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Journal of Asian Natural Products Research

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713454007>

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To cite this Article Fei, Dong-Qing , Han, Yi-Feng , Wu, Gang and Gao, Kun(2006) 'Two new eremophilanolides from *Ligularia lapathifolia*', Journal of Asian Natural Products Research, 8: 1, 99 – 103

To link to this Article: DOI: 10.1080/10286020500480233

URL: <http://dx.doi.org/10.1080/10286020500480233>

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Two new eremophilanolides from *Ligularia lapathifolia*

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(Received 30 May 2005; revised 10 October 2005; in final form 19 October 2005)

From the roots of *Ligularia lapathifolia* two new eremophilane-type sesquiterpenes have been isolated. Their structures were established as 3 β -angeloyloxy-8 β -hydroxy-6 α ,15 β -epoxy-eremophil-7(11)-en-12,8 α -olide (**1**) and 8 β H-eremophil-3,7(11)-dien-12,8 α (15,6 α)-diolide (**2**) by spectroscopic methods including 2D NMR experiments.

Keywords: *Ligularia lapathifolia*; Compositae; Eremophilanolide; Sesquiterpene

1. Introduction

The genus *Ligularia* (Compositae; tribe: senecionean) consists of more than 110 species occurring in China, of which about 27 species have been used as traditional or folk Chinese herbs [1,2]. *Ligularia lapathifolia* (Franch.) Hand.-Mazz. is mainly distributed in the southwest of China and its roots have been used to treat coughs and inflammation [2]. A previous phytochemical investigation of the roots and rhizomes of *L. lapathifolia* collected in Lijiang Prefecture of Yunnan Province, China resulted in the isolation of several eremophilane-type sesquiterpenes [3,4]. In order to compare the influence of different ecological environments on the chemical constituents of plants, we studied the dried roots of *L. lapathifolia* collected at high elevation place (altitude: 3600 m) in Muli county, Sichuan Province, China. Two new eremophilane-type sesquiterpene lactones 3 β -angeloyloxy-8 β -hydroxy-6 α ,15 β -epoxy-eremophil-7(11)-en-12,8 α -olide (**1**) and 8 β H-eremophil-3,7(11)-dien-12,8 α (15,6 α)-diolide (**2**) were isolated from this species. The new compounds were characterised by detailed spectroscopic analysis (NMR, MS, UV and IR) and comparison of their spectral data with the reported values in literatures.

2. Results and discussion

Compound **1** was obtained as colourless plates. Its molecular formula was established as C₂₀H₂₆O₆ on the basis of HRESI-MS at m/z 380.2071 [M + NH₄]⁺ and the degree of

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Table 1. ^1H NMR and ^{13}C NMR data of compounds **1** and **2** (300 MHz).

Position	1		2	
	δ_{H} (α/β)	δ_{C} (DEPT)	δ_{H} (α/β)	δ_{C} (DEPT)
1	1.46 m/2.17 m	21.1 (CH ₂)	1.74 m/2.04 m	21.8 (CH ₂)
2	1.61 m/1.82 m	25.6 (CH ₂)	2.23 m/2.33 m	22.0 (CH ₂)
3	5.26 ddd (3.0,3.0,3.0)	66.4 (CH)	6.85 dd (3.0, 3.0)	136.9 (CH)
4	2.01 m	40.6 (CH)	–	129.6 (C)
5	–	44.3 (C)	–	44.0 (C)
6	4.55 q (1.8)	83.3 (CH)	5.14 q (1.8)	81.8 (CH)
7	–	157.9 (C)	–	155.9 (C)
8	–	104.1 (C)	4.68 dd (9.3, 4.2)	77.4 (CH)
9	1.76 m/2.17 m	36.4 (CH ₂)	1.08 m/2.23 m	33.0 (CH ₂)
10	2.32 m	35.0 (CH)	2.15 m	33.6 (CH)
11	–	125.6 (C)	–	125.4 (C)
12	–	172.4 (C)	–	173.4 (C)
13	1.95 d (1.8)	8.3 (CH ₃)	2.00 d (1.8)	9.4 (CH ₃)
14	1.37 s	21.8 (CH ₃)	1.42 s	27.0 (CH ₃)
15	3.69 m/3.92 m	66.6 (CH ₂)	–	168.3 (C)
OAng				
1'		167.3 (C)		
2'		127.3 (C)		
3'	6.11 qq (7.2,1.5)	139.4 (CH)		
4'	1.91 dq (7.2,1.5)	15.7 (CH ₃)		
5'	1.99 dq (1.5,1.5)	20.8 (CH ₃)		

Measured in CDCl₃, all values are in ppm, coupling constant in Hz.

unsaturation was 8. The IR spectrum showed absorptions at 1758, 1714 and 1647 cm⁻¹ for two α,β -unsaturated esters and 3360 cm⁻¹ for a hydroxyl group. In its ^1H NMR, ^{13}C NMR and DEPT spectra, there were signals for an angeloyloxy group (table 1). This was supported by the fragment ion peak at m/z 262 [M–AngOH]⁺ in its EI–MS. In addition to five carbons of the angeloyloxy moiety, there were 15 carbon signals in the ^{13}C NMR and DEPT spectra (table 1), including two methyls, four methylenes, four methenyls and five quaternary carbons. An ester carbonyl signal at δ 172.4 (C) and two olefinic carbon signals at δ 157.9 (C) and 125.6 (C) indicated the presence of an α,β -unsaturated γ -lactone [5]. The signal at δ 104.1 (C) implied the presence of a hemiacetal moiety. This information showed that **1** should be an 8-hydroxy-eremophil-7(11)-en-12,8-olide (figure 1) [5]. Except for the 7 degrees of unsaturation from eremophilinolide skeleton and one angeloyloxy, this compound should have another ring. The two carbon signals at δ 83.3 (CH) and 66.6 (CH₂) seem to be due to an epoxide, and the former (δ 83.3) should be an oxygen-bearing methine

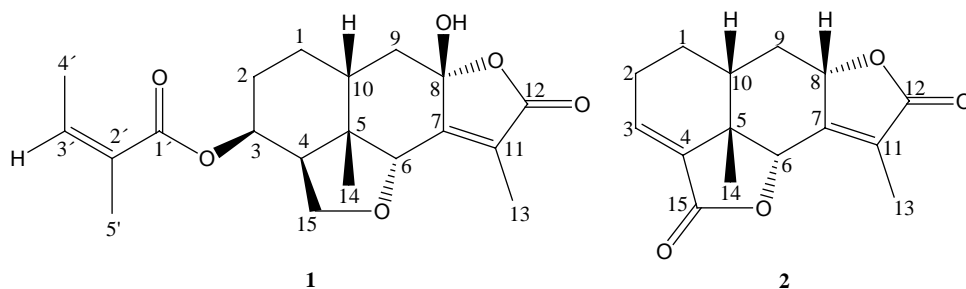


Figure 1. Chemical structures of the new eremophilinolides (**1** and **2**).

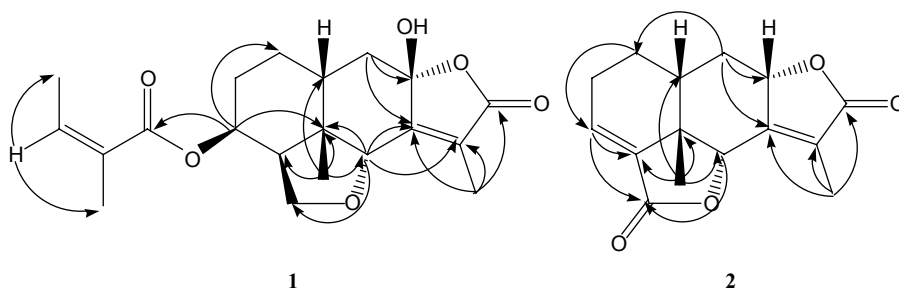


Figure 2. The important HMBC correlations of **1** and **2**.

bonded with an olefinic carbon, showing the presence of 6,15-epoxy. This was confirmed by the correlations in the HMBC spectrum (figure 2) and the HMBC correlation also exhibited that the angeloyloxy was at the C-3. So the planar structure of compound **1** was determined as 3-angeloyloxy-8-hydroxy-6,15-epoxy-eremophil-7(11)-en-12,8-olide.

Stereochemically, C-14 and C-15 were in β -orientations [6]. The rings A/B *cis* arrangement was determined by the NOE correlation between H₃-14 and H-10 in NOE different spectrum. The stereochemistry of H-3 and H-4 was assigned as α -orientation due to no NOE correlation between H-14 and H-3; H₃-14 and H-4, which was confirmed by the coupling pattern of H-3 α (ddd with $J_{3\alpha,2\alpha} = J_{3\alpha,2\beta} = J_{3\alpha,4\alpha} = 3$ Hz) due to the coupling of H-3 α (equatorial proton) with three vicinal protons (one equatorial and two axial protons) [7]. Because the NOE between H-14 and H-6 was observed, the H-6 must be β -oriented. Due to the presence of homoallylic coupling between H-6 and H₃-13 in the ¹H NMR, the hydroxyl group at C-8 position must be β -oriented [8]. Therefore, the structure was established as depicted in the formula **1**.

Compound **2** was also obtained as colourless plates, and the molecular formula C₁₅H₁₆O₄ was deduced by the [M + H]⁺ peak at *m/z* 261.1122 in HRESI-MS. The IR spectrum showed the presences of an α,β -unsaturated γ -lactone (1732, 1675 cm⁻¹) and a saturated γ -lactone (1769 cm⁻¹). The ¹H NMR, ¹³C NMR and DEPT spectra (table 1) indicated that **2** contained two methyls, three methylenes, four methenyls (one double bond CH and two CH bonded with acyloxys) and six quaternary carbons (two ester carbonyls and three double bond carbons). The information mentioned above and biogenetic considerations suggested that **2** was an eremophilane sesquiterpene lactone and its structure was similar to that of the rings A/B *cis*-fused 8 β H-eremophil-7(11)-en-12,8 α (15 β ,6 α)-diolide [5,8] except for the presence of an additional double bond between C-3 and C-4 in **2**. This was further confirmed by downfield shifted signals of H-3 at δ 6.86, C-3 at δ 136.9 and C-4 at δ 129.6. In combination with the NOE different spectrum and HMBC spectrum, the structure of **2** was determined as 8 β H-eremophil-3,7(11)-dien-12, 8 α (15,6 α)-diolide.

3. Experimental

3.1 General experimental procedures

Melting points were determined on a Kofler hot-stage instrument and are uncorrected. Optical rotations were recorded on a Perkin-Elmer model 341 polarimeter. IR spectra

were taken on a Nicolet NEXUS 670 FT-IR spectrometer. UV spectra were obtained on a UV-VIS spectrometer Tu-1901. NMR spectra were recorded on a Varian Mercury-300BB NMR instrument (^1H NMR spectra at 300 MHz and ^{13}C NMR at 75 MHz) with TMS as the internal standard and CDCl_3 as solvent. EI-MS were measured on a VG ZAB-HS MS instrument at 70 eV and the positive HRESI-MS was carried out on a Bruker APEX II. Silica gel (200–300 mesh) used for column chromatography (CC) and silica GF_{254} (10–40 μ) for TLC were supplied by the Qingdao Marine Chemical factory, Qingdao, P.R. China. TLC plates were detected at 254 nm or by heating after being sprayed with 5% H_2SO_4 in $\text{C}_2\text{H}_5\text{OH}$ (v/v).

3.2 Plant material

The roots of *Ligularia lapathifolia* were collected in August 2003 from Muli county of Sichuan Province, P.R. China, and identified by Professor Guo-Liang Zhang, Department of Biology, Lanzhou University. A voucher specimen has been deposited in the College of Chemistry and Chemical Engineering, Lanzhou University.

3.3 Extraction and isolation

The dried and powdered roots of *L. lapathifolia* (3.6 kg) were extracted with petroleum ether/ Et_2O /acetone (1:1:1) three times (7 days/time) at room temperature. The combined extracts were evaporated to dryness (270 g) under reduced pressure. The residue was separated by column chromatography over 1500 g silica gel (200–300 mesh) with a gradient of petroleum/acetone (50:1–0:1). Seven fractions were collected. The second fraction (petrol/acetone, 20:1) was isolated by repeated column chromatography on silica gel with petrol/ethyl acetate (3:1) yielding **1** (20 mg). The fourth fraction (petrol/acetone, 5:1) was isolated by repeated column chromatography on silica gel with chloroform/acetone (6:1) yielding **2** (10 mg).

3.3.1 Compound 1. Colourless plates, mp 167–169°C, $[\alpha]_D^{20} + 111.0$ (*c* 0.95, CH_3OH), UV λ_{max} (CH_3OH) nm (log ϵ): 238 (2.66). IR (KBr) ν_{max} (cm^{-1}): 3360, 1758, 1714, 1647, 1449, 1233 1139. HRESI-MS m/z 380.2071 $[\text{M} + \text{NH}_4]^+$ (calcd for $[\text{C}_{20}\text{H}_{26}\text{O}_6 + \text{NH}_4]^+$, 380.2068). EI-MS m/z : 344, 262, 247, 244, 229, 83, 55. ^1H NMR and ^{13}C NMR data: see table 1.

3.3.2 Compound 2. Colourless plates, mp 230–231°C, $[\alpha]_D^{20} + 28.0$ (*c* 0.20, CHCl_3), UV λ_{max} (CH_3OH) nm (log ϵ): 238 (2.65). IR (KBr) ν_{max} (cm^{-1}): 1769, 1739, 1679, 1445, 1258, 1148. HRESI-MS m/z : 261.1122 $[\text{M} + \text{H}]^+$ (calcd for $[\text{C}_{15}\text{H}_{16}\text{O}_4 + \text{H}]^+$, 261.1121). EI-MS m/z : 260, 231, 163, 84. ^1H NMR and ^{13}C NMR data: see table 1.

Acknowledgements

This work was supported by the NSFC (No. 20372029 and No. 20021001) and by the Key Project of Chinese Ministry of Education (No. 104178).

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