Notes

Bioactive Nortriterpenoids from *Schisandra grandiflora*

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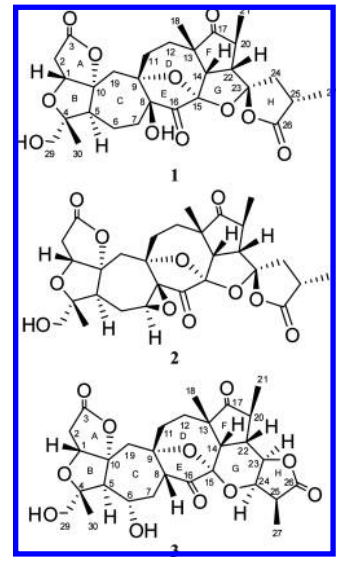
Three new nortriterpenoids, schigrandilactones A−C (**1**−**3**), along with eight known compounds, were isolated from an organic solvent extract of *Schisandra grandiflora*. Compounds **1** and **2** feature a spirocyclic moiety in their structures, and compound **3** was characterized with a new oxygenated pattern. The relative configurations of **1** and **3** were determined through single-crystal X-ray experiments. In addition, compounds **1** and **2** displayed cytotoxic activity against two human cancer cell lines, and compound **3** showed anti-HIV-1 inhibition in infected C8166 cells.

The genus *Schisandra* of the family Schisandraceae is economically and medicinally valuable and is used widely in traditional Chinese medicine. Recent research by our group on *Schisandra* species has resulted in the characterization of a series of structurally interesting secondary metabolites, the *Schisandra* nortriterpenoids.[1] *Schisandra* nortriterpenoids have highly oxygenated and complex polycyclic structures and may be classified into the schisanartane,[1,2] schiartane,[1,3] 18-norschiartane,[1,4,5] 18(13/14)-*abeo*-schiartane,[1,6] preschisanartane,[1,7] and wuweiziartane[1,8] types, in terms of their carbon framework and patterns of oxygenation. Some of these compounds exhibit anti-HIV-1[3,5] and cytotoxic[9] activities.

Schisandra grandiflora (Wall.) Hook. f. & Thoms. is a climbing plant distributed in the northwestern part of mainland China, Bhutan, India, and Myanmar. Its fruits are eaten locally. There has been only one report on the chemical constituents of this species to date.[10] In a continuing search for bioactive natural products from plants of the genus *Schisandra*, we have investigated the leaves and stems of *S. grandiflora*. The present study has resulted in the identification of three new nortriterpenoids, schigrandilactones A−C (**1**−**3**), along with eight known compounds, lancifodilactones C, D,[11] K, L, and N,[12] micrandilactone A,[2] and henridilactones A and B.[13] The structures of **1**−**3** were identified by interpretation of their spectroscopic data, aided by single-crystal X-ray studies on **1** and **3**. Herein, we report the isolation and structural elucidation of compounds **1**−**3** and their biological activities.

Powdered dried leaves and stems of *S. grandiflora* were extracted with 70% aqueous acetone. The filtrate was concentrated and partitioned between H_2O and EtOAc. The EtOAc fraction was evaporated under reduced pressure and at low temperature and then submitted to successive chromatographic fractionation and purification steps, to yield compounds **1**−**3** and eight known compounds.

Schigrandilactone A (**1**), $[\alpha]^{24.5}_D$ +95.1 (*c* 0.20, CH_3OH), showed a pseudomolecular ion peak at *m/z* 583 $[M + Na]^+$ in the ESIMS, and the molecular formula, $C_{29}H_{36}O_{11}$, was established by HRESIMS (*m/z* 583.2260 $[M + Na]^+$), corresponding to 12 degrees of unsaturation. The ^1H NMR spectrum displayed signals due to two tertiary methyls and two secondary methyls. The ^{13}C NMR spectrum of **1** exhibited signals for 29 carbons, including two ester groups, two carbonyl groups, seven quaternary carbons, six methines (including an oxygenated one), eight methylenes (including an oxygenated one), and four methyls (Table 1). Comparison of the 1D NMR spectroscopic data of **1** with those of the known *Schisandra* nortriterpenoid, lancifodilanctone C,[11] showed that several characteristic signals for this kind of nortriterpenoid skeleton were observed for **1**, such as the proton signals at H-1 (δ_H 4.29, d, $J = 6.3$ Hz) and H-19 (δ_H 2.18 and 2.55, AB d, $J = 15.9$ Hz) and carbon signals at δ_C 82.0 (C-1), 97.0 (C-10), and 219.9 (C-17). Thus, the structure of **1** was determined by comparison with the NMR spectroscopic data of lancifodilactone C and the analysis of two-dimensional NMR data of **1**.



Differences found between **1** and lancifodilactone C were the methyl group at C-29, the oxygenated methine at C-7, and the methine at C-8 in lancifodilactone C being replaced, respectively,

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Table 1. ^{1}H and ^{13}C NMR Data for Schigrandilactones A−C (**1**−**3**)[a]

	1		**2**		**3**	
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	82.0 CH	4.29 (d, 6.3)	80.7 CH	4.28 (d, 6.4)	81.9 CH	4.41 (d, 6.5)
2α	35.4 CH_2	2.65 (br d, 18.3)	35.2 CH_2	2.65 (br d, 18.6)	35.5 CH_2	2.79 (overlapped)
2*β*		2.92 (overlapped)		3.05 (dd, 6.4, 18.6)		3.07 (dd, 6.5, 16.7)
3	175.7 C		174.4 C		175.6 C	
4	86.9 C		86.4 C		87.7 C	
5	56.2 CH	2.85 (m)	49.7 CH	2.98 (m)	63.2 CH	3.14 (d, 6.7)
6α	19.6 CH_2	2.20 (m)	27.7 CH_2	2.42 (m)	67.9 CH	4.17 (m)
6*β*		1.71 (m)		1.45 (m)		
7α	32.3 CH_2	2.30 (m)	62.8 CH	3.82 (overlapped)	37.8 CH_2	2.50 (m)
7*β*		2.00 (m)				2.76 (overlapped)
8	83.1 C		59.5 C		50.1 CH	2.88 (dd, 5.0, 13.5)
9	78.3 C		78.7 C		81.9 C	
10	97.0 C		95.3 C		94.1 C	
11α	36.0 CH_2	2.40 (m)	35.5 CH_2	2.22 (overlapped)	41.1 CH_2	1.90 (m)
11*β*		1.95 (m)		1.84 (overlapped)		1.57 (m)
12α	31.8 CH_2	1.90 (m)	30.7 CH_2	1.95 (m)	30.9 CH_2	1.80 (m)
12*β*		1.70 (m)		1.85 (overlapped)		1.41 (m)
13	48.7 C		49.3 C		50.2 C	
14	60.3 CH	3.31 (d, 6.8)	60.7 CH	3.17 (d, 7.1)	45.2 CH	2.69 (d, 7.0)
15	106.0 C		107.4 C		98.9 C	
16	214.8 C		207.6 C		211.7 C	
17	219.9 C		218.7 C		220.3 C	
18	26.2 CH_3	0.93 (s)	26.6 CH_3	0.95 (s)	26.0 CH_3	0.88 (s)
19α	43.0 CH_2	2.18 (AB d, 15.9)	41.4 CH_2	2.20 (AB d, 16.0)	43.5 CH_2	2.28 (AB d, 16.1)
19*β*		2.55 (AB d, 15.9)		2.34 (AB d, 16.0)		2.39 (AB d, 16.1)
20	44.4 CH	2.93 (m)	43.7 CH	2.76 (m)	44.9 CH	2.60 (m)
21	18.1 CH_3	1.23 (d, 6.7)	17.6 CH_3	1.29 (d, 7.3)	14.9 CH_3	1.08 (d, 7.0)
22	53.1 CH	2.98 (m)	53.9 CH	2.90 (m)	40.2 CH	2.81 (overlapped)
23	118.3 C		116.9 C		75.3 CH	4.60 (br s)
24α	38.0 CH_2	2.78 (br d, 6.1)	37.1 CH_2	2.58 (br d, 6.1)	69.3 CH	5.25 (br d, 1.6)
24*β*				2.24 (overlapped)		
25	35.7 CH	2.82 (m)	35.8 CH	2.81 (m)	42.0 CH	3.18 (m)
26	178.6 C		177.8 C		177.9 C	
27	17.1 CH_3	1.47 (d, 7.4)	16.7 CH_3	1.40 (d, 7.4)	8.1 CH_3	1.29 (d, 7.1)
29	67.7 CH_2	3.63 (d, 11.5)	67.3 CH_2	3.78 (d, 11.6)	69.1 CH_2	4.12 (d, 11.4)
		3.78 (d, 11.5)		3.85 (d, 11.6)		4.07 (d, 11.4)
30	17.0 CH_3	1.17 (s)	16.5 CH_3	1.08 (s)	16.6 CH_3	1.46 (s)

[a] Data were recorded in C_5D_5N at 125 MHz (^{13}C NMR) and 500 MHz (^{1}H NMR); chemical shifts (δ) are expressed in ppm with reference to the most downfield signal of C_5D_5N (δ 8.71 ppm) for ^{1}H and to the center peak of the most downfield signal of C_5D_5N (δ 149.9 ppm) for ^{13}C, respectively.

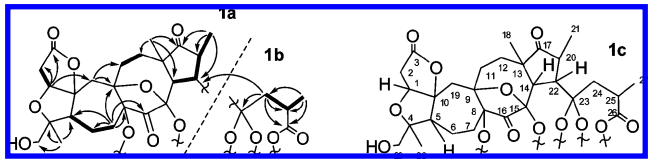

Figure 1. Selected HMBC (→) and $^{1}H-^{1}H$ COSY (−) correlations of **1**.

by an oxygenated methylene (C-29, δ_C 67.7), a methylene (C-7, δ_C 32.3), and an oxygenated quaternary carbon (C-8, δ_C 83.1) in **1**, which were further confirmed by HMBC and $^{1}H-^{1}H$ COSY correlations (Figure 1). A side-by-side comparison of **1** and lancifodilactone C allowed the structural subunit **1a** to be established (Figure 1). Furthermore, HMBC correlations observed from H-27 (δ_H 1.47 d, J = 7.4 Hz) to C-24 (δ_C 38.0), C-25 (δ_C 35.7), and C-26 (δ_C 178.6) and from H-25 (δ_H 2.82) to C-23 (δ_C 118.3), C-26, and C-27 (δ_C 17.1), together with the $^{1}H-^{1}H$ COSY correlations, H-24/H-25/H-27, allowed the construction of the structural subunit **1b** (Figure 1). In addition, HMBC correlations from H_2-24 (δ_H 2.78, br d, J = 6.1 Hz) to C-22 and C-23 required the direct connectivity of C-22 with C-23 and permitted subunits **1a** and **1b** to be joined to form **1c** (Figure 1). Since C-8, C-16, C-23, and C-26 are quaternary carbons, it was not easy to determine the exact connectivities among these carbons by spectroscopic evidence alone. Therefore, a single crystal of **1** was obtained from methanol after repeated recrystallization, and an X-ray diffraction experiment was conducted (Figure 2), which indicated a spirocyclic moiety (ring H) located at C-23 and a hydroxy group located at C-8.

The relative configuration of **1** was also determined from the X-ray analysis, together with a ROESY NMR experiment (Figure 3). On biogenetic grounds, H-5 was taken as α-oriented. The ROESY correlations observed between H_2-29/H-5 and CH_3-30/H-1 demonstrated that H-1 is *β*-oriented. The ROESY correlations of CH_3-18/CH_3-21, CH_3-18/H-14, and CH_3-18/H-22 showed that CH_3-21, H-14, and H-22 are located on the same side of the molecule as CH_3-18. They were further determined to be *β*-oriented by the X-ray diffraction experiment. In addition, according to the IUPAC sequence rule,[14] based on the chiral center with the lowest locant, the relative configurations of carbons C-8, C-9, C-10, C-15, C-23, and C-25 were deduced as *S*, *S*, *R*, *R*, *R*, and *S*, respectively.

Compound **2** was obtained as white crystals and was assigned the molecular formula $C_{29}H_{34}O_{11}$, as deduced by HRESIMS (found *m*/*z* $[M + Na]^+$ 581.2109, calcd 583.2101). The ^{13}C NMR data of **2** were very similar to those of **1** (Table 1). Differences found were the appearance of two carbons with signals at δ_C 62.8 (d, C-7) and 59.5 (s, C-8) in **2** that replaced a methylene (C-7) and an oxygenated quaternary carbon (C-8) in **1**. This evidence, coupled with the proton signal observed at δ_H 3.82 (H-7), indicated the presence of a trisubstituted epoxide in **2**. This epoxide group was located between C-7 and C-8 on the basis of the HMBC correlations of H-5 (δ_H 2.98) and H_2-6 (δ_H 1.45, 2.42) with C-7, H-7 with C-6 (δ_C 27.7) and C-8 (δ_C 59.5), and H_2-19 (δ_H 2.20, 2.34, each AB d, J = 16.0 Hz) with C-8. In addition, a ROESY correlation of H-5 with H-7 indicated the latter group to be α-oriented. The other chiral centers were deduced to be the same as those of **1** by comparison of the chemical shifts and analysis of the ROESY spectrum. Therefore,

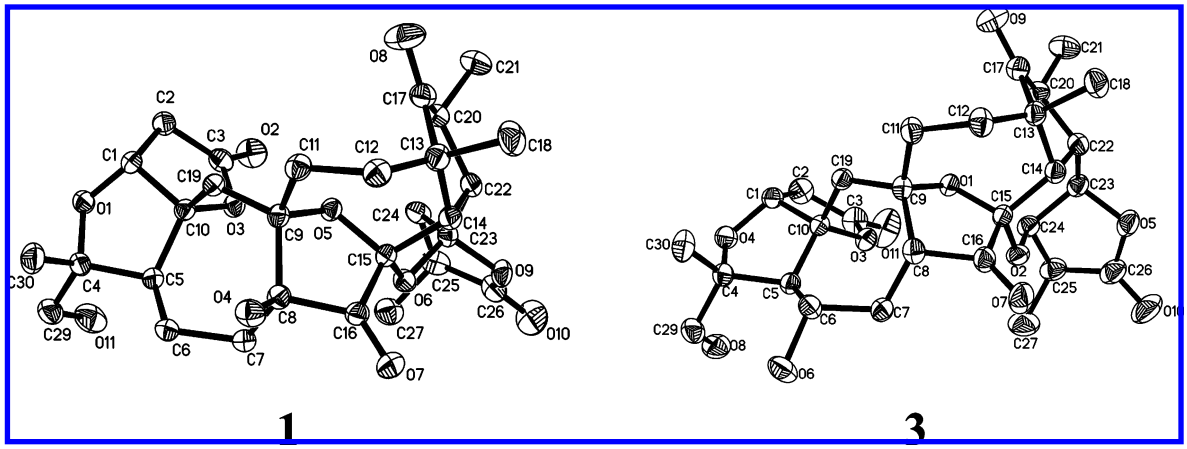

Figure 2. ORTEP drawings of **1** and **3**.

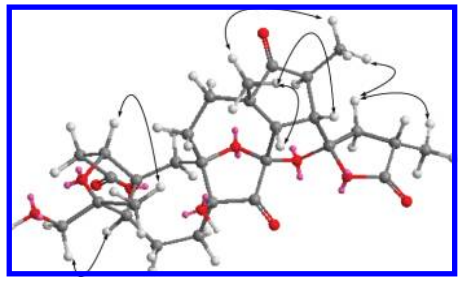

Figure 3. Selected ROESY correlations of **1**.

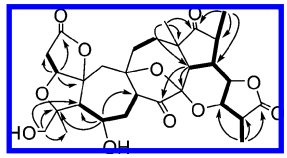

Figure 4. Selected HMBC (→) and $^1H-^1H$ COSY (−) correlations of **3**.

compound **2** was established as shown and has been accorded the trivial name schigrandilactone B.

The molecular formula of **3** was deduced as $C_{29}H_{36}O_{11}$ from its HRESIMS (found $[M + Na]^+$ 583.2255, calcd 583.2258) and ^{13}C NMR data. The ^1H and ^{13}C NMR spectroscopic data were very close to those of lancifodilactone C.[11] Comparison of 1D NMR spectral data suggested that CH_3-29 in the latter compound is replaced by an oxygenated methylene in **3**, with a hydroxy group occurring at C-6 in **3** instead of at C-7. This deduction was determined by HMBC correlations of H-29 with C-4, C-5, and CH_3-30, and H-6 with C-4, C-5, and C-8 (Figure 4). The ROESY correlations of H-6 with H-8 and CH_3-30 established H-6 as being β-oriented. The other chiral centers in **3** were also determined by the ROESY experiment and finally confirmed by an X-ray diffraction experiment (Figure 2). Therefore, the structure of **3** (schigrandilactone C) was determined as shown.

Compounds **1**−**3** were tested for their ability to prevent the cytopathic effects of HIV-1 in C8166 cells, and their cytotoxicity was measured in parallel with the determination of antiviral activity, using AZT as a positive control (EC_{50} 0.0045 μg/mL and CC_{50} > 200 μg/mL).[15] Compounds **1**−**3** displayed EC_{50} values of 80.2, 20.8, and 5.1 μg/mL, and a selectivity index of 1.1, 4.0, and 12.7, respectively. In addition, compounds **1** and **2** were further evaluated for their cytotoxicity against two human tumor cell lines, K562 and HepG2, using a bioassay method previously described, with cisplatin as the positive control (IC_{50} 0.40 and 0.59 μg/mL, respectively).[16] Compounds **1** and **2** showed IC_{50} values of 0.13 and 3.19 μg/mL for K562 cells and IC_{50} values of 0.19 and 0.20 μg/mL for HepG2 cells, respectively. Compound **3** was not further tested for its activity due to the limited amount available.

Experimental Section

General Experimental Procedures. Melting points were obtained on a XRC-1 micro melting point apparatus and are uncorrected. Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A Tenor 27 spectrophotometer was used for scanning IR spectroscopy with KBr pellets. 1D and 2D NMR spectra were recorded on Bruker AM-400 and DRX-500 spectrometers. Unless otherwise specified, chemical shifts (δ) are expressed in ppm with reference to the solvent signals. Mass spectra were obtained on a VG Autospec-3000 spectrometer at 70 eV. Column chromatography was performed using silica gel (200−300 mesh; Qing-dao Marine Chemical, Inc., Qingdao, People's Republic of China). Semipreparative HPLC was performed on a Hewlett-Packard instrument (column: Zorbax SB-C_{18}, 250 × 9.4 mm; DAD detector). Fractions were monitored by TLC, and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH.

Plant Material. The leaves and stems of *S. grandiflora* were collected in July 2006 from Jilong County of Tibet, People's Republic of China. The specimen was identified by Prof. Xi-Wen Li. A voucher specimen, no. KIB 06-07-11, has been deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. Air-dried and powdered stems and leaves (2.5 kg) were extracted with 70% aqueous acetone (4 × 4 L) at room temperature and concentrated in vacuo to give a crude extract (95.4 g), which was partitioned between H_2O and EtOAc. The EtOAc part (65.0 g) was chromatographed on a silica gel column eluting with $CHCl_3-CH_3OH$ (9:1, 8:2, 2:1, 1:1, and 0:1) to afford fractions I−V. Fraction II (8.1 g) was chromatographed on a silica gel column to afford five subfractions, II(a)−II(e). Subfraction II(c) was then purified by semipreparative HPLC (CH_3OH-H_2O, 40:60, and $CH_3OH-CH_3CN-H_2O$, 15:40:45) to furnish compounds **1** (10 mg), **2** (7 mg), micrandilactone A (19 mg), and henridilactone A (4 mg). Fraction III (10.9 g) was further chromatographed on a silica gel column, eluting with $CHCl_3-Me_2CO$ (9:1, 8:2, 2:1, 1:1), to afford subfractions III(a)−III(f). Subfraction III(b) (2.0 g) was purified by crystallization and repeated chromatography over silica gel, RP-18, and Sephadex LH-20 (CH_3OH), followed by semipreparative HPLC (CH_3CN-H_2O, 35:65, CH_3OH-H_2O, 37:63, and $CH_3OH-CH_3CN-H_2O$, 10:33:57) to yield compounds **3** (4 mg), lancifodilactone C (5 mg), lancifodilactone D (10 mg), lancifodilactone L (6 mg), and lancifodilactone N (15 mg). Subfraction III(d) (1.5 g) was chromatographed by passage over Sephadex LH-20 (CH_3OH), followed by semipreparative HPLC (CH_3CN-H_2O, 40:60), to afford compounds lancifodilactone K (3 mg) and henridilactone B (7 mg).

Bioassays. A cytotoxicity assay against C8166 (permanent human T-cell) cells (CC_{50}) was carried out using the MTT method, and an anti-HIV-1 activity inhibition assay for the cytopathic effects of HIV-1 (EC_{50}) was determined using a literature method.[15] Cytotoxicity against two human tumor cell lines, K562 (human erythromyeloblastoid

leukemia cell) and HepG2 (human hepatocellular liver carcinoma cell), was evaluated by a bioassay method previously described.[16]

Schigrandilactone A (1): white crystals; mp 195−196 °C; $[\alpha]^{24.5}_D$ +95.1 (*c* 0.20, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 203 (3.41) nm; IR (KBr) ν_{max} 3432, 2967, 1776, 1708, 1643, 1445, 1430, 1357, 1280, 1081, 590 cm^{-1}; ^1H and ^{13}C NMR data, Table 1; ESIMS *m*/*z* 583 $[M + Na]^+$; HRESIMS *m*/*z* 583.2260 $[M + Na]^+$ (calcd 583.2258 for $C_{29}H_{36}O_{11}Na$).

Schigrandilactone B (2): white crystals; mp 186−187 °C; $[\alpha]^{25.0}_D$ +91.5 (*c* 0.16, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 203 (3.51) nm; IR (KBr) ν_{max} 3426, 2958, 1779, 1720, 1654, 1450, 1381, 1184, 1021, 591 cm^{-1}; ^1H and ^{13}C NMR data, Table 1; ESIMS *m*/*z* 581 $[M + Na]^+$; HRESIMS *m*/*z* 581.2109 $[M + Na]^+$(calcd 581.2101 for $C_{29}H_{34}O_{11}Na$).

Schigrandilactone C (3): white crystals; mp 175−176 °C; $[\alpha]^{25.1}_D$ +94.5 (*c* 0.15, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 206 (3.75) nm; IR (KBr) ν_{max} 3433, 2931, 1779, 1740, 1630, 1455, 1388, 1175, 1014, 580 cm^{-1}; ^1H and ^{13}C NMR data, Table 1; ESIMS *m*/*z* 583 $[M + Na]^+$; HRESIMS *m*/*z* 583.2255 $[M + Na]^+$ (calcd 583.2258 for $C_{29}H_{36}O_{11}$).

X-ray Crystal Structure of Schigrandilactone A (1). A crystal, $C_{29}H_{36}O_{11}$, M_r = 560.60, orthorhombic, space group $P2_12_12_1$, a = 12.406(1) Å, b = 13.593(1) Å, c = 16.490(1) Å, V = 2780.8(3) $Å^3$, Z = 4, d = 1.339 g/cm^3, crystal dimensions 0.05 × 0.40 × 0.50 mm, was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator ($\omega-2\theta$ scans, $2\theta_{max}$ = 50.0°), using Mo Kα radiation. The total number of independent reflections measured was 2832, of which 2515 were observed ($|F|^2 \geq 2\sigma|F|^2$). Final indices: R_1 = 0.061, wR_2 = 0.137. The crystal structure of **1** was solved by direct methods using SHELX-97[17] and expanded using difference Fourier techniques, refined by the program and method NOMCSDP[18] and full-matrix least-squares calculations. The CIF file of X-ray data of **1** has been deposited in the Cambridge Crystallographic Data Centre (deposition number: 729789). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk].

X-ray Crystal Structure of Schigrandilactone C (3). A crystal, $C_{29}H_{36}O_{11}$, M = 560.60, orthorhombic, space group $P2_12_12_1$, a = 10.825(1) Å, b = 11.335(1) Å, c = 22.723(1) Å, V = 2788.3(4) $Å^3$, Z = 4, d = 1.335 g/cm^3, crystal dimensions 0.20 × 0.30 × 0.50 mm, was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator ($\omega-2\theta$ scans, $2\theta_{max}$ = 50.0°), using Mo Kα radiation. The total number of independent reflections measured was 2875, of which 2665 were observed ($|F|^2 \geq 3\sigma|F|^2$). Final indices were R_1 = 0.0394, wR_2 = 0.1041 ($w = 1/\sigma|F|^2$), S = 1.067. The crystal structure of **3** was solved using the same methods as used for **1**.[17,18] The CIF file of X-ray data of **3** was deposited in the Cambridge Crystallographic Data Centre (deposition number: 729790). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk].

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Supporting Information Available: 1D and 2D NMR spectra of schigrandilactones A−C (**1**−**3**). These materials are available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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