Chinese Chemical Letters Vol. 16, No. 11, pp 1477-1480, 2005
http://www.imm.ac.cn/journal/ccl.html

A Novel Dimeric Eremophilane from *Ligularia virgaurea* spp. *oligocephala*

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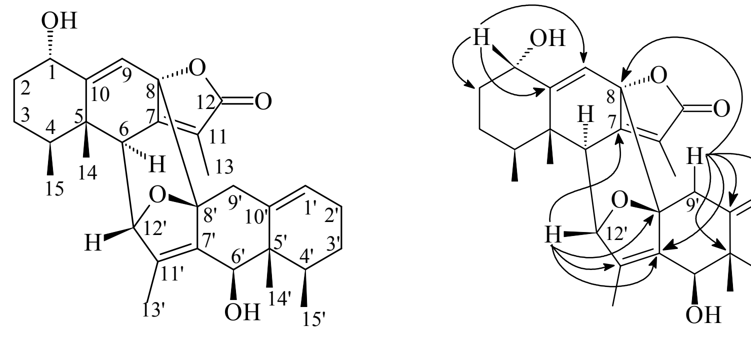
Abstract: A novel dimeric eremophilane, ligulolide B, was isolated from the alcoholic extract of the whole plant of *Ligularia virgaurea* spp. *oligocephala*. The structure was elucidated by various spectroscopic methods including intensive 2D NMR techniques (^{1}H-^{1}H COSY, gHMQC, gHMBC and ^{1}H-^{1}H NOESY) and HR-ESI-MS.

Keywords: *Ligularia virgaurea* spp. *oligocephala*, sesquiterpene, dimeric eremophilane.

Ligularia virgaurea spp. *oligocephala* has long been used as a traditional folk medicine for the treatment of stomachache and nausea [1]. We invested the whole plant of this species and found a novel dimeric eremophilane sesquiterpene. In this paper, we describe the isolation and structural elucidation of compound **1**.

Figure 1 The structure and significant gHMBC correlations of compound **1**



Compound **1** was obtained as colorless gum, $[\alpha]_D^{17}$ -15 (*c* 1.49, CH_2Cl_2). Its HR-ESI-MS provided a *quasi*-molecular ion peak $[M+NH_4]^+$ at *m/z* 496.3048 (calcd. 496.3057), suggesting the molecular formula as $C_{30}H_{38}O_5$ and 12 degrees of unsaturation. The IR spectrum showed the absorption bands for hydroxyl (3450 cm^{-1}) and α, β-

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unsaturated-γ-lactone (1740 cm^{-1}), as well as double bond (1702 cm^{-1}). The ^{13}C-NMR spectrum (**Table 1**) displayed 30 carbons including six methyls, five methylenes, eight methines and eleven quaternary carbons, assigned by DEPT experiment. In the upfield region of NMR spectrum, there were six methyl signals: δ_H 1.70 (*s*, 3H), 1.80 (*d*, 3H, *J*=2.0 Hz) and δ_C 7.67, 11.20 (olefinic methyl groups); δ_H 1.00 (*s*, 3H), 0.89 (*s*, 3H) and δ_C 20.13, 14.87; δ_H 0.95 (*d*, 3H, *J*=6.8 Hz), 0.97 (*d*, 3H, *J*=6.8 Hz) and δ_C 14.87, 16.73, which were the typical methyl signals of eremophilane [2-9]. Along with the molecular formula, we known compound **1** was a dimeric eremophilane sesquiterpene. In the downfield region of the NMR spectrum, there were some characteristic signals at δ_C 153.79, 114.03; δ_C 164.00, 116.62; δ_C 127.15, 135.04; δ_C 137.69, 135.93 and δ_H 5.99

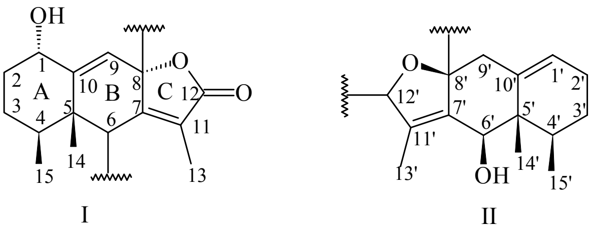
Table 1 NMR spectral data of compound **1** in CDCl$_3$

No	^{1}H NMR^a	^{13}C NMR^b	gCOSY	gHMBC^c	NOESY
1	4.15 (m)	69.29 d	2, 3	2, 9, 10	14
2	2.05 (m) 2.07 (m)	35.90 t	1, 3		
3	1.68 (m) 1.60 (m)	29.01 t	1, 2	4	
4	2.10 (m)	35.48 d	15	5, 14, 15	
5		47.59 s			
6	2.77 (d, 2.0)	46.28 d	12′	5, 7, 8, 10, 11, 14	1, 13, 14, 15, 12′, 13′
7		164.00 s			
8		85.21 s			
9	5.99 (d, 2.0)	114.03 d		1, 5, 7, 10	
10		153.79 s			
11		116.62 s			
12		174.70 s			
13	1.70 (s)	7.67 q		7, 11, 12	
14	1.00 (s)	20.13 q		4, 5, 6, 10	1, 6, 15
15	0.95 (d, 6.8)	14.87 q	4	3, 4, 5	6, 14, 12′
1′	5.70 (t, 3.0)	127.15 d	2′	2′, 3′, 5′	
2′	2.02 (m) 1.99 (m)	22.79 t	1′		
3′	1.23 (m) 1.50 (m)	27.08 t		1′, 2′, 4′, 5′, 15′	
4′	1.90 (m)	33.42 d	15′	2′, 3′, 5′, 15′	6′
5′		44.24 s			
6′	4.12 (d, 2.4)	77.24 d			4′
7′		137.69 s			
8′		88.64 s			
9′	2.55 (d, 14.0) 2.38 (d, 14.0)	37.13 t		8, 1′, 5′, 7′, 8′, 10′	
10′		135.04 s			
11′		135.93 s			
12′	4.60 (d, 2.0)	83.74 d	6, 13′	7, 7′, 8′, 11′	6, 15
13′	1.80 (d, 2.4)	11.20 q	12′	7′, 11′, 12′	
14′	0.89 (s)	14.87 q		4′, 5′, 6′, 10′	15′
15′	0.97 (d, 6.8)	16.73 q	4′	3′, 4′, 5′	14′

[a] recorded at 400.16 MHz, [b] recorded at 100.63 MHz, multiplicity deduced by HMQC, [c] protons showing long-range correlation with indicated carbon, δ in ppm and TMS as the intensive standard.

(*d*, 1H, J=2.0 Hz) and δ_H 5.70 (*t*, 1H, J=3.0 Hz) ascribed to four double bond functions, and δ_C 174.70 to a carbonyl group, indicating an α,β-unsaturated-γ-lactone, along with δ_C 69.29 and δ_H 4.15 (*m*, 1H); δ_C 77.24 and δ_H 4.12 (*d*, 1H, J=2.4 Hz) and δ_C 83.74 and δ_H 4.60 (*d*, 1H, J=2.0 Hz) due to oxymethines, addition to δ_C 85.21, 88.64 for two oxygen-bonded quaternary carbons. Taking into account the twelve degrees of unsaturation, compound **1** was a heptacyclic structure with an ester carbonyl carbon, four double bonds and two hydroxyl groups. Extensive analysis of gHMBC data (**Table 1**) led to two substructures (I & II, **Figure 2**). Substructure I was assembled on the basis of gHMBC correlations (H-1/C-2, 9, 10, H-4/C-5, 14, 15, H-6/C-5, 7, 8, 10, 11, 14, H-9/C-1, 5, 7, 10, H-13/C-7, 11, 12, H-14/C-4, 5, 6, 10 and H-15/C-3, 4, 5). Substructure II was also deduced on the basis of gHMBC correlations (H-1′/C-2′, 3′, 5′, H-3′/C-1′, 2′, 4′, 5′, 15′, H-4′/C-2′, 3′, 5′, 15′, H-9′/C-1′, 5′, 7′, 8′, 10′, H-12′/C-7′, 8′, 11′, H-13′/C-7′, 11′, 12′, H-14′/C-4′, 5′, 6′, 10′ and H-15′/C-3′, 4′, 5′). The two substructures could be assembled into a structure (**Figure 1**) by key gHMBC correlations between H-9′ with C-8 and H-12′ with C-7 as well as gCOSY cross peak between H-6 with H-12′.

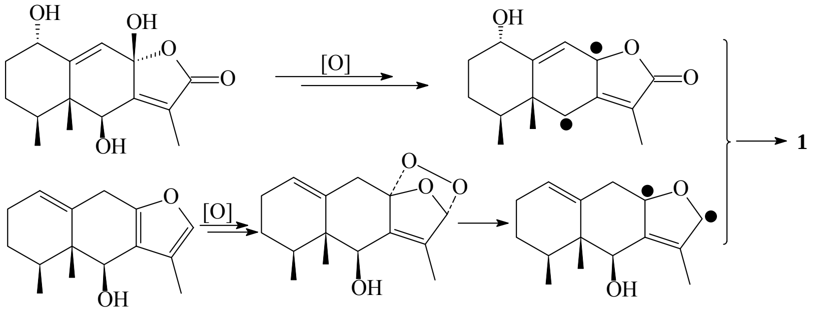
Figure 2 Substructures from two-dimensional NMR for **1**



The relative stereochemistry of the ring system in **1** could be determined on the basis of key NOESY correlations. H_3-14 correlated with H-1 and H_3-15. If CH_3-14 and CH_3-15 were appointed to β-orientation, the OH-1 was α-configuration. Although H-6 correlated with H_3-14 and H_3-15, H-6 was as a α-orientated for H-6 as equatorial bond in the stereostructure [6]. H_3-14′ with H_3-15′ and H-4′ with H-6′ indicated the CH_3-14′, CH_3-15′ and 6′-OH have the identical orientation. H-6 correlated with H-12′ and the smaller couple constant of $J_{6,12'}$ = 2.0 Hz in ^{1}H-NMR showed that the dihedral angle between H-6 and H-12′ was almost 90°. From the literature [3,7], in the A/B ring *trans*-series, the methyl singlet (H_3-14′) was upfield from the methyl doublet (H_3-15′), vice versa, the A/B *cis*-series the methyl doublet (H_3-15) upfield, together with the identical relative configuration by comparing to known compounds 6β, 8α-dihydroxy-1-oxoeremophila-7(11), 9(10)-dien-12,8-olide [2] and toluccanolide A, B and C [4,8], which have been obtained from this plants, we concluded that 8-OR was α-configuration and 8′-OR was β-configuration. Hence, compound **1** was elucidated as the **Figure 1**, and named ligulolide B after the genus *Ligularia*.

A plausible biosynthetic pathway was showed in **Figure 3**. The route of which was previously discussed in the case of eremophilanes [3,9].

Figure 3 Possible biosynthetic pathway to **1**



Acknowledgments

This work was supported by the Foundation for the "Bairen Jihua" of Chinese Academy of Sciences (CAS) in 2000 and the National Natural Science Foundation of China (NNSFC 20021001, 20372029, 20475057).

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Received 31 January, 2005