentic sample).

A small amount of hemiacetal was crystallized from petroleum ether (m.p. 133.5-134.5°) and characterized. IR (Fig.1): (no carbonyl absorption), OH 1160, 1130, 1118, 1043 cm^{-1}. PMR (Fig. 1) ($CDCl_3$): $-\overset{t}{\underset{t}{C}}-\underline{Me}$ (6H, s, 0.98 ppm; 3H, s, 1.02 ppm), C$\underline{H}$OC (1H, d, 3.58 ppm, J_{gem}= 9Hz; 1H, q, 3.82 ppm, J_{gem}= 9Hz, J_{vic}= 3Hz). D_2O exchangeable $\underline{OH}$ (1H, bs 2.90 ppm); $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24% found C, 76.07; H, 9.93%. Mass: Ten most intense peaks, M^+ 236 (100%), 165 (43%), 153 (80%), 152 (85%), 121 (33%), 107 (90%), 105 (40%), 95 (42%), 93 (46%), 91 (96%).

6.1.7. Deuteration of hydrazine with D_2O

Anhydrous hydrazine (NH_2NH_2, b.p. 113-114°/715 mm, 15 ml) was placed in a three necked 500 ml flask assembled with two dropping funnels and an efficient total-condensation-partial-take-off condenser. D_2O (50 ml) was added from one funnel, refluxed for 30 minutes and distilled azeotropically with dry xylene (130 ml) delivered from the second funnel. This process was repeated four times with more D_2O (40 ml, 35 ml, 35 ml, and 30 ml) with xylene (115 ml, 110 ml, 110 ml and 80 ml) respectively. Finally the resulting hydrazine hydrate-D_6 ($ND_2ND_2D_2O$) was distilled, b.p. 118-120°/715 mm in a current of dry nitrogen.

6.1.8. Deuteration of Diethylene glycol

Diethylene glycol (125 ml) was deuterated by adding D_2O (75 ml), refluxing for half an hour and distilling the water off. This process was repeated thrice with more D_2O (50 ml, 50 ml and 50 ml).

6.1.9. Methyl isolongifolate-3,4,4,5,5-d_5 (21a)

6.1.9.1. Wolff-Kishner Reduction of ketoacid 28 using potassium as base: Potassium (1.7 gm) was dissolved (in several portions) in diethylene glycol-Od_2 (30 ml), placed in a three necked flask

(assembled with a reflux condenser, dropping funnel and downward distillation condenser) under nitrogen, with cooling and occasional swirling, when all the potassium had dissolved (in 8 hours), ketoacid 28 (4.8 gm) and D_2O (10 ml) were added, refluxed for 10 minutes and water was distilled off. This process was repeated three more times with D_2O (8 ml, 7 ml and 5 ml) (to deuterate the active methylene protons to carbonyl group). Hydrazine hydrate-d_6 ($ND_2ND_2D_2O$, 3 ml) was then added and refluxed for two hours under N_2 in an oil bath (145-155°). Excess of hydrazine hydrate-d_6 and D_2O were removed by distillation. The dropping funnel and distillation condenser were removed and the reaction mixture was refluxed for four hours under nitrogen. The product was diluted with water (100 ml) and extracted with ether-benzene (1:1, 50 ml x 4) to remove neutral material. The aqueous portion after acidification with dil HCl and extraction with ether-benzene (1:1, 50 ml x 4) gave the crude acid (4.6 gm, m.p. 125-130°), esterified with diazomethane and the ester was distilled (4.2 gm, b.p. 128-130°/1.5 mm, m.p. 39-45°, GLC. methyl isolongifolate-d_5 (95%) and methyl longifolate-d_5 (5%).

6.1.9.2. Using t-BuOK as base*: Ketoacid (4.9 gm) was dissolved

*This method was more convenient to generate KOD. In the first method there is always danger of fire during the addition of potassium, besides this process takes a long time for the metal to dissolve.

in diethylene glycol-Od_2 (30 ml). t-BuOK (6.4 gm) in D_2O (15 ml) was added to this, refluxed for half an hour and excess of t-BuOD and D_2O were distilled off. Similar work up procedure was followed as in the above experiment. In this method also we got same yield of ester 21a with same deuterium content; methyl isolongifolate (4.8 gm, m.p. 41-47°): GLC methyl isolongifolate-d_5 (95%), and methyl longifolate (5%). Methyl isolongifolate 21 (m.p. 54-55°). PMR (Fig. 5A): $-\overset{|}{\underset{|}{C}}-$Me (3H, s, 0.89 ppm; 3H, s, 0.95 ppm; 3H, s, 1.01 ppm), methylene protons (13H, spanned between 1.12 2.2 ppm), CHCOOMe (1H, d, 2.83 ppm, J = 4Hz), COOMe (3H, s, 3.59 ppm). Methyl isolongifolate-d_5, 21a (m.p. 41-47°C). PMR (Fig. 5B): $-\overset{|}{\underset{|}{C}}-$Me (3H, s, 0.89 ppm; 3H, s, 0.95 ppm; 3H, s, 1.01 ppm), methylene protons (8.5H, spanned between 1.12-2.2 ppm), CHCOOMe (0.3H, d, 2.83 ppm J = 4Hz) COOMe (3H, s, 3.59 ppm).

Mass spectrum: Deuterium content of the W.K. reduction product i.e. methyl isolongifolate-d_5 21a

Product	No. of deuteriums incorporated in the product							Total D/mol
	0	1	2	3	4	5	6	
K as base	0	0	0	5.28	56.76	37.80	0.16	4.32
t-BuOK as base	0	0	0	8.46	48.64	42.90	-	4.34

6.1.10. Isolongifolol-3,4,4,5,5-d_5 (22a)

Methyl isolongifolate (9.0 gm) in ether (150 ml) was reduced with LAH (2.6 gm) in ether (120 ml). After work up (as described in section 6.1.9) and crystallization resulted crystalline isolongifolol-3,4,4,5,5-d_5 22a (7.4 gm, m.p. 112.5-113.5°).

6.1.11. Isolongifolyl tosylate

Isolongifolol (2.5 gm) was dissolved in pyridine (30 ml) and cooled to 0° in an ice bath, p-toluene sulphonyl chloride (4.0 gm) was added in one lot. After keeping the reaction mixture at 5° for 7 hours and at 25° for 12 hrs, it was diluted with ice cold water (160 ml) containing much of crushed ice (with stirring). The tosylate was filtered off, washed with ice cold water and dried over P_2O_5 under vacuum (1.5 mm) for 4 hours. Isolongifolyl tosylate (m.p. 68.5-69.5°, 4.8 gm; lit.[24] m.p. 68-69°). IR: SO 1180, 1097, 948 cm^{-1}, aromatic 1580 cm^{-1}. PMR: $-\overset{t}{\underset{t}{C}}-$Me (3H, s, 0.77 ppm; 3H, s, 0.93 ppm; 3H, s, 0.97 ppm), Tos-Me (3H, s, 2.45 ppm); CHOTs (2H, d, 4.08 ppm, J_1 = 7Hz), aromatic protons (2H, d, 7.30 ppm, J_1 =7.5Hz; 2H, d, 7.73 ppm, J_1= 7.5Hz).

Similar treatment of isolongifolol-d_5 22a (4.0 gm) in pyridine (40 ml) with p-toluene sulfonyl chloride (6.0 gm)

gave pure crystalline isolongifolyl tosylate (m.p. 67-69°, 7.16 gm).

6.1.12. Longifolene-4,4,5,5-d_5 (22a)

Isolongifolyl tosylate (3.6 gm) in petroleum ether (100 ml, 2/3 v/w of alumina) was loaded on dry packed column (4 cm x 20 cm) of alumina (N/I, 1.50 gm). At the end of 12 hours, longifolene (1) was eluted out with petroleum ether (350 ml) and distilled; longifolene (b.p. 91-93°/3 mm, 2.0 gm, 90% GLC pure, 9% isolongifolene). IR: = CH_2 1650, 875 cm^{-1}. PMR (Fig. 6A): $-\overset{t}{\underset{t}{C}}-$Me (3H, s, 0.90 ppm; 3H, s, 0.95 ppm; 3H, s, 1.00 ppm), methylene protons (11H, spanned between 1.1- 1.8 ppm), methine protons (1H, bs, 2.08 ppm; 1H, bs, 2.61 ppm) = CH_2 (1H, s, 4.48 ppm; 1H, s, 4.63 ppm).

Similarly isolongifolyl tosylate-3,4,4,5,5-d_5 (7.1 gm) in petroleum ether (190 ml, 2/3 v/w of alumina) was loaded on dry packed column (4 cm x 30 cm) of alumina (N/I, 245 gm) and after 12 hrs, longifolene-d_4 (1b, 3.5 gm) was eluted out as described above. PMR (Fig. 6B): $-\overset{t}{\underset{t}{C}}-$Me (3H, s, 0.90 ppm; 3H, s, 0.95 ppm; 3H, s, 1.00 ppm) methylene protons (7.5H, spanned between 1.1 -1.8 ppm), methine protons (1H, s, 2.08 ppm; 1H, s, 2.61 ppm), = CH_2 (1H, s, 4.48 ppm; 1H, s, 4.63 ppm). Mass: 0.9% d_1, 7.6% d_2, 35.0% d_3, 49.3% d_4 and 7.2% d_5.

6.2. ISOMERIZATION OF LONGIFOLENE TO ISOLONGIFOLENE

6.2.1 With $BF_3 \cdot Et_2O$/AcOD[2,38]

Longifolene (26.64 gm), borontrifluoride etherate (25 ml) and AcOD (125 ml; 98% isotopic purity) were mixed and stirred at room temperature (30°) for 20 minutes. Just after the mixing, the colour of the mixture was yellow, which soon changed to pale pink, then to reddish pink and finally the mixture turned to a dark reddish pink homogeneous solution. This was poured into water (250 ml) contained in a separating funnel, shaken well and extracted with pentane-ether (1:1, 100 ml x 3). The ethereal layer was washed with water (100 ml x 3), aq. sodium bicarbonate (10%, 50 ml x 2) and brine, dried ($MgSO_4$) and then freed from solvent to give a yellow residue (28.98 gm). This was separated into hydrocarbon and acetate fractions by passing over a column (1.6 x 6 cm) of alumina (gr. I, 350 gm). The hydrocarbon fraction, eluted with petroleum ether, was distilled (b.p. 102-105°/6.5 mm) to give pure deuterated isolongifolene 2a (17.92 gm).

This general procedure mentioned above was used to isomerize different substrates to isolongifolene in deuterio and nondeuterio acid media employing standard conditions; hydrocarbons (1 gm), AcOH/AcOD (5 ml); $BF_3 \cdot Et_2O$ (1 ml).

PMR and mass spectral analysis are given in Table 5 and 1 respectively for the isolongifolene obtained from different substrates for different reaction time.

6.2.2. With $BF_3.Et_2O$ in benzene[2]

A solution of longifolene-4,4,5,5-d_4 (1b, 8.5 gm) in dry benzene (30 ml) containing BF_3Et_2O (0.3 ml) was kept at 25° for 2 hours then the reaction mixture was diluted with satured sodium carbonate (20 ml), benzene layer separated and aqueous layer extracted twice with ether (20 ml x 2). Combined organic extracts were washed with water (20 ml x 3). The residue (8.5 gm), after removal of solvent, was distilled, b.p. 94-95°/2 mm (8.1 gm). PMR (Fig. 7B): $-\underset{|}{\overset{|}{C}}-$Me (3H, s, 0.83 ppm; 6H, s, 0.96 ppm; 3H, s, 1.03 ppm); methylene and methine protons (8H, spanned between 1.1-2 ppm); =CH (1H, t, 5.13 ppm, J_1 = J_2 = 3.5Hz). Mass: 2.6% d_1, 13.9% d_2, 29.1% d_3, 42.6% d_4 and 11.8% d_5.

6.3. LOCATION OF DEUTERIUMS IN ISOLONGIFOLENE

6.3.1. 9-Oxoisolongifolene 8[38]

Isolongifolene 2 was oxidized to α,β-unsaturated ketone 8 according to the procedure of Sukh Dev and co-workers[11]; 9-oxoisolongifolene (8) m.p. 53-54°C. IR: CO 1670, C=C 920, 901 cm^{-1}. PMR: $-\underset{|}{\overset{|}{C}}-$ Me (3H, s, 1.00 ppm; 6H, s, 1.07 ppm; 3H, s, 1.17 ppm); =CH (1H, s, 5.5 ppm).

Table 5: PMR SPECTRA OF ISOLONGIFOLENE DERIVED FROM DIFFERENT SUBSTRATE WITH BF_3Et_2O-AcOH/AcOD

Expt. No.	Starting hydrocarbon	Acid Medium AcOH/ AcOD	Reaction time	No. of protons in Methyls at δ			Olefinic protons at δ 5-13	Ring protons	Total D/mol.
				0.83	0.96	1.03			
1.	Longifolene	AcOH	20 min	3.0	6.0	3.0	1.0	11.0	0
2.	Longifolene	AcOD	20 min	3.0	3.5 to 4.0	1.8 to 2.0	0.4	11.0	3-3.7
3.	Product of 2	AcOH	20 minx2	3.0	4.4	2.3	1.0	11.0	2.3
4.	Product of 2	AcOH	24 hrs	3.0	5.6	3.0	1.0	11.0	0.4
5.	Isolongifolene	AcOD	20 min	3.0	6.0	3.0	0.5	11.0	0.5
6.	Product of 5	AcOH	20 min x2	3.0	6.0	3.0	1.0	11.0	0
7.	Isolongifolene	AcOD	27 hrs	3.0	6.0	2.2	0.4	10.0	2.2
8.	Product of 7	AcOH	20 min x2	3.0	6.0	2.3	1.0	10.0	1.7
9.	Product of 7	AcOH	24 hrs	3.0	6.0	2.4	1.0	11.0	0.6

Isolongifolene-d (2a) (2.5 gm) was oxidized to ketone 8a (0.78 gm). PMR: $-\overset{|}{C}-$Me (3H, s, 1.00 ppm; 3.3H, s, 1.07 ppm, 2H, s, 1.17 ppm); = CH (0.5 H, s, 5.5 ppm). Mass: 5.65% d_0, 5.75% d_1, 12.33% d_2, 27.47% d_3, 20.45% d_4, 16.34% d_5, 12.94% d_6, and 3.8% d_7.

Ketone 8a was treated with alcoholic KOH for 2 hours under nitrogen and its deuterium content was analysed by mass: 3.98% d_0, 6.36% d_1, 15.43% d_2, 22.78% d_3, 21.06% d_4, 15.73% d_5, 10.83% d_6 and 3.79% d_7.

6.3.2. Isolongifolene epoxide 9

To isolongifolene (60.6 gm, 0.3 mol), dissolved in dry benzene (120 ml, cooled to 0°, $[\alpha]_D$-26.5°), was added dropwise a benzene solution (1 lit., precooled to 5°) of perbenzoic acid (40.4 gm, 0.3 mol) during 20 min. At the end of 12 hours, at 5-8°C the reaction was almost complete and was worked up by extraction with 5% aq KOH (250 ml x 3). The organic layer was washed with water (250 ml x 3) followed by brine and dried. A colourless liquid residue (66 gm) was obtained after removal of solvent. This was diluted with n-hexane (75 ml) and chilled in dry ice (-60°) to give a white solid (m.p. 37-39°, 32.5 gm). Three subsequent crystallization from n-hexane gave white crystalline isolongifolene oxide, m.p. 40-41°. IR: epoxide 1240, 920, 808 cm^{-1}. PMR: $-\overset{|}{C}-$ Me (3H, s, 0.75 ppm; 6H, s,

0.85 ppm; 3H, s, 0.9 ppm), CHOC (1H, t, 3.02 ppm).

Similarly isolongifolene-d_4(2b) (7.1 gm, derived from longifolene-4,4,5,5-d_4 1b) in dry benzene (15 ml) was treated with perbenzoic acid (5 gm) in benzene (95 ml). Usual work up (as described above) gave the solid epoxide 9b (m.p. 39-41°, 3.6 gm).

Isolongifolene-d_7 2a (10.54 gm) was oxidized to get pure epoxide 9a (m.p. 40-41°, 4.23 gm).

6.3.3. Rearrangement of Isolongifolene epoxide on alumina

Isolongifolene epoxide (4.9 gm) in hexane (10 ml) was loaded on a dry packed column of alumina (gr. I,/N, 150 gm, 1.5 cm x 75 cm) and was immediately eluted out by methanol benzene (1:1, 1 ltr.) to yield crystalline cycloisolongifolol (4.85 gm) which was crystallized from acetonitrile to furnish needles (m.p. 96-98°, 2.26 gm); the mother liquor on chromatography (alumina N/I, 45 gm, 1.5 cm x 30 cm) gave dehydroisolongifolene (0.815 gm) with petroleum ether and cycloisolongifolol (0.723 gm) with benzene methanol (1:1, 400 ml). Combined cycloisolongifolol was recrystallized from acetonitrile (m.p. 96.98°, 2.83 gm). IR: OH 3300, 1018 cm^{-1}. PMR: $-\overset{|}{\underset{|}{C}}-Me$ (3H, s, 0.82 ppm; 3H, s, 0.9 ppm; 6H, s, 0.93 ppm); CHOH. (1H, t, 4.13 ppm).

The reaction was repeated with deuterated isolongifolene epoxide-d_7 (9a; 1.4 gm) which yielded deuterated cycloisolongifolol (10a, m.p. 97-98°; 0.537 gm). Mass spectral analysis indicated 1.1% d_0, 4.6% d_1, 12.8% d_2, 21.2% d_3, 22.2% d_4, 19.5% d_5, 13.7% d_6 and 4.9% d_7.

Isolongifolene epoxide-d_4 (9b) (2.14 gm, m.p. 39-41°) gave cycloisolongifolol-d_4 (10b) (m.p. 95-96°, 2.215 gm), Mass spectral analysis dictated 1.0% d_0, 2.5% d_1, 9.1% d_2, 23.7% d_3, 51.7% d_4 and 12.0% d_5.

6.3.4. Dehydrocycloisolongifolene (11) and Homoallylic Alcohol (12)

Cycloisolongifolol (10, 528 mg), gl. AcOH (3 ml) and 50% (v/v) aq H_2SO_4 (0.05 ml) were mixed and left aside at 8-10° for 12 hours (monitored by TLC). The light pink coloured product was diluted with water (50 ml) and extracted with n-hexane (50 ml x 4). The organic layer was washed with 5% aq $NaHCO_3$ (50 ml x 3) and water followed by brine and dried. Solvent was removed, residue (530 mg). Prog. GLC: dehydrocycloisolongifolene 11 (34%), cycloisolongifolyl acetate (0.5%), acetate of alcohol 12 (54%), alcohol 12 (4.5%) and alcohol 10 (7%). It was chromatographed (silica gel II, 50 gm) 1.5 cm x 32 cm) with TLC monitoring (solvent, 5% EtOAc in benzene).

Fr. 1	pet ether	(50 ml x 3)	121 mg	liquid
Fr. 2	pet ether	(50 ml x 1)	-	-
Fr. 3	50% pet ether in benzene	(50 ml x 2)	252 mg	liquid
Fr. 4	benzene	(50 ml x 2)	51 mg	semisolid
Fr. 5	benzene methanol (1:1)	(50 ml x 2)	60 mg	solid.

Fraction 1 was distilled, 90-110°(bath)/1.5 mm and identified; dehydrocycloisolongifolene (12). IR: olefinic 1640, 755 cm^{-1}. PMR: (Fig. 9A): $-\overset{|}{C}-Me$ (3H, s, 0.82 ppm; 3H, s, 0.88 ppm; 3H, s, 0.95 ppm; 3H, s, 1.05 ppm); = CH (1H, d, 5.97 ppm; J_1 = 10Hz; 1H, m, spanned between 5.13-5.53 ppm).

Fraction 3 was distilled, b.p. 145-155°(bath)/1.5 mm, identified as acetate of alcohol 12. IR: CO 1730, 1024, C=C 850, 820 cm^{-1}. PMR: $-\overset{|}{C}-Me$ (3H, s, 0.85 ppm; 3H, s, 0.98 ppm; 3H, s, 1.03 ppm; 3H, s, 1.07 ppm); CH_3CO (3H, s, 1.95 ppm); CHOAc (1H, dd, 4.80 ppm, J_1 = 3Hz, J_2 = 6Hz); = CH (1H, t, 5.33 ppm).

Fraction 5 was a mixture of alcohols 10 and 12.

Acetate of alcohol (12) (655 mg) was refluxed with 5% alcoholic KOH (15 ml) on a waterbath for one hour. After completion of the reaction (monitored by TLC, 5% EtOAc in benzene), the product was diluted with water (150 ml), saturated with NaCl and extracted with petroleum ether (100 ml x 4). The organic layer was washed with water (150 ml x 4) followed by

brine and dried. Solvent was removed, the residue, white solid (m.p. 70-76°, 646 mg), was crystallized from acetonitrile to give a white crystalline solid alcohol 12 (m.p. 88.5-90°, 400 mg). IR: OH 3240, 1045, C=C 842, 817, 783 cm^{-1}. PMR (Fig. 10A): $-\overset{|}{C}-$Me (3H, s, 0.84 ppm; 6H, s, 0.98 ppm; 3H, s, 1.15 ppm); CHOH (1H, dd, 3.80 ppm; J_1 = 3Hz, J_2 = 6Hz); = CH (1H, t, 5.23 ppm). $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%; found C, 81.68; H, 10.98%. Mass: Ten most intense peaks; 220 (35%), 176 (51%), 160 (51%), 132 (46%), 119 (100%), 118 (51%), 105 (78%), 91 (61%), 77 (38%), 41 (75%).

When in the above experiment, deuterated cycloisolongifolol-d_7 (10a, 1.0 gm) was employed, it gave deuterated dehydrocycloisolongifolene-d_7 11a (210 mg). PMR (Fig. 9B): $-\overset{|}{C}-$Me (1H, s, 0.82 ppm; 3H, s, 0.88 ppm; 2H, s, 0.95 ppm; 3H, s, 1.05 ppm); = CH (1H, m, centred at 5.35 ppm, 0.5H, d, 5.97 ppm); and deuterated alcohol-d_7 12a (m.p. 88-90°, 277 mg). PMR: (Fig. 10B): $-\overset{|}{C}-$Me (3H, s, 0.84 ppm; 3H, s, 0.98 ppm; 3H, s, 1.15 ppm); CHOH (1H, dd, 3.80 ppm); = CH (0.5H, t, 5.23 ppm), Mass: 2.0% d_0, 5.2% d_1, 12.6% d_2, 21.6% d_3, 21.8% d_4, 18.3% d_5, 14.0% d_6 and 4.8% d_7.

Cycloisolongifolol-d_4 (10b, 870 mg) under identical conditions, gave homoallylic alcohol 12b (m.p. 87-88°, 320 mg). PMR (Fig. 10C): $-\overset{|}{C}-$Me (3H, s, 0.84 ppm; 6H, s, 0.98 ppm; 3H, s, 1.15 ppm); CHOH (1H, bs, 3.80 ppm); = CH (1H, t, 5.23 ppm). Mass: 2.2% d_1, 8.5% d_2, 22.9% d_3, 53.7% d_4 and 12.7% d_5.

6.3.5. 5-Oxoisolongifolene (13)

To a cooled (0^{o}) solution of 5-hydroxyisolongifolene (12, 550 mg) in acetone (20 ml) was added dropwise, Jone's reagent (1 ml) till it became orange. The reaction mixture was kept at room temperature (28^{o}) for 3 hours and then diluted with water (150 ml) and extracted with n-hexane (100 ml x 3). The organic layer was washed with 5% aq $NaHCO_3$ (100 ml x 3) and water (75 ml x 2) followed by brine and dried. The residue, after solvent removal and distillation, gave the ketone 13 (540 mg) b.p. 120-130^{o}(bath)/1.5 mm. IR: CO 1740, C=C 810 cm^{-1}. PMR (Fig. 11A): $-\overset{|}{\underset{|}{C}}-$Me (3H, s, 0.77 ppm; 3H, s, 1.02 ppm; 3H, s, 1.09 ppm; 3H, s, 1.14 ppm); = CH (1H, t, 5.47 ppm) $C_{15}H_{22}O$ requires C, 82.51; H, 10.16%; found C, 82.69; H, 10.59%. Mass: Ten most intense peaks, 218 (100%), 175 (78%), 162 (22%), 159 (15%), 147 (44%), 134 (23%), 119 (28%), 105 (23%), 91 (24%), 77 (14%).

Oxidation of the deuterioalcohol-d_7 12a (200 mg) gave ketone 12a (195 mg). PMR (Fig. 11B): $-\overset{|}{\underset{|}{C}}-$ Me (3H, s, 0.77 ppm; 3H, s, 1.02 ppm; 2H, s, 1.09 ppm; 1H, s, 1.14 ppm); = CH (0.54, t, 5.47 ppm). Mass: 1.7% d_0, 5.0% d_1, 12.2% d_2, 20.4% d_3, 22.9% d_4, 19.7% d_5, 14.3% d_6 and 5.1% d_7.

Ketone 13a (80 mg) in ethanol (1.5 ml) was mixed with aq. 1N NaOH (0.2 ml) and kept for 16 hours at room temperature (30^{o})

under nitrogen atmosphere. The reaction mixture was neutralized with AcOH, diluted with water (30 ml) and extracted with petroleum ether (30 ml x 3). The organic layer was washed with water. The residue (70 mg), free from solvent, was distilled, b.p. 120-130°(bath)/1.5 mm. Mass: 2.1% d_0, 5.6% d_1, 14.7% d_2, 20.4% d_3, 21.3% d_4, 16.6% d_5, 15.3% d_6 and 4.3% d_7.

Ketone-d_4 13b (70 mg) was obtained from alcohol-d_4 12b (100 mg) by oxidation with Jone's reagent . Mass: 1.0% d_0, 2.6% d_1, 9.3% d_2, 26.2% d_3, 58.0% d_4 and 2.9% d_5.

The above ketone 13b (30 mg) was refluxed with 10% alc. KOH for 16 hours and worked up as described above. Mass spectral analysis of this ketone indicated; 9.5% d_0, 15.0% d_1, 47.7% d_2, 30.5% d_3 and 5.9% d_4.

6.3.6. Action of HCl-$CHCl_3$ on Isolongifolene epoxide 9

A $CHCl_3$ solution of dry HCl (0.5%, 5 ml) was chilled to -11 ± 1^0 and isolongifolene epoxide (530 mg) was added in one lot and shaken till dissolved. The solution was left at the same temperature for one hour and then at -5^0 for 10 hours (monitored by TLC, 5% EtOAc in benzene). The product was then diluted with 5% aq. Na_2CO_3 (50 ml) and extracted with petroleum ether (30 ml x 3). The organic extracts were washed with water

(25 ml x 3) followed by brine (40 ml) and dried. Solvent was removed and the residue (522 mg) was chromatographed (Al_2O_3, N/III, 15.5 gm, 1 cm x 21 cm).

Fr. 1	petroleum ether	(3 ml x 4)	35.2 mg solid m.p.36-38°, epoxide(TLC)
Fr. 2	Pet ether	(5 ml x 18)	340 mg liquid
Fr. 3	75% pet ether in benzene	(5 ml x 4)	
Fr. 4	50% pet ether in benzene	(5 ml x 3)	107 mg solid
Fr. 5	benzene	(5 ml x 4)	102 mg solid m.p. 103-111°

Fraction 5 after four crystallizations from n-hexane, yielded white feather-like crystals of alcohol 14 (m.p. 123-124°, 60 mg). IR: OH 3250, 1040; C=C 844, 822 cm^{-1}. PMR (Fig. 12A) ($CDCl_3$): $-\overset{|}{C}-Me$ (3H, s, 0.83 ppm; 3H, s, 0.92 ppm; 3H, s, 1.03 ppm; 3H, s, 1.08 ppm); CHOH (1H, t, 3.87 ppm); = CH (1H, d, 5.67 ppm J_1 = 3Hz). Mass: Ten most intense peaks, 220 (17%), 193 (17%), 177 (89%), 164 (100%), 149 (17%), 136 (16%), 121 (23%), 105 (19%), 91 (28%), 77 (18%).

Similar experiment with isolongifolene-epoxide-d_7 9a (610 mg) gave alcohol-d_7 14a (m.p. 123-124°, 90 mg). PMR: (Fig. 12B): ($CDCl_3$): $-\overset{|}{C}-Me$ (1H, s, 0.83 ppm; 2H, s, 0.92 ppm; 3H, s, 1.03 ppm; 3H, s, 1.08 ppm); CHOH (0.5H, t, 3.87 ppm);

=C<u>H</u> (1H, d, 5.67 ppm, J_1 = 3Hz). Mass: 1.8% d_0, 5.4% d_1, 13.6% d_2, 24.5% d_3, 20.7% d_4, 16.8% d_5, 13.1% d_6 and 4.2% d_7.

Isolongifolene epoxide-d_4 <u>9b</u> (500 mg) on similar treatment gave unsaturated alcohol <u>14b</u> (m.p. 122-123°, 30 mg). PMR (Fig. 12C): ($CDCl_3$): $-\overset{|}{\underset{|}{C}}-$<u>Me</u> (3H, s, 0.83 ppm; 3H, s, 0.92 ppm; 3H, s, 1.03 ppm; 3H, s, 1.08 ppm); C<u>H</u>OH (1H, t. 3.87 ppm); =C<u>H</u> (0.25 H, s, 5.67 ppm). Mass: 2.9% d_1, 9.9% d_2, 25.9% d_3, 50.1% d_4 and 11.2% d_5.

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37. We wish to emphasize that because D-assays in fragment ions are inherently inaccurate these estimates are crude, and only qualitative conclusion should be drawn from them.

38. This experiment was carried out by Dr.R. Soman of this laboratory.

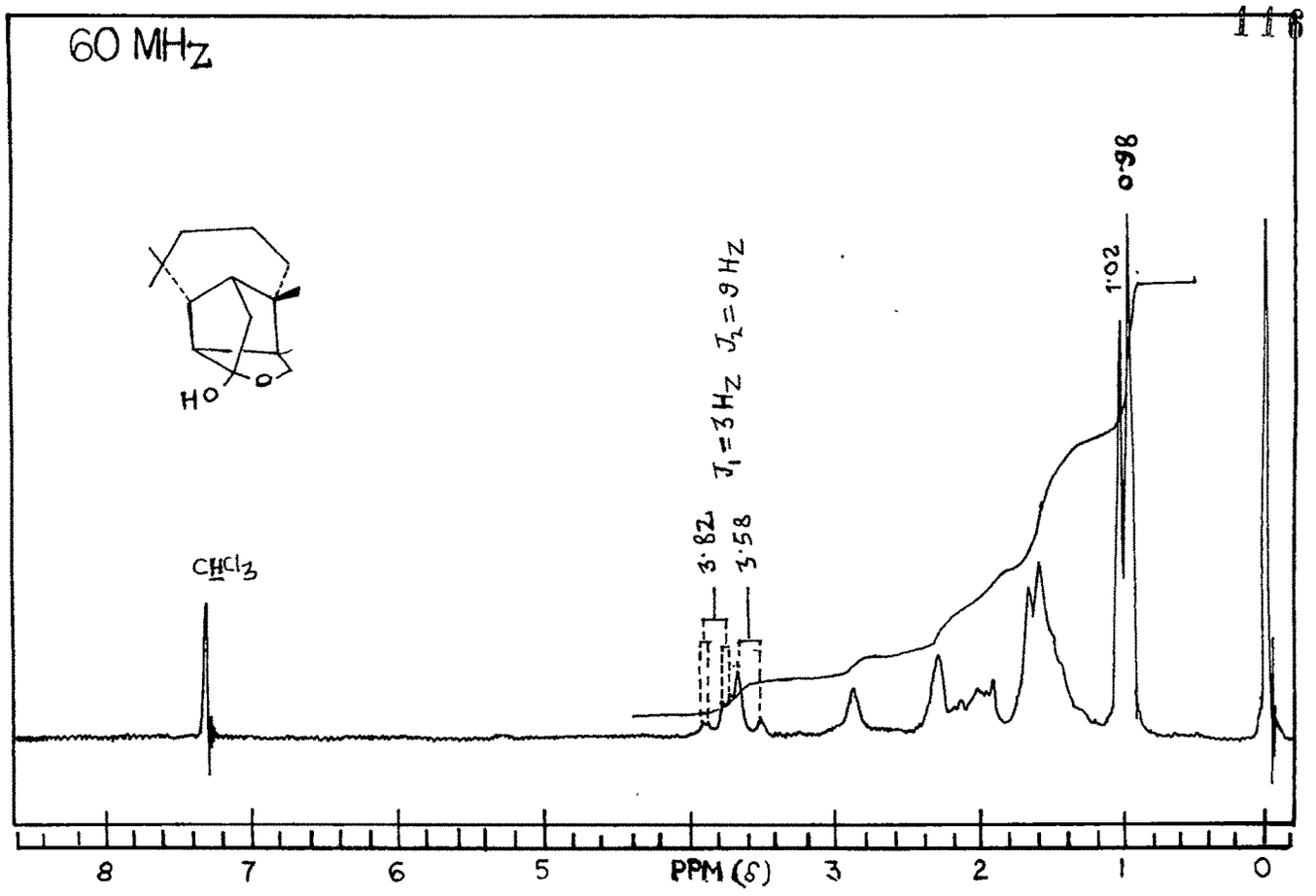


FIG: 1: PMR SPECTRUM : 4-OXOISOLONGIFOLOL HEMIACETAL (26)

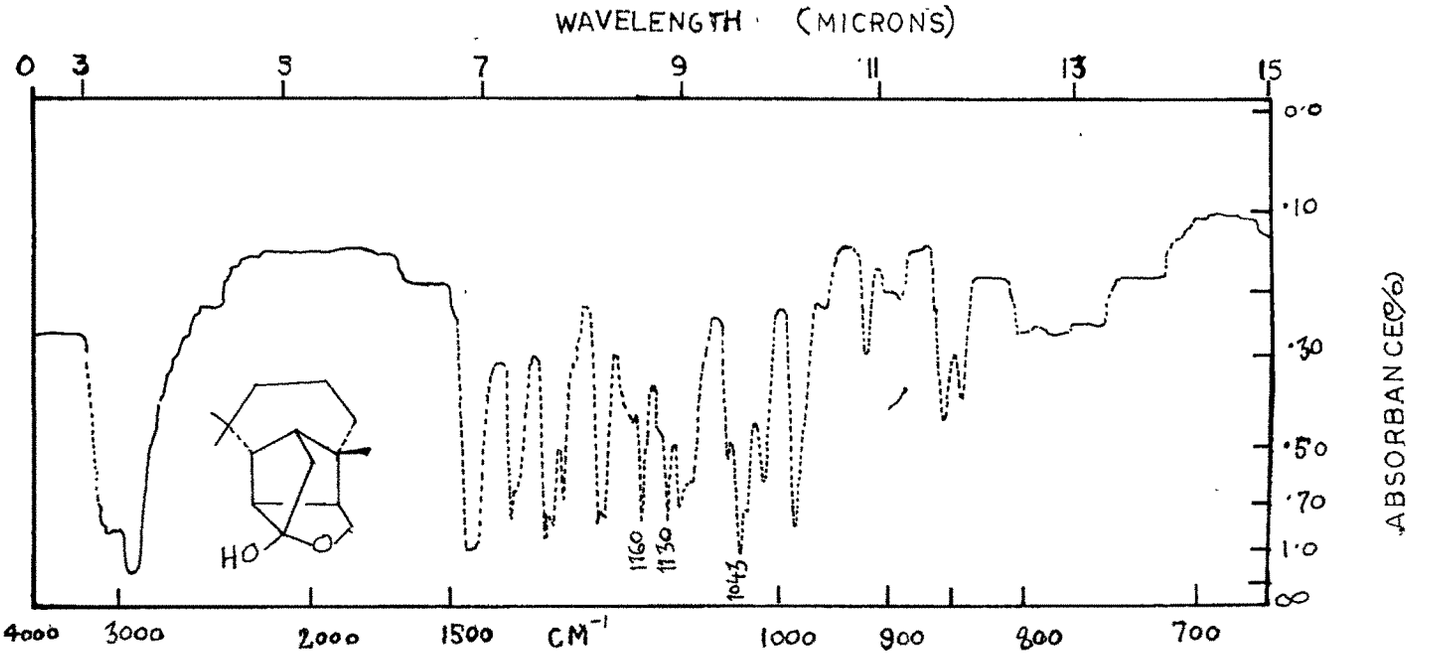


FIG: 2: IR SPECTRUM: 4-OXOISOLONGIFOLOL HEMIACETAL (26)

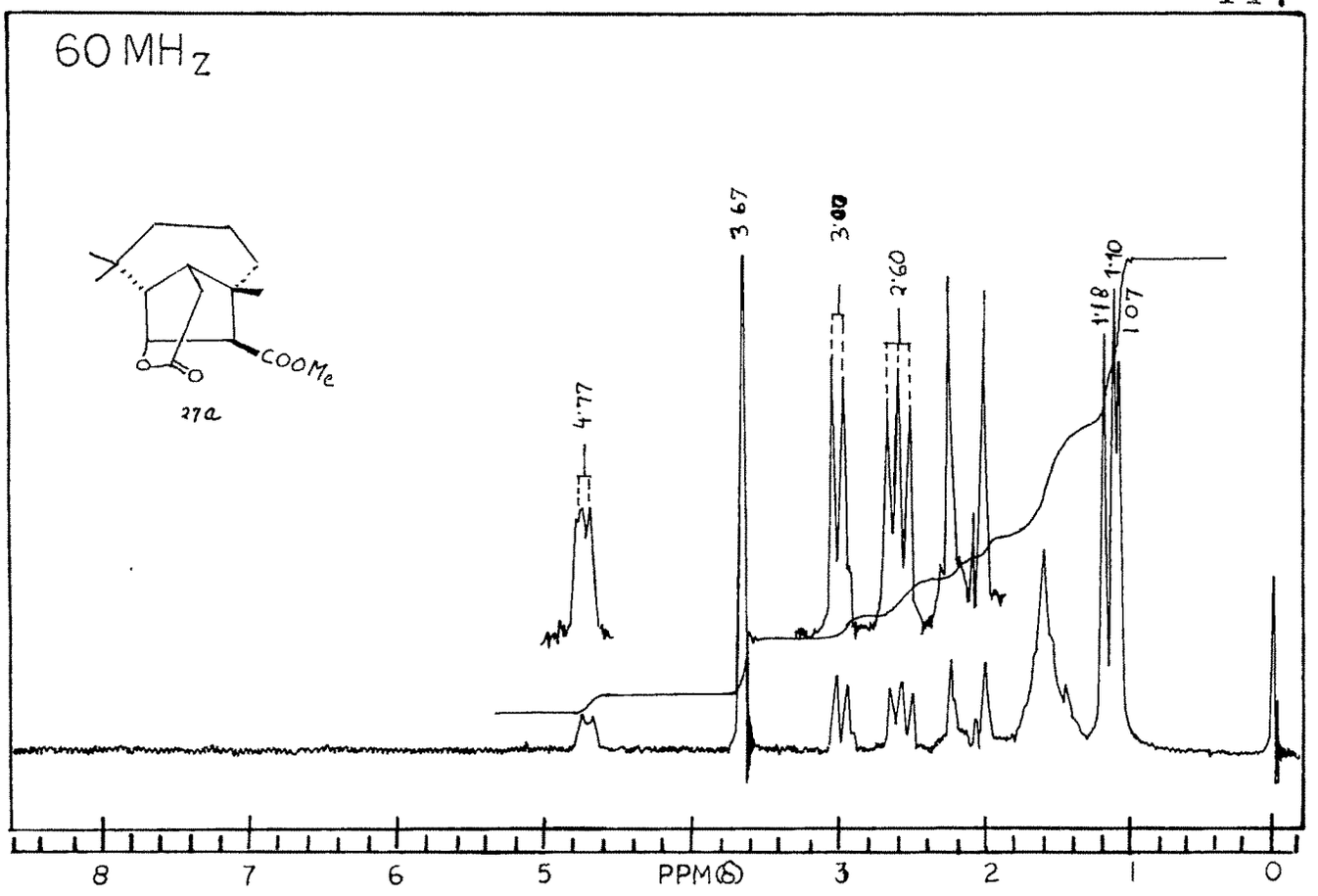


FIG:3: PMR SPECTRUM: LACTONE ESTER (27a)

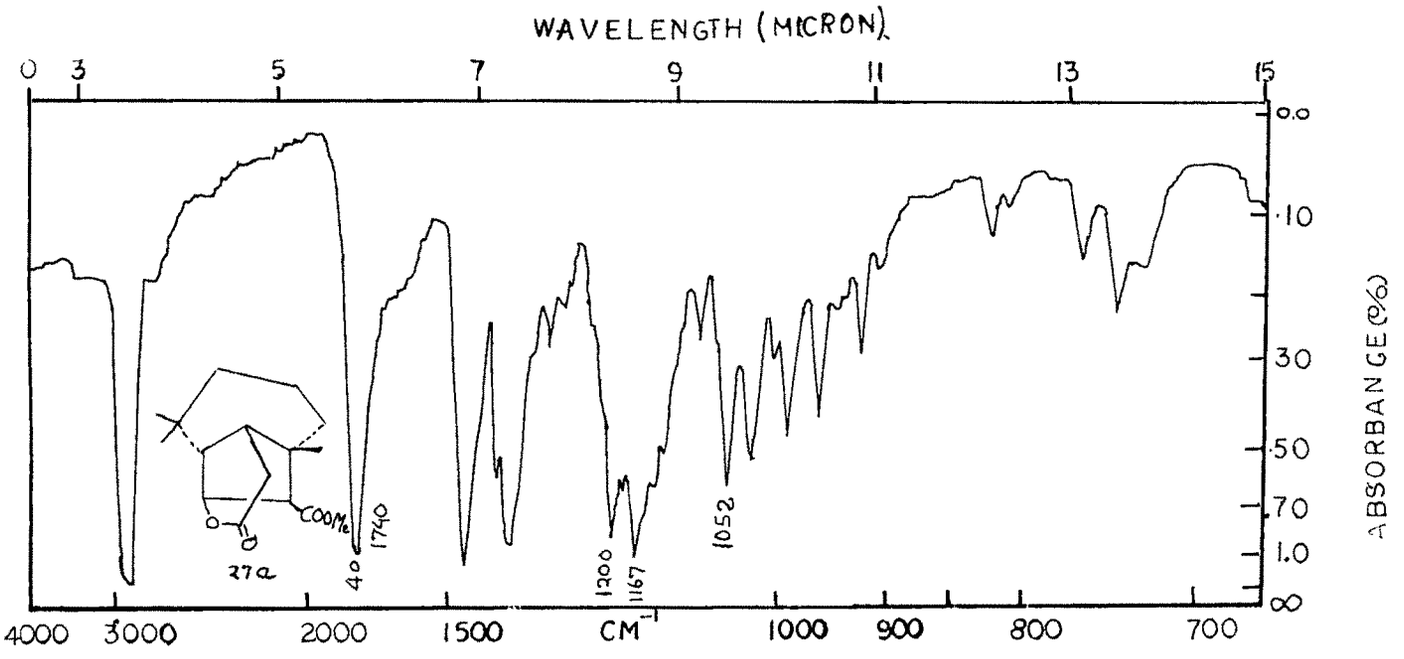
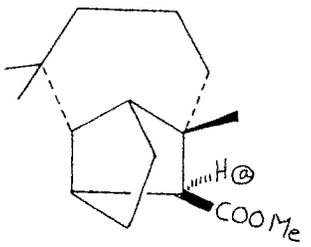


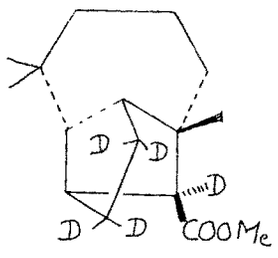
FIG:4: IR SPECTRUM: LACTONE ESTER (27a)

FIG 5A



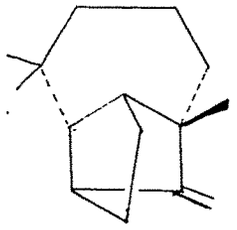
21

FIG 5B.



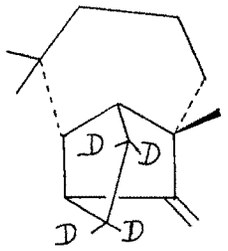
21a

FIG. 6A



LONGIFOLENE(1)

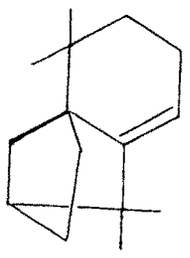
FIG. 6B:



LONGIFOLENE-4,4,5,5-d_4-(1b)

FIG 7A

120



ISOLONGIFOLENE(2)

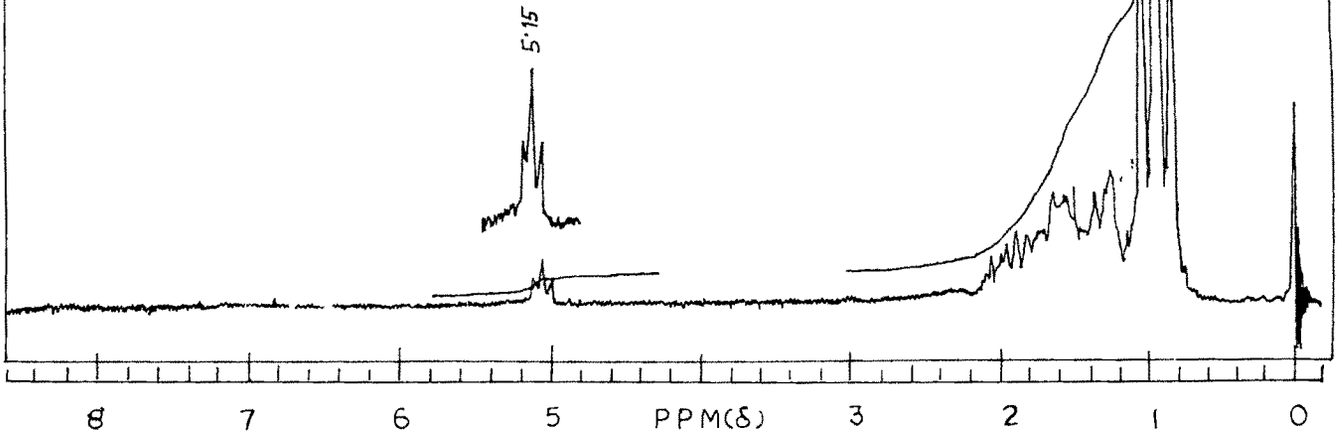
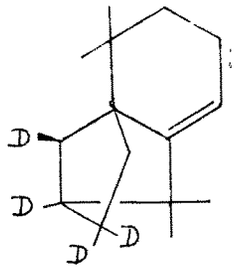


FIG. 7B.



2b

ISOLONGIFOLENE - d_4(2b)

FIG: 8A:

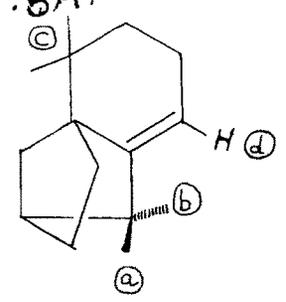


FIG: 8B:

LONGIFOLENE $\xrightarrow[20\,\text{MIN.}]{\text{AcOD-}BF_3Et_2O}$ ISOLONGIFOLENE-d_7 (2a)

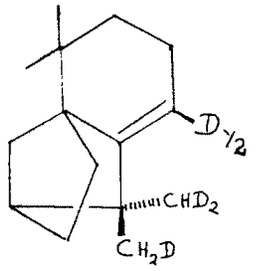


FIG: 8C

ISOLONGIFOLENE $\xrightarrow[27\,\text{hrs}]{\text{AcOD-}BF_3Et_2O}$ ISOLONGIFOLENE-d_7 (2c)

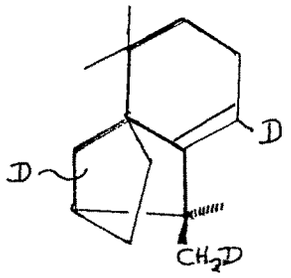
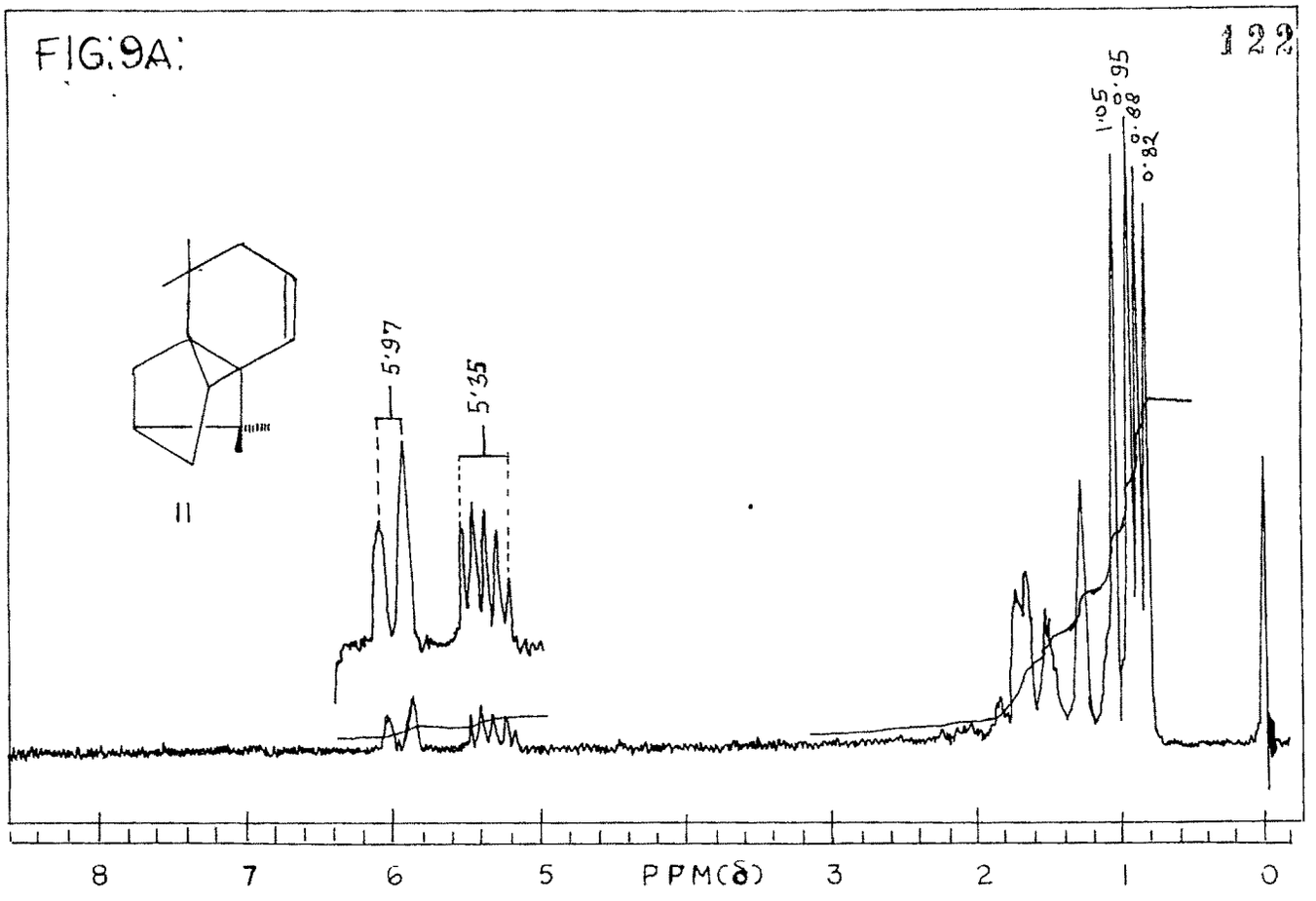
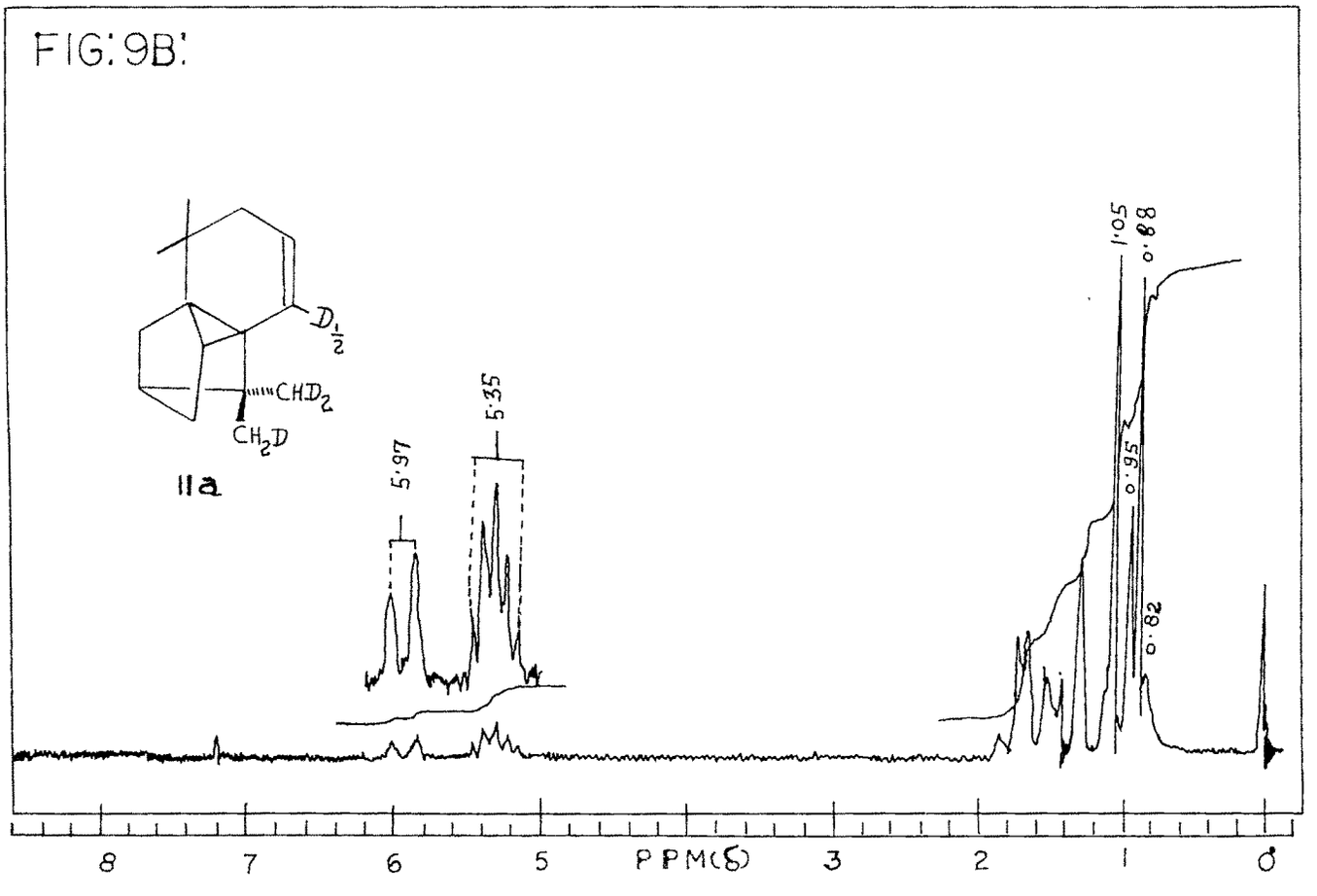


FIG: 9A:



II

FIG: 9B:



IIa

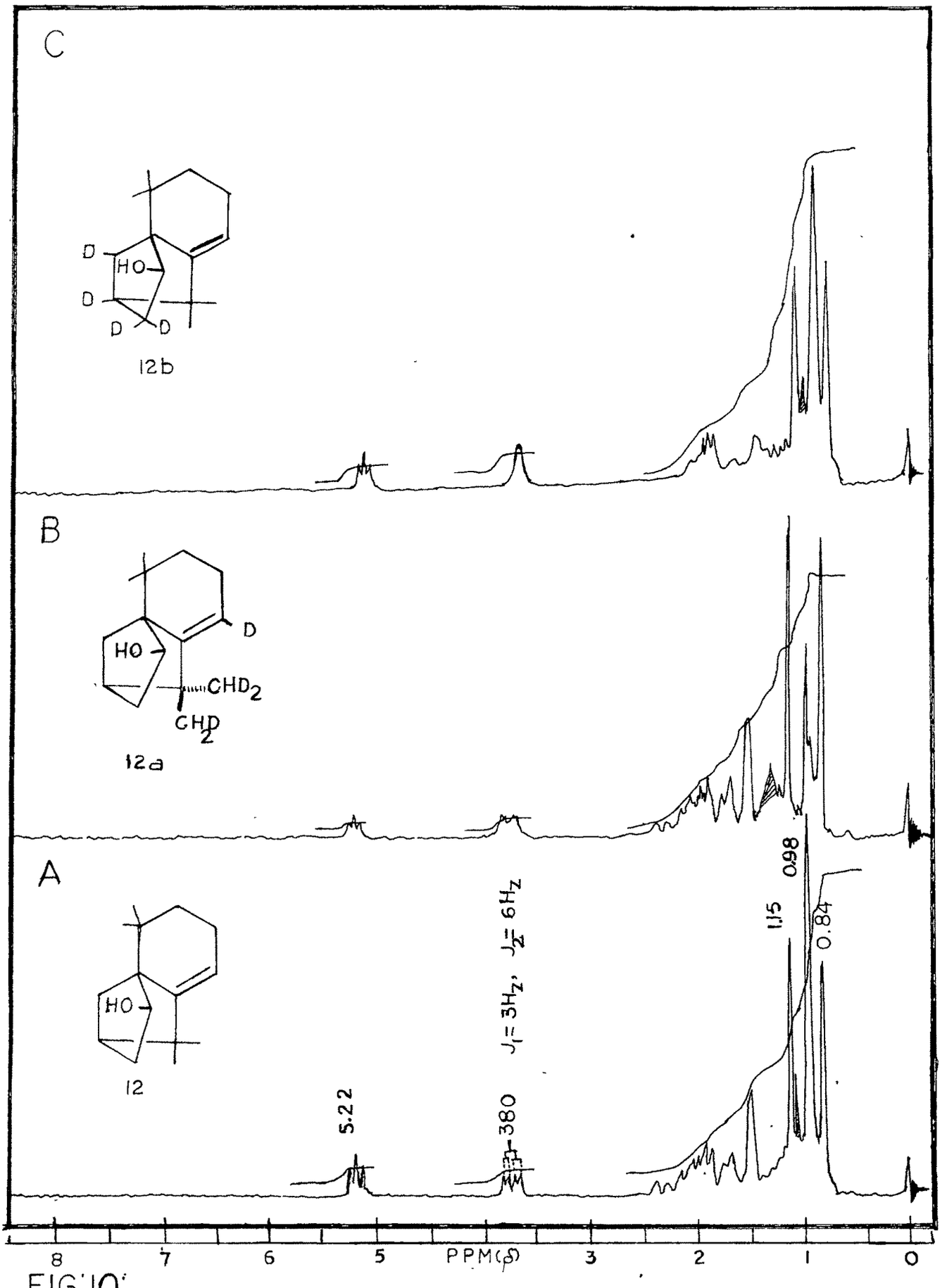

C
D
HO
D
D
D
12b
B
HO
D
CHD2
CHD2
12a
A
HO
12
5.22
3.80
J1= 3Hz, J2= 6Hz
1.15
0.98
0.84
8
7
6
5
PPM(δ)
3
2
1
0

FIG. 10.

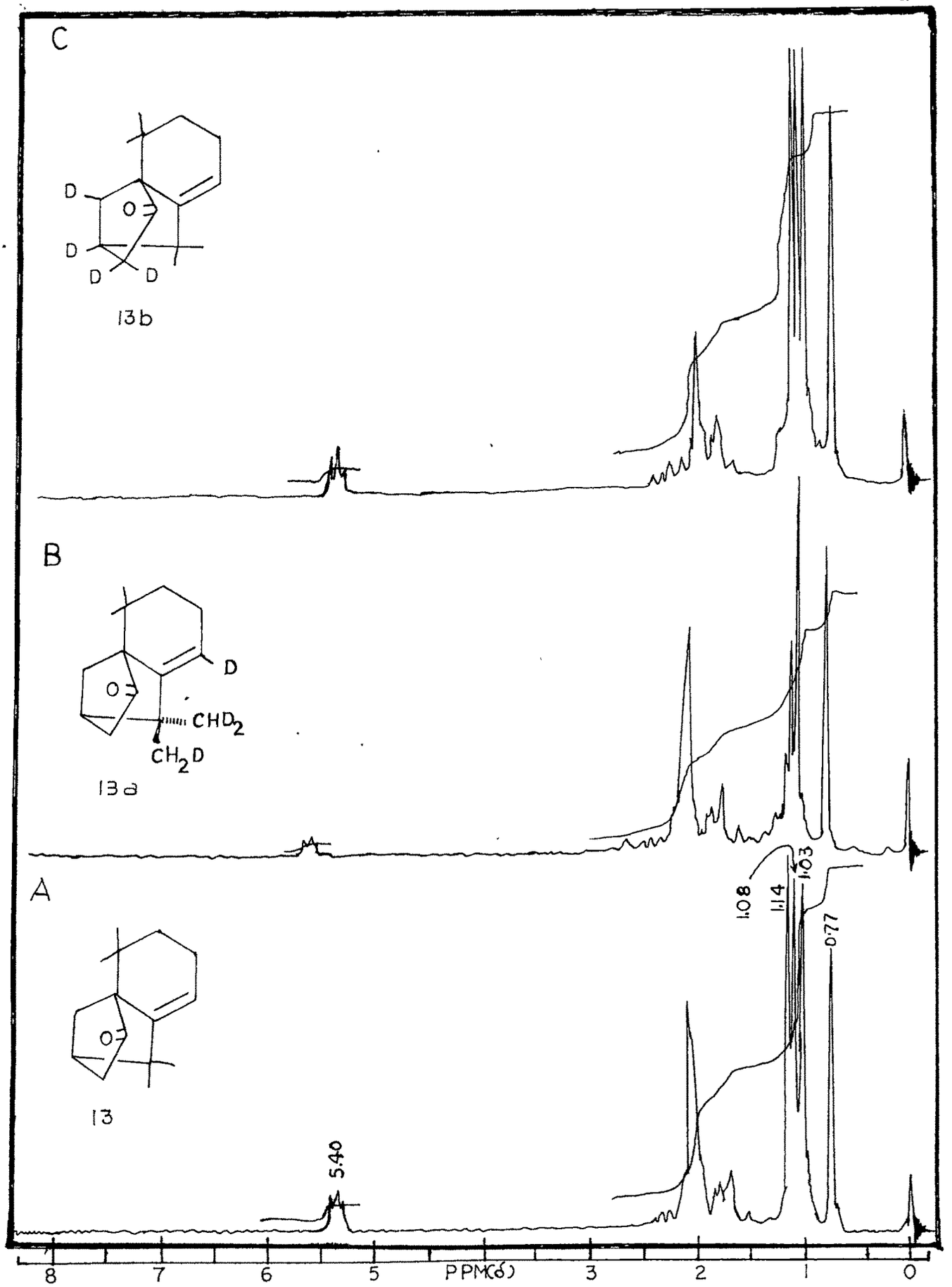

C
D
O
D
D
D
13b
B
D
O
CHD2
CH2D
13a
A
O
13
5.40
1.08
1.14
1.03
0.77
8
7
6
5
PPM(δ)
3
2
1
0

FIG.11.

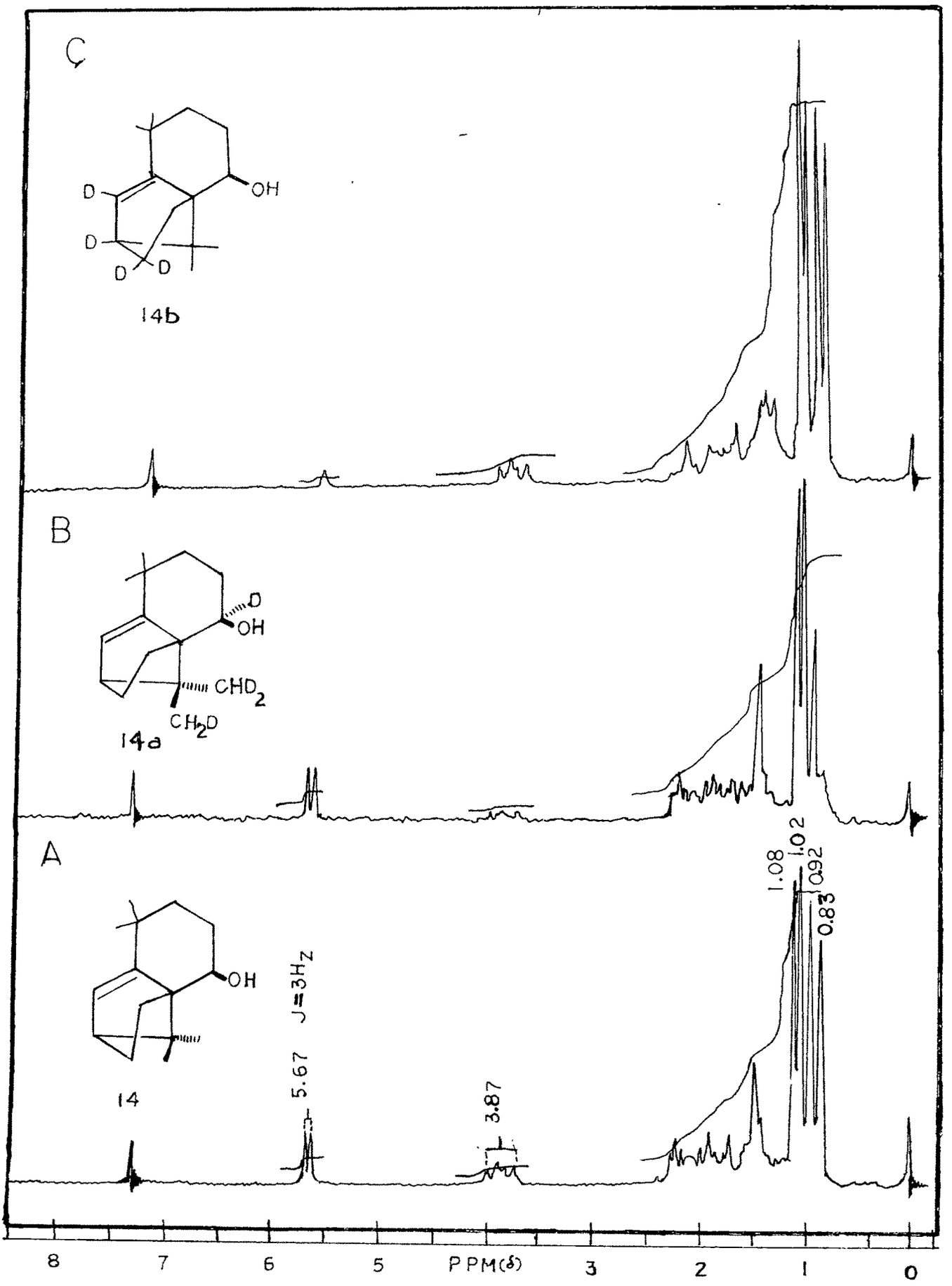

C
D
D
D
D
OH
14b
B
D
OH
CHD2
CH2D
14a
A
OH
14
J=3Hz
5.67
3.87
1.08
1.02
.92
0.83
8
7
6
5
PPM(δ)
3
2
1
0

FIG:12:

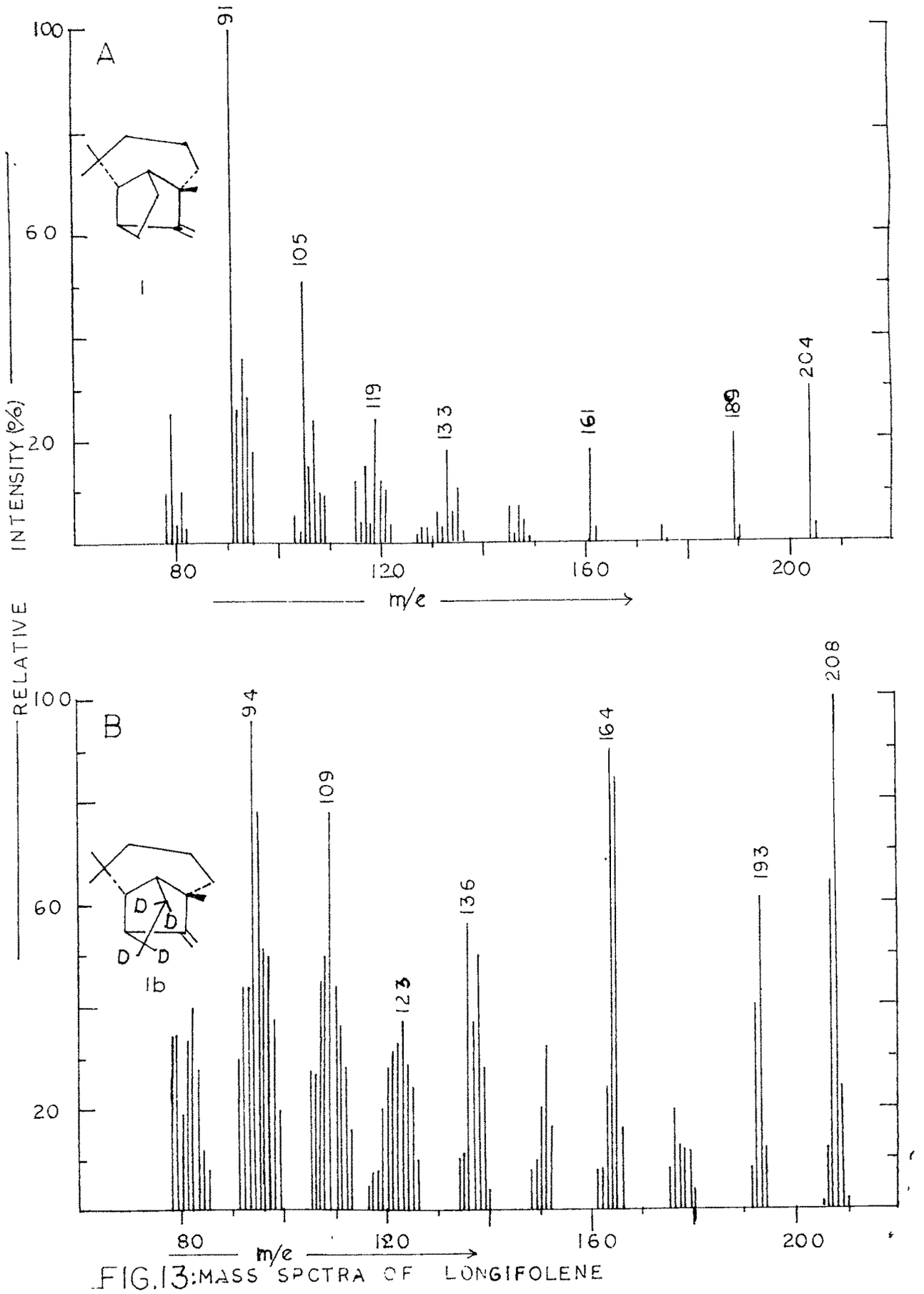


FIG.13: MASS SPCTRA OF LONGIFOLENE

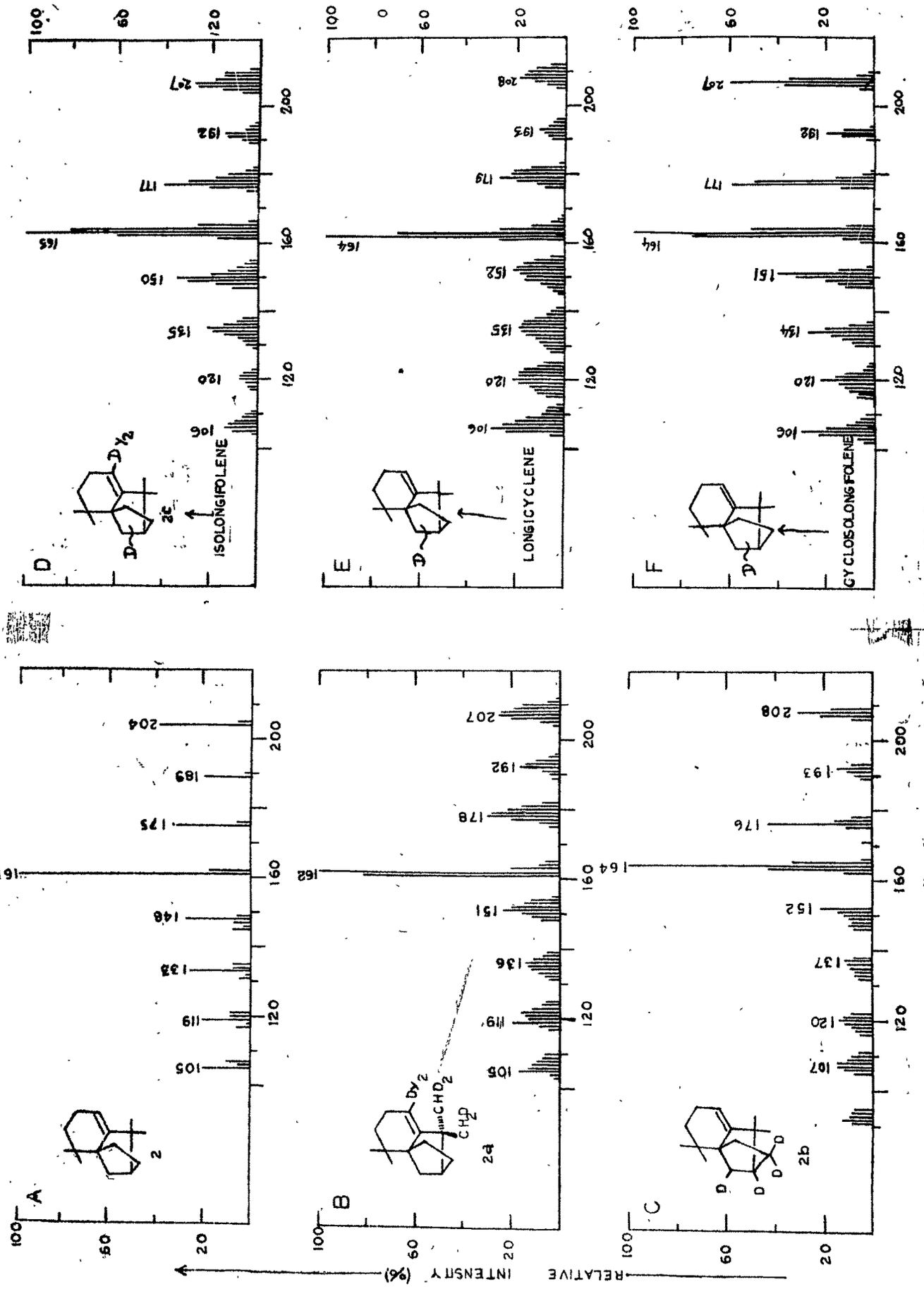


FIG.14 MASS SPECTRA OF ISOLONGIFOLENE

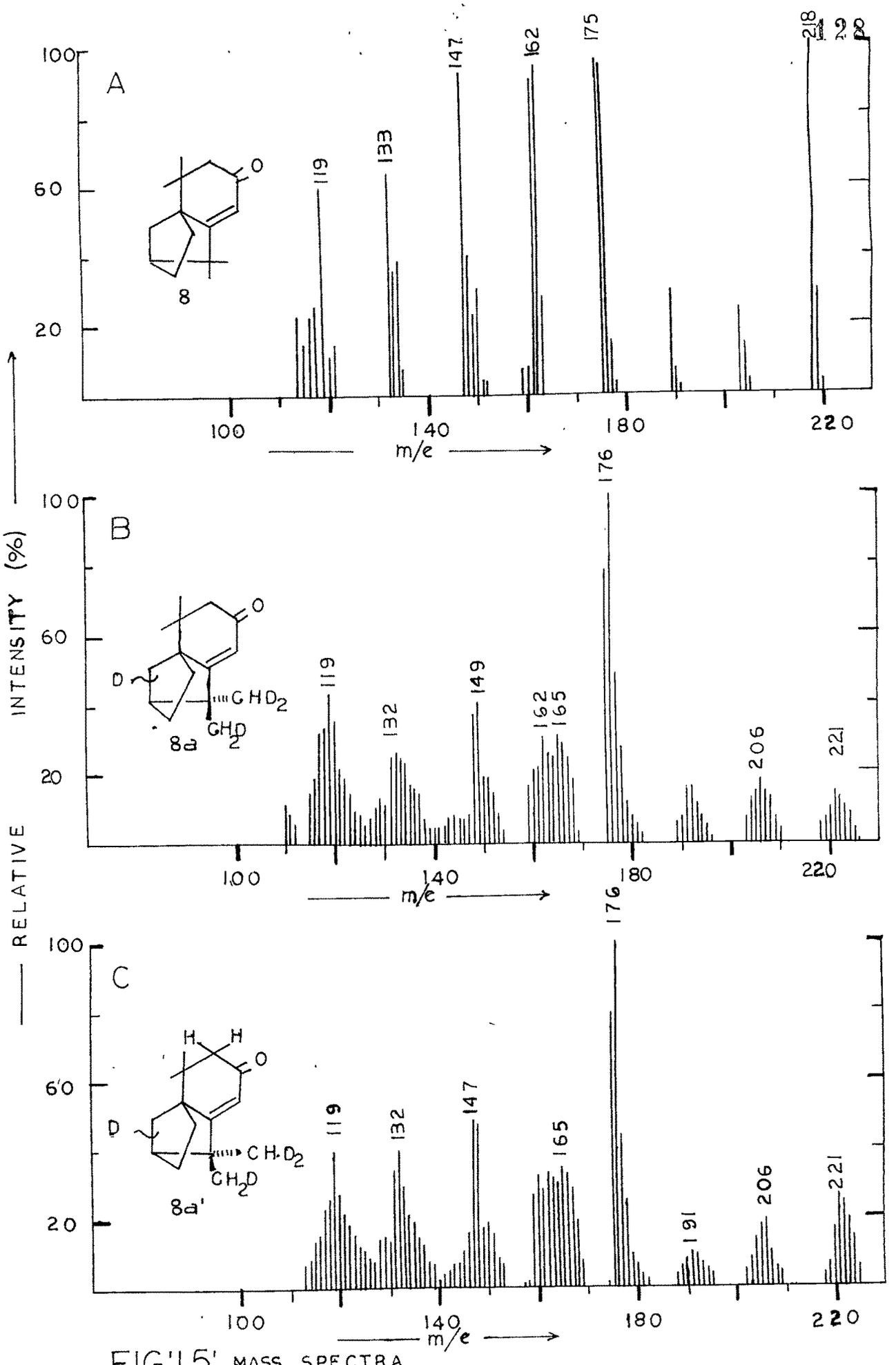


FIG. 15. MASS SPECTRA

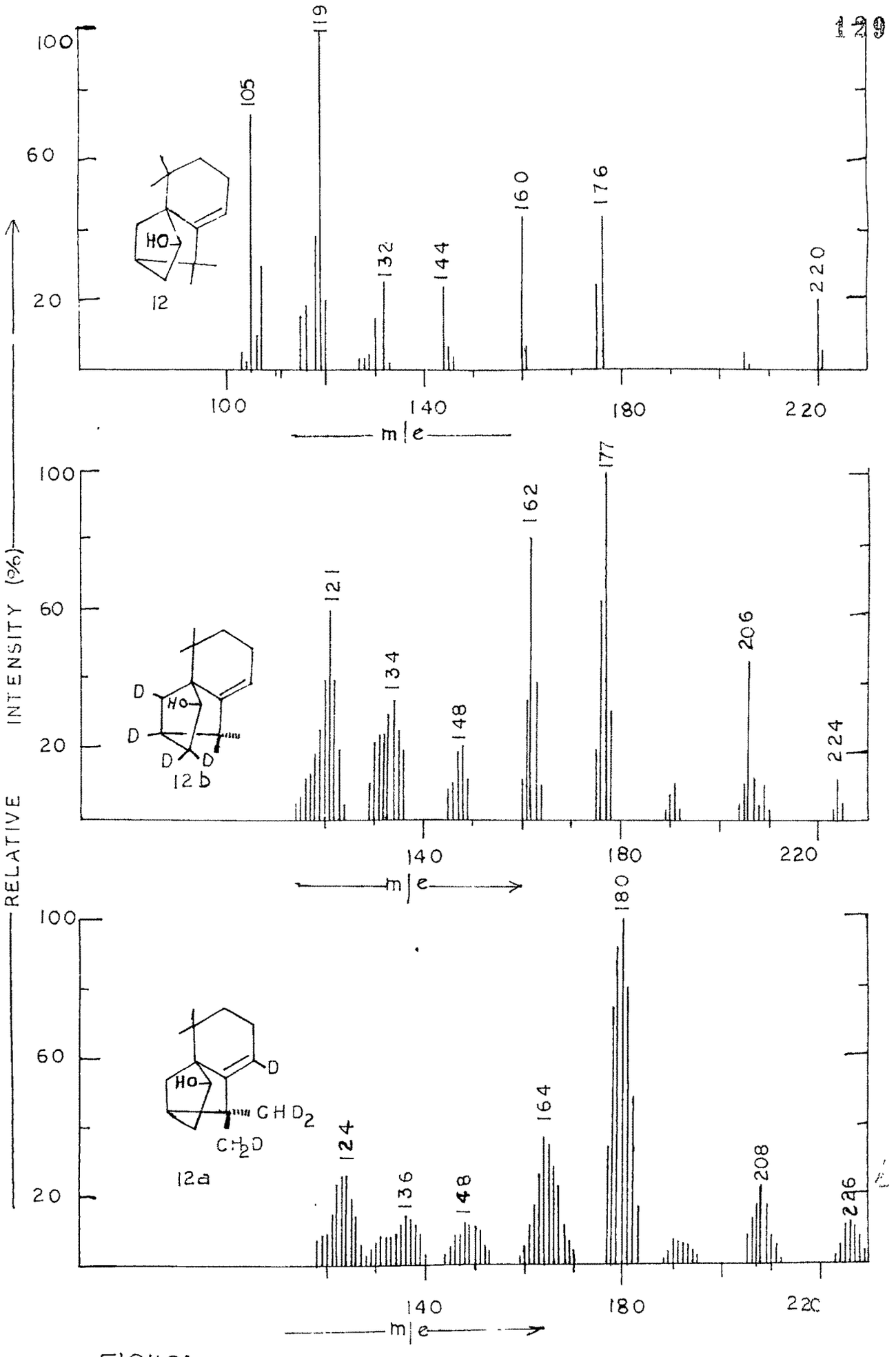


FIG.16: MASS SPECTRA

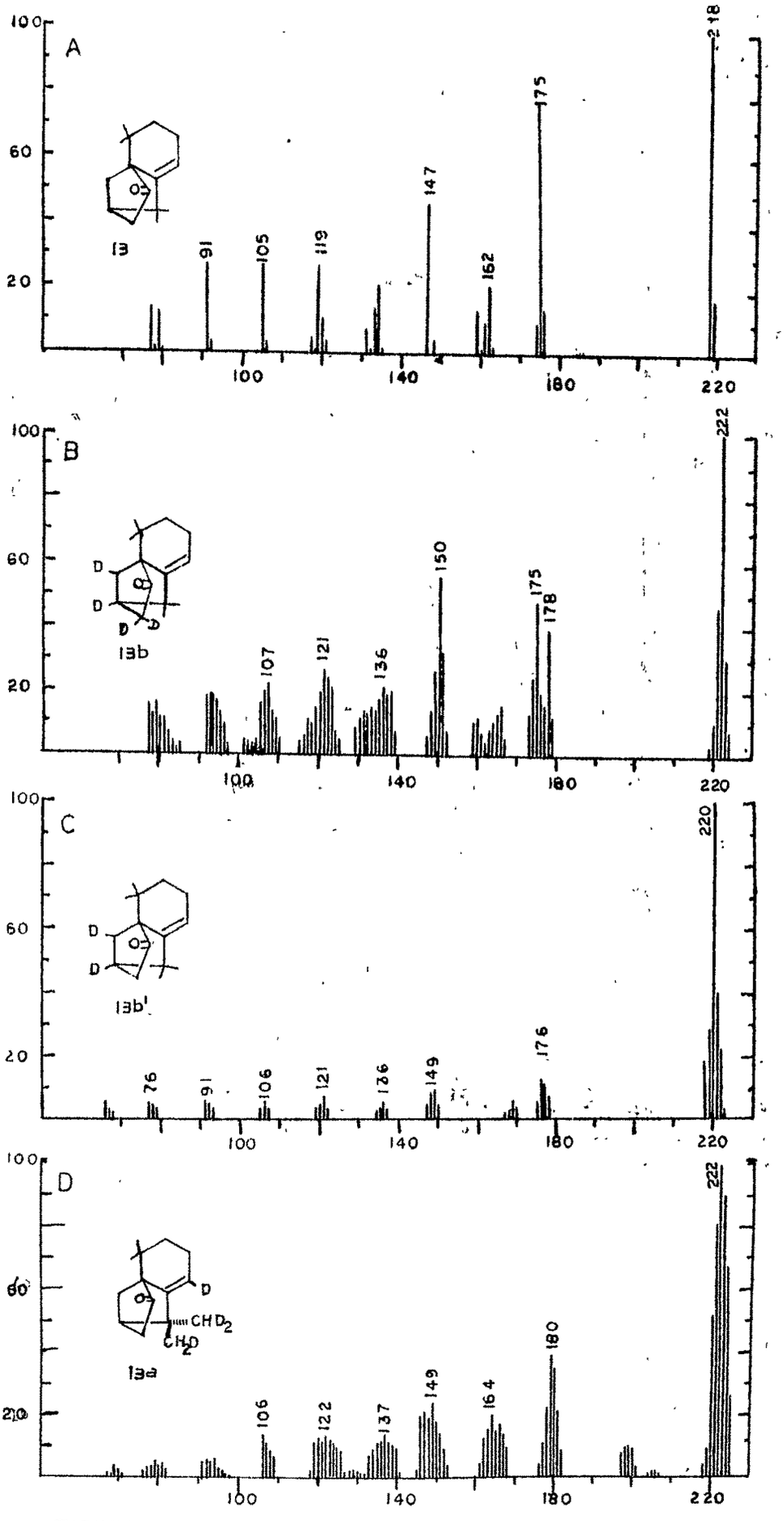


FIG.17: MASS SPECTRA

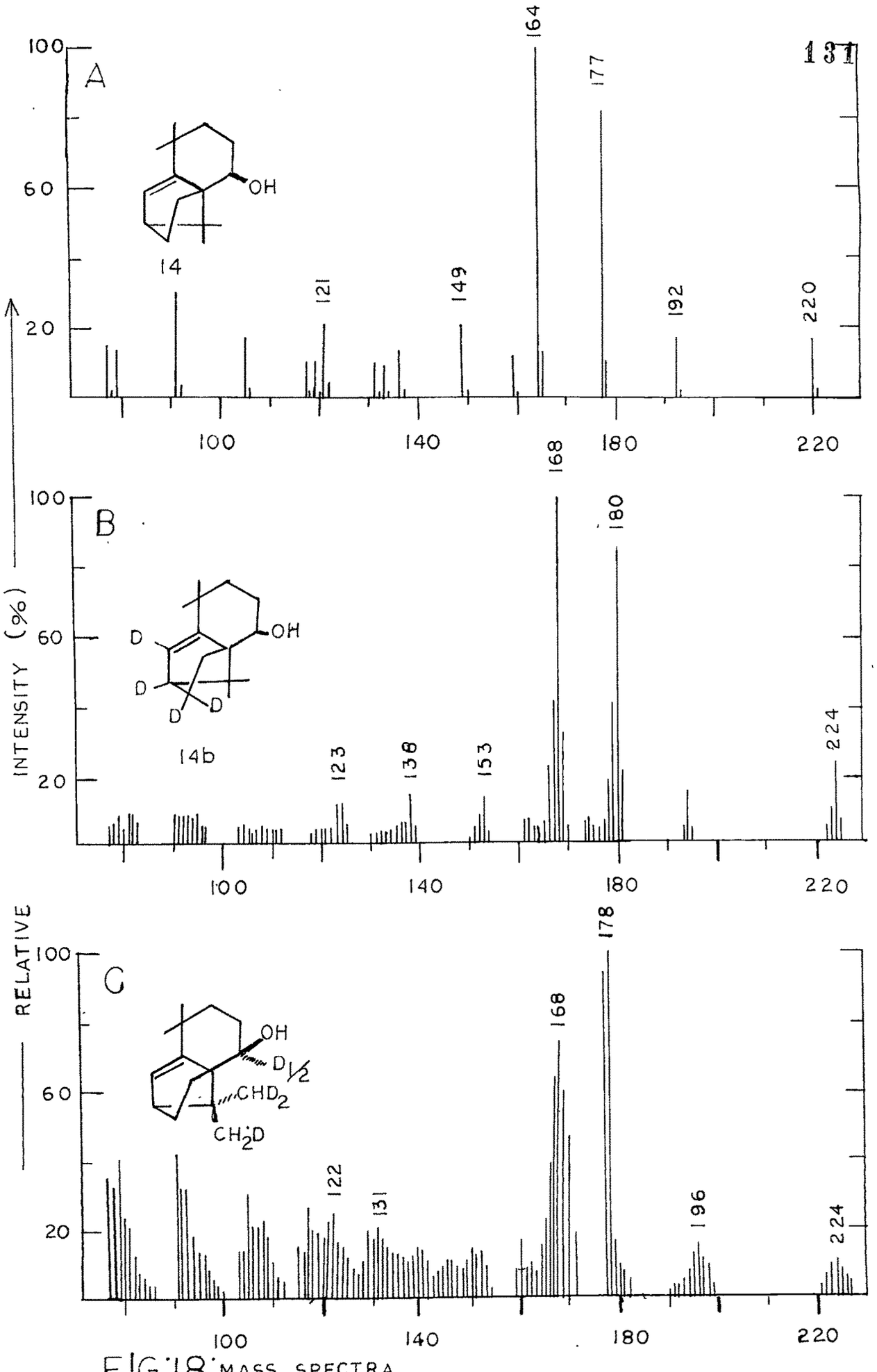


FIG. 18. MASS SPECTRA.