Phytochemistry 72 (2011) 514–517

Contents lists available at ScienceDirect

Phytochemistry

journal homepage: www.elsevier.com/locate/phytochem

Eremophilane-type sesquiterpene lactones from *Ligularia hodgsonii* Hook

Hong-Li Huang [1], Yang-Jun Xu [1], Hong-Li Liu, Xiao-Qing Liu, Ji-Ning Shang, Guang-Tian Han, Ming-Jun Yao, Cheng-Shan Yuan *

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, PR China

ARTICLE INFO

Article history:
Received 24 January 2010
Received in revised form 3 September 2010

Keywords:
Ligularia hodgsonii Hook.
Compositae
Eremophilane sesquiterpene lactone
Biliguhodgsonolide
(4*S*,5*S*,6*R*,10*R*)-8,9-*seco*-12-hydroxyeremophil-7 (11)-en-14,6;12,8-diolid-9-al

ABSTRACT

A dimeric eremophilane sesquiterpene lactone with a cyclobutane ring, biliguhodgsonolide (**1**) and an uncommon seco-sesquiterpene derivative, (4*S*,5*S*,6*R*,10*R*)-8,9-*seco*-12-hydroxyeremophil-7(11)-en-14,6;12,8-diolid-9-al (**2**), were isolated from the roots and rhizomes of *Ligularia hodgsonii* Hook. Their structures, including the absolute stereochemistry, were elucidated by spectroscopic data and CD analysis. The cyclobutane ring was confirmed by single-crystal X-ray diffraction.

1. Introduction

Plant species in the Compositae are well-known for their structurally diverse sesquiterpenoids (Kim et al., 2002; Macías et al., 1998; Wu et al., 2006). Within this family, the genus *Ligularia* contains more than 110 species in China (Delectis Florae Reipublicae Popularis Sinicae Agendae Academiae Sinicae Edita, 1989). The roots of *L. hodgsonii* Hook., used as a traditional herbal medicine, have antibiotic, antiphlogistic and antitumor properties (Xu et al., 2006). In prior reports, sesquiterpenes (Ishizaki et al., 1974, 1979; Liao et al., 2002; Xu et al., 2006, 2009) and pyrrolizidine alkaloids (Lin et al., 2000) were isolated from *L. hodgsonii*. We investigated the EtOH extract of roots and rhizomes of *L. hodgsonii* and obtained two new eremophilane-type sesquiterpenes. Here we describe the isolation and structure elucidation of **1** and **2** (Fig. 1).

2. Results and discussion

Biliguhodgsonolide (**1**) was isolated as colorless needles. Its molecular formula ($C_{30}H_{32}O_8$) was determined by HRESIMS (Fig. S1, Supplementary material). The IR (Fig. S3, Supplementary material) absorption at 1780 cm^{-1} implied the presence of ester carbonyl functionality. From the ^1H and ^{13}C NMR spectra (Table 1, Figs. S4 and S5, Supplementary material), the number of signals observed was half of that expected, suggesting that **1** had a symmetrical structure and should consist of two identical units. The ^{13}C NMR spectrum displayed 15 carbons, including two methyls, three methylenes, four methines, and six non-protonated carbons, assigned by DEPT experiment (Fig. S5, Supplementary material). Among them, two carbonyls (δ_C 170.3 and 174.3) corresponding to two lactone groups, and resonances for two olefinic carbons at δ_C 150.8 and 131.0 were observed. Considering the two typical Me signals at δ_H 1.99 (d, $J = 1.5$ Hz) and 1.36 (s), and an oxygenated CH proton resonance at 5.30 (d, $J = 1.5$ Hz), the unit was deduced to be an eremophilanolide, specifically an eremophil-7(11)-en-14,6;12,8-diolide (Moriyama and Takahashi, 1976; Zhao et al., 1995).

The NMR spectrum of **1** was somewhat similar to that of eremophil-7(11)-en-14β,6α;12,8α-diolide (Moriyama and Takahashi, 1976; Zhao et al., 1995), except for the presence of a quaternary carbon and a methine in **1** instead of the corresponding methine and methylene in the latter compound at C-8 and C-9, respectively. Furthermore, the HMBC correlation (Fig. 2 and Fig. S6, Supplementary material) observed from H-9 to C-9′ and the absence of an HMBC correlation for H-8 to C8′ indicated a symmetrical dimer containing two identical units linked at the C-8 and C-9 positions. The relative stereochemistry of **1** was inferred from coupling constants, NOESY correlations (Fig. 3 and Fig. S8, Supplementary material), and molecular modeling. The ^1H NMR spectrum of **1** (Fig. S4, Supplementary material) showed the presence of homoallylic coupling between H-6 [δ_H 5.30 (d, $J = 1.5$ Hz) with H_3-13 [δ_H 1.99 (d, $J = 1.5$ Hz)] (Moriyama and Takahashi, 1976). The large coupling constant observed for H-9 [δ_H 2.17 (1H, d, $J = 8.4$ Hz)] with H-10 [δ_H 2.58 (1H, dd, $J = 8.4, 5.7$ Hz)], indicated that H-9 and H-10 have a trans stereochemical relationship. The NOESY correlations of

---

* Corresponding author. Tel.: +86 0931 8912500; fax: +86 0931 8915557.
E-mail address: yuancs@lzu.edu.cn (C.-S. Yuan).

[1] These authors contributed equally to this work.

0031-9422/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2011.01.008

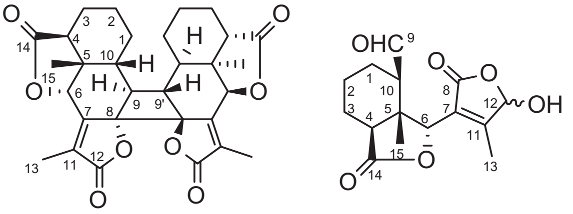

Fig. 1. Structures of compounds **1** and **2**.

Table 1
^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectroscopic data of **1** (in CDCl$_3$) and **2** (in DMSO-d$_6$).

No.	1		2	
	δ_H (*J*, Hz)	δ_C	δ_H (*J*, Hz)	δ_C
1(1′)	1.46 m, 1.92 m	23.9	1.36 m, 1.89 m	21.4
2(2′)	1.23 m, 1.82 m	20.8	1.43 m, 1.85 m	24.8
3(3′)	1.30 m, 1.88 m	18.9	1.28 m, 1.76 m	19.3
4(4′)	1.86 m	41.7	3.09 dd (8.7, 3.0)	47.0/47.4
5(5′)		45.3		44.0/44.2
6(6′)	5.30 d (1.5)	82.1	5.39 s/5.43 s	81.8
7(7′)		150.8		123.0/123.4
8(8′)		92.2		170.4/170.5
9(9′)	2.17 d (8.4)	47.8	9.39 s/9.40 s	203.6/203.7
10(10′)	2.58 dd (8.4, 5.7)	41.8	2.39 m	53.5/53.6
11(11′)		131.0		167.1
12(12′)		170.3	5.90 d (9.3)/5.88 d (8.7)	99.2/99.3
13(13′)	1.99 d (1.5)	10.4	2.00 s	12.7/12.9
14(14′)		174.3		176.4
15(15′)	1.36 s	20.1	1.07 s	16.6/16.7
OH			7.75 d (9.3)/7.86 d (8.7)	

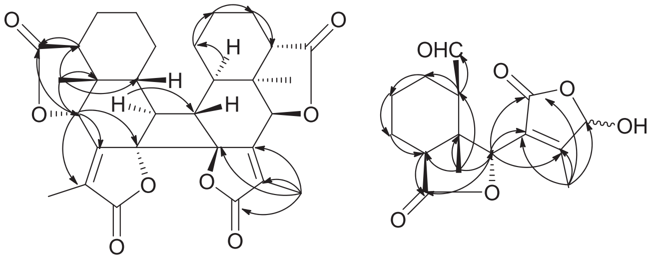

Fig. 2. Key HMBC correlations (H → C) of **1** and **2**.

H$_3$-15/H-6 and H-10, and H-9/H-4, indicated that H-6, H-10 and H$_3$-15 protruded on one side of the molecule, and H-4, H-9, and the α,β-unsaturated γ-lactone ring were on the other side of the molecule.

To confirm the structure, **1** was crystallized for X-ray crystallographic analysis, which (Fig. 4) showed that **1** was an eremophil-7(11)-en-14,6;12,8-diolide derivative. The atomic distances, 1.567 Å and 1.574 Å, between C8-C8′ and C9-C9′, respectively, which are very close to the average bond length of C–C single bond (1.54 Å), indicating the formation of the dimer with a 1,2,3,4-tetra-substituted cyclobutane ring. Consequently, the structure of **1** was confirmed.

The absolute configuration of **1** was determined by analysis of the CD spectrum (Fig. S9, Supplementary material). According to the sector rule of Jennings et al. for the saturational γ-lactone (Jennings et al., 1965), the positive Cotton effect, $[\theta]_{216}$ = +209,612 deg cm^2/dmol, indicated that the methyl group at C-5 falls to a positive sector, the absolute configuration at C-5 was assigned to *S*. The positive Cotton effect, $[\theta]_{252}$ = +62,090 deg cm^2/dmol (O(3)═C(12)–C(11)═C(7), −177.6(4)°), and $[\theta]_{224}$ = +251,036 deg cm^2/dmol (O(4)–C(8)–C(7)═C(11), 6.1(4)°), indicated that the absolute configuration at C-8 was assigned to *S* (Beecham, 1972). Those at C-4, C-6, C-9, C-10, C-4′, C-5′, C-6′, C-8′, C-9′, C-10′ were fixed to be *S*, *R*, *S*, *R*, *S*, *S*, *R*, *S*, *S*, and *R*, respectively. Thus, the structure of **1** was assigned and named biliguhodgsonolide.

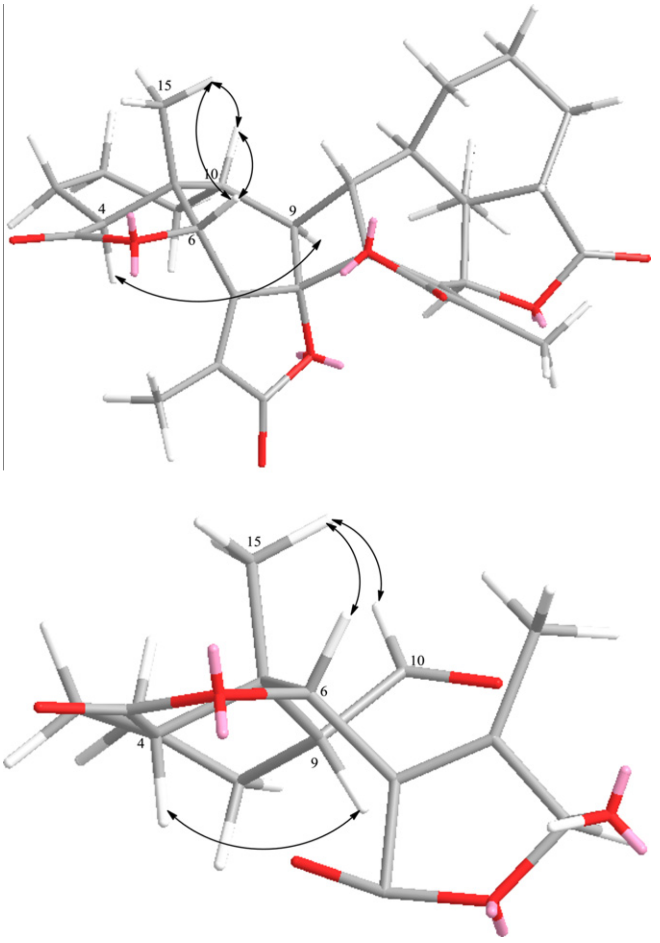

Fig. 3. Selected NOESY correlations (H ↔ H) of **1** and Selected NOE correlations (H ↔ H) of **2**.

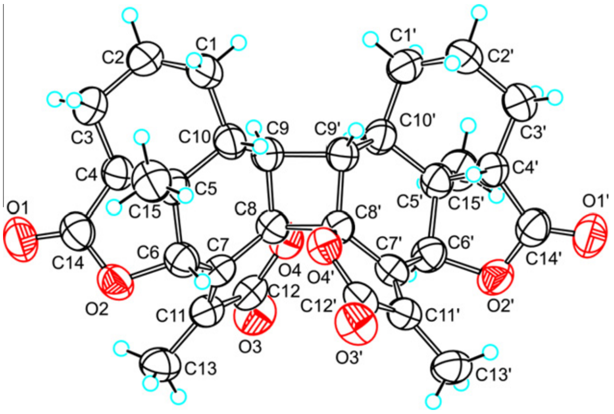

Fig. 4. X-ray crystal structure of **1**.

Compound **2**, a colorless amorphous powder, has the molecular formula C$_{15}$H$_{18}$O$_6$. Its IR spectrum (Fig. S12, Supplementary material) suggested the presence of an hydroxyl group (3315 cm^{-1}) and