Two Eudesmane Sesquiterpenes from *Laggera pterodonta*

By: Y.-B. Liu, W. Jia, W.-Y. Gao, A.-H. Zhao, Y.-W. Zhang, Y. Takaishi, and H.-Q. Duan

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Abstract:

The phytochemical study of the aerial parts of *Laggera pterodonta* afforded two new eudesmane sesquiterpenes, 3α,4β,11-trihydroxyenantioeudesmane (pterodontriol E) (**1**) and 4β,8β,11-trihydroxyenantioeudesmane (pterodontriol F) (**2**), along with seven known compounds. Their structures were elucidated on the basis of spectroscopic data.

Article:

INTRODUCTION

Laggera pterodonta (DC.) Benth is widely distributed in southwestern China, mainly in Yunnan province. The aerial part of *L. pterodonta* has been used as folk medicine dating from ancient times. Pharmacological research indicated that extract of *L. pterodonta* has anti-leukaemia, anti-bacterial, anti-inflammatory and anti-malarial activities [1-3]. Many eudesmane sesquiterpenes and related glucosides, as well as flavonoids, have been reported from *L. pterodonta* [3-13]. In our search for pharmacologically active compounds from crude drugs of plant origin, the chemical constituents of *L. pterodonta* were studied. This paper deals with the isolation and structural elucidation of two new and seven known compounds (**1**–**9**) from the aerial parts of *L. pterodonta*.

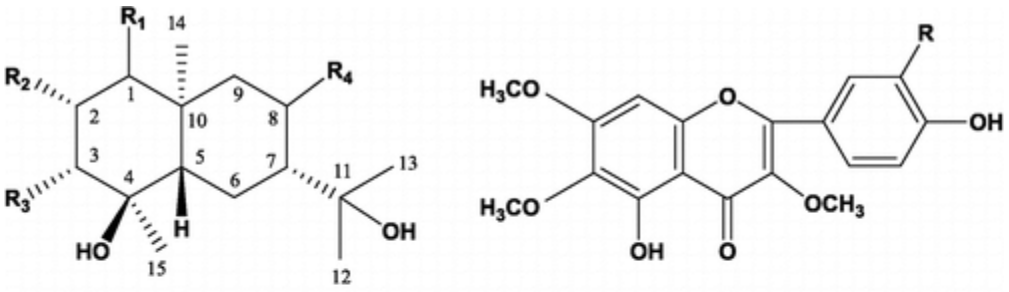
RESULTS AND DISCUSSION

The ethyl acetate-soluble fraction from *Lagger pterodonta* was separated by repeated silica-gel column chromatography, HPLC and gel permeation chromatography (GPC), to give two new sesquiterpenes, named pterodontriol E (**1**) and pterodontriol F (**2**), as well as seven known compounds (**3**–**9**).

Pterodontriol E (**1**) was obtained as an amorphous powder, exhibiting a molecular ion peak at *m/z* 279.1939 $[M+ Na]^+$ (HR FTMS), indicating a molecular formula of $C_{15}H_{28}O_3$ for 1. The IR spectrum showed the presence of hydroxyl group (3321 cm^{-1}). The ^1H NMR spectral data of 1 revealed the presence of four methyl groups [δ_H 1.29, 1.28, 1.05, and 0.91 (each 3H, s)] and one oxygenated methine proton signal [δ_H 3.45 (1H, dd, J = 4.5, 11.9 Hz)]. Its ^{13}C NMR spectral data showed 15 carbons, including four methyls, five methylenes, one oxygenated methine, two oxygenated quaternary carbons and other three carbon signals. Based on the above facts,

compound **1** was proposed to be a eudesmane sesquiterpene, the same as pterodontriols A–D isolated from the same plant [3-5]. The ^{13}C NMR spectral data of **1** were similar to those of pterodondiol [5], except for C–2 and C–3. In the HMBC spectrum of **1**, the proton signal at δ_H 0.91 (H-14) was correlated with the carbon signals at δ_C 47.2 (C-5), 41.3 (C-9), 39.7 (C-1) and 34.3 (C-10), the signal at δ_H 1.05 (H-15) was correlated with the signals at δ_C 79.9 (C-3), 76.5 (C-4), and 47.2 (C-5), while the signal at δ_H 3.45 (H-3) was correlated with the signals at δ_C 76.5 (C-4), 27.5 (C-2), and 15.7 (C-15). Therefore, the hydroxyl group was located at the C-3 position. Thus, compound **1** should be a 3-hydroxy pterodondiol.

In the NOESY spectrum, the proton signal at δ_H 3.45 (H-3) was correlated with the signals at δ_H 1.68 (H-5) and 1.42 (H-1β); the methyl signal at δ_H 0.91 (H-14) was correlated with the signal at δ_H 1.05 (H-15). Furthermore, the coupling constant of H-3 (J = 4.5, 11.9 Hz) indicated that it has axial orientation. Thus, the relative configurations of two hydroxyl groups were determined as 3α and 4β. According to the literature [3-5,11,12], all the pterodontriols isolated from *L. pterodonta* (including known compounds **3**–**7**, see section 3) have positive $[\alpha]_D$ values and their structures were determined as enantio-eudesmantriol by comparing with $[\alpha]_D$ values to those of eudesmantriols. Therefore, the positive $[\alpha]_D$ value (+78.6) of 1 indicated pterodontriol E (**1**) was apparently also an enantio-eudesmantriol. The structure of pterodontriol E was thus determined as shown in figure 1.



	R_1	R_2	R_3	R_4
1	H	H	OH	H
2	H	H	H	–OH
3	H	OH	H	H
4	–OH	H	H	H
5	H	H	H	–OH
6	oxo	H	H	H
7	H	H	H	H

	R
8	H
9	OCH_3

Figure 1: Structures of compounds **1**–**9**.

Pterodontriol F (**2**) had the molecular formula $C_{15}H_{28}O_3$, the same as **1**. The ^1H NMR spectral data of **2** showed the presence of four methyl groups [δ_H 1.65, 1.58, 1.35, and 0.99 (each3H, s)], and one oxygenated methine proton signal [δ_H 4.66 (1H, ddd, J = 8.1, 8.1, 5.3 Hz)]. Comparing the ^{13}C NMR spectral data of **2** with those of **1**, compound **2** also appeared to be a eudesmane sesquiterpene with three hydroxyl groups (table 1). In the HMBC spectrum of **2**, the methyl proton signal at δ_H 0.99 (H-14) was correlated with the carbon signals at δ_C 49.0 (C-5), 43.4 (C-

1), and 52.6 (C-9), the signal at δ_H 1.81 (H-9a) was correlated with the signals at δ_C 21.2 (C-14), 69.8 (C-8), 47.1 (C-7), while the signal at δ_H 2.66 (H-6a) was correlated with the signals at δ_C 35.4 (C-10) and 69.8 (C-8). In turn, the methine signal at δ_H 4.66 (H-8) was correlated with the signal at δ_C 74.9 (C-11). Thus, the secondary hydroxyl group was located at the C-8 position. In the NOESY spectrum, the methyl proton signal at δ_H 0.99 (H_3-14) was correlated with the signals at δ_H 1.35 (H-15) and 4.66 (H-8). Thus, the two hydroxyl groups have 4β and 8β orientations. Therefore, pterodontriol F (**2**) was determined as 4β,8β,11-trihydroxyenantioeudesmane (figure 1).

Table 1: ^{1}H NMR and ^{13}C NMR spectral data of 1 and 2.

	1 ($CDCl_3$)		***2*(C_5D_5N)**	
No.	**^{13}C**	**^{1}H[a]**	**^{13}C**	**^{1}H[a]**
1	39.7	1.42,1.22 (m)	43.4	1.48,1.27 (m)
2	27.5	1.71,1.51 (m)	21.4	1.69,1.53 (m)
3	79.9	3.45 (dd, 4.5, 11.9)	44.8	1.97,1.71 (m)
4	76.5	–	71.7	–
5	47.2	1.68 (m)	49	2.27 (m)
6	20.4	2.09 (brd, 13.6), 1.49 (m)	21.5	2.68 (dt, 14.2, 4.4), 1.70 (m)
7	41.3	1.67 (m)	47.1	2.30 (m)
8	21.3	1.75,1.65 (m)	69.8	4.66 (ddd, 8.1, 8.1, 5.3)
9	41.3	1.47,1.19 (m)	52.6	2.05, 1.81 (m)
10	34.3	–	35.4	–
11	74.9	–	74.9	–
12	29.6	1.29 (s)	30.2	1.58 (s)
13	30	1.28 (s)	31.9	1.65 (s)
14	18.8	0.91 (s)	21.2	0.99 (s)
15	15.7	1.05 (s)	23.3	1.35 (s)

[a] The chemical shift of proton signals was read by HSQC spectrum.

Several known compounds were identified by their spectroscopic data in comparison with literature values as follows: pterodontriol A (**3**) [5], pterodontriol B (**4**) [5], pterodontriol C (**5**) [3], laggerone A (**6**) [3], pterodondiol (**7**) [5], pendultin (**8**) [13], chrysosptertin (**9**) [13].

EXPERIMENTAL

General experimental procedures

NMR analysis of samples were performed with a Bruker AVANCE 300 instrument (^{1}H 300 MHz, ^{13}C 75 MHz), both with teramethylsilane as an internal standard. HR FTMS data and EIMS data were obtained on Bruker Apex 7.0 Tesla and VG ZAB-HS (70 eV) instruments, respectively. Column chromatography was performed on silica-gel (Qingdao Haiyang Chemical Co. Ltd), Sephadex LH-20 (Amersham Pharmacia Biotech) and Toyopearl HW-40 (TOSOH). HPLC was a JASCO Gulliver Series with PU-1580 (pump), RI-1530 and UV-1575 (detector). Preparative HPLC column was used as follows: ODS (YMC-Pack ODS-A, SH-343-5), GPC (Shodex, Asahipak GS-310, 20 G, MeOH), Si-HPLC (Hibar RT 250-25, Lichrosorb, Si60 7 μm). IR spectra were recorded on a FTS3000 Infrared Fourier Transform sepectrometer (Bio-Rad). Optical rotation was measured with a MC 241 digital polarimeter (Perkin-Elmer).

Plant material

Laggera pterodonta (DC.) Benth was purchased from Kunming, Yunnan province of China in August 2002 and identified by Professor Wen-Yuan Gao. A voucher specimen (D20020818) is deposited at the College of Pharmaceutical Science and Biotechnology, Tianjin University, China.

Extraction and isolation

The dried aerial parts (0.85 kg) of *L. pterodonta* were crushed and extracted three times with EtOH (95%, 10 L each) at 60°C for 6 h. The EtOH extract was concentrated under reduced pressure to give a residue (110 g), which was suspended in H_2O, and then partitioned with petroleum ether, EtOAc and n-BuOH, respectively. The EtOAc layer was concentrated to afford a residue (12 g), which was subjected to column chromatography with silica gel, and was eluted with solvents of increasing polarity [$CHCl_3$/MeOH (95:5, 9:1, 8:2, MeOH)] to yield eight fractions. Fraction 7 (439 mg) was chromatographed on Sephadex LH-20 (MeOH) to give four fractions (fr. 7.1–7.4). Fraction 7.2 (298 mg) was purified by HPLC (ODS, MeOH/H_2O 8:2, and then 7:3) to give **1** (13.8 mg) and **4** (11 mg). Fraction 5 (643 mg) was chromatographed on Toyopearl HW-40 ($CHCl_3$/MeOH, 2:1) to give three fractions (fr. 5.1-5.3). Fraction 5.2 (349 mg) was chromatographed on ODS column (MeOH/H_2O 8:2) to give seven fractions (fr. 5.2.1–5.2.7). Fraction 5.2.4 (22 mg) was purified by HPLC (GPC, MeOH) to give **2** (8.5 mg). Fraction 5.2.3 (35 mg) was separated by Si-HPLC ($CHCl_3$/MeOH, 95:5) to give **5** (4.5 mg) and **6** (4 mg). Fraction 4 (1.5 g) was chromatographed on Sephadex LH-20 (MeOH) to give four fractions (fr .4.1–4.4). Fraction 4.3 was further chromatographed on a silica-gel column [$CHCl_3$/MeOH (95:5, 9:1)] to give three fractions (fr. 4.3.1–4.3.3). Fraction 4.3.2 (346 mg) was separated by HPLC (ODS, MeOH/H_2O 8:2) to give **7** (55 mg). Fraction 8 (513 mg) was chromatographed on LH-20 (MeOH) to give four fractions (fr. 8.1–8.4). Fraction 8.3 (110 mg) was separated by HPLC (ODS, MeOH/H_2O 8:2, and then Si-60, $CHCl_3$/MeOH, 85:15) to give **3** (18.6 mg). Fraction 3 (1.2 g) was chromatographed on silica-gel column [$CHCl_3$/MeOH (99:1, 98:2, 95:5, 9:1)] to give five fractions (fr. 3.1–3.5). Fraction 3.4 (463 mg) was chromatographed on Toyopearl HW-40 ($CHCl_3$–MeOH, 2:1) to give four fractions (fr. 3.4.1–3.4.4). Fraction 3.4.3 (110 mg) was separated by Si-HPLC ($CHCl_3$/MeOH, 97:3) to give **8** (6.7 mg) and **9** (13.6 mg).

Pterodontriol E (**1**) was isolated as an amorphous powder, $[\alpha]_D^{25}$ +78.6 (*c* 1.5, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3321, 2945, 1459, 1406, 1387, 1265, 1220, 1186, 1150, 1089, 1067, 1035, 984, 907, 859. EI-MS: *m/z* 256 $[M]^+$(1), 238 (10), 220 (8), 205 (9), 179 (31), 147 (21), 123 (31), 95 (30), 59 (55), 43 (100), 27 (9). HR-FTMS *m/z* 279.1939 $[M+ Na]^+$ (calcd for $C_{15}H_{28}O_3Na$ 279.1931). ^1H NMR and ^{13}C NMR ($CDCl_3$) data are listed in table 1.

Pterodontriol F (**2**) was isolated as an amorphous powder, $[\alpha]_D^{25}$ +45.2 (*c* 0.8, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3369, 2930, 1459, 1384, 1173, 1101, 1050, 942, 914, 756. EI-MS: *m/z* 256 $[M]^+$(1), 238 (2), 220 (10), 205 (12), 177 (53), 162 (49), 109 (29), 95 (45), 59 (54), 43 (100), 27 (11). HR-FTMS *m/z* 279.1944 $[M+Na]^+$ (calcd for $C_{15}H_{28}O_3Na$ 279.1931). ^1H NMR and ^{13}C NMR (C_5D_5N) data are listed in table 1.

$[\alpha]_D$ values of **3**–**7**: **3**, $[\alpha]_D^{25}$ 22.7 (*c* 0.22, MeOH); **4**, $[\alpha]_D^{25}$ 31.8 (*c* 0.26, MeOH); **5**, $[\alpha]_D^{25}$ 88.6 (*c* 0.7, MeOH); **6**, $[\alpha]_D^{25}$ 42.4 (*c* 0.67, MeOH); **7**, $[\alpha]_D^{25}$ 27.3 (*c* 2.2, $CHCl_3$).

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