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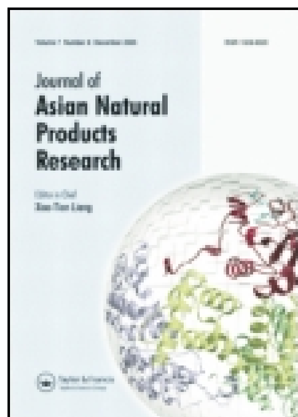

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A new ursane-type triterpenoid from Schefflera heptaphylla (L.) Frodin

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A new ursane-type triterpenoid from *Schefflera heptaphylla* (L.) Frodin

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A new ursane-type triterpenoid (**1**), together with 15 known compounds (**2–16**), was isolated from the barks of *Schefflera heptaphylla* (L.) Frodin. The structure of the new compound was determined on the basis of extensive spectroscopic data including IR, HR-ESI-MS, 1D and 2D NMR, and further confirmed by single-crystal X-ray diffraction. Compounds **2–6** were isolated from *Schefflera* genus for the first time.

Keywords: Araliaceae; *Schefflera heptaphylla*; ursane-type triterpene; X-ray crystallographic analysis

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1. Introduction

Schefflera heptaphylla (L.) Frodin (Araliaceae) is a medicinal plant mainly distributed in the tropical and subtropical areas of Asia [1]. The bark of the plant is used as a folk remedy for the treatment of pains, inflammations, and common cold [2], and it is a principal ingredient of an herbal tea formulation widely used to treat common cold in southern China [3]. Chemical studies of *S. heptaphylla* indicated that triterpenoids and saponins are the major constituents of the plant [1,3–9]. Our chemical investigation on the 95% ethanol extract of this species led to the isolation of one new triterpene, 3α,13-dihydroxyurs-11-en-23,28-dioic acid-13,28-lactone (**1**), together with 15 known compounds, namely dysodensiol D (**2**) [10], 15-nor-10-hydroxy-oplopan-4-oic acid (**3**) [11], dysodensiol E (**4**) [10], vanillic acid (**5**) [12], (+)-balanophonin (**6**) [13], 3,5-di-*O*-caffeoyl quinic acid methyl ester (**7**) [14], 3α-hydroxy-lup-20(29)-en-23,28-dioic acid (**8**) [15], oleanolic acid (**9**) [16], 3-*oxo*-urs-12-en-28-oic acid (**10**) [17], 3-oxooleanolic acid (**11**) [18], scheffursoside F (**12**) [19], scheffoleoside A (**13**) [20], scheffoleoside D (**14**) [19], scheffursoside D (**15**) [19], and acankoreoside A (**16**) [21]. Compounds **2–6** were obtained for the first time from *Schefflera* genus. The known compounds were identified by comparing their spectral data with the reported data in the literature. In this paper, we report the isolation and structural elucidation of compound **1**.

2. Results and discussion

Compound **1** was obtained as a white powder, $[\alpha]_D^{25}$ +15 (c = 1.30, CH_3OH). Its molecular formula was determined to be $C_{30}H_{44}O_5$ based on its HR-ESI-MS data at m/z 507.3085 $[M + Na]^+$, suggesting that **1**

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Table 1. ^{1}H and ^{13}C NMR spectral data of compound **1** (in pyridine-d_5, 400 MHz for ^{1}H).

No.	δ_C (DEPT)	$\delta_{(\alpha\text{-H})}$	$\delta_{(\beta\text{-H})}$	Coupling in HMBC
1	32.5 (t)	1.71 (m, 1H)	1.90 (m, 1H)	C-2
2	20.9 (t)	1.60 (m, 1H)	1.85 (m, 1H)	C-3, 4, 10
3	72.8 (d)		4.27 (br s, 1H)	C-1, 5, 23, 24
4	51.7 (s)			
5	44.5 (d)	2.54 (br d, 1H, 10.4)		C-9, 10, 23, 24, 25
6	31.6 (t)	1.68 (m, 1H)	1.16 (m, 1H)	C-5
7	30.0 (t)	1.28 (m, 1H)	1.28 (m, 1H)	C-6, 26
8	42.6 (s)			
9	53.4 (d)	2.32 (br s, 1H)		C-5, 8, 10, 11, 12, 25
10	36.7 (s)			
11	133.6 (d)	5.64 (dd, 1H, 10.3, 3.2)		C-8, 9, 13
12	129.3 (d)	6.09 (d, 1H, 10.3)		C-9, 13, 14
13	89.4 (s)			
14	42.3 (s)			
15	25.8 (t)	1.69 (m, 1H)	2.30 (m, 1H)	C-8
16	23.1 (t)	1.26 (m, 1H)	2.04 (m, 1H)	
17	45.2 (s)			
18	60.5 (d)		1.59 (br s, 1H)	C-12, 13, 14, 28, 29
19	38.1 (d)	1.71 (m, 1H)		C-20
20	40.3 (d)		0.72 (m, 1H)	
21	30.9 (t)	1.17 (m, 1H)	1.39 (m, 1H)	C-19, 20
22	31.9 (t)	1.82 (m, 1H)	1.59 (m, 1H)	C-17, 20
23	179.2 (s)			
24	17.4 (q)		1.44 (s, 3H)	C-3, 5, 23
25	17.8 (q)		0.99 (s, 3H)	C-1, 5, 9, 10
26	19.7 (q)		1.24 (s, 3H)	C-8, 9, 14
27	16.0 (q)	1.01 (s, 3H)		C-8, 13, 14, 15
28	179.4 (s)			
29	18.4 (q)		0.94 (d, 3H, 6.0)	C-18, 19, 20
30	19.0 (q)	0.81 (d, 3H, 6.0)		C-19, 20, 21

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is a triterpenoid. The IR spectrum of **1** showed absorption bands for γ-lactone at 1760 cm^{-1} and for carboxyl group at 1724 cm^{-1}. The ^{1}H NMR spectrum (Table 1) exhibited four tertiary methyl signals at δ_H 0.99 (3H, s, H-25), 1.01 (3H, s, H-27), 1.24 (3H, s, H-26), and 1.44 (3H, s, H-24), two secondary methyl signals at δ_H 0.81 (3H, d, $J = 6.0$ Hz, H-30) and 0.94 (3H, d, $J = 6.0$ Hz, H-29), an oxygenated methine signal at δ_H 4.27 (1H, br s, H-3) and two olefinic proton signals at δ_H 5.64 (1H, dd, $J = 10.3$, 3.2 Hz, H-11) and 6.09 (1H, d, $J = 10.3$ Hz, H-12). The ^{13}C NMR and DEPT spectra (Table 1) revealed 30 carbon signals, including six methyl carbons at δ_C 16.0 (C-27), 17.4 (C-24), 17.8 (C-25), 18.4 (C-29), 19.0 (C-30), and 19.7 (C-26), one oxygenated methine carbon at δ_C 72.8 (C-3), two olefinic carbons at δ_C 129.3 (C-12) and 133.6 (C-11), as well as two carbonyl groups at δ_C 179.2 (C-23) and 179.4 (C-28), respectively. The other carbon signals were observed and assigned to eight methylene, five methine, and six quaternary carbons. These NMR spectral data indicated that compound **1** was an ursane-type triterpenoid [22]. The NMR signals assigned to ring A of **1** (Table 1) were very similar to those of aceriphyllic acid C [23], suggesting that **1** had 3α-hydroxy group and a carboxyl carbon at C-23. The α-configuration of the hydroxyl group at C-3 was confirmed by the ROESY correlations from H-3 (δ_H 4.27) to H-2β (δ_H 1.85), H-24 (δ_H 1.44), H-1β (δ_H 1.90), and H-25 (δ_H 0.99), as well as by the

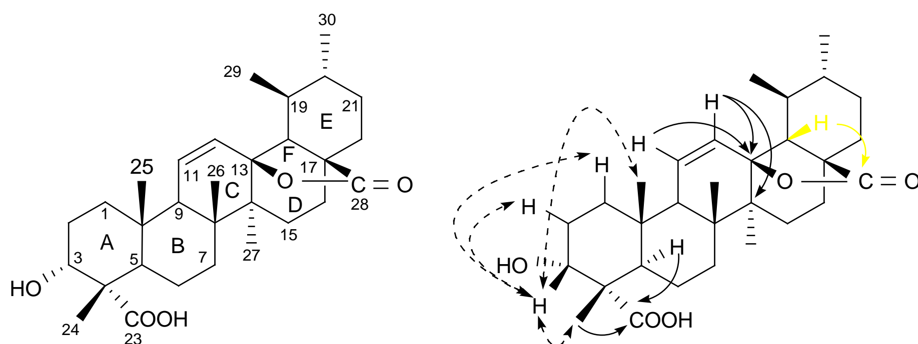

Figure 1. The chemical structure, key HMBC (H → C), and ROESY (H- - -H) correlations of **1**.

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absence of the ROESY correlation between H-3 (δ_H 4.27) and H-5 (δ_H 2.54; Figure 1). In the HMBC spectrum, the correlations from both H-24 (δ_H 1.44) and H-5 (δ_H 2.54) to the carbonyl carbon at δ_C 179.2 also indicated that this carbonyl group is located at C-23 (Figure 1). On the other hand, comparison of the ^{13}C NMR spectral data of **1** with those of 3-*epi*-corosolic acid lactone (2α,3α-dihydroxyurs-11-en-13β,28-olide) [24] revealed that both signals appearing from the rings C–E were essentially identical (Table 1), suggesting that **1** also possessed 13,28-lactone and the double bond between C-11 and C-12. Especially, the quaternary carbon signals at δ_C 89.4 (C-13) and 179.4 (C-28), along with the IR absorption at 1760 cm^{-1}, indicated the presence of a γ-lactone ring between C-13 and C-28 [24]. The olefinic proton signals at δ_H 5.64 and 6.09 were assigned to H-11 and H-12, respectively, by the HMBC correlations between H-11 (δ_H 5.64) and C-13 (δ_C 89.4), between H-12 (δ_H 6.09) and C-13 (δ_C 89.4), and between H-12 (δ_H 6.09) and C-14 (δ_C 42.3; Figure 1). Finally, the structure of **1** was determined as 3α,13-dihydroxyurs-11-en-23,28-dioic acid-13,28-lactone (Figure 1). The molecular structure and its stereochemistry were further confirmed by X-ray crystallographic analysis (Figure 2). The molecule is composed of five six-membered rings (A–E) and one five-membered ring (F). The stereochemistry of the ring juncture is A/B *trans*, B/C *trans*, C/D *trans*, and D/E *cis*, while ring F is bridged on ring D at C-13 and C-17 making a dihedral angle at 106.0° with ring D. The cyclohexane rings A, B, D, and E adopt normal chair conformations, while ring C exists in a half-chair form owing to the double bond between C-11 and C-12. This is also indicated by the small torsion angle C9–C11–C12–C13 = –1.2(6)°. The five-membered ring F adopts an envelope conformation with C18 displaced by 0.747 Å from the mean plane of the remaining four atoms (C13, O5, C28, and C17). This model also reveals that the skeleton is twisted strongly at the C17–C18 bond because of the *cis* fusion between the rings D and E. It is noteworthy that the final refinement on CuKα diffraction data resulted in a small Flack parameter 0.0 (5), allowing an unambiguous assignment of the absolute structure as shown in Figure 2.

3. Experimental

3.1 General experimental procedures

Optical rotations were carried out using a JASCO P-1030 automatic digital polarimeter. IR spectra were measured on a JASCO FT/IR-480 plus infrared spectrometer with KBr pellets. 1D and 2D NMR spectra were recorded on a Bruker AV-500 or AV-400 spectrometer with TMS as the internal standard, and

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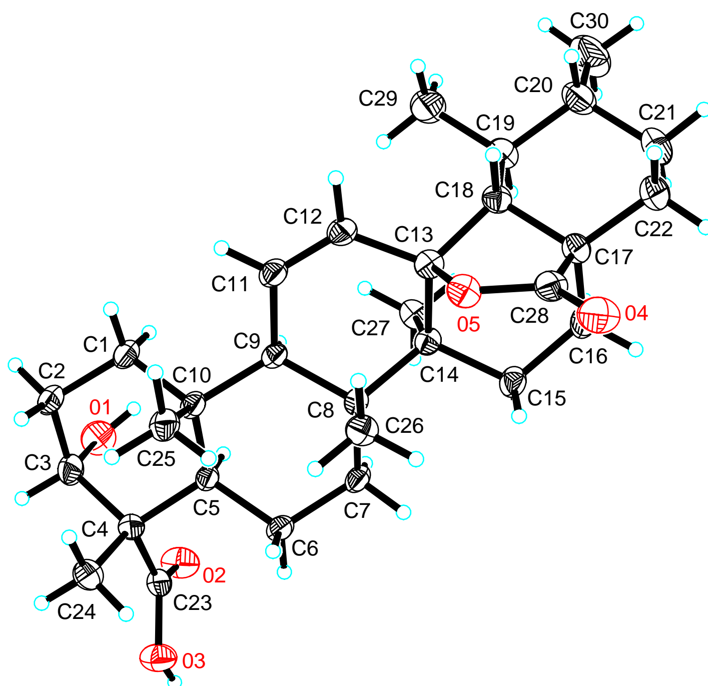

Figure 2. X-ray crystal structure of **1** with atom-labeling scheme.

chemical shifts were expressed in δ values (ppm). HR-ESI-MS data were detected on an Agilent 6210 LC/MSD TOF mass spectrometer. Silica gel (200–300 mesh, Qingdao Marine Chemical Inc., Qingdao, China), ODS silica gel (50 μm, YMC, Kyoto, Japan), and Sephadex LH-20 (Pharmacia, Uppsala, Sweden) were used for column chromatography (CC). Preparative HPLC was carried out on a Varian instrument equipped with UV detectors (Varian, Palo Alto, CA, USA) and a reversed-phase (RP) C_{18} column (5 μm, 20 × 250 mm; Cosmosil, Kyoto, Japan). Thin-layer chromatography (TLC) was performed using pre-coated silica-gel plates (GF254, Yantai Chemical Industry Research Institute, Yantai, China). X-ray crystallographic data collection was performed on a Gemini S Ultra using graphite-monochromated radiation. All the reagents were purchased from Tianjin Damao Chemical Company (Tianjin, China).

3.2 Plant material

The barks of *S. heptaphylla* were collected from Yulin, Guangxi, China, and were authenticated by Mr Zhenqiu Mai, a senior herbalist at the Chinese Medicinal Material Company, Guangdong, China. A voucher specimen with accession No. 20090301 has been deposited in the herbarium of College of Pharmacy, Jinan University.

3.3 Extraction and isolation

The dried and powdered barks of *S. heptaphylla* (10 kg) were soaked in 95% ethanol and extracted by percolation. The ethanol solution was evaporated under reduced pressure to obtain an extract. This extract was suspended in distilled water, and then partitioned with petroleum ether, ethyl acetate, and *n*-butanol, respectively. The ethyl acetate extract (200 g) was subjected to silica-gel CC (200–300

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mesh, 1.5 kg) eluted with cyclohexane–ethyl acetate (100:0–0:100) in gradient to yield 14 fractions (fractions 1–14). Fraction 9 (7.0 g) was applied to silica-gel CC (200–300 mesh, 140 g) using gradient mixtures of cyclohexane–ethyl acetate (100:1–50:50) as eluants to afford seven subfractions (subfractions 1–7). Subfraction 2 (510 mg) was subjected to an ODS column using gradient mixtures of MeOH–H_2O (70:30–95:5) as eluants to yield compound **10** (14.6 mg) and compound **11** (6.3 mg). Fraction 11 (12.6 g) was applied to silica-gel CC (200–300 mesh, 200 g) using gradient mixtures of $CHCl_3$–MeOH (100:1–50:50) as eluants to afford eight fractions (fractions A–H). Fraction C (300 mg) was separated on a silica-gel column eluting with $CHCl_3$–MeOH (95:5–50:50) to yield 11 subfractions (subfractions 1–11). Compound **5** (57.0 mg) was obtained upon recrystallization in $CHCl_3$–MeOH (70:30) from subfraction 8 (70 mg). Fraction D (750 mg) was applied to Sephadex LH-20 ($CHCl_3$–MeOH, 1:1, v/v) CC to afford compound **1** (10.3 mg) and compound **3** (22.0 mg). Fraction E (680 mg) was applied to Sephadex LH-20 ($CHCl_3$–MeOH, 1:1, v/v) CC to yield nine subfractions (subfractions 1–9). Compound **2** (13.5 mg) was obtained upon recrystallization in $CHCl_3$–MeOH (1:1) from subfraction 3 (53 mg). Subfraction 6 (98 mg) was subjected to a silica-gel CC (200–300 mesh, 3.0 g) using gradient mixtures of $CHCl_3$–MeOH (100:0–90:10) as eluants to afford compound **4** (9.7 mg), compound **8** (17.0 mg), and compound **9** (23.5 mg). Compound **6** (10.7 mg) was isolated from fraction 13 (10 g) by silica-gel CC (200–300 mesh, 200 g) using $CHCl_3$–acetone (80:20) as solvents. The *n*-BuOH extract (100 g) was separated by silica-gel CC (200–300 mesh, 800 g) using gradient mixtures of $CHCl_3$–MeOH (90:10–60:40) as eluants to afford 40 fractions (fractions 1–40). Fraction 14 (510 mg) was subjected to a preparative HPLC (MeOH–H_2O, 63:37) to give **14** (54.8 mg), **15** (159.2 mg), and **16** (16.7 mg), respectively. Fraction 24 (330 mg) was purified by a preparative HPLC (MeOH–H_2O, 60:40) to afford **12** (41.9 mg) and **13** (12.3 mg). Fraction 28 (280 mg) was also subjected to a preparative HPLC (MeOH–H_2O, 45:55) to yield compound **7** (20.1 mg).

Compound **1**, white amorphous powder; $[\alpha]_D^{25}$ +15 ($c = 1.30$, CH_3OH). IR (KBr) ν_{max}: 1760, 1724 cm^{-1}. ^1H and ^{13}C NMR spectral data (C_5D_5N): see Table 1. HR-ESI-MS: *m/z* 507.3085 $[M + Na]^+$ (calcd for $C_{30}H_{44}O_5$ Na, 507.3081).

3.4 X-ray crystallographic analysis of 1

X-ray analysis. Colorless blocks, $C_{30}H_{44}O_5$, Mr = 484.65, monoclinic, $P2_1$, $a = 12.5001(4)$, $b = 6.9690(2)$, $c = 14.8731(5)$ Å, $\beta = 93.711(3)$, $V = 1292.93(7)$ Å^3, $Z = 2$, $d_x = 1.245$ Mg/m^3, $F(000) = 528$, μ(Mo-Kα) = 0.657 mm^{-1}. Data collection was performed on a Gemini S Ultra using graphite-monochromated radiation ($\lambda = 1.54184$ Å); 2460 unique reflections were collected to $\theta_{max} = 60.69°$, in which 2269 reflections were observed [$F^2 > 4\sigma(F^2)$]. The structures were solved by direct methods (SHELXTL version 5.1) and refined by full-matrix least squares on F^2. In the structure refinements, non-hydrogen atoms were refined anisotropically. Hydrogen atoms bonded to carbons were placed on geometrically ideal positions by the 'ride on' method. Hydrogen atoms bonded to oxygen were located by the difference Fourier method and were included in the calculation of structure factors with isotropic temperature factors. The final indices were $R = 0.0508$, $R_w = 0.0536$, and $S = 1.090$. Crystallographic data for structure **1** have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication No. CCDC 804653. Copies of the data can be obtained

free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; Email: deposit@ccdc.cam.ac.uk).

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