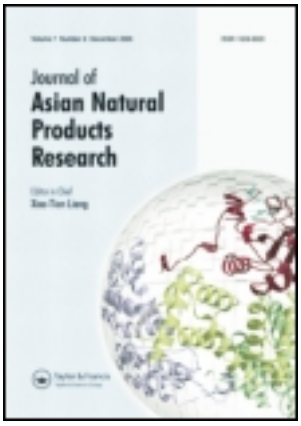

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A new highly oxygenated nortriterpenoid from *Schisandra chinensis*

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A new highly oxygenated nortriterpenoid, 2β-hydroxy-micrandilactone C (**1**), and three related known triterpenoids (**2**–**4**) have been isolated from the leaves and stems of *Schisandra chinensis*. The structure of the new compound was elucidated by means of NMR and MS spectroscopic analyses.

Keywords: Schisandraceae; *Schisandra chinensis*; *Schisandra* nortriterpenoid

1. Introduction

The *Schisandra* nortriterpenoids are a structurally intriguing group of highly oxygenated, polycyclic, fused heterocyclic natural products produced by the plants of the genus *Schisandra* (Schisandraceae) [1]. These structurally complex molecules have attracted great interest to chemists as challenging targets for total synthesis [2,3] as well as biosynthetic studies [4,5]. Knowledge of this fascinating group of metabolites was recently widened by H.-D. Sun and other researchers by the discovery of a new series of *Schisandra* nortriterpenoids, which result from ring cleavage or rearrangement, from a different species of the genus *Schisandra*. Many *Schisandra* species have a long history of use as folk medicines in China. For example, the fruits of *S. chinensis* have been used as sedative and tonic agents and used for the treatment of hepatitis for over 2000 years in China.

S. chinensis (Turcz.) Baill. is a climbing plant that is widely found in northeastern China, Korea, and Japan. This plant has been reported to contain dibenzocyclooctadiene lignans, which were found to have some important pharmacological effects that include antihepatitis, antitumor, and anti-HIV activities [6,7]. Due to its notable medicinal properties, the plant of *S. chinensis* has been studied extensively, and in recent years, several novel *Schisandra* nortriterpenoids were isolated and reported [8,9]. In the course of our search for bioactive metabolites from Chinese medicinal plants [10,11], we made a collection of *S. chinensis* from Jiangxi Province, China, resulting in the discovery of a new schiartane-type nortriterpenoid, 2β-hydroxy-micrandilactone C (**1**), together with three related known compounds, namely, micrandilactone B (**2**), anwuweizic acid (**3**), and ganoderic acid U (**4**). This paper describes the isolation and structure elucidation of the new compound **1**.

2. Results and discussion

The powdered leaves and stems of *S. chinensis* were extracted with MeOH. The MeOH extract was partitioned consecutively between H_2O and petroleum ether,

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H_2O and EtOAc. The EtOAc fraction was repeatedly chromatographed over MCI gel, silica gel, Sephadex LH-20, and RP-HPLC to afford compounds **1**–**4**, respectively (Figure 1).

Compound **1** was obtained as an optically active amorphous powder, $[\alpha]_D^{23} + 17.5$ ($c = 0.04$, CH_3OH). Its molecular formula of $C_{29}H_{42}O_{10}$ was determined by an HR-ESI-MS pseudomolecular ion peak at *m/z* 573.2651 $[M + Na]^+$ (calcd 573.2676), indicating 9 degrees of unsaturation. The IR spectrum of **1** showed that absorptions revealed the presence of hydroxyl (3452 cm^{-1}) and carbonyl (1756, 1729 cm^{-1}) functionalities. The ^1H NMR spectral data (Table 1) of **1** displayed the presence of five methyls [δ 1.16 (3H, s, H-30), 1.33 (3H, s, H-29), 1.34 (3H, d, $J = 4.8$ Hz, H-21), 1.48 (3H, s, H-18), and 1.83 (3H, s, H-27)] and one olefinic proton [δ 7.22 (1H, br s, H-24)]. The ^{13}C NMR and DEPT spectral data (Table 1) were in good agreement with the above analysis, and showed 29 carbon signals consisting of five methyls, six methylenes, ten methines, and eight quaternary carbons. The ^1H and ^{13}C NMR spectral data, in combination with the molecular composition, clearly showed compound **1** to be a C_{29} nortriterpenoid dilactone with six rings.

The planar structure of **1** was mainly determined by the extensive study of 2D NMR (^1H–^1H COSY, HSQC, and HMBC) spectra. Analysis of ^1H–^1H COSY and HSQC spectra of **1** readily identified four spin systems [**a** (C-1 to C-2), **b** (C-5 to C-8), **c** (C-11 to C-12), and **d** (C-15 to C-23)] (Figure 2). The HMBC spectrum was used to confirm the above proton spin-system assignments and establish the connectivities among the fragments **a**–**d**. A series of significant HMBC correlations between H-1/C-3, C-4, and C-10, H-5/C-4 and C-10, H-29/C-4 and H-30/C-4 suggested that fragments **a** and **b** were connected through the quaternary carbons C-3, C-4, and C-10. The cross-peaks of H-8/C-9 and H-11/C-9 gave rise to the connectivity of fragments **b** and **c** through C-9. The tertiary methyl at δ_H 1.48 (3H, s, H-18) showed that HMBC correlations with C-12, C-13, and C-14, in combination with the correlation of H-15/C-14, required the attachment of fragments **c** and **d** through C-13 and C-14. The presence of a five-membered α-methyl-α,β-unsaturated-γ-lactone ring (ring F) was revealed by the correlations between H-27/C-25 and C-26, H-23/C-26, and H-24/C-26. Taking the above data into account, the planar structure of **1** was completely assembled as shown in Figure 2.

The relative stereochemistry of **1** was deduced from the analysis of its ROESY spectrum. As depicted in the Chemdraw 3D molecular model (Figure 2), the strong ROESY correlations H-1/Me-30, H-1/H19β, H19β/H-8, H-8/OH-14, OH-14/Me-18, Me-18/H-15, Me-18/H-16β, and Me-18/H-20 revealed that H-1, Me-30, H-8, Me-18 H-15, OH-14, and 17-side chain were cofacial and were arbitrarily assigned to be β-oriented. While the ROESY cross-peaks of H-2/Me-29, H-2/H-5, H-5/H-19α, H-19α/OH-9, and H-17/H-16α revealed that H-2, H-5, OH-9, H-17, and Me-29, were α-oriented. A search of the literature revealed that the structure of **1** was very

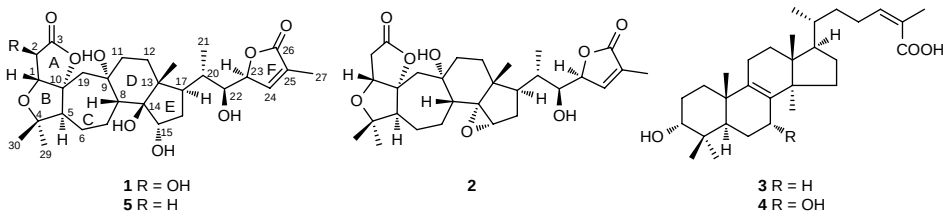

Figure 1. Structures of compounds **1**–**5**.

Table 1. ^{1}H and ^{13}C NMR spectral data of compound **1**[a] and ^{13}C NMR spectral data of **5** in pyridine-d_5.

	1		**5** [12]
Position	δ_H (mult, J in Hz)	δ_C	δ_C
1	4.48 (br s)	87.3 (d)	82.8 (d)
2α	4.72 (br s)	73.7 (s)	37.2 (t)
3		177.4 (s)	177.6 (s)
4		85.8 (s)	86.2 (s)
5β	2.80 (m)	59.0 (d)	60.2 (d)
6α	1.41 (m)	28.7 (t)	29.3 (t)
6β	1.87 (m)		
7α	2.25 (m)	24.7 (t)	24.7 (t)
7β	2.74 (m)		
8β	2.06 (d, 11.5)	56.6 (d)	56.8 (d)
9		72.4 (s)	73.3 (s)
10		100.4 (s)	101.3 (s)
11α	2.79 (m)	38.3 (t)	38.5 (t)
11β	1.90 (m)		
12α	1.66 (m)	39.1 (t)	39.6 (t)
12β	1.69 (m)		
13		45.9 (s)	46.3 (s)
14		86.8 (s)	87.6 (s)
15β	4.53 (br s)	77.0 (d)	77.2 (d)
16α	2.23 (m)	36.2 (t)	36.0 (t)
16β	2.57 (m)		
17	2.58 (m)	54.3 (d)	54.7 (d)
18	1.48 (s)	18.4 (q)	18.2 (q)
19α	2.92 (ABd, 16.0)	48.6 (t)	47.0 (t)
19β	2.40 (ABd, 16.0)		
20	2.59 (m)	37.9 (d)	38.3 (d)
21	1.34 (d, 4.8)	18.6 (q)	18.2 (q)
22	4.07 (d, 6.3)	73.7 (d)	73.8 (d)
23	5.29 (br s)	82.8 (d)	83.6 (d)
24	7.22 (br s)	148.7 (d)	149.9 (d)
25		130.2 (s)	131.3 (s)
26		174.9 (s)	177.0 (s)
27	1.83 (s)	10.7 (q)	10.6 (q)
29	1.33 (s)	30.1 (q)	30.0 (q)
30	1.16 (s)	23.9 (q)	23.5 (q)
9-OH	7.47 (br s)		
14-OH	5.76 (br s)		

Notes: [a]Data were recorded on a Bruker DRX 400 spectrometer; assignments were deduced by the analysis of 1D and 2D NMR spectra.

similar to the model compound **5** (micrandilactone C), which was previously isolated from *Schisandra micrantha* [12]. In fact, the ^{13}C NMR spectral data of **1** and **5** (Table 1) were almost the same except that a methylene at δ 37.2 in **5** was replaced by an oxymethine at δ 73.7 in agreement with the 16 mass units difference (-O-) between them. The relative configurations of **1** at C-22 and C-23 were assigned as the same as those of **2** [12] and **5** mainly on the basis of the analysis of coupling constants, splitting patterns, and ROESY correlations between **1**, **2**, and **5**, whereas the relative configuration at C-20 was tentatively deduced as the same as that of **2** on the basis of biogenetic considerations. Thus, the structure of **1** was established as shown in Figure 1.

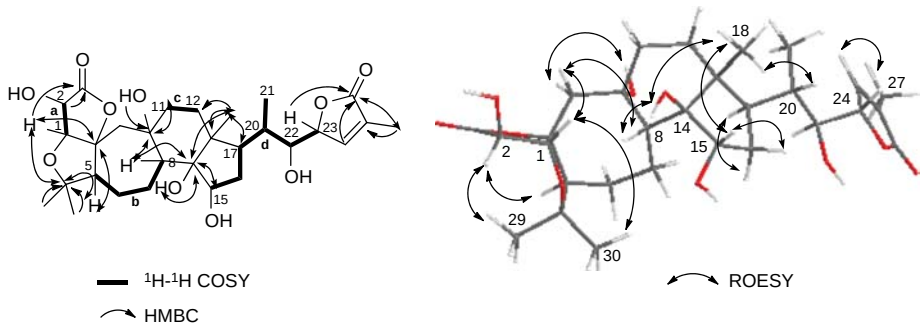

Figure 2. Selected 2D NMR correlations for compound **1**.

The three known compounds were readily identified as micrandilactone B (**2**) [12], anwuweizic acid (**3**) [13], and ganoderic acid U (**4**) [14], by the analysis of their NMR spectra, and by the comparison of spectroscopic and MS data with those reported in the literature. It may be worth to point out that among these metabolites, compounds **2** and **3** were isolated from the species for the first time.

As we mentioned above, *S. chinensis* is an important medicinal plant in China. However, no phytochemical investigation has been done on this plant that is distributed in Jiangxi province. To the best of our knowledge, this is the first report on the chemical constituents of this plant collected in Jiangxi province. Additionally, compounds **1**–**4** were evaluated for their inhibitory activity against human protein tyrosine phosphatase 1B, a key target for the treatment of type II diabetes and obesity [15]. Unfortunately, the results indicated that compounds **1**–**4** were all inactive. Other bioassays such as antibacterial and cytotoxic activities are currently ongoing.

3. Experimental

3.1 General experimental procedures

Optical rotation was measured on a Perkin-Elmer polarimeter 341. UV spectrum was recorded on a 756 CRT spectrophotometer. CD spectrum was obtained on a JASCO 810 spectrometer. IR spectrum was recorded on a Nicolet-Magna FT-IR 750 spectrometer. The NMR spectra were measured on Bruker DRX 400 and Varian Inova 600 spectrometers. Chemical shifts were expressed in δ (ppm) and coupling constants (J) in Hz. The ^{1}H and ^{13}C NMR assignments were supported by ^{1}H–^{1}H COSY, HSQC, HMBC, and ROESY experiments. ESI-MS and HR-ESI-MS spectra were recorded on a Q-TOF Micro LC-MS-MS mass spectrometer. Reversed-phase HPLC analysis was performed on an Agilent 1100 series liquid chromatography using a VWD G1314A detector at 210 nm and a semi-preparative ZORBAX ODS column (250 mm × 9.4 mm i.d., 5 μm particle size). Silica gel (Marine Chemical Factory, Qingdao, China), MCI gel (CHP20P, 75–150 μM, Mitsubishi Chemical Industries Ltd, Tokyo, Japan), and Sephadex LH-20 gel (Amersham Pharmacia Biotech AB, Uppsala, Sweden) were used for column chromatography (CC). Precoated silica gel plates GF-254 (Marine Chemical Factory) were used for analytical TLC.

3.2 Plant material

The leaves and stems of *S. chinensis* were collected in Jiuliansan, Jiangxi Province, China, in August 2009. The sample was identified by Prof. Ren-Lin Liu, Department of Chemistry and Biological Science, Gan Nan Normal College. A voucher sample (09-P-57) is available for inspection at the Herbarium of Shanghai Institute of Materia Medica, CAS.

3.3 Extraction and isolation

The powdered leaves and stems of *S. chinensis* (2.5 kg) were extracted with MeOH at r.t. (20 liters × 3, each for 7 days). After removing MeOH under vacuum, it formed a residue (242 g), which was subsequently dissolved in water to form a suspension (1 liter) and extracted successively with petroleum ether (60–90°C, 2 × 1.5 liters) and EtOAc (3 × 1.5 liters). The EtOAc extract (40 g) was chromatographed over MCI gel CC using 30% MeOH/H_2O, 70% MeOH/H_2O, and 100% MeOH as the eluents. The fraction (23 g) that was eluted by 70% MeOH/H_2O was further purified by silica gel CC eluted with a gradient of petroleum ether/EtOAc (80:20–0:100) to give eight fractions. Fraction 2 (0.8 g) was chromatographed over silica gel with petroleum ether and EtOAc (80:20 and 70:30) to yield compounds **3** (18.5 mg) and **4** (10.7 mg), respectively. Fraction 4 (0.6 g) was subjected to a column of Sephadex LH-20 eluted with $CHCl_3$–CH_3OH (50:50), and was then purified by reversed-phase HPLC eluted with CH_3OH and H_2O (40:60–70:30) to yield **2** (4.8 mg) and **1** (12.5 mg), respectively.

3.3.1 2β-Hydroxy-micrandilactone C (*1*)

Amorphous powder; $[\alpha]_D^{23}$ + 17.5 (c = 0.04, CH_3OH); CD (CH_3OH) $\Delta\varepsilon_{221nm}$ −10.7; UV λ_{max} (log ε) 213 (3.53) nm; IR (KBr) ν_{max}: 3452, 2975, 2936, 1756, 1729, 1631, 1455, 1386, 1203, 1076, and 998 cm^{-1}; ^1H and ^{13}C NMR spectral data (Table 1); ESI-MS: *m/z* 573.3 $[M + Na]^+$, 1123.6 $[2M + Na]^+$; HR-ESI-MS: *m/z* 573.2651 $[M + Na]^+$ (calcd for $C_{29}H_{42}O_{10}Na$, 573.2676).

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References

[1] W.L. Xiao, R.T. Li, S.X. Huang, J.X. Pu, and H.D. Sun, *Nat. Prod. Rep.* **25**, 871 (2008).
[2] L.A. Paquette and K. Wah Lai, *Org. Lett.* **10**, 3781 (2008).
[3] S. Maity, K. Matcha, and S. Ghosh, *J. Org. Chem.* **75**, 4192 (2010).
[4] W.L. Xiao, L. Chun, J. Ren, T.G. Liao, J.X. Pu, C.U. Pittman Jr, Y. Lu, Y.T. Zheng, H.J. Zhu, and H.D. Sun, *Chem. Eur. J.* **14**, 11584 (2008).
[5] C. Lei, S.X. Huang, W.L. Xiao, X.N. Li, J.X. Pu, and H.D. Sun, *J. Nat. Prod.* **73**, 1337 (2010).
[6] Y.H. Kuo, L.Y. Kuo, and C.F. Chen, *J. Org. Chem.* **62**, 3242 (1997).
[7] J.B. Chang, J. Reiner, and J.X. Xie, *Chem. Rev*. **105**, 4581 (2005).
[8] S.X. Huang, L.B. Yang, W.L. Xiao, C. Lei, J.P. Liu, Y. Lu, Z.Y. Weng, L.M. Li, R.T. Li, J.L. Yu, Q.T. Zheng, and H.D. Sun, *Chem. Eur. J.* **13**, 4816 (2007).
[9] S.X. Huang, J. Yang, H. Huang, L.M. Li, W.L. Xiao, R.T. Li, and H.D. Sun, *Org. Lett.* **9**, 4175 (2007).
[10] Z.Y. Li, P. Chen, H.G. Xu, Y.M. Yang, S.Y. Peng, Z.Z. Zhao, and Y.W. Guo, *Org. Lett.* **9**, 477 (2007).
[11] W. Zhang, Y.W. Guo, and K. Krohn, *Chem. Eur. J.* **12**, 5122 (2006).
[12] R.T. Li, Q.B. Han, Y.T. Zheng, R.R. Wang, L.M. Yang, Y. Lu, S.Q. Sang, Q.T. Zhao, and H.D. Sun, *Chem. Comm.* **23**, 2936 (2005).
[13] J. Liu, M. Huang, and Y. Tao, *Can. J. Chem.* **66**, 414 (1988).
[14] J.O. Toth, B. Luu, and G. Ourisson, *Tetrahedron Lett.* **24**, 1081 (1983).
[15] J.C.H. Byon, A.B. Kusari, and J. Kuseti, *Mol. Cell. Biochem.* **182**, 101 (1998).