CHAPTER - 4

PARTIAL SYNTHESIS OF MARSUPELLONE AND MARSUPELLOL

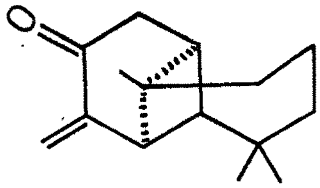
Abstract

The present Chapter describes partial synthesis of optical antipode of naturally occurring (+)-marsupellol and (-)-marsupellone. Base-catalyzed isomerization of (+)-α-longipinene epoxide and photo-oxygenation of (+)-α-longipinene gave optical antipode of (+)-marsupellol, pyridinium chlorochromate oxidation of which gave optical antipode of (-)-marsupellone.

INTRODUCTION

During investigations on terpene constituents of liverworts, several enantiomeric sesquiterpenoids, which are antipodal to those from higher plants, have been isolated by Matsuo <u>et al.</u>[1-4] From a methanol extract of <u>Marsupella emarginata</u> (Ehrh.) Subsp. <u>tubulosa</u> (Steph.) N. Kitag., three new <u>ent</u>-longipinane type sesquiterpenoids, named (-)-marsupellone (<u>1</u>), (+)-marsupellol (<u>2</u>) and (+)-acetoxymarsupellone (<u>3</u>), were isolated (Fig. 1). The structures and absolute configurations of these compounds were determined by the chemical and spectral evidence.[5]

(-)-Marsupellone (<u>1</u>) was isolated as a major constituent of the extract and the spectroscopic evidence showed that the compound was a tricyclic α,β-unsaturated sesquiterpene ketone having a ketone group in conjugation with an exocyclic methylene. The ^{1}H-NMR spectrum of this ketone (<u>1</u>) had a close-resemblence to that of pinocarvone[6], a bicyclic α,β-unsaturated monoterpene ketone, except an additional tertiary methyl and three normal methylenes. The ketone (<u>1</u>), when subjected to hydrogenation over 5% Pd-C in ethanol followed by $LiAlH_4$ reduction, furnished a saturated secondary alcohol (<u>4</u>), which was then treated with $POCl_3$ to give an unsaturated hydrocarbon(<u>5</u>),



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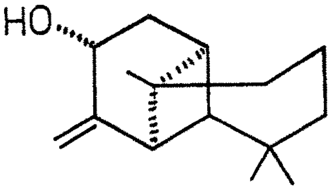

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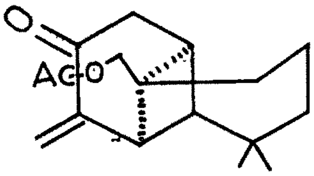

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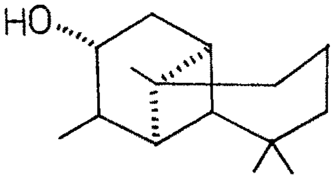

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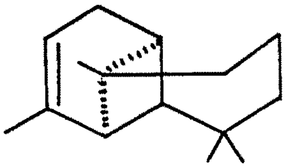

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Fig. 1. New ent-longipinane type sesquiterpenoids isolated from *Marsupella emarginata* (Enrh).

identified as (-)-α-longipinene ($\underline{5}$)[1], the enantiomer of (+)-α-longipinene ($\underline{9}$), based on coincidence of the spectral data and specific rotation[7]. Thus the absolute configuration of (-)-marsupellone ($\underline{1}$) was determined.

(+)-Marsupellol ($\underline{2}$) was isolated as a minor constituent whose IR, ^{1}H-NMR and mass spectra closely resembled with those of (-)-marsupellone ($\underline{1}$) and its reduced alcohol ($\underline{4}$) suggesting that marsupellol would be a reduction product ($\underline{2}$) of marsupellone ($\underline{1}$). The Sarett oxidation (CrO_3/pyridine) of the alcohol ($\underline{2}$) provided an α,β-unsaturated ketone, which was identified with (-)-marsupellone ($\underline{1}$) in the spectral data and optical rotation.

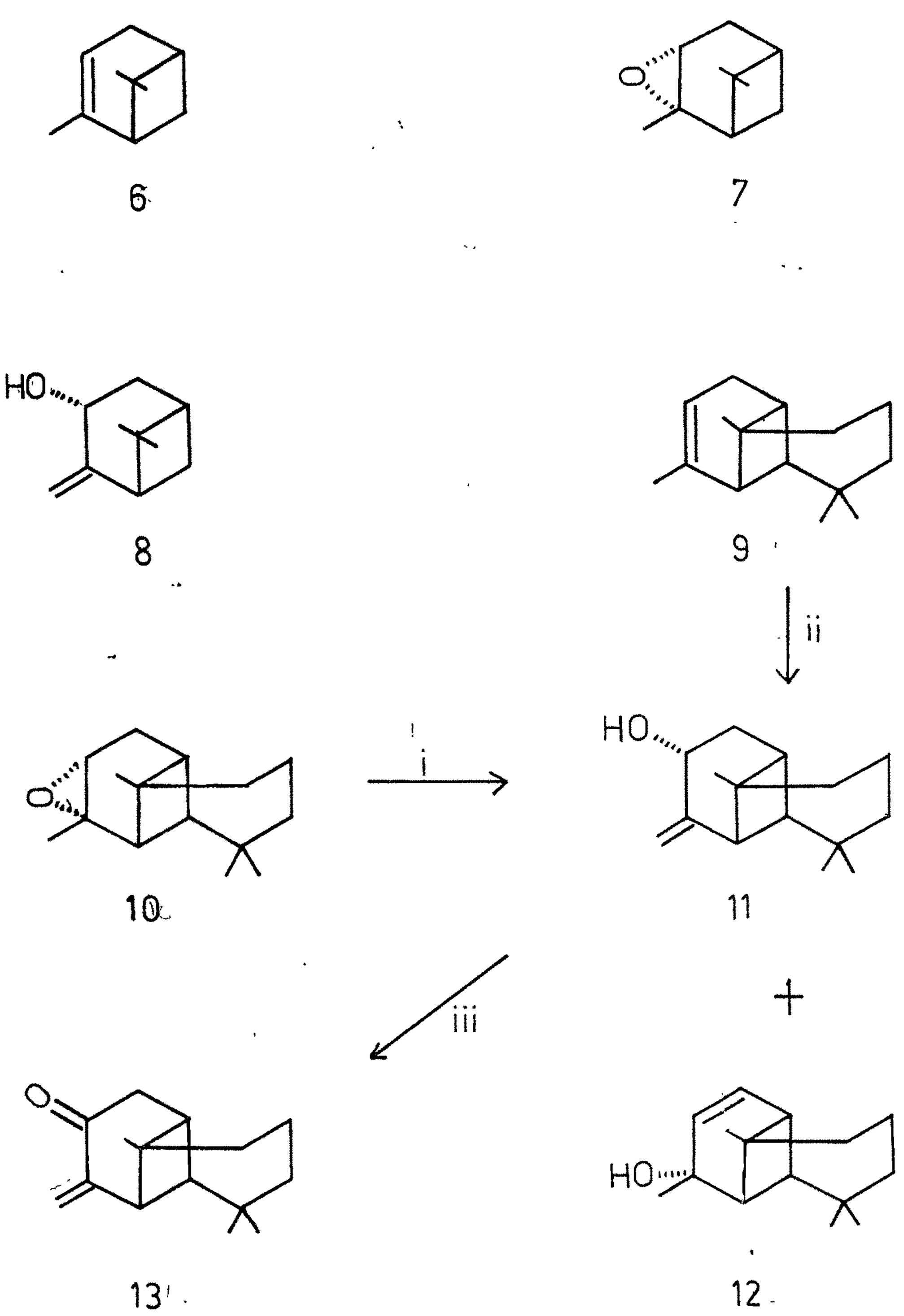
PRESENT WORK

Optical antipode of naturally occurring (+)-marsupellol was synthesized by two independent routes. The first started with (+)-α-longipinene epoxide ($\underline{10}$) which on base-induced eliminative opening of the oxirane gave $\underline{11}$ in a manner similar to that known for α-pinene epoxide ($\underline{7}$) (described in Chapter-1, Part I). The second route is based on photooxygenation of (+)-α-longipinene (9).

Base-catalyzed isomerization of (+)-α-longipinene epoxide. The formation of trans-pinocarveol (8), as the major product of base-catalyzed isomerization of α-pinene oxide (7) is discussed earlier (Chapter-1, Part-I). Applying similar conditions, (+)-α-longipinene epoxide (10) on base-catalyzed isomerization using DMSO-KOH gave (-)-marsupellol (11) as the major product (80-85%, ^{1}H-NMR) alongwith minor amount of unwanted 3°-allylic alcohol (12) (15-20%, ^{1}H-NMR). Pyridinium chlorochromate[8] oxidation and subsequent chromatography of the above mixture gave pure marsupellone (13) (Fig. 2).

Photooxygenation of (+)-α-longipinene (9). Reaction of singlet oxygen with mono-olefins having an allylic hydrogen available produces allylic hydroperoxide in which the double bond has migrated[9]. Further studies have revealed that the transition state for photo-oxygenation is reactant-like and that steric effects largely determine the reaction course.[10,11]

Regardless of the nature of the mechanism, photo-induced hydroperoxidation of both α-pinene (6) and (+)-α-longipinene (9) forma~~l~~lly involve C-O bond making either at



Reagents: i) DMSO-KOH

ii) hv

iii) Pyridinium chlorochromate

Fig. 2. Partial synthesis of Marsupellone and Marsupellol.

C(2) or C(3) with associated hydrogen abstraction either at C(4) or C(10); these processes pass through, what are called, the enclinal and ectoclinal modes* respectively. Moreover, as each mode has exo and endo sides, singlet oxygen attacks the allylic moiety in four modes (Fig. 3),(Scheme-1).

Partitioning of oxygen attack between these modes will depend on the relative importance of electronic, stereoelectronic and steric factors in the transition states corresponding to each mode. It has been already amply demonstrated that C-O bond making is sensitive to steric hindrance,[11,13,14] whereas ease of rupture of the allylic C-H bond depends on its orientation with respect to the double bond. When σ-π overlap is good, abstraction by singlet oxygen of allylic hydrogen is easy[13,15]. In conformationally free cyclohexene derivatives, which exist preferentially in unemcumbered half-chair configurations, the quesi-axial allylic hydrogen is abstracted some three times more easily than quasi-equatarial hydrogen by singlet oxygen.[10]

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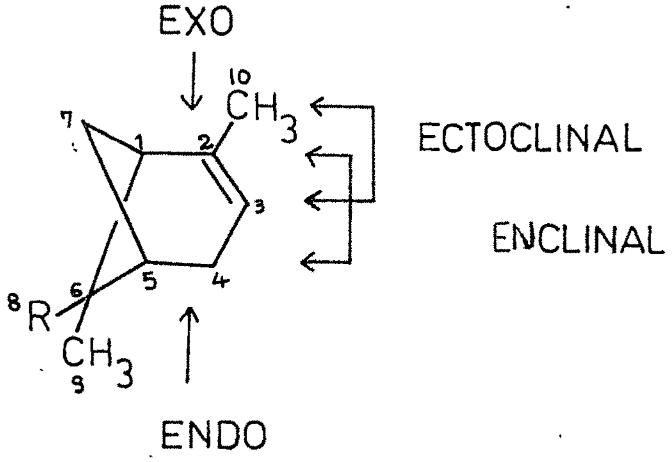
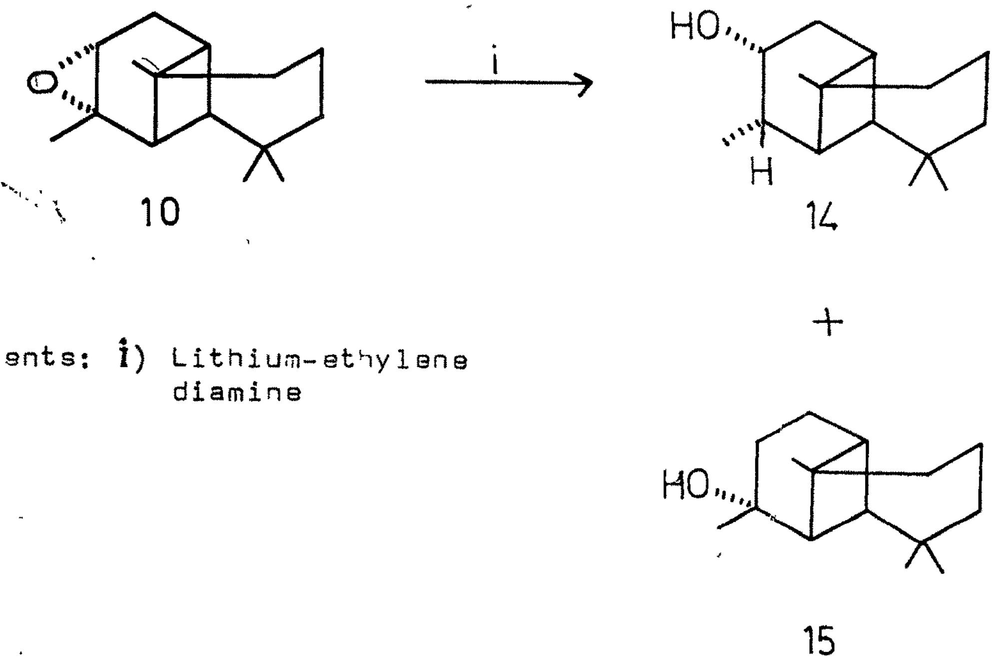
*To avoid ambiguity with the terms exo and endo commonly employed with bridged bicyclic olefins, the prefixes ecto and en have been chosen to designate placement of the double bond or the attacking reagent with respect to the outside or inside of the ring.



Scheme 1. Modes of attack by singlet oxygen and (+)- -longipinene.
I) Exo-ectoclinal, II) exo-enclinal,
III) endo-ectoclinal and IV) endo-enclinal.



Reagents: i) Lithium-ethylene diamine

Scheme 2. Reduction products of (+)-α-longipinene epoxide.

Fig. 3.

In (+)-α-longipinene (9) and α-pinene (6) as well, the cyclohexene moiety is held flat by the *gem*-dialkylmethylene bridge.[16] Consequently, stereoelectronic preferences springing from axiality of the ring allylic C-H bond should be effectively suppressed. However, the C(10) methyl group will be unaffected and its C-H bonds will be able to adopt the best overlap possible with the double bond. The proportion of ectoclinal to clearly reflects the paramouncy of the stereoclectronic factor. It might also be argued that favouring of ectoclinal mode could be due to the switching of the double bond out of what is tantamount to a cyclopentene ring to the thermodynamically more favourable ectocyclic position. The overwheling diposition for the *exo*-ectoclinal mode demonstrates that stearic and stereoelectronic effects work together and simalteneously in the transition state.

Finally, photooxygenation of (+)-α-longipinene (9) was carried out in acetonitrile-methanol using Rose Bengal as sensitizer and a 500 W tungston lamp as light source. The hydroperoxide so obtained was reduced with sodium borohydride in methanol,[12] to furnish

(-)-marsupellol as the exclusive product along with unreacted olefin (Fig. 2). (-)-Marsupellol (11) was further purified by chromatography over SiO_2-gel/IIA.

In addition to this, optical antipode (14) of saturated secondary alcohol (4)[5a] was prepared by reductive clevage of (+)-α-longipinene epoxide (10) (Fig. 3). Exposure of (+)-α-longipinene epoxide (10) to lithium-ethylene diamine[17,18] resulted in a product consisting of (14) as the major product which is optical andipode of (4) and minor amount of (+)-longipinanol (15) along with traces of unidentified hydrocarbon (Fig. 3) (Scheme-2).

EXPERIMENTAL

For general remarks see pg. No. 71.

Isomerization of (+)-longipinene epoxide (10)

A solution of KOH powder (0.28 g, 0.005 mole) in dry DMSO (4 ml) was prepared by stirring it at 90° (30 mins) under dry conditions. (+)-α-Longipinene epoxide (10, 1.15 g, 0.0056 mole) was then added at R.T. The contents of the flask were stirred at 130 ± 3° for 6 hr, and TLC (solvent: 15% EtOAc in toluene) indicated essentially complete conversion. The reaction mixture was then diluted with water (5 ml) and extracted with light pet. (25 ml x 3). After the usual work-up 1.142 g of crude product (99.3%) obtained was distilled to furnish distillate (0.926 g, 80.52%, b.p. 103-107°/2 mm) to be a mixture of 11 (85-90%) and 12 (10-15%), shown by ^1H-NMR

Photooxygenation of (+)-α-longipinene (9)

In a typical experiment, a vigorously stirred solution of an accurately weighed sample of (+)-α-longipinene (9, 1.5 g, 0.0074 mole) and Rose Bengal (100 mg) in acetonitrile-methanol (60 + 10 ml) was irradiated under an atmosphere of oxygen using 500 W Tungston lamp. Absorption decreased sharply as the uptake of the theoritical amount of oxygen was approached (25 hr), when TLC (solvent: 15% EtOAc in toluene) indicated maximum conversion. At this point, irradiation was stopped and the resulting solution of hydroperoxides was reduced by adding a solution of excess of sodium borohydride (400 mg, 0.011 mole) in dry methanol (20 ml) while stirring at 0°C. After 2 hr solvent was removed and the residue was taken up in water (60 ml). The product was extracted with ether (20 ml x 4). The crude product (1.73 gm) obtained after usual work-up was chromatographed (SiO_2 gel/IIA, 1.7 x 33 cm) where the eluent (2-4% EtOAc in light pet., 50 ml x 5) eluted GLC pure marsupellol (<u>11</u>, 1.09 gm, 66.46% yield). Physical properties and spectral data were compared with reported[5] values (Table-1, Fig. 4).

<u>Pyridinium chlorochromate oxidation of (-)-marsupellol(11)</u>

To the solution of (-)-marsupellol (<u>11</u>, .286 gm, 0.0013 mole) in dichloromethane (15 ml, dry), was added pyridinium chlorochromate (.700 gm, 0.0032 mole) at 25°c in portions. After 8 hr of stirring, the dark red mixture was filtered through a column (SiO_2G/IIA, 1.7 x 10 cm) and the column was washed with dry ether (90 ml). The combined organic solution was distilled under reduced pressure (100 mm) to leave behind (0.271 gm, 95.1%) of the crude product which was chromatographed (SiO_2G/IIA, 1.7 x 15 cm); 1% EtOAc in light pet. (50 ml x 3) eluted pure massupellone (0.134 gm, 47%). Physical and spectral data were compared with the values reported[5] (Table-2, Fig. 5).

Reduction of (+)-α-longipinene epoxide (10)

To a mixture of 10 (2.75 g, 0.0125 mole) and dry ethylenediamine (15 ml), maintained at 50-55° (N_2), Li (2.0 gm, 0.288 g. atoms; small pieces) was portionwise, introduced with stirring during 4 hr. At the end, the blue mixture was cooled (ice), crushed ice (150 gr) added and the product taken up in ether (50 ml x 4) after saturating aqueous phase with sodium chloride. The ether phase after usual work-up gave the crude product (2.966 gm) was shown by TLC(solvent, 15% EtOAc in toluene) to be a mixture of two components along with some trace of hydrocarbons. The above product (2.5 gm) was chromatographed over Al_2O_3/III (75 gm, 1.7 x 33 cms) with TLC (solvent: 15% EtOAc in toluene) monitoring of fractions obtained with light pet. and light pet. containing increasing quantities of EtOAc (1-10%) and finally with EtOAc. Different fractions were further processed as follows.

Hydrocarbons: The material (0.26g, 10.4%) eluted with light petroleum (100 ml x 2) was essentially a mixture of the hydrocarbons, not investigated.

Longipinanol (15): The material (0.5463 gm, 20.6%, viscous colourless liquid) eluted with 1-2% EtOAc in light pet. was crystallized in acetonitrile (tit$\overset{u}{\wedge}$ration) at 0-5°C, which was identified as (+)-longipinanol (15).

Secondary alcohol (14): The material (1.555 g, 62.2%, white solid) eluted with 2-10% EtOAc in light pet. was crystallized in light pet., which was identified as optical antipode of the known saturated secondary alcohol (4). The physical and spectral data of both (15) and (14) were compared with reported[5] values (Table-3 and 4, Fig. 6 & 7).

Table-1: COMPARISON OF THE PHYSICAL CHARACTERISTICS AND SPECTRAL PROPERTIES OF THE (-)-MARSUPELLOL (11) WITH THAT OF (+)-MARSUPELLOL (2)^{5}

Sr.No.		Properties	
		(-)-Marsupellol	(+)-Marsupellol
1.	m.p.	56-57^{0}	oil
2.	$[\alpha]_D$	-14.7($CHCl_3$,c 3.4%)	+13.4 ($CHCl_3$, c,1.34%);
3.	^{1}H-NMR (Fig.8)	-CHOH(1H,d, 4.36 ppm, J = 8.0 Hz)	(1H, d, 4.47 ppm, J = 7.0 Hz)
		-C=CH_2(1H each br.s, 4.69 and 4.86 ppm).	(1H, each br,s, 4.79 and 4.95 ppm)
		Me-C (3H,s, 0.58 ppm)	(3H, s, 0.62 ppm)
		(6H, s, 0.901 ppm)	(6H, s. 0.92 ppm)
4.	IR(KBr)(Fig.9'):	3380, 3260, 3086, 1650, 1381, 1369, 951 and 900 cm^{-1}	3590, 3435, 3050, 1642 and 893 cm^{-1}.

Fig. 4.

Table 2: COMPARISON OF THE PHYSICAL CHARACTERISTICS AND SPECTRAL PROPERTIES OF THE MARSUPELLONE (13) and (-)-MARSUPELLONE (1)^5

Sr. No.	Properties	
	Marsupellone (13)	(-)-Marsupellone (1)
1. M.p.	oil	oil
2. $[\alpha]_D$	not easily detected	-1.94 ($CHCl_3$, c, 3.5%)
3. ^1H-NMR (Fig. 10):		
	$-C=CH_2$ (1H each, d, 4.88 and 5.83 ppm, J = 2.0 Hz)	(1H each, d, 4.91 and 5.77 ppm, J = 1.5 Hz)
	$CH_2-C=O$ (2H, dd, 2.52 ppm, J = 8 and 3 Hz)	(2H, complex, 2.48 ppm)
	Me-C (3H, s, 0.766 ppm)	(3H, s, 0.76 ppm)
	(6H, s, 0.933 ppm).	(6H, s, 0.92 ppm)
	Methines (1H, s, 1.36 ppm)	(1H, s, 1.34 ppm)
	(1H, complex, 2.3 ppm)	(1H, dt, 2.24 ppm, J = 6.5 and 3.0 Hz)
	(1H, d, 2.83, J = 6.5 Hz)	(1H, d, 2.77, J = 6.5 Hz)
4. IR (Fig. 11):	2932, 1709, 1628, 1413 and 933 cm^{-1}	3015, 1710, 1630, 1415, and 935 cm^{-1}

Fig. 5

Table 3. COMPARISON OF THE PHYSICAL CHARACTERISTICS AND SPECTRAL PROPERTIES OF THE (+)-LONGIPINANOL (<u>15</u>) WITH THAT OF ITS OPTICAL ANTIPODE[19]

Sr. No.	Properties	(+)-Longipinanol (<u>15</u>)	(-)-Longipinanol[19]
1.	m.p.	85-86.5°C	82.5-83°C
2.	$[\alpha]_D$	+50 ($CHCl_3$, <u>c</u>, 1.6%)	-50
3.	^1H-NMR <u>Me</u>-C	(3H, s, 0.89 ppm)	(3H, s, 0.9 ppm)
		(6H, s. 0.90 ppm)	(6H, s. 0.90 ppm)
	<u>Me</u>-C-OH	(3H, s, 1.27 ppm)	(3H, s, 1.35 ppm)
4.	IR (KBr):	3460-3401, 1471, 1459, 1381, 1368, 1169, 1092, 921, 900 and 888 cm^{-1}	3370, 1385, 1368, 1165, 1098, 900, 979, 920 and 985 cm^{-1}

Fig. 6

Table 4. COMPARISON OF THE PHYSICAL CHARACTERISTICS AND SPECTRAL PROPERTIES OF THE 2°-ALCOHOL (14) WITH THAT OF ITS OPTICAL ANTIPODE

		Properties	
Sr.No.		2°-Alcohol (14)	2°-Alcohol (4)^5
1.	m.p.	108-109°C	113.5-114.5°C
2.	$[\alpha]_D$	+16.34°(CHCl$_3$, c, 1.87)	-46.9°(CHCl$_3$, c, 0.647).
3.	^{1}H-NMR: CHOH	(1H, m, 3.95 ppm)	(1H, td, 4.32ppm, J = 10.0 and 5.0 Hz)
	2°-methyl	(3H, d, 1.14 ppm J = 7.0 Hz)	(3H, d, 1.05 ppm, J = 7.0Hz)
	Me-C	(9H, s, 0.90 ppm)	(6H, s, 0.87 ppm) (3H, s, 1.03 ppm)
4.	IR (KBr):	3350, 3320, 3008, 1472, 1450, 1370, 1360, 1275, 1038, 1016, 990 and 948 cm^{-1}	3630 and 3450 cm^{-1}

Fig. 7

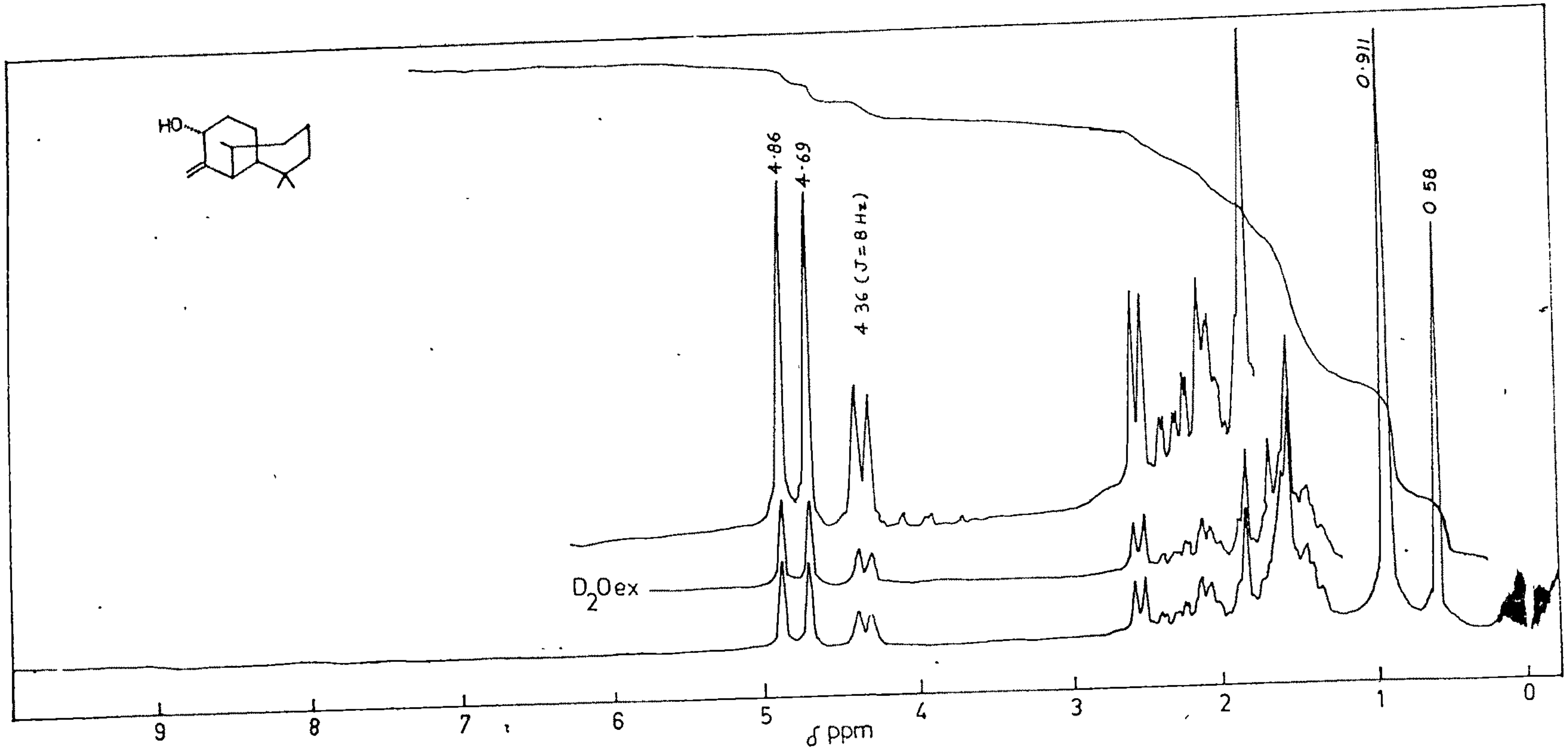


FIG.8 : ^{1}H-NMR SPECTRUM OF (-)-MARSUPELLOL(11)

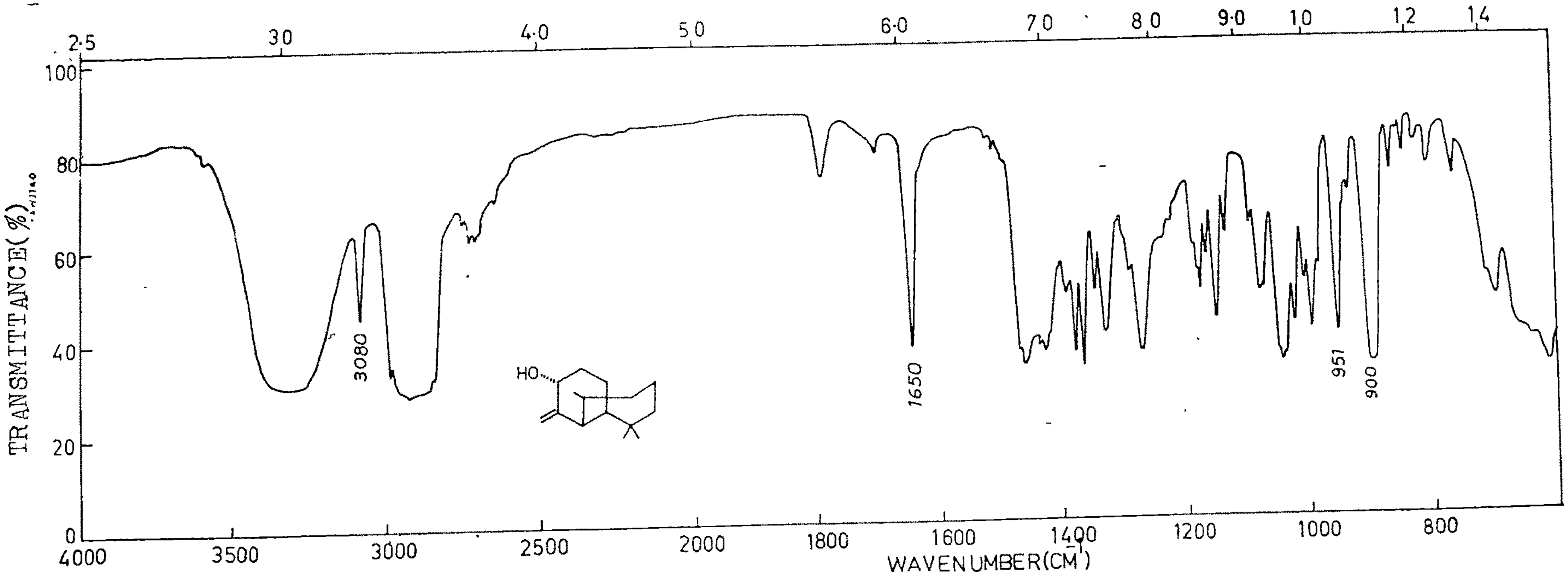


FIG.9 : IR SPECTRUM OF (-)-MARSUPELLOL(11)

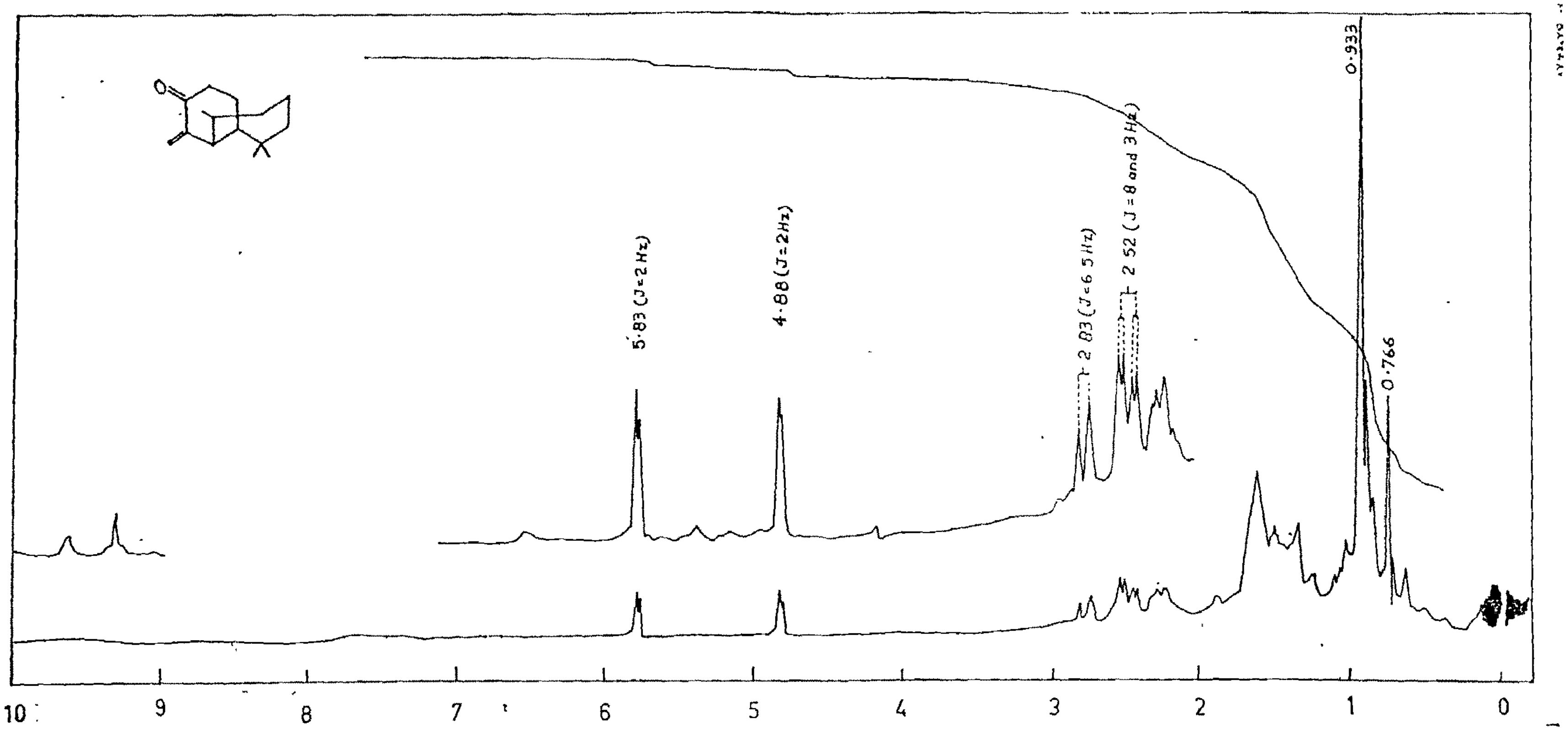


FIG.10 : ^{1}H-NMR SPECTRUM OF MARSUPELLONE(13)

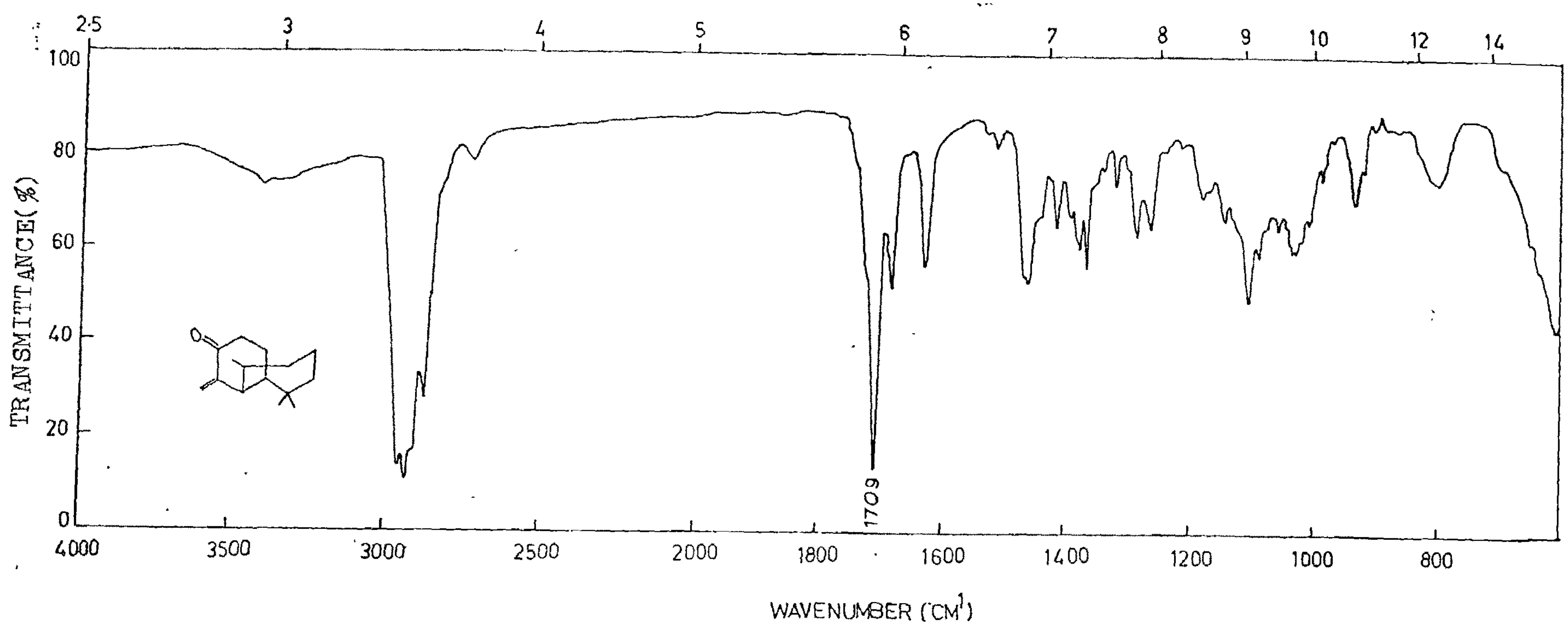


FIG.11 : IR SPECTRUM OF MARSUPELLONE(13)

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