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A new elemanolide sesquiterpene lactone from *Elephantopus scaber*

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A new elemanolide sesquiterpene lactone, named elescaberin (**1**), together with two known compounds, namely, isodeoxyelephantopin (**2**) and deoxyelephantopin (**3**), was isolated from the whole plant of *Elephantopus scaber*. The structure of **1** was elucidated on the basis of spectroscopic analysis. All three compounds exhibited significant inhibitory activities against human SMMC-7721 liver cancer cells *in vitro* (IC₅₀ 8.18–14.08 μmol/l).

Keywords: *Elephantopus scaber*; Compositae; sesquiterpene lactone; anticancer; elescaberin

1. Introduction

The whole plant of *Elephantopus scaber* L. (Compositae) is used in Chinese medicine as a diuretic, antifebrile, antiviral, and antibacterial agent as well as for the treatment of hepatitis and bronchitis,¹ and sesquiterpenoids were discovered as antitumor constituents of *E. scaber*.² In our present study, we have further investigated the constituents of *E. scaber* collected from Guangxi Province of China, and obtained a new elemanolide sesquiterpene lactone, elescaberin (**1**), together with two known germacranolides, namely, isodeoxyelephantopin (**2**) and deoxyelephantopin (**3**). All the three compounds exhibited significant inhibitory activities against human SMMC-7721 liver cancer cells *in vitro* (IC₅₀ 8.18, 9.53, and 14.08 μmol/l, respectively). Here, we report the isolation and structure elucidation of **1** (Figure 1).

2. Results and discussion

Elescaberin (**1**) obtained as colourless needles with $[\alpha]_D^{25} + 43$ (*c* 0.004, MeOH), whose

molecular formula, C₂₀H₂₄O₇, was inferred by HR-ESI-MS at *m/z* 377.1595 [M + H]⁺. Its ¹³C NMR and DEPT spectra showed 20 resonance lines, indicating three methyls, three methylenes, seven methines, and seven quaternary carbons. The IR spectrum of **1** showed the absorption bands of a γ-lactone moiety at 1770 cm⁻¹ and two α,β-unsaturated carbonyl moieties at 1714 and 1702 cm⁻¹. Analysis of the overall NMR spectral data revealed the presence of an angelate group.³ The ¹H NMR signals at δ 6.04 (1H, dq, *J* = 7.2, 1.4 Hz), 1.81 (3H, dd, *J* = 7.2, 1.4 Hz), and 1.72 (3H, brs) were assigned as H-18, H-19, and H-20, respectively. The chemical shifts of a carbonyl carbon at δ 166.2, two olefinic carbons at δ 127.2 and 137.2, and two methyl carbons at δ 15.3 and 20.0, respectively, were assigned as C-16, C-17, C-18, C-19, and C-20. And the ion peak at *m/z* 277 [M + H - CH₃ - CH=C(CH₃)-COOH]⁺ in its mass spectrum also supported the presence of an angelate group.

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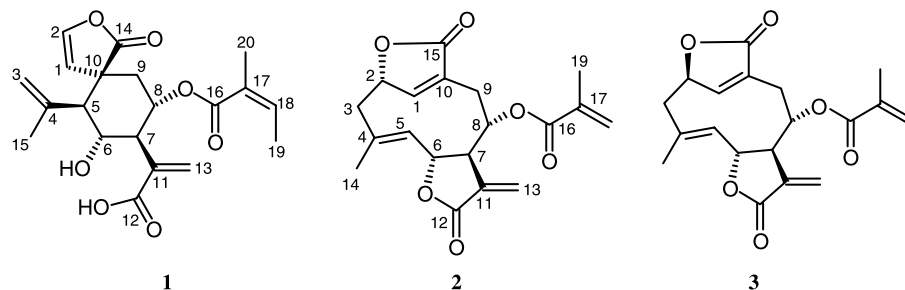


Figure 1. The structures of compounds **1**–**3**.

In ^1H – ^1H COSY spectrum, the methine H-7 at δ 2.88 coupled with two oxygenated methine H-6 at δ 4.22 and H-8 at δ 5.52, respectively. H-6 was also coupled with H-5 at δ 2.39 and the hydroxyl proton at δ 4.71, and H-8 with the methylene H-9 at δ 1.91. These connectivities defined the presence of system **I** (Figure 2). The remaining methines H-1 at δ 5.64 and H-2 at δ 7.05 showed to be correlated with each other and suggested the presence of system **II**. The remaining protons included a methyl H-15 at δ 1.62 and two methylenes H-3 at δ 4.84, 4.70, and H-13 at δ 5.64, 6.23. All the carbon signals were assigned through the HMQC experiment and the above fragments were connected on the basis of HMBC experiment. In the HMBC spectrum, H-2 showed correlations to the ester carbonyl carbon C-14 at δ 179.3 and the quaternary carbon C-10 at δ 51.0, and both H-5 and H-9 correlated with C-14, and H-6 with C-10, which allowed the connection of two fragments **I** and **II** and the presence

of a *spiro*- β,γ -unsaturated- γ -lactone ring (Figure 3). In addition, H-5 correlated with an olefinic methylene carbon C-3 at δ 114.0, a quaternary olefinic carbon C-4 at δ 142.3, and a methyl carbon C-15 at δ 22.9, respectively, and H-15 correlated with C-3 and C-5. H-7 also showed correlations to a quaternary olefinic carbon C-11 at δ 140.8, a carboxyl carbon C-12 at δ 167.8, and an olefinic methylene carbon C-13 at δ 125.0, respectively, and H-13 correlated with C-12 (Figure 3). These observed correlations suggested an elemanolide sesquiterpene lactone skeleton for **1** with an angelate group.^{4–7} The long-range correlation between H-8 and the carbonyl carbon (δ 166.2) of the angelate group revealed that an angelate group was linked at C-8.

In the ^1H NMR spectrum of **1**, H-5 appeared as a well-defined doublet ($J_{5,6} = 11$ Hz). H-6 was shown as a triplet with large coupling constants with H-5 and H-7 ($J_{5,6} = J_{6,7} = 10.8$ Hz). H-7 appeared as

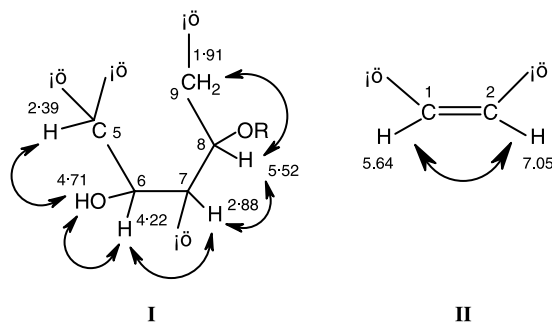


Figure 2. ^1H – ^1H COSY correlations for systems **I** and **II**.

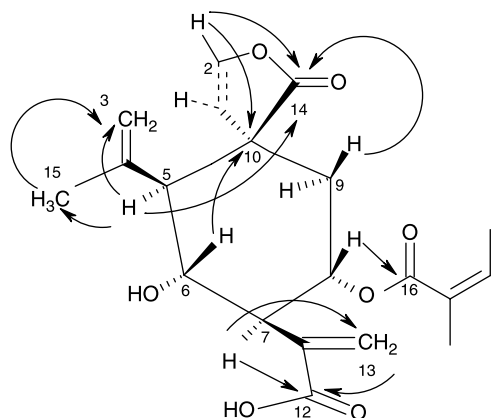


Figure 3. Key HMBC correlations of **1** (H \rightarrow C).

the same triplet coupling with H-6 and H-8 ($J_{6,7} = J_{7,8} = 10.8$ Hz). This implied *trans*-axial relationships between H-5, H-6, H-7, and H-8, i.e. H-5 α , H-6 β , H-7 α , and H-8 β -orientations. These assignments were based on the assumption that H-7 is α -oriented as in all other naturally occurring sesquiterpenoids,⁸ and were also supported by the NOESY correlation between H-7 α and H-5 α (Figure 4). Moreover, in the NOESY spectrum of **1**, the correlations between H-1 and H-5 α and H-9 α were observed.

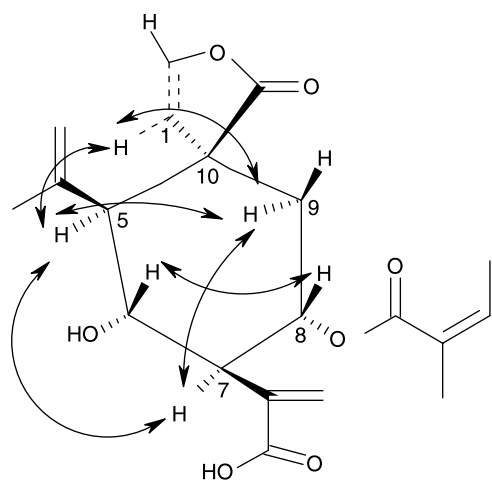


Figure 4. Key NOE correlations in NOESY spectrum of **1**.

This indicated that the carbonyl carbon at C-10 is β -oriented, which is in agreement with the constructed molecular model. From the above evidence, the structure of **1** was elucidated as 6 α -hydroxy-8 α -angeloyloxyl-12-carboxyl-eleman-1(2),3(4),11(13)-triene-2,14 β -olide.

Two known compounds were identified, by comparing their physical and spectral data with literature values,⁸ as isodeoxyelephantopin (**2**) and deoxyelephantopin (**3**). And careful analyses of the ¹H, ¹³C NMR, HMQC, HMBC, and NOESY spectra of compound **3** led to ¹³C signal reassignment, different from those in the literature,⁸ especially at positions C-2 and C-6.

Germacranolides are characteristic metabolites in the genus *Elephantopus*,^{8,9} whereas the elemanolide was found in the titled species for the first time, and elescaberin was the first reported natural elemanolide sesquiterpene lactone with a *spiro*- γ -lactone ring at C-10.

3. Experimental

3.1 General experimental procedures

Melting points were determined on an X₄ micro-melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. IR spectra were obtained on a Nicolet Impact infrared spectrophotometer with KBr pellets. NMR spectra were recorded on a Bruker DRX-400 spectrometer, using CDCl₃ and DMSO-*d*₆ as solvent. Chemical shifts are reported on the δ scale in parts per million, downfield from TMS. ESI-MS were obtained on an Agilent 110 MSD mass spectrometer. Column chromatography were made of silica gel (100–200 and 200–300 mesh, Marine Chemical Factory in Qingdao) and Sephadex LH-20 (Pharmacia, Stockholm, Sweden); TLC were performed on pre-coated silica gel plates (HSG and HSF254, Yantai Chemical Factory, Shandong Province, China), and spots were detected by spraying with vanillin-sulfuric acid reagent, followed by heating.

Table 1. The ^1H and ^{13}C NMR spectral data for compounds **1**, **2** in CDCl_3 and **3** in $\text{DMSO}-d_6$.

Position	1 (δ_{H} , J)	1 (δ_{C})	2 (δ_{C})	3 (δ_{C})
1	5.64 d (3.5)	115.6	149.3	153.3
2	7.05 d (3.5)	141.4	79.5	81.4
3	4.84 brs, 4.70 brs	114.0	40.1	41.5
4		142.3	135.3	135.8
5	2.39 d (10.8)	55.4	125.4	133.6
6	4.22 t (10.8)	68.8	78.7	78.0
7	2.88 t (10.8)	50.2	49.8	52.58
8	5.52 ddd (10.8, 10.9, 5.0)	69.1	74.0	71.6
9	1.91 m	37.3	30.1	33.7
10		51.0	131.5	128.7
11		140.8	134.0	134.2
12		167.8	169.4	169.4
13	6.23 brs, 5.64 brs	125.0	123.1	123.7
14		179.3	21.6	20.2
15	1.62 brs	22.9	174.3	172.4
16		166.2	166.6	166.4
17		127.2	135.5	136.0
18	6.04 dq (7.2, 1.4)	137.2	126.8	126.7
19	1.81 dd (7.2, 1.4)	15.3	18.2	18.3
20	1.72 brs	20.0		
OH	4.71 brs			
COOH	12.2 brs			

3.2 Plant material

The whole plant of *E. scaber* L. was collected in the summer of 1999 from Guangxi province, China, and identified by Dr Yongbing Wang (Department of Pharmacognosy, China Pharmaceutical University, Nanjing, China). A voucher specimen (No. 991019) is deposited in the herbarium of China Pharmaceutical University.

3.3 Extraction and isolation

The air-dried plant material (about 10 kg) was extracted with 80% ethanol. After concentration, the dark green solution was partitioned between H_2O and EtOAc. The EtOAc-soluble fraction (220 g) was concentrated and subjected to silica gel column chromatography, eluted with petroleum ether–EtOAc (10:1), followed by stepwise addition of EtOAc to yield eight fractions (1–8). Fraction 2 was further subjected to silica gel column chromatography (petroleum ether–EtOAc, 100:11) to afford compound **2** (80 mg).

Fraction 3 was subjected to silica gel column chromatography (petroleum ether–EtOAc, 100:21), and was further recrystallized from petroleum ether–EtOAc, to give compound **3** (300 mg). Fraction 6 was subjected to silica gel column chromatography (CHCl_3 – CH_3OH , 100:1–100:20) and purified by Sephadex LH-20 (CH_3OH) column chromatography to give compound **1** (30 mg).

3.3.1 *Elescaberin* (**1**)

Colourless needles (CH_3OH); mp 218–220°C; $[\alpha]_{\text{D}}^{20} + 43$ (c 0.004, MeOH); IR(KBr) ν_{max} : 3413–2400 (br), 1770, 1714, 1702, 1633, 1620, 1384, 1236, 1163, 977 cm^{-1} ; ^1H and ^{13}C NMR ($\text{DMSO}-d_6$) spectral data see Table 1; positive-ion HR-ESI-MS m/z : 377.1595 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{20}\text{H}_{25}\text{O}_7$, 377.1600).

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