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NEW SESQUITERPENES FROM THE ROOTS OF
LIGULARIA VEITCHIANA

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ABSTRACT.—The roots of *Ligularia veitchiana* were found to contain three previously un-reported eremophilane derivatives **1–3**. Their structures were established by high field tech-niques and chemical transformations.

Many eremophilane sesquiterpenes and pyrrolizidine alkaloids have been isolated from the genus *Ligularia* belonging to the tribe Senecioneae of the Compositae (1,2). Among approximately 100 Chinese *Ligularia* species, of which 27 have been used since ancient times as folk remedies, only a few have been studied chemically (3,4). The re-cently reported norditerpene with a novel carbon skeleton from *Ligularia sagitta* (4) in-creased our interest in the chemistry of this genus. We now report the results of our in-vestigation of the roots of *Ligularia veitchiana* (Hemsl.) Greenm.
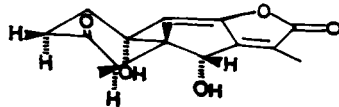
RESULTS AND DISCUSSION

The extract of *L. veitchiana* afforded, by repeated cc and preparative tlc over Si gel, two eremophilanolides, **1** and **2**, and the *n*-undecanoyl eremophilane derivative **3**.
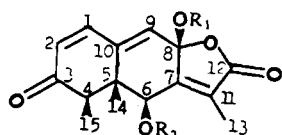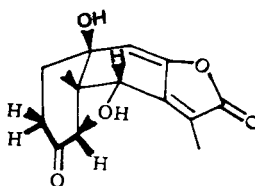

1 R$_1$=R$_2$=H
6 R$_1$=Ac, R$_2$=H
7 R$_1$=R$_2$=Ac
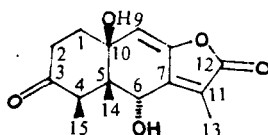
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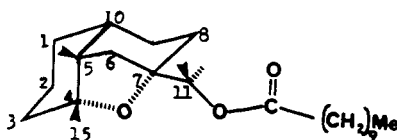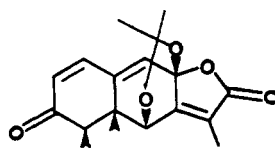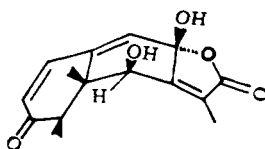
Lactone **1** yielded colorless needles (MeOH), mp 193–194°, $[\alpha]^{25}D + 12.0°$ ($c =$ 0.5, MeOH); $C_{15}H_{16}O_5$ was indicated by its eims (m/z 276 $[M]^+$) and elemental analysis. The ^{13}C-nmr spectrum, accompanied by 90° and 135° DEPT pulse sequences, showed 15 carbon resonance lines consisting of two carbonyls, five quaternary (three sp^2 and two sp^3), five methine (three sp^2 and two sp^3), and three methyl groups (in total $C_{15}H_{14}$). The other two protons in the molecule had to exist as hydroxyls, as evidenced by hydroxyl ir absorption bands at 3487 and 3240 cm^{-1} and the eims, which exhibited prominent peaks at m/z 258 and 240 ascribable to the successive losses of H_2O from $[M]^+$ (m/z 276). In the ^1H-nmr spectrum of **1**, a quartet ($J = 7.4$ Hz, H-4, δ 2.94) and a three-proton doublet ($J = 7.4$ Hz, H-15, δ 1.44) were evident. A set of downfield vinylic proton signals at δ 6.10 (dd, $J = 10.0, 2.6$, H-2), 6.76 (dd, $J = 10.0, 1.5$ Hz, H-1), and 6.63 (brs, H-9) established a γ,δ-disubstituted α,β,γ,δ-unsaturated ketone system. The typical ir absorption band at 1690 cm^{-1} as well as the uv λ max at 284 nm further evidenced this conjugated unit and explained the upfield ketone carbon resonance to δ 201.7 ppm. Furthermore, an olefinic methyl doublet at δ 2.02 split by homoallylic coupling with the H-6 signal at δ 4.98 ($J = 1.4$ Hz) revealed information concerning a 6-hydroxy-7(11)-ene-13-methyl-12-lactone moiety in **1** and was reinforced by a γ-lactone ir absorption band at 1755 cm^{-1} and a group of carbon signals arising from C-6–C-8 and C-11–C-13 in the ^{13}C-nmr spectrum (Table 1) (5,6). The quartet (H-4) and the doublet (H-15) were both shifted downfield compared to the corresponding shift for secondary methyl groups as reported in the literature (5,6). Other information suggested that the structure of **1** was as indicated to permit the magnitude of $J_{1,2} = 10$ Hz characteristic of hexene derivatives (7,8). The splitting pattern of the H-6 and H-9 proton signals provided further support for the structure of eremophilanolide **1**. The C-4 and C-5 stereochemistry assignments followed from biogenetic considerations. Moreover, acetonation of **1** gave an isopropylidene derivative **4**, demonstrating that the two hydroxyls were cis-oriented. NOe spectroscopy revealed that the Me-14 had an effect on the Me-15 (16%) but that it had no effect on H-6, which eliminated the possibility of H-6β. Furthermore, the 8β-monoacetyl deriva-

TABLE 1. ^{13}C-nmr Data of Compounds **1** and **2**.[a]

Carbon	Compound			
	1 (CD$_3$OD)	DEPT	**2** (Me$_2$CO-d_6)	DEPT
C-1	158.7	CH	20.3	CH$_2$
C-2	128.2	CH	40.0	CH$_2$
C-3	201.7	C	206.9	C
C-4	43.7	CH	41.4	CH
C-5	52.6	C	51.0	C
C-6	76.0	CH	74.3	CH
C-7	160.1	C	158.7	C
C-8	101.6	C	149.3	C
C-9	129.3	CH	125.0	CH
C-10	146.5	C	84.8	C
C-11	124.8	C	124.0	C
C-12	168.8	C	171.5	C
C-13	8.7	Me	8.2	Me
C-14	13.7	Me	12.2	Me
C-15	17.3	Me	17.7	Me

[a]Assignments were accomplished by comparing the data with those of analogues in Jia *et al.* (5) and Sugama *et al.* (6).

tive **6** shifted only the singlet of H-9 downfield to δ 6.99 ppm while in the diacetyl derivative **7**, the Me-14 was shifted downfield to δ 1.28 ppm when compared with that of **1** (δ 1.01 ppm). Inspection of the model also showed the presence of 6β-,8β-OH groups was most likely because both 6α- and 8α-OH were widely separated and it was spatially impossible for acetonation to occur (see the conformational formula **5**). The same substitution could be observed in eremophilanolides isolated from the aerial parts of this species (5).

The ^{1}H- and ^{13}C-nmr and ir spectral data of compound **2** were close to those of **1** and revealed that it also contained an eremophilan-12,8-olide with $\Delta^{7(11)}$ olefin unit. The molecular formula $C_{15}H_{18}O_5$ was assigned on the basis of the elemental analysis and the molecular ion peak at m/z 278 in the eims. Two hydroxyls in **2** were deduced from the intense fragment ions at m/z 260 $[M - H_2O]^+$ and 242 $[M - 2 \times H_2O]^+$ and from the hydroxyl ir absorption band at 3560 cm^{-1} (br). In the ^{1}H-nmr spectrum of **2** the splitting pattern and the lowfield shifts of H-2, H-4, and H-15 (Table 2) established the 3-ketone group while the lowfield shift of H-6 ($J = 1.6$ Hz) indicated the presence of a 6-OH. In the ^{13}C-nmr spectrum the semiketal quaternary sp^3 carbon signal observed at δ 101.6 in the case of **1** was missing and was replaced by a non-protonated sp^2 carbon resonance line at δ 149.3. In the ir spectrum, the α,β-unsaturated γ-lactone absorbed at a higher frequency (1765 cm^{-1}) than that of **1** (1755 cm^{-1}), indicating the presence of an enol γ-lactone unit. All these spectral features could be explained by assuming an 8,9 double bond. Moreover, the last oxygen-bonded quaternary carbon (δ 84.8) led to the proposal of a 10β-OH, in accordance with 4β-,5β-Me groups. The W-type long range coupling ($J = 3.0$ Hz) between H-2α and H-4α confirmed the cis-fusion of the decalin nucleus **8** whereas the trans fused isomer **9** would have an axially oriented 4α-proton which could not exhibit W-type coupling. As for the stereochemistry of H-6, the model showed that the 6β-, 10β-OH were all axial and should form an isopropylidene derivative like compound **1**. However, acetonation of **2** failed, which suggested that a 6β-OH was not present (the presence of the 10β-OH had already been shown). NOe experiments showed that H-6 had a clear effect on Me-14 (12%) but had no effect on H-4α, supporting the presence of a 6α-OH. Furthermore, the model indicated that the dihedral angle between H-6α and Me-13 was nearly 30° while that between H-6β and Me-13 was nearly 80°, which allowed homoallylic coupling in the case of **2** ($J_{6,13} = 1.6$ Hz).

TABLE 2. ^{1}H-nmr Data of Compounds **1**, **2**, **6**, and **7**.[a]

Proton	Compound			
	1 (CD$_3$OD)	**6** (CDCl$_3$)	**7** (CDCl$_3$)	**2** (Me$_2$CO-d_6)
H-1 . . .	6.76 dd (10.0, 1.5)	6.59 dd (10.0, 1.5)	6.58 dd (10.0, 1.5)	0.9–1.4 m
H-2α . .				2.46 dddd (10.0, 4.0, 4.0, 3.0)
	6.10 dd (10.0, 2.6)	6.10 dd (10.0, 2.6)	6.10 dd (10.0, 2.6)	
H-2β . .				1.79 ddd (10.0, 8.0, 4.0)
H-4 . . .	2.94 q (7.4)	2.90 q (7.4)	2.92 q (7.3)	2.18 dq (7.0, 3.0)
H-6 . . .	4.98 q (1.4)	4.95 q (1.4)	5.92 q (1.4)	4.98 q (1.6)
H-9 . . .	6.63 br s	6.99 br s	7.08 br s	6.24 br s
H-13 . . .	2.02 d (1.4)	2.06 d (1.4)	1.96 d (1.4)	1.99 d (1.6)
H-14 . . .	1.01 s	1.05 s	1.28 s	0.91 s
H-15 . . .	1.44 d (7.4)	1.43 d (7.4)	1.40 d (7.3)	1.26 d (7.0)

[a]Coupling constants in Hz are in parentheses.

TABLE 3. ^{1}H- and ^{13}C-nmr Data of Compound **3** (CDCl$_3$).[a]

Position	^{1}H	^{13}C	DEPT
1	⎫	22.68	CH$_2$
2	⎬ 1.45–1.75 m	24.80[b]	CH$_2$
3	⎭	31.92	CH$_2$
4	—	74.42	C
5	—	38.74	C
6α	2.13 dd (11.8, 4.5)	⎫ 37.83[c]	CH$_2$
6β	1.82 d (11.8)	⎭	
7	—	82.22	C
8	⎫	37.72[c]	CH$_2$
9	⎬ 1.45–1.75 m	25.63[b]	CH$_2$
10	⎭	44.53	CH
11	—	87.90	C
12	1.28 s	24.71[d]	CH$_3$
13	1.30 s	26.91[d]	CH$_3$
14	1.12 s	22.86	CH$_3$
15	1.36 s	30.48	CH$_3$
1'	—	179.55	C
2'	2.34 t (7.5)	38.11[c]	CH$_2$
3'	⎫	34.03	CH$_2$
4'	⎪	29.67[e]	CH$_2$
5'	⎪	29.67[e]	CH$_2$
6'	⎬ 1.20–1.38 m	29.65[e]	CH$_2$
7'	⎪	29.43[e]	CH$_2$
8'	⎪	29.35[e]	CH$_2$
9'	⎭	29.24[e]	CH$_2$
10'		29.07[e]	CH$_2$
11'	0.88 t (7.5)	14.00	Me

[a]Coupling constants in Hz are given in parentheses.
[b-e]Assignments with the same superscript may be interchangeable.

The spectral features of compound **3** and the molecular formula C$_{26}$H$_{46}$O$_3$ [based on eims data, the DEPT spectrum, and the nmr data which were assigned by comparison with those of previously reported eremophilane derivatives (5, 6, 9–11)] indicated that **3** was most likely a sesquiterpene undecanoyl ester. Moreover, the three-proton singlets at δ 1.28, 1.30, and 1.36, along with a further singlet at δ 1.12, were typical of the methyl groups of an eremophilane derivative (9) and indicated the presence of oxygen atoms at C-4 and C-11. Subtracting two oxygen atoms due to the ester function (ir absorption band at 1734 cm^{-1} and the ^{13}C resonance at 179.6), no unsaturated bond was required by the nmr data. However, the four degrees of unsaturation of C$_{26}$H$_{46}$O$_3$, three of which were ascribable to an ester group and two ring systems in the decalin nucleus, indicated that an oxide ring was also present. The lowfield shifts of three oxygen-bonded quaternary carbons (δ$_C$ 87.9, 82.2, and 74.2) eliminated the possibility of an epoxide or simultaneous oxygen attachment to C-4 and C-10 (γ effect). It was spatially impossible for C-4 and C-11 to be connected through an oxygen atom on the basis of the proposed stereochemistry (*cis*-decalin derivative with 4β-Me and 7β-isopropyl groups if C-7 and C-11 are not sp^2 carbons) (10,11). The C-4 and C-7 oxide ring closure with C-11 carrying the above-mentioned undecanoyl group is consistent with the chemical shifts of C-7 and C-11 (both being moved downfield by the β effect on each other).

EXPERIMENTAL

spectra were recorded in a Bruker AM-400 FT-nmr spectrometer using TMS as internal standard. Eims were obtained on a VG ZAB-HS spectrometer at 70 eV. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. Uv spectra were taken on a DU-7 uv-vis spectrophotometer in EtOH.

PLANT MATERIAL.—The roots of *L. veitchiana* were collected in Zhang County, Gansu Province, People's Republic of China. A voucher specimen was identified by Prof. R.N. Zhao and deposited in the Herbarium of the Department of Pharmacy, Lanzhou Medical College.

EXTRACTION AND ISOLATION.—The air-dried roots (2.5 kg) were pulverized and extracted at room temperature with petroleum ether (60°–90°)-Et$_2$O-Me$_2$CO (2:4:1) (7 days × 3). The resulting extract was concentrated under vacuum to a residue (50 g), which was subjected to cc over 900 g Si gel and eluted with a gradient of CHCl$_3$-Me$_2$CO (1:0↦1:1). The fractions 3–6 (30 mg) mainly contained compound **3**, which was crystallized (12 mg) from petroleum ether-Et$_2$O (1:1). Fractions 11–20 (100 mg) were combined and re-chromatographed on Si gel (30 g) and eluted with CHCl$_3$-Me$_2$CO (6:1) to give a fraction which was then separated by repeated preparative tlc to afford **2** (24 mg) and **1** (38 mg).

Compound **1**.—Colorless needles (MeOH): mp 193–194°; [α]^{25}D +12.0 (c = 0.5, MeOH); uv λ max nm (log ε) 284 (4.39), 220 (4.12); found C 65.20, H 5.78 (calcd for C$_{15}$H$_{16}$O$_6$, C 65.22, H 5.80); ir (KBr) ν max 3487, 3240, 1755, 1690 cm^{-1}; ^{1}H nmr see Table 2; ^{13}C nmr see Table 1; eims m/z (% rel. int.) [M]$^+$ 276 (6), [M − H$_2$O]$^+$ 258 (17), 248 (6), [M − 2H$_2$O]$^+$ 240 (12), 230 (11), 229 (14), 212 (14), 187 (11), 175 (9), 135 (24), 107 (20), 91 (41), 77 (22), 40 (100).

Acetonation of **1**.—A solution of **1** (10 mg) in anhydrous Me$_2$CO (5 ml) was kept at 80° for 2 h with *p*-toluenesulfonic acid (2 mg). The resultant mixture was purified by preparative tlc [CHCl$_3$-Me$_2$CO (10:1)], affording the acetonide of **1**: compound **4** (9 mg). Compound **4**: colorless gum; found C 68.32, H 6.32 (calcd for C$_{18}$H$_{20}$O$_5$, C 68.33, H 6.33); ir (KBr) ν max 1760, 1687, 1470, 1383, 735 cm^{-1}; eims m/z (% rel. int.) [M]$^+$ 316 (29), 301 (46), 286 (42), 268 (21), 162 (25), 149 (78), 105 (28), 41 (100); ^{1}H nmr δ (ppm) (CDCl$_3$) 6.90 (1H, dd, J = 10.5, 1.6 Hz, H-1), 6.08 (1H, dd, J = 10.5, 2.5 Hz, H-2), 5.00 (brs, 1H, H-6), 6.75 (1H, brs, H-9), 2.16 (3H, brs, H-13), 0.98 (3H, brs, H-14), 1.40 (3H, d, J = 7.2 Hz, H-15), 2.29 and 2.33 (each 3H, s, isopropylidene methyls).

Neutral acetylation of **1**.—A solution of **1** (10 mg) in Ac$_2$O (2 ml) was kept at 70° for 3 h. It was purified by preparative tlc [CHCl$_3$-Me$_2$CO (6:1)] to afford **6** (8 mg): ^{1}H nmr see Table 2.

Basic acetylation of compound **1**.—Compound **1** (10 mg) was dissolved in Ac$_2$O-pyridine (1:1) and left for 24 h at room temperature. Preparative tlc [CHCl$_3$-Me$_2$CO (10:1)] of the product afforded **7** (9 mg): ^{1}H nmr see Table 2.

Compound **2**.—Colorless needles (Me$_2$CO): mp 148–149°; [α]^{25}D +42.6° (c = 0.5, Me$_2$CO); uv λ max nm (log ε) 230 (4.20); found C 64.72, H 6.45 (calcd for C$_{15}$H$_{18}$O$_5$, C 64.75, H 6.47); ir (KBr) ν max 3560 (OH), 1718, 1770 cm^{-1}; eims m/z (% rel. int.) [M]$^+$ 278 (8), [M − H$_2$O]$^+$ 260 (28), 242 [260 − H$_2$O]$^+$ (15), 232 (34), 225 (16), 214 (25), 158 (100).

Compound **3**.—Colorless powder (CHCl$_3$): mp 84–84°; [α]^{25}D −23.0 (c = 0.5, CHCl$_3$); found C 76.86, H 11.30 (calcd for C$_{26}$H$_{46}$O$_3$, C 76.85, H 11.33); ir (KBr) ν max 2917, 2649, 1734, 1463, 1382, 721 cm^{-1}; eims m/z (% rel. int.) [M]$^+$ 406 (5), 391 (2), 368 (12), 354 (7), 340 (8), 325 (6), 312 (10), 284 (13), 256 (9), 238 (12), 223 (14), 205 (9), 187 (7), 185 (6), 97 (12), 73 (31), 57 (28), 43 (100); ^{1}H and ^{13}C nmr see Table 3.

ACKNOWLEDGMENTS

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