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Two New Eremophilane Sesquiterpene Lactones from *Ligularia myriocephala* Ling

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Abstract: Two new eremophilane sesquiterpene lactones, 1β-angeloyloxy-6β, 10β-dihydroxy-8β-methoxyeremophila-7(11)en-8α,12-olide and 1β-angeloyloxy-6β,10α-dihydroxy-8α-methoxyeremophila-7(11)en-8β,12-olide were isolated from the extract of the whole plant of *Ligularia myriocephala* Ling. Their structures and stereochemistry were elucidated by various spectroscopic methods including intensive 2D-NMR techniques (COSY, gHMQC, gHMBC and ^{1}H-^{1}H NOESY) and HR-ESIMS.

Keywords: *Ligularia myriocephala* Ling, Compositae, sesquiterpene lactones, eremophilanolide.

The genus *Ligularia* (Compositae) for its pharmaceutical value, has been studied by our group for several years[1, 2], and it was found to be an important source of sesquiterpenes with eremophilane type. On going our investigation on natural sesquiterpenes, we selected *Ligularia myriocephala*, because its chemical constituents have not been reported and two eremophilanolides **1**-**2** have been found for the first time from the species. In this paper, we describe the structural elucidation of **1** and **2**.

Compound **1** was obtained as colorless needle crystals, m.p.180-181℃, $[\alpha]_D^{20}$ +186 (*c* 0.70, CHCl$_3$). Its molecular formula was assigned as $C_{21}H_{30}O_7$ (seven degrees of unsaturation) on the basis of the HRESIMS (*m/z* = 417.1884 [M+Na]$^+$, calcd. 417.1889 for $C_{21}H_{30}O_7Na$). The IR (ν, KBr) spectrum showed the absorption bands for the hydroxyl group (3474.0 and 3435.4 cm^{-1}) and the α,β-unsaturated-γ-lactone (1644.9, 1704.4 and 1776.0 cm^{-1}) corresponding UV absorption band at a λ_{max} 220 nm. Except for the typical carbon signals of angeloyl group (**Table 1**) and methyloxyl group (δ_C 51.1 ppm; δ_H 3.25 ppm, s, 3H), the ^{13}C-NMR spectrum (**Table 1**) showed 15 carbons including three methyls, three methylenes, three methines, and six quaternary carbons, assigned by DEPT experiment, which revealed that **1** was as a sesquiterpenoid. By detailed inspection of the ^{1}H- and

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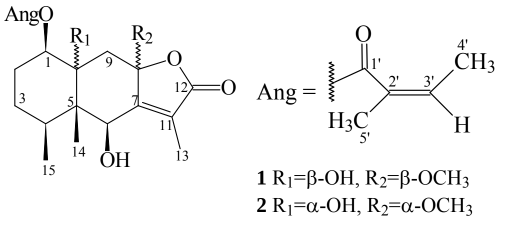
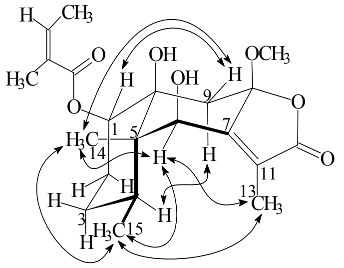
^{13}C-NMR, and comparison of its spectral data with those of known sesquiterpene lactones [2-5], **1** was further confirmed as eremophilanoide with one angeloyl, one methoxyl and two hydroxyl groups, particularly, for typical eremophiliane methyl groups: δ_H 0.86 (d, 3H, J = 6.7 Hz), 1.33 (s, 3H) and δ_C 16.1, 12.7, as well as δ_H 1.91 (s, 3H) and δ_C 8.9 (olefinic methyl groups, ppm). The location of the angeloyloxy moiety was established by the gHMBC correlation of H-1 (δ_H 4.85, t, J = 2.8 Hz) with C-1′ (δ_C 167.7), C-10 (δ_C 76.2), C-9 (δ_C 43.7) and C-5 (δ_C 47.4). The methoxyl group attached at C-8 was deduced by the gHMBC correlation of the methoxyl protons (-OCH_3) with C-8 (δ_C 105.4). The hydroxyl group attached to C-10 was deduced as β-oriented because rings A and B were *cis*-fused (A/B-*cis*) from the chemical shift of protons of the 14-CH_3 (δ_H 1.33, s, 3H) downfield to the 15-CH_3 [2-4]. This was also supported by a cross-peak between H-4α and H-9α in the NOESY spectrum (**Figure 2**). The hydroxyl group at C-6 was β-oriented indicated by the cross-peak between H-6α and H-15 in the NOESY experiment (**Figure 2**). The pattern and smaller J values between H-1 and H_2-2 ($J_{1e,2e}$ = $J_{1e,\,2a}$ = 2.8 Hz) showed that the angeloyl group at C-1 was β-oriented. Considering all the above informations, the structure of **1** was determined to be a 1β-angeloyloxy-6β, 10β-dihydroxy-8β-methoxyeremophila-7(11)en-8α,12-olide.

Figure 1 Structures of compounds **1** and **2**



1 R_1=β-OH, R_2=β-OCH_3
2 R_1=α-OH, R_2=α-OCH_3

Figure 2 Key correlations in NOESY of **1**



Compound **2** was obtained as colorless needle crystals, m.p. 170-171℃, $[\alpha]_D^{20}$ −11 (c 1.12, $CHCl_3$). Its molecular formula was assigned as $C_{21}H_{30}O_7$ (seven degrees of unsaturation) on the basis of the HRESIMS (m/z = 395.2065 $[M+H]^+$, calcd. 395.2064 for $C_{21}H_{31}O_7$). The IR (ν, KBr) spectrum showed the absorption bands for a hydroxyl group (3474.0 and 3435.4 cm^{-1}) and a α,β-unsaturated-γ-lactone (1646.3, 1679.3 and 1739.4 cm^{-1}) corresponding UV absorption band at λ_{max} 220 nm. The ^{1}H- and ^{13}C-NMR spectra were very similar to those of **1** except for the doublet of methyl group H-15 (δ_H 1.21, d, 3H, J = 7.6 Hz) was downfield shifted from H-14 methyl singlet (δ_H 0.96, s, 3H). This suggested compounds **2** was a *trans*-eremophilane, which attributed to decide the hydroxyl group at C-10 and methoxy group at C-8 were α-oriented [3, 6]. The homoallylic coupling (J = 1.6 Hz) between H-6α and Me-13 protons also showed the methoxyl group at C-8 was α-oriented. Then, the structure of **2** was determined to be 1β-angeloyloxy-6β, 10α-dihydroxy-8α-methoxyeremophil-7(11)en-8β, 12-olide.

Table 1 ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and DEPT data of compound **1** and **2** ($CDCl_3$, TMS, δ ppm, *J* Hz)*

No.	**1** δ_H	**1** δ_C	**2** δ_H	**2** δ_C	DEPT
1	4.85 t (2.8)	75.5	5.29 dd (9.2, 4.8)	73.7	CH
2α	1.76 m	27.1	1.83 m	21.4	CH_2
2β	1.72 m		1.89 m		
3α	1.57 m	25.7	1.50m	26.3	CH_2
3β	1.37 m		1.91 m		
4	1.27 m	33.4	2.13 m	31.05	CH
5		47.4		50.8	C
6	4.51 s	72.1	4.81 d (1.6)	70.4	CH
7		153.7		156.5	C
8		105.4		103.9	C
9α	2.25 d (14.8)	43.7	2.50 d (14.0)	41.3	CH_2
9β	2.43 d (14.8)		1.75 d (14.0)		
10		76.2		75.0	C
11		127.4		127.5	C
12		170.6		171.6	C
13	1.91 s	8.9	2.07 d (1.6)	8.9	CH_3
14	1.33 s	12.7	0.96 s	12.5	CH_3
15	0.86 d (6.7)	16.1	1.21 q (7.6)	16.8	CH_3
1′		167.7		166.5	C
2′		127.3		127.8	C
3′	6.10 qq (7.2, 1.2)	139.6	6.02 qq (7.2, 1.2)	138.1	CH
4′	1.98 dq (7.2, 1.6)	15.8	1.94 dq (7.2, 1.6)	15.8	CH_3
5′	1.92 m	20.7	1.88 m	20.6	CH_3
OCH_3	3.25 s	51.1	3.08 s	50.1	CH_3

*Assignments of chemical shifts of **1** and **2** were confirmed by DEPT, gHMQC, gHMBC and ^{1}H-^{1}H NOESY experiments.

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