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Three Novel Eremophilanolides from *Ligularia virgaurea* spp. *oligocephala*

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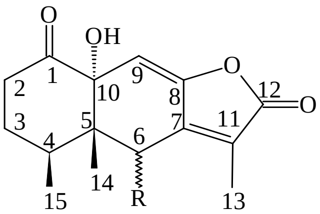
Abstract From the alcoholic extract of the whole plant of *Ligularia virgaurea* spp. *oligocephala*, three novel eremophilane sesquiterpene lactones, 6α, 10α-dihydroxy-1-oxoeremophila-7(11), 8(9)-dien-8, 12-olide, 6β, 10α-dihydroxy-1-oxoeremophila-7 (11), 8 (9)-dien-8, 12-olide and 10α-hydroxy-1-oxoeremophila-7(11), 8(9)-dien-8, 12-olide were isolated. Their structures were elucidated by various spectroscopic methods including intensive 2D NMR techniques (COSY, HMQC, HMBC and ^1H-^1H NOESY) and HR-MS.

Keywords: *Ligularia virgaurea* spp. *oligocephala*, Compositae**,** sesquiterpene lactones, eremophilanolides.

Liguaria genus (Compositae) is the most important resource of sesquiterpenes, particularly, eremophilane type sesquiterpenes. In a continuing investigation on occurring sesquiterpenoids, we selected *Ligularia virgaurea* spp. *oligocephala*, which has long been used as a traditional folk medicine for the treatment of stomachache and puke[1], and three eremophilanolides **1**-**3** have been found for the first time from the species. We describe herein the isolation and structural elucidation of **1**-**3**.

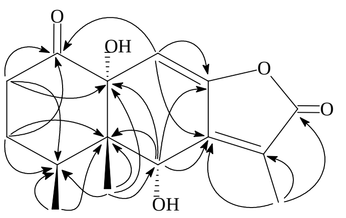
Compound **1** was obtained as colorless gum, $[\alpha]_D^{26}$ -38 (*c* 0.14, $CHCl_3$). The molecular formula was assigned as $C_{15}H_{18}O_5$ on the basis of the HRESIMS (*m/z* = 574.2641 $[2M+NH_4]^+$). Its IR spectrum showed the absorption bands for hydroxyl (3425 cm^{-1}) and ketone carbonyl (1722 cm^{-1}) functions, as well as α,β-unsaturated- γ-lactone

Figure 1



1 R=α-OH
2 R=β-OH
3 R=H

Figure 2 Relative peaks of HMBC in **1**



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(1775 cm^{-1}) and double bond (1670 cm^{-1}). The ^{13}C-NMR spectrum displayed 15 carbons including three methyls, two methylenes, three methines and seven quaternary carbons, assigned by DEPT experiment, which revealed that **1** was as a sesquiterpenoids. In the downfield region of the NMR spectrum, there were some characteristic signals at δ_C 207.10 due to a ketone carbonyl group, and δ_C 146.51, 127.31; δ_C 150.15, 104.41 and δ_H 6.18 ascribed to two double bond functions, and δ_C 170.32 to a carbonyl group, indicating an α,β-unsaturated-γ-lactone, along with δ_C 68.62 and δ_H 4.50 (1H, s) due to oxymethine, addition to δ_C 79.99 for an oxygen-bonded quaternary carbon. Then, compound **1** was considered to be a α, β-unsaturated-γ-lactone sesquiterpene with a ketone and two hydroxyl groups. By detailed inspection of the ^{1}H- and ^{13}C-NMR, and comparison of its spectral data with those of known sesquiterpene lactones$^{2-8}$, **1** was further confirmed as eremophilanolide, particularly, with typical eremophilane methyl groups: δ_H 2.05 (s, 3H) and δ_C 8.78 (olefinic methyl groups), δ_H 0.57 (d, 3H, J = 6.8), 1.06 (s, 3H) and δ_C 13.15, 14.11.

Table 1 ^{1}H-NMR spectral data of compounds **1**, **2** and **3** (400.16MHz)[a]

No	**1** ($CDCl_3$)	**2** ($CDCl_3$)	**3** (Acetone-d_6)
2α	3.15 ddd (7.8,13.6, 13.6)	3.15 ddd (7.8, 13.2, 13.2)	3.14 ddd (8.4, 13.6, 13.6)
2β	2.32 dd (4.4, 13.6)	2.12 dd (4.8, 13.2, 4.8)	2.28 dd (5.2, 13.6)
3α	1.93 m 1.62 dddd	1.77 m 1.53 dddd	1.88 m 1.60 dddd
3β	(4.4,13.6,13.6,13.6)	(4.8,13.2,13.2,13.2)	(5.2,13.6,13.6,13.6)
4α	3.12 m	2.82 m	2.64 m
6	4.50 s	5.19 s	2.75 d (16.8) 2.53 d (16.8)
9	6.18 s	5.96 s	6.12 s
13	2.05 s	2.00 s	1.92 s
14	0.57 s	0.61 s	0.64 s
15	1.06 d (6.8)	1.11 d (6.8)	0.93 d (7.6)

[a] Assignment of **1**-**3** was aided by spin splitting patterns, DEPT, COSY, HMBC experiments. δ in ppm and TMS as the intensive standard.

The location of the carbonyl group was assigned by the COSY with correlations of H-2αβ (δ_H 3.15, 2.32) with H-3αβ (δ_H 1.62, 1.93), H-3αβ with H-4α (δ_H 3.12), and H-4α with H-15 (δ_H 1.06), together with the HMBC correlation of H-2α (δ_H 3.15), H_2-3, H-9 (δ_H 6.18) with C-1 (δ_C 207.10). The hydroxyl group attached at C-10 was deduced as α-oriented because rings A and B of **1** was of *trans* fusion (A/B-*trans*), they possess chair-like conformation and H-2 and H-3 have the respective span splitting pattern and J value, in particular, H-3β for dddd, $J_{3\beta,2\beta}$=4.4, $J_{3\beta,2\alpha}$ =$J_{3\beta,3\alpha}$ =$J_{3\beta,4\alpha}$ =13.6Hz in the ^{1}H-NMR (**Table 1**). The relative stereochemistry of C-6 of **1** could be determined on the basis of the correlations between H-6β and H-14, H-15, H-13 in the NOESY experiment. Hence, the compound **1** was elucidated as 6α, 10α–dihydroxy-1-oxoeremophila-7(11), 8 (9)-dien-8, 12-olide (**Figure 1**).

Table 2 ^{13}C-NMR spectral data of compounds **1**，**2** and **3**（100.32MHz）[a]

No	**1**	**2**	**3**
1	207.10 s	207.84 s	208.5 s
2	36.47 t	36.57 t	36.35 t
3	29.16 t	31.93 t	29.92 t
4	28.17 d	34.21 d	32.88 d
5	47.37 s	52.19 s	45.72 s
6	68.62 d	71.81 d	30.47 t
7	146.51 s	150.06 s	146.12 s
8	150.15 s	151.27 s	151.97 s
9	104.41 d	105.34 d	103.86 d
10	79.99 s	79.26 s	78.47 s
11	127.31 s	125.56 s	124.21 s
12	170.32 s	171.35 s	170.49 s
13	8.78 q	8.44 q	8.72 q
14	13.15 q	9.41 q	13.50 q
15	14.11 q	18.22 q	14.46 q

[a] Assignment of **1-3** was aided by spin splitting patterns, DEPT, HMQC, HMBC experiments. δ in ppm and TMS as the intensive standard. Multiplication determined by DEPT experiments.

Compound **2** was obtained as colorless gum, $[\alpha]_D^{20}$ -109 (*c* 0.18, $CHCl_3$). Its molecular formula was assigned as $C_{15}H_{18}O_5$ on the basis of the HREIMS (*m/z* = 278.1137 $[M]^+$), which could be supported by ^{13}C-NMR and DEPT experiments (3×CH_3, 2×CH_2, 3×CH and 7×C). The IR spectrum showed the absorption bands for hydroxyl (3360 cm^{-1}), α,β-unsaturated-γ-lactone (1755 cm^{-1}) and double bond (1665cm^{-1}) functions. The ^{1}H- and ^{13}C-NMR spectra of **2** were close to those of **1** (**Tables 1** and **2**), and revealed that they contained the same molecular background carbon skeleton. The careful inspection of the ^{1}H- and ^{13}C-NMR of compounds **2** and **1** suggested that the compound **2** was also eremophilanolide, and the only difference between **2** and **1** was 6β-OH of **2**, because of several chemical shift changes at H-6 (**Table 1**) and C-5, C-6, C-7, Me-14, Me-15 (**Table 2**). Hence, compound **2** was elucidated as 6β, 10α-dihydroxy-1-oxoeremophila-7 (11), 8 (9)-dien-8, 12-olide (**Figure 1**).

Compound **3** was obtained as colorless needle, mp=177-178°C, $[\alpha]_D^{26}$ -87 (*c* 0.17, $CHCl_3$), with molecular formula $C_{15}H_{18}O_4$ deduced from the HRESIMS (*m/z*=263.1277 $[M+H]^+$), ^{13}C-NMR and DEPT spectra (**Table 2**). Its IR spectrum showed the absorptions for hydroxyl (3446 cm^{-1}), ketone carbonyl (1717 cm^{-1}) functions and α,β-unsaturated-γ-lactone (1772 cm^{-1}) and double bond (1647 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra of **3** (**Tables 1** and **2**) were very similar with those of **1**, and revealed that they contained the same molecular background. The intensive inspection of the data of ^{1}H- and ^{13}C-NMR of compounds **3** and **1** indicated the 6α-hydroxyl group in **1** was disappear in **3,** an oxygen-bearing methine (CH-OH: δ_H 4.50, s, δ_C 68.62) in **1** changed into a methylene group (6-CH_2: δ_H 2.53, d, δ_H 2.75, d, and δ_C 30.47) in **3**. Consequently, the molecular structure of compound **3** could be elucidated as 10α-hydroxy-1-oxoeremophila-7 (11), 8 (9)-diene-8, 12-olide.

Acknowledgments

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