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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 Si, Jian-Yong , Chen, Di-Hua and Tu, Guan-Zhong(2005) 'Siraitic Acid F, a New nor-Cucurbitacin With Novel Skeleton, from the Roots of *Siraitia Grosvenorii*', *Journal of Asian Natural Products Research*, 7: 1, 37 – 41

To link to this Article: DOI: 10.1080/10286020310001609010

URL: <http://dx.doi.org/10.1080/10286020310001609010>

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Siraitic acid F, a new nor-cucurbitacin with novel skeleton, from the roots of *Siraitia grosvenorii*

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(Received 22 April 2003; revised 3 June 2003; in final form 9 June 2003)

A new cucurbitane triterpene, siraitic acid F (**1**), has been isolated from the roots of *Siraitia grosvenorii* (Swingle) C. Jeffrey, and its structure has been elucidated as 29-nor-4,24-diene-3,11-dioxo-19-hydroxy-6,19-cyclocucurbitane-26-oic acid on the basis of spectroscopic evidences, including a series of 2D NMR analyses.

Keywords: *Siraitia grosvenorii*; Cucurbitaceae; Siraitic acid F

1. Introduction

The fruits of *Siraitia grosvenorii* (Swingle) C. Jeffrey (Cucurbitaceae) have been used as a traditional medicine as recorded in the Chinese pharmacopoeia (2000 edition). It has also been used as an expectorant as well as a natural sweet food [1]. During our search for new antitumor agents from plants, we found that the ethanolic extract of the roots of the plant exhibited significant activity against both KB and HCT cells *in vitro*. Chemical investigation of the ethanolic extract of the roots has led to the isolation of a new cucurbitacin, the structural elucidation of which is reported here.

2. Results and discussion

Siraitic acid F (**1**) was obtained as white needles (acetone), mp 220–222°C, $[\alpha]_D^{20} + 33.3$ (*c* 0.21, MeOH), and has a molecular formula $C_{29}H_{40}O_5$ established by HRMS (m/z 468.2875). In the UV spectrum, absorption bands at 215 and 252 nm showed that **1** has an α,β -unsaturated keto system. The IR spectrum displayed α,β -unsaturated carboxylic acid and α,β -unsaturated ketone bands (3300–2500, 1670, 1660, 1620 cm^{-1}). The ^{13}C and DEPT NMR spectra of **1** showed 29 carbon signals, including one carboxyl carbon (δ 170.2), two carbonyl carbons (δ 211.0, 199.7), four olefinic carbons (δ 142.2, 129.0, 164.6, 122.8), four

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tertiary methyls (δ 11.5, 12.8, 16.9, 18.9), one secondary methyl (δ 18.4), and eight methylenes (δ 24.2, 25.7, 26.7, 29.2, 33.6, 35.3, 38.7, 50.5). In addition, the spectra also showed six other methines, including a hydroxy-bearing methine (δ 35.7, 40.5, 41.3, 48.2, 49.2, 76.2) and three quaternary carbons (δ 47.1, 51.8, 62.1). The ^1H NMR spectrum indicated an olefinic proton (δ 7.19), two tertiary methyls (δ 0.94, 1.18), two methyls (δ 1.82, 2.09) connected to olefinic carbon, and a secondary methyl (δ 0.99).

However, the structure could not be deduced from 1D NMR data and, therefore, a series of 2D NMR measurements were carried out, including ^1H - ^1H COSY, ^1H - ^1H TOCSY, HMQC, HMBC (figure 1) and NOESY spectra. Detailed analyses of these spectra led us to deduce that **1** consists of rings A–E and a side chain.

The TOCSY spectrum of **1** showed one group of signals in an independent spin system at δ 1.65 (H-1), 2.35, 2.58 (H-2) and 3.40 (H-10). In the ^1H - ^1H COSY spectrum, the methylene protons at δ 1.65 gave a cross-peak with the methylene signals at δ 2.35, 2.58 and the methine signal at δ 3.40. From the HMBC spectrum, the signal at δ 1.65 showed long-range correlations with the signals at δ 164.6 (C-5) and 170.6 (C-3). Correlations between δ 2.58 (H-2b) and 122.0 (C-4); δ 1.83 (H-28) and 164.6 (C-5), δ 170.6 (C-3) gave ring A. The partial structures B–E and the side chain were deduced in similar fashion.

These partial structures suggested that **1** is a nor-cucurbitacin, having a structure similar to siraitic acid **2**, the structure of which has been determined by X-ray diffraction analysis [2]. Comparison of ^{13}C NMR data of **1** with **2** (table 1) [3] showed similar chemical shifts except for C-1–C-10. This suggested that the ring C–D and the side chain were the same for both compounds. Considering the degree of unsaturation in **1** and the unassigned hydroxyl-bearing methine (C-19), as well as the chemical shift difference between C-6 as well C-9 in compounds **1** and **2**, gave good reasons for suggesting that the oxygenated carbon signal appearing at δ 76.2 (C-19) forms a new ring with the methine at δ 48.2 (C-6) and the quaternary carbon at δ 62.1 (C-9). This deduction was supported by the cross-peaks between δ 3.17 (H-6) and 4.59 (H-19) in the ^1H - ^1H COSY spectrum and the long-range correlations between δ 3.17 (H-6) and 62.1 (C-9); δ 1.57, 2.19 (H-7) and 76.2 (C-19); δ 4.59 (H-19) and 24.2 (C-7) in the HMBC spectrum. The relative stereochemistry of **1** was determined by analysis the NOESY spectrum, in which correlations were observed between H₃-30 and

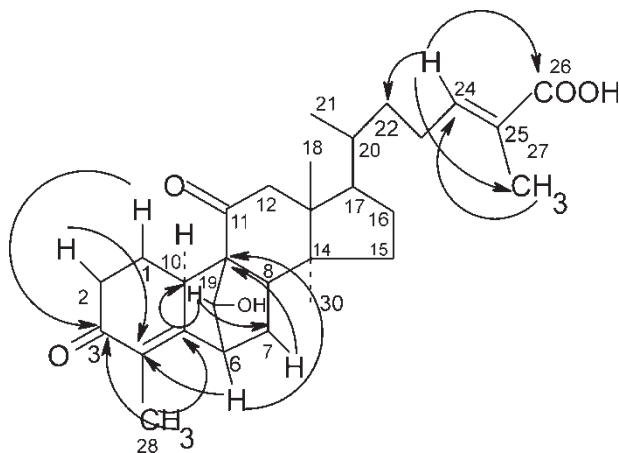


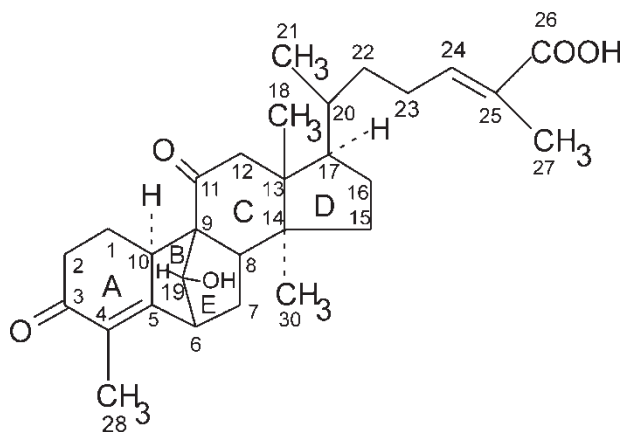
Figure 1. Significant HMBC correlations of **1**.

Table 1. NMR spectral data of compounds **1** and **2** (500 MHz for ^1H and 125 MHz for ^{13}C NMR in $\text{C}_5\text{D}_5\text{N}$).

Position	<i>I</i>	
	^{13}C	^1H
1	26.7	1.65 (2H, m)
2	38.7	2.35 m, 2.58 m
3	197.7	
4	122.8	
5	164.6	
6	48.2	3.17 m
7	24.2	1.57 m, 2.19 m
8	40.5	3.66 (t, 10)
9	62.1	
10	41.3	3.40 (t, 8)
11	211.0	
12	50.5	2.62, 2.64 (d, 12)
13	47.1	
14	51.8	
15	33.6	1.28 (2H, m)
16	29.2	1.32 m, 2.06 m,
17	49.2	1.66, m
18	16.9	0.94 (3H, s)
19	76.2	4.59 brs
20	35.8	1.35 m
21	18.4	0.90 (3H, d, 6.)
22	35.3	1.17 m, 1.56 m
23	25.7	2.11 m, 2.27 m
24	142.2	7.19 m
25	129.0	
26	170.6	
27	12.8	2.09 (3H, s)
28	11.5	1.83 (3H, s)
30	18.9	1.18 (3H, s)

Recorded in CDCl_3 .

H_α -10; H_β -30 and H_α -17; H_β -18 and H_β -8; H-19 and H-1, H-6. Considering cucurbitacin biogenesis [4] and undisplayed NOE correlations between H-19 and H-10(α -H), H-30 (α - CH_3) in the NOESY spectrum, the C-6, C-19 ring should be β orientated. Thus, the structure of **1** was assigned as 29-nor-4,24-diene-3,11-dioxo-19-hydroxy-6,19-cyclocucurbitane-26-oic acid (figures 2 and 3).

Figure 2. Structure of compound **1**.

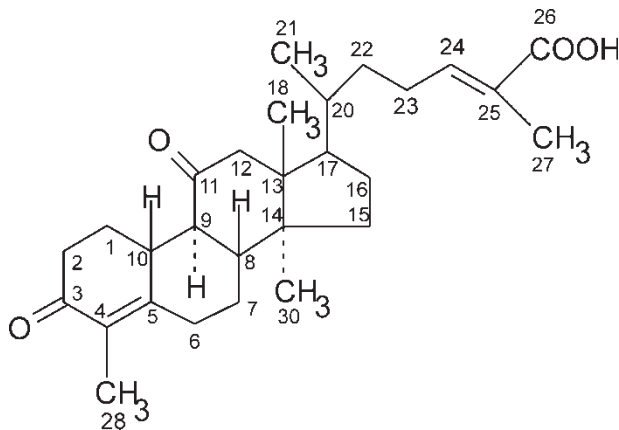


Figure 3. Structure of compound 2.

3. Experimental

3.1 General experimental procedures

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were obtained on a Perkin–Elmer 341 polarimeter. IR spectra were recorded on a Perkin–Elmer 983G spectrometer. NMR spectra were measured on a Bruker Am-500 (500 MHz) instrument, and chemical shifts were referenced to TMS. EIMS data were recorded on a Zabspec instrument.

3.2 Plant material

The roots of *Siraitia grosvenorii* (Swingle) C. Jeffrey were collected in Yongfu county, Guanxi Province of China in August 1995, and were identified by Professor Shou-quan Lin. A voucher specimen has been deposited in the herbarium of the institute.

3.3 Extraction and isolation

The powdered air-dried roots of *Siraitia grosvenorii* (26 kg) were extracted exhaustively with 80% EtOH under reflux. The alcoholic solution was concentrated *in vacuo* to yield a syrup-like extract (3.3 kg) which was dissolved in water. The water-soluble fraction was placed on a column of macroporous absorption resin (D101) and eluted with MeOH to give fraction F₃ (410 g), which was then subjected to column chromatography over silica gel (100–200 mesh, 2 kg) and eluted with an eluent of CHCl₃–MeOH (10:90), yielding fractions 1–30. Fraction 25 was rechromatographed on silica gel (100–200 mesh, 400 g), eluted with hexane–acetone (3:2), to afford **1** (15 mg, 0.00075%).

Siraitic acid F (**1**): white needle (acetone), mp 220–222°C, $[\alpha]_D^{20} + 33.3$ (c 0.21, MeOH). IR (KBr) ν_{\max} (cm⁻¹): 3350–2500, 1670, 1665, 1620, 1240, 1200, 1180. UV (MeOH) λ_{\max} (nm): 215, 252. HRMS m/z 468.2875 (calcd. for C₂₉H₄₀O₅, 468.2876), EIMS m/z (%): 468 (100), 440 (90), 422 (40), 297 (20), 205 (50), 162(50). ¹H and ¹³C NMR data: see table 1.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No. 29672052).

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