9-Hydroxynerolidol Esters and Bicyclic Sesquiterpenoids from Dittrichia viscosa

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9-HYDROXYNEROLIDOL ESTERS AND BICYCLIC SESQUITERPENOIDS FROM *DITTRICHIA VISCOSA*[1]

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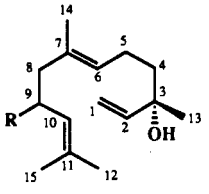
ABSTRACT.—The following new sesquiterpenoids have been identified from *Dittrichia viscosa* (Compositae): 9-isobutyroxynerolidol [**3**], 9-isovaleroyloxynerolidol [**4**], 9-(2-methylbutyroxy)-nerolidol [**5**], 11-methoxy-3,7,11-trimethyldodeca-1,6,9-trien-3-ol [**7**], and 2,5-peroxyeudesma-3,11(13)-dien-12-oic acid [**11**]. Some known nerolidol derivatives, eudesmane sesquiterpenoids, triterpenoids, and aromatic derivatives were also isolated.

Dittrichia viscosa (L.) W. Greuter [syn. *Inula viscosa* (L.) Aiton, Compositae, Tribe Inuleae] is a herbaceous perennial plant widespread in the Spanish Comunidad Valenciana and has been used for years in folk medicine of the Mediterranean area (1–3).

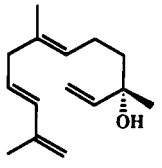
Previous phytochemical studies on this plant, including ours, reported the isolation of flavonoids (4–8), triterpenoids (9), sesquiterpene lactones (10–12), and sesquiterpene acids structurally related to ilicic acid (11–14). In this paper we describe the isolation of some new sesquiterpenoids, as well as several known terpenoids, from the roots and aerial parts of this plant.

A re-examination of the dewaxed C_6H_6 extract of the roots led us to identify 3-methoxy-4-isopropylbenzyl isobutyrate (15) and the triterpenes dammaradienyl acetate (16), friedelin (17,18), and 3-*epi*-friedelinol (18).

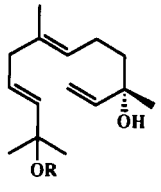
Si gel chromatographic separation of the dewaxed Me_2CO extract of the aerial parts gave nerolidol [**1**] (19), fokienol [**2**] (20), a mixture of 9-isobutyrate [**3**], 9-isovalerate



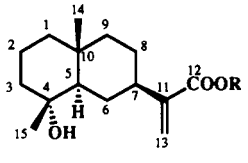
1 R=H
3 R=OCOCHMe$_2$
4 R=OCOCH$_2$CHMe$_2$
5 R=OCOCHMeCH$_2$Me
6 R=OH



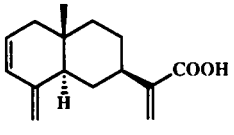
2



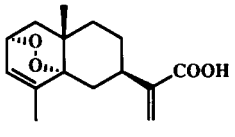
7 R=Me
8 R=H



9 R=H



10



11

[1]Presented in part at the "XX Reunión Bienal de la Real Sociedad Expañola de Química," Castellón, Spain, September 1984.

[**4**], and 9-(2-methylbutyrate) [**5**], 3,7,11-trimethyldodeca-1,6,10-triene-3,9-diol [**6**] (20), 11-methoxy-3,7,11-trimethyldodeca-1,6,9-trien-3-ol [**7**], 3,7,11-trimethyldodeca-1,6,9-triene-3,11-diol [**8**] (20), the sesquiterpene acids ilicic acid [**9**] (21,22), eudesma-2,4(15),11(13)-trien-12-oic acid [**10**] (13), and 2,5-peroxyeudesma-3,11(13)-dien-12-oic acid [**11**], and the sesquiterpene lactones 2-deacetoxyxanthinin (5) and inuviscolide (5,23). Sesquiterpenes **3**, **4**, **5**, **7**, and **11** have not been described previously.

Compounds **3**, **4**, and **5** were isolated as a mixture. The ir spectrum showed the presence of tertiary hydroxyl (3450 cm^{-1}), ester (1720, 1185, 1155 cm^{-1}), and alkene functionalities (3075, 1630, 990, 915, 825 cm^{-1}). Saponification of the mixture of esters gave **6** (20) as the sole neutral product. The identification of the esters as isobutyrate, isovalerate, and 2-methylbutyrate was deduced from the ^{1}H- and ^{13}C-nmr spectral data of the mixture (Tables 1, 2) and confirmed also by the presence of ms fragments at *m/z* 71 (isobutyrate), and *m/z* 85 (isovalerate and 2-methylbutyrate). These esters must be attached to C-9, as deduced from the observed shielding of the geminal proton to the secondary hydroxyl group obtained by saponification.

Compound **6**, $[\alpha]_D$ +11.4, was identified as 3,7,11-trimethyldodeca-1,6,10-triene-3,9-diol, as its ^{1}H-nmr spectrum (Table 1) was quite similar to that of known nerolidol derivatives (19). It showed a signal at δ 4.43 (1H, dt, J = 8.5 Hz, and J = 6.5 Hz), for one allylic proton geminal to one hydroxyl group, which was coupled with a signal at δ 2.13 (2H, brd, J = 6.5 Hz), assigned to one allylic methylene group (C-8). These data were in agreement with those reported for racemic 9-hydroxynerolidol (20).

Treatment of diol **6** with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid in Me_2CO gave a mixture of fokienol [**2**], 9-methoxynerolidol, and a compound identical to **7**, which showed signals of one quaternary methoxyl group (δ 3.07, s) and two trans coupled vinylic protons [δ 5.45 (dd, J = 15.8 and 6 Hz) and 5.33 (d, J = 15.8 Hz)]. These data allowed identification of compound **7** as (6*E*,9*E*)-11-methoxy-3,7,11-trimethyldodeca-1,6,9-trien-3-ol.

The ir and ^{1}H-nmr spectra of **8** were very similar to those of **7**. The only significant difference was the absence of the signal assigned to the methoxyl group in the ^{1}H- and ^{13}C-nmr spectra (Tables 1, 2). The spectral data of **8** were in agreement with those described in the literature for 3,7,11-trimethyldodeca-1,6,9-triene-3,11-diol (20).

Compounds **2**, **7**, and **8** may be artifacts formed from the nerolidol esters during extraction. However, it should be pointed out that the crude extract was in contact with aqueous MeOH only when the concentrated Me_2CO extract was fractionated with *n*-hexane at room temperature (see Experimental).

Compound **9** was isolated as a solid (mp 175–177°; $[\alpha]_D$ −34.7) and was identified as ilicic acid (=vachanic acid) by spectroscopic methods (11,21,22). Treatment of **9** with CH_2N_2 gave **9** methyl ester and a pyrazoline derivative [mp 127–129°, lit. (21) 120°].

Compound **10** was also isolated as a solid (mp 97–98°, $[\alpha]_D$ +59.4). The ms showed a molecular ion at *m/z* 232, in agreement with a molecular formula $C_{15}H_{20}O_2$. The ir spectrum showed absorption bands of a conjugated carboxylic group (3500–2500, 1675 cm^{-1}) and double bonds (1610, 950, 875, 680 cm^{-1}). The ^{1}H nmr spectrum showed the signals of a quaternary methyl group [δ 0.78 (s)], an α-methylene group conjugated with a carboxylic acid [δ 5.72 (t, J = 1.1 Hz) and 6.37 (d, J = 1.1 Hz)], and four olefinic protons at δ 4.77 (1H, br s), 4.86 (1H, br s), 5.67 (1H, m), and 6.13 (1H, dd, J = 9.9 Hz and J = 2.8 Hz) ppm, suggesting the presence of the conjugated diene -CH=CH-C=CH_2. Comparison of these data with those of **9** suggested that **10** was an α-methylene eudesmane acid, with additional unsaturations at 2 and 4 (15). The presence of a conjugated diene was confirmed by the uv spectrum which

TABLE 1. ^{1}H-nmr Data for Nerolidol and Related Compounds (200 MHz, TMS, $CDCl_3$).

Proton	Compound					
	1	**2**	**3–5**	**6**[a]	**7**	**8**
H-1*trans*	5.22 dd (1.3, 17.4)	5.22 dd (1.3, 17.3)	5.20 dd (1.4, 17.3)	5.19 dd (1.5, 17.0)	5.14 dd (1.4, 17.3)	5.19 dd (1.3, 17.3)
H-1*cis*	5.07 dd (1.3, 10.7)	5.06 dd (1.3, 10.7)	5.05 dd (1.4, 10.7)	5.06 dd (1.5, 10.5)	4.98 dd (1.4, 10.7)	5.05 dd (1.3, 10.7)
H-2	5.93 dd (10.7, 17.4)	5.91 dd (10.7, 17.3)	5.90 dd (10.7, 17.3)	5.96 dd (10.5, 17.0)	5.84 dd (10.7, 17.3)	5.90 dd (10.7, 17.3)
H-4	1.60 m	1.59 m	1.54 t (7.0)	1.60 m	1.48 m	1.62 m
H-5	2.10 m	2.02 m	2.10 m	2.06 m	2.00 m	2.00 m
H-6	5.12 br t (6.0)	5.18 br t (7.1)	5.17 br t (7.0)	5.15 br t	5.08 tq (1.4, 6.8)	5.14 br t (7.2)
H-8	2.10 m	2.75 d (7.4)	2.10 m	2.13 br d (6.5)	2.61 d (6.0)	2.66 d (5.9)
H-9	2.10 m	5.61 dt (7.4, 15.6)	5.62 m	4.43 dt (8.5, 6.5)	5.45 dd (15.8, 6.0)	5.55 dd (15.6, 5.9)
H-10	5.15 br t (6.0)	6.14 d (15.6)	5.08 dq (1.3, 9.0)	5.10 m	5.33 d (15.8)	5.63 d (15.6)
H-12	1.69 s	4.88 br s	1.71 br s	1.75 br s	1.21 s	1.30 s
H-13	1.29 s	1.29 s	1.27 s	1.29 s	1.18 s	1.26 s
H-14	1.61 s	1.60 s	1.63 br s	1.69 br s	1.51 br s	1.56 br s
H-15	1.61 s	1.84 s	1.70 br s	1.72 br s	1.21 s	1.30 s
OMe	—	—	—	—	3.07 s	—

Esters	H-2′	H-3′	H-4′	H-5′
3: isobutyrate	2.49 m	1.12 d (7.0)	1.12 d (7.0)	—
4: isovalerate	2.30 m	—	0.92 d (6.4)	0.92 d (6.4)
5: 2-methylbutyrate	—	—	0.91 t (6.9)	1.01 d (6.9)

[a]Recorded at 60 MHz.

TABLE 2. ^{13}C-nmr Data for Nerolidol and Related Compounds ($CDCl_3$, TMS).

Carbon	1	2	3–5	7	8
C-1	111.8	111.8	111.7	111.7	111.8
C-2	145.3	145.2	145.1	145.2	145.1
C-3	73.5	73.5	73.4	73.4	73.6
C-4	42.3	42.2	42.0	42.2	42.1
C-5	22.9	22.9	22.8	22.9	22.9
C-6	124.5	125.4	124.0	125.4	125.3
C-7	135.7	134.2	136.8	134.2	134.3
C-8	39.9	43.0	45.4	42.7	42.4
C-9	26.9	128.7	69.6	128.4	125.5
C-10	124.5	134.2	127.8	136.9	139.5
C-11	131.6	145.2	131.2	74.9	70.8
C-12	25.8	114.7	25.7	26.0	29.9
C-13	28.0	27.9	27.9	27.9	27.9
C-14	16.2	16.3	16.3	16.1	16.2
C-15	17.8	18.8	18.5	26.0	29.9
MeO	—	—	—	50.2	—

Esters	C-2′	C-3′	C-4′	C-5′
3: isobutyrate	34.2	19.1	19.1	—
4: isovalerate	43.8	26.8	22.4	22.4
5: 2-methylbutyrate	41.3	26.8	11.6	16.6

showed λ max (EtOH) at 229 nm (log ε 4.44). The positive Cotton effect exhibited by **10** at 229 nm agrees with the absolute configuration shown for this substance.

Compound **10** was previously reported as an oil (13), and the optical rotation was not quoted, so that the proposed absolute configuration could not be justified. The isolation of this sesquiterpenoid was published a few months after we communicated its structure in a Symposium (see footnote 1).

The structure of compound **11** (mp 146–147°, $[\alpha]_D$ +13.6) was deduced from spectroscopic data. The ir spectrum was very similar to that of **10**, and the ^{1}H nmr showed signals of two methyl groups at δ 0.94 (3H, s, Me-C) and 1.84 (3H, d, J = 1.7 Hz, Me-C=CH). A signal of an allylic proton geminal to oxygen [δ 4.52 (1H, ddd, J = 6.2 and J = 2.1 Hz)] was coupled to a vinylic proton at δ 6.23 (1H, dq, J = 6.2 Hz and J = 1.7 Hz, CH=C) which was also coupled to the vinylic methyl group at δ 1.84. The characteristic signals for the CH_2=C-COOH group [δ 5.68 (1H, t, J = 1.1 Hz); 6.33 (1H, d, J = 1.1 Hz)] were also observed. The ^{13}C-nmr spectrum of **11** (Table 3) showed deshielded carbon atom signals (geminal to oxygen) at δ 71.5 (d) and 81.6 (s), assignable to a tertiary and a quaternary carbon atom, respectively.

The preceding data, and the absence of free hydroxyl groups, suggested the presence of an endoperoxide bridge between C-2 and C-5. The easy thermal loss of O_2 in this type of compound explains the absence of the molecular ion in its ms: the highest mass fragment was observed at *m/z* 232 which can be ascribed to the ion $[C_{15}H_{20}O_4 - O_2]^+$. The stereochemistry shown in the formula **11** was proposed by comparison of the ^{1}H-nmr signal for H-7 with those of H-7 in compounds **9** and **10**. Also, the α orientation of the endoperoxide bridge can explain the observed shielding of C-7 and C-9 by a γ-gauche effect of the C-5 oxygen on these carbon atoms.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv spectra were recorded in EtOH. Melting points are

TABLE 3. ^{13}C-nmr Spectral Data for Sesquiterpenes **9** Methyl Ester, **10**, and **11** ($CDCl_3$, TMS).

Carbon	**9** methyl ester	**10**	**11**
C-1	41.1	40.9	40.3
C-2	20.2	126.9	71.5
C-3	43.5	130.1	124.3
C-4	72.0	145.3[a]	143.3[a]
C-5	55.0	45.1	81.6
C-6	26.6	27.5	30.2
C-7	40.6	39.1	34.6
C-8	27.4	29.7	26.4
C-9	44.6	42.8	36.2
C-10	34.6	33.6	33.2
C-11	145.9	146.0[a]	144.2[a]
C-12	167.9	172.5	171.1
C-13	122.3	125.1	125.9
C-14	18.7	17.0	17.4
C-15	22.5	109.6	25.1
COO*Me*	51.7	—	—

[a]These signals may be interchanged.

uncorrected. ^{1}H nmr (60 and 200 MHz) and ^{13}C nmr (50.3 MHz) spectra were recorded in $CDCl_3$ using TMS as internal standard. The ^{13}C-nmr multiplicities were deduced from DEPT experiments. Mass spectra were obtained at 70 eV.

PLANT MATERIAL.—*D. viscosa* was collected at the end of October 1982 at "Peña las Aguilas," Elche, Alicante, Spain. The plant material was identified by Dr. A. Escarré from the Biology Department at the University of Alicante, where voucher specimens are deposited (4).

EXTRACTION AND ISOLATION.—Air-dried roots (1500 g) of *D. viscosa* were extracted with hot MeOH, and the crude extract (6.26 % of the roots' wt) was extracted with $CHCl_3$ (2.80 g). The neutral part of this fraction (2.0 g) was subjected to chromatography on Si gel (*n*-hexane/C_6H_6 and *n*-hexane/EtOAc, which yielded pure samples of 3-methoxy-4-isopropylbenzyl isobutyrate (300 mg), dammaradienyl acetate (370 mg), friedelin (70 mg), and 3-*epi*-friedelinol (40 mg).

The aerial parts of the air-dried and finely ground plant (7185 g) were extracted with hot Me_2CO, and the crude extract (345 g, 4.8% of the dry plant wt) was suspended in H_2O/MeOH and extracted with *n*-hexane as described previously (4).

The *n*-hexane-soluble fraction (125 g, 36.2% of the crude Me_2CO extract) was chromatographed on Si gel with *n*-hexane/EtOAc mixtures. After repeated chromatographies and/or crystallizations, pure samples of the following components were isolated: **1** (90 mg), **2** (600 mg), **3**, **4**, and **5** (500 mg), **7** (520 mg), **8** (600 mg), **9** (3.580 g), **10** (200 mg), **11** (50 mg) and fatty esters of 2-(4-hydroxyphenyl)-ethanol. The lactones 2-deacetoxyxanthinin (70 mg) and inuviscolide (250 mg) were isolated from the $CHCl_3$-soluble fraction of the crude Me_2CO extract (4), as well as ferulic aldehyde (18 mg) and 2′,4′-dihydroxy-6′-methoxyacetophenone (20 mg).

3,7,11-Trimethyldodeca-1,6,10-triene-3,9-diol [**6**].—The mixture of 9-isobutyrate, 9-isovalerate, and 9-(2-methylbutyrate) of **6** was purified by cc on $AgNO_3$-Si gel (2:8), with *n*-hexane–EtOAc (8:2): ir ν max (film) 3450, 3075, 1720, 1630, 1440, 1370, 1255, 1185, 1155, 990, 915, 825 cm^{-1}; ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

Saponification of the mixture of esters (240 mg) gave the diol **6** (172 mg): $[\alpha]_D$ +25.5 (c = 0.5, $CHCl_3$); ir ν max (film) 3370, 3070, 1630, 1435, 1405, 1370, 1105, 990, 915, 830 cm^{-1}; ^{1}H nmr see Table 1; eims *m/z* $[M - H_2O]^+$ 220 (0.5), 202 (1), 187 (1), 136 (14), 135 (5), 121 (14), 119 (8), 107 (17), 93 (35), 85 (100), 83 (18), 80 (10), 68 (43), 55 (19).

11-Methoxy-3,7,11-trimethyldodeca-1,6,9-trien-3-ol [**7**].—Compound **7** was purified by cc on Si gel with CH_2Cl_2-EtOH (98:2): $[\alpha]_D$ +9.9 (c = 0.6, $CHCl_3$); ir ν max (film) 3430, 3075, 1610, 1375, 1360, 1165, 1070, 990, 970, 915, 845 cm^{-1}; ^{1}H nmr see Table 1; ^{13}C nmr see Table 2; eims *m/z* 220 (1), 202 (9), 187 (13), 159 (13), 146 (10), 145 (16), 134 (16), 133 (16), 132 (10), 131 (17), 119 (60), 107 (53), 106 (21), 105 (56), 93 (100), 85 (7), 79 (69), 71 (17), 67 (44).

REACTION OF **6** WITH 2,2-DIMETHOXYPROPANE/*p*-TsOH: 9-METHOXY-3,7,11-TRIMETHYLDODECA-1,6,10-TRIEN-3-OL.—To a stirred solution of **6** (120 mg) in Me_2CO (10 ml), *p*-toluensulfonic acid (2 mg) and 2,2-dimethoxypropane (0.5 ml) were added. After 15 min, solid Na_2CO_3 was added and the mixture was filtered, dried, and evaporated. The residue (120 mg) was chromatographed on Si gel and eluted with *n*-hexane/EtOAc mixtures to give fokienol [**2**] (20 mg), methoxytrienol **7** (35 mg), and 9-methoxy-3,7,11-trimethyldodeca-1,6,10-trien-3-ol (15 mg): $[\alpha]_D$ +7.4 (c = 0.9, $CHCl_3$); ir ν max ($CHCl_3$) 3580, 3480, 1600, 1435, 1370, 1200, 1185, 990, 920, 835 cm^{-1}; ^1H nmr (60 MHz, $CDCl_3$) δ 5.93 (1H, dd, X part of ABX, J_{BX} = 17 Hz, J_{AX} = 10.5 Hz, H-2), 5.16 (1H, dd, B part of ABX, J_{BX} = 17 Hz, J_{AB} = 1.5 Hz, H-1t), 5.03 (1H, dd, A part of ABX, J_{AX} = 10.5 Hz, J_{AB} = 1.5 Hz, H-1c), 4.03 (1H, m, H-9), 3.19 (3H, s, OMe), 2.16 (2H, m, H-8), 1.66 (9H, m, Me-12, Me-14 and Me-15), 1.23 (3H, s, Me-13); eims *m/z* 202 (3), 187 (4), 119 (16), 107 (16), 105 (17), 99 (100), 93 (32), 91 (26), 81 (10), 79 (21), 77 (19), 71 (8), 69 (12), 67 (30), 65 (15), 55 (33).

Eudesma-2,4(15),11(13)-trien-12-oic acid [**10**].—Cc on Si gel with *n*-hexane–EtOAc (19:1) as the eluent, followed by extraction with aqueous saturated solution of $NaHCO_3$ and recrystallization, gave **10**: mp 97–98° (*n*-hexane); $[\alpha]_D$ +59.4 (c = 0.5, $CHCl_3$); uv λ max (EtOH) 229 nm (log ϵ 4.44); ir ν max (KBr) 3500–2500, 1675, 1610, 1420, 1370, 1285, 1150, 950, 875, 820, 680, 635 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 6.37 (1H, d, J = 1.1 Hz, H-13), 6.13 (1H, dd, J = 9.9 Hz, J = 2.8 Hz, H-3), 5.72 (1H, t, J = 1.1 Hz, H-13), 5.67 (1H, m, H-2), 4.86 (1H, br s, H-15), 4.77 (1H, br s, H-15), 2.57 (1H, br t, J = 9.5 Hz, H-7α), 2.18 (1H, br d, J = 9.6 Hz, H-5α), 2.10 [1H, d (AB), J = 16.4 Hz, H-1α], 1.95 (1H, dd, J = 16.4 Hz, J = 5.1 Hz, H-1β), 0.78 (3H, s, Me-14); ^{13}C nmr see Table 3; eims *m/z* $[M]^+$ 232 (100), 217 (17), 203 (12), 199 (26), 191 (11), 187 (20), 171 (36), 157 (18), 145 (29), 131 (25), 119 (50), 105 (44), 91 (58), 79 (29), 77 (29); cd positive Cotton effect at 229 nm.

2,5-Peroxyeudesma-3,11(13)-dien-12-oic acid [**11**].—Compound **11** was purified by cc on Si gel with *n*-hexane–EtOAc (1:1): mp 146–147° (*n*-hexane/C_6H_6); $[\alpha]_D$ +13.6 (c = 0.2, $CHCl_3$); ir ν max (KBr) 3400, 3030, 1675, 1615, 1430, 1370, 1285, 1260, 1165, 1130, 1020, 965, 935, 920, 855, 790, 760, 680 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ 6.33 (1H, d, J = 1 Hz, H-13), 6.23 (1H, dq, J = 6.2 Hz, J = 1.7 Hz, H-3), 5.68 (1H, t, J = 1.1 Hz, H-13), 4.52 (1H, ddd, J = 6.2 Hz, J = 2.1 Hz, H-2), 2.96 (1H, tt, J = 11.5 Hz, J = 5.0 Hz, H-7α), 1.84 (3H, d, J = 1.7 Hz, Me-15), 1.32 (1H, dd, J = 13 Hz, J = 2.1 Hz, H-1α), 0.94 (3H, s, Me-14); ^{13}C nmr see Table 3; eims *m/z* $[M-O_2]^+$ 232 (29), 218 (4), 203 (3), 199 (24), 187 (2), 181 (4), 175 (4), 171 (31), 143 (25), 119 (22), 105 (29), 91 (38), 81 (17), 79 (31), 77 (34), 76 (25), 53 (44), 41 (100).

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