Dibenzocyclooctadiene Lignans from *Schisandra lancifolia* and Their Anti-human Immunodeficiency Virus-1 Activities

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Three new dibenzocyclooctadiene lignans, schilancifolignans A—C (1—3), together with thirteen known ones, were isolated from the leaves and stems of *Schisandra lancifolia*. The structures of 1—3 were elucidated by spectroscopic methods, including extensive 1D- and 2D-NMR techniques. Compounds 1—3 were tested for their anti-human immunodeficiency virus-1 activities and showed weak bioactivities.

Key words *Schisandra lancifolia*; dibenzocyclooctadiene lignan; schilancifolignan A; schilancifolignan B; schilancifolignan C; anti-human immunodeficiency virus-1 activity

Previous studies of *Schisandra* species have reported lignans with various beneficial pharmacological effects such as antihepatitis, antitumor, and anti-human immunodeficiency virus (HIV) activities as typical of this genus.[1—4] Recent researches also showed that some triterpenoids isolated from this genus exhibited anti-HIV activities and inhibitory activities toward cholesterol biosynthesis.[5—9] *Schisandra lancifolia*, one of species of this genus, is a climbing plant mainly distributed in Mainland of China.[10] In our previous work, some new highly oxygenated nortriterpenoids were isolated from this plant.[11—17] To search for more new bioactive compounds from this plant, we examined the leaves and stems of *S. lancifolia*, which led to the isolation of three new dibenzocyclooctadiene lignans, schilancifolignans A—C (**1**—**3**), along with thirteen known compounds. In addition, the anti-HIV-1 activities of new compounds **1**—**3** were evaluated. Described in this paper are their structure elucidation and biological activities.

Results and Discussion

A 70% aq. acetone extract prepared from the leaves and stems of *S. lancifolia* was partitioned between EtOAc and H_2O. The EtOAc layer was subjected repeatedly to column chromatography on Si gel, Sephadex LH-20, RP-18 and preparative HPLC to afford compounds **1**—**16**, including 3 new lignans named schilancifolignans A—C (**1**—**3**), together with 13 known, kadsuralignan A (**4**),[18] methylisogomisin O (**5**),[19] kadsuranin (**6**),[20] isogomisin O (**7**),[21] 12-demethylwuweilignan I (**8**),[22] angeloylisogomisin O (**9**),[21] schisandrin A (**10**),[23] gomisin N (**11**),[24] (+)-gomisin K_2 (**12**),[25] gomisin J (**13**),[26] (+)-schizandrin (**14**),[26] bznzoylgomisin Q (**15**),[27] angeloygomisin Q (**16**).[28] The structures of the compounds **1**—**16** were as shown in Fig. 1.

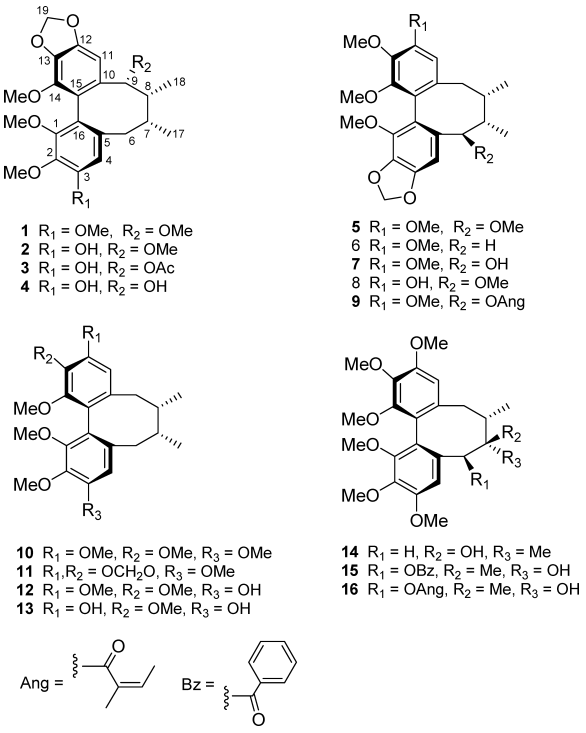

Fig. 1. The Structures of Compounds **1**—**16**

Compound **1** was obtained as yellow gum. Its molecular formula was determined as $C_{24}H_{30}O_7$ by HR-electrospray ionization (ESI)-MS *m*/*z* 453.1886 $[M+Na]^+$ (Calcd 453.1889). Its ^{1}H- and ^{13}C-NMR spectra showed signals to 30 hydrogens and 24 carbons, respectively, corresponding to two aromatic rings with two aromatic protons (δ_H 6.99 s, δ_H 6.73 s), one methylene carbon (δ_C 37.8 t), two methine carbons (δ_C 36.3 d, δ_C 38.7 d), one oxidated methine carbon (δ_C 90.0 d), two methyl groups (δ_C 15.3 q, δ_C 20.0 q; δ_H 0.82 d, J=6.9 Hz, δ_H 0.99 d, J=7.0 Hz), five methoxy groups (δ_C 55.7, δ_C 55.9, δ_C 60.6, δ_C 60.7, δ_C 60.8; δ_H 3.09, δ_H 3.79, δ_H 3.86, δ_H 3.88, δ_H 3.92), one methylenedioxy group (δ_C 101.2 t) (Table 1). UV absorption bands at 210 and 243 nm, and ^{1}H–^{1}H correlation spectroscopy (COSY) correlations of H-6/H-7/H-8/H-9, H-7/H-17, and H-8/H-18, together with heteronuclear multiple bond connectivity (HMBC) correlations of H-11 (δ_H 6.73 s) with C-9 (δ_C 90.0 d), C-10 (δ_C 137.0 s), and C-15 (δ_C 121.2 s), and of H-4 (δ_H 6.99 s) with C-5 (δ_C 135.9 s), C-6

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Table 1. ^{13}C-NMR Data of Compounds **1**—**3** (δ in ppm, Data Obtained in Pyridine-d_5)

No.	1	2	3	No.	1	2	3
1	152.0 s	152.3 s	152.1 s	14	141.9 s	141.5 s	141.6 s
2	140.2 s	140.1 s	139.6 s	15	121.2 s	121.8 s	121.7 s
3	153.9 s	150.9 s	150.5 s	16	122.7 s	122.9 s	123.2 s
4	110.3 d	111.0 d	111.2 d	17	15.3 q	15.4 q	15.2 q
5	135.9 s	136.3 s	135.1 s	18	20.0 q	20.0 q	20.1 q
6	37.8 t	39.0 t	37.9 t	19	101.2 t	101.2 t	101.3 t
7	36.3 d	38.1 d	36.4 d	1′	55.7 q	55.9 q	169.9 s
8	38.7 d	39.9 d	38.8 d	2′			21.0 q
9	90.0 d	90.0 d	83.7 d	1-OMe	60.8 q	60.8 q	60.3 q
10	137.0 s	138.1 s	137.3 s	2-OMe	60.8 q	60.9 q	60.6 q
11	105.0 d	106.6 d	105.4 d	3-OMe	55.9 q		
12	149.1 s	149.2 s	148.8 s	14-OMe	60.6 q	60.5 q	60.0 q
13	136.7 s	138.1 s	136.2 s				

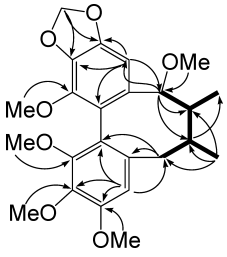

Fig. 2. Selected HMBC (→) and ^{1}H–^{1}H COSY (—) Correlations of **1**

(δ_C 37.8 t), C-16 (δ_C 122.7 s), implied that **1** could be a dibenzocyclooctadiene lignan. The ^{1}H- and ^{13}C-NMR spectra of **1** are similar to those of kadsuralignan A (**4**).[18] The obvious differences are the chemical shift of C-9 with δ_C 83.9 (d, δ_H 4.61 d, J=11.7 Hz) in **4** downfield shift to δ_C 90.0 (d, δ_H 4.10 d, J=8.2 Hz) in **1**, and an additional methoxy group (δ_H 3.09) in **1**. The methoxy group located at C-9 in **1** was deduced by HMBC correlation of the proton signals (δ_H 3.09) with C-9 (δ_C 90.0 d). In addition, the HMBC correlations of δ_H 3.79 with C-14 (δ_C 141.9 s), δ_H 3.89 with C-1 (152.0 s), δ_H 3.92 with C-2 (δ_C 140.2 s), δ_H 3.86 with C-3 (δ_C 153.9 s), showed that other four methoxy groups were located at C-1, C-2, C-3, and C-14, respectively. HMBC correlations of H-19 (δ_H 5.99, δ_H 5.89) with C-12 (149.1 s) and C-13 (136.7 s) showed the methylenedioxy group located at C-12 and C-13. Thus, the planar structure of **1** was established.

The configuration of the biphenyl groups in all isolated dibenzocyclooctadiene lignans were determined based on their characteristic circular dichroism (CD) spectra. The CD spectra *S*-biphenyl configuration lignans showed a positive cotton effect at 215—225 nm and a negative cotton effect at 240 nm and 260 nm. However, the *R*-biphenyl configuration lignans showed a negative cotton effect at 215—225 nm and a positive cotton effect at 240 nm and 260 nm.[26,29,30] The CD spectrum of **1** had a negative Cotton effect at 251 nm and a positive Cotton effect at 224 nm, indicating that **1** has an *S*-biphenyl configuration. The rotating frame Overhauser enhancement spectroscopy (ROESY) correlations between H-4/CH$_3$-17 and H-11/H-8 in **1** suggested a twist-boat-chair (TBC) conformation for the cyclooctadiene ring (Fig. 3).[26] The configuration of OMe-9 was deduced as α-orientation by the ROESY correlation between H-11/H-9β (Fig. 3).[18] In addition, H-7 and H-8 were both correlated with H-9β,

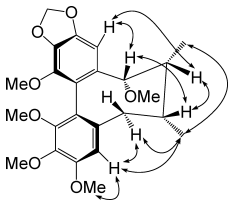

Fig. 3. Key ROESY Correlations of **1**

revealing the α-orientations of both Me-17 and Me-18. This was also supported by the ROESY correlations observed between Me-17 and Me-18, and between the Me-17 and the aromatic H-4.[18] Therefore, the structure of **1** was determined unambiguously as shown in Fig. 1, and given the name as schilancifolignan A.

Compound **2** was obtained as yellow gum, showed a quasi-molecular weight of 439.1735 $[M+Na]^+$ in HR-ESI-MS (Calcd 439.1733), corresponding to the molecular formula $C_{23}H_{28}O_7$. Its ^{1}H- and ^{13}C-NMR showed the signals of two aromatic rings with two aromatic protons, one methylene carbons, two methine carbons, one oxidated methine carbon, two methyl groups, four methoxy groups, one methylenedioxy group. The ^{1}H- and ^{13}C-NMR spectra of **2** were very similar to these of **1**. Detailed comparison of 1D NMR spectra between **1** and **2** showed the only difference was a methoxy group in **1** was substituted by a hydroxyl group in **2** on aromatic rings, which was supported by the disappearance of singal of a methoxy group in **2**. Analysis of HMBC spectrum of **2** showed that the four methoxy groups were at C-1, C-2, C-9, and C-14, respectively. Accordingly, the hydroxy group was deduced to be located at C-3. In addition, the CD spectrum of **2** had a negative Cotton effect at 252 nm and a positive Cotton effect at 222 nm, indicating that **2** has an *S*-biphenyl configuration,[26] which is the same as that of **1**. The substituent positions and stereochemistry assignments of **2** were also determined by the comparison of the ROESY correlations and coupling constants of **2** (H-9, J=8.3 Hz) with those of **1** (H-9, J=8.2 Hz). Thus, the structure of **2** was established.

Compound **3**, obtained as yellow gum, was assigned the molecular formula $C_{24}H_{28}O_8$ by HR-ESI-MS *m/z* 467.1686 $[M+Na]^+$ (Calcd 467.1682). Its ^{1}H- and ^{13}C-NMR spectra showed signals of two aromatic rings with two aromatic protons, one methylene carbon, two methine carbons, one oxidated methine carbon, two methyl groups, three methoxy groups, one methylenedioxy group, and one acetoxy group (δ_C 169.9 s, 21.0 q; δ_H 2.03 s). The ^{1}H- and ^{13}C-NMR spectra of **3** were very similar to those of **2**. The differences were resulted from the appearance of an acetyl group, and lack of a methoxy group in **3**. The HMBC correlation of H-9 (5.66, 1H, d, J=8.4 Hz) with carbonyl carbon (δ_C 169.9 s) showed that acetyl group was attached to C-9. In addition, the CD spectrum of **3** had a negative Cotton effect at 252 nm and a positive Cotton effect at 222 nm, indicating that **3** has an *S*-biphenyl configuration,[26] which is the same as those of **1** and **2**. Therefore, the configuration of the acetyl group at C-9 can be determined to be α-orientation by the ROESY correlation of H-11 with H-8 and H-9. The other substituent positions and stereochemistry assignments of **3** were also determined by the comparison of the ROESY correlations and coupling

Table 2. Anti-HIV Activities of Compounds **1**—**3**

Compound	EC_{50} ($\mu g\,ml^{-1}$)	CC_{50} ($\mu g\,ml^{-1}$)	TI[a)]
1	2.32	18.6	8.02
2	3.88	48.5	12.5
3	3.62	35.2	6.96

a) $TI=EC_{50}/CC_{50}$.

constants of **3** with those of **1** and **2**. Accordingly, the structure of **3** was determined as shown.

Since some of dibenzocyclooctadiene lignans from *Schisandra* genus species exhibited modest or strong anti-HIV activities, new compounds **1**—**3** were tested for their potencies in preventing the cytopathic effects of HIV-1 in C8166 and cytotoxicity measured in parallel with the determination of antiviral activity, using 3′-azidodeoxythymidine (AZT) as a positive control (0.0043 μM and CC_{50} >200 μM).[31] The results were showed in Table 2. Compounds **1**—**3** showed weak anti-HIV-1 activities with therapeutic index (TI) values of 8.02, 12.5 and 6.96, respectively.

Experimental

General Experimental Procedures 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. CD spectra were measured on a JASCO J-810 spectropolarimeter. 1D and 2D NMR spectra were recorded on DRX-500 spectrometers with tetramethylsilane (TMS) as internal standard. Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to the solvent signals. HR-ESI-MS was performed on an API QSTAR time-of-flight spectrometer and a VG Autospec-3000 spectrometer, respectively. Preparative HPLC was performed on a Shimadzu LC-8A preparative liquid chromatograph with a ZORBAX PrepHT GF (21.2 mm×25 cm, 7 μm) column or a Venusil MP C18 (20 mm×25 cm, 5 μm) column. Column chromatography was performed with Si gel (200—300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China), Lichroprep RP-18 gel (40—63 μm, Merck, Darmstadt, Germany) and MCI gel (75—150 μm, Mitsubishi Chemical Corporation, Tokyo, Japan). The fractions were monitored by TLC, and spots were visualized by heating Si gel plates sprayed with 5% H_2SO_4 in EtOH.

Plant Material The stems of *S. lancifolia* were collected in Erlang Mountain area of Sichuan Province, P. R. China, in September 2007. The identification of plant material was verified by Prof. Xi-Wen Li. A voucher specimen (KIB-07-09-28) has been deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, P. R. China.

Extraction and Isolation The air-dried and powdered leaves and stems of *S. lancifolia* (3.2 kg) were extracted four times with 70% aqueous Me_2CO (4×3.5 l) at room temperature and filtered to yield a filtrate, which was successively evaporated under reduced pressure and partitioned with EtOAc (3×4 l). The EtOAc partition (158 g) was applied to Si gel (200—300 mesh) column chromatography eluting with a $CHCl_3$–MeOH gradient system (20 : 1, 9 : 1, 8 : 2, 7 : 3, 6 : 4, 5 : 5) to give five fractions A—E. The separation of fraction A (46.5 g) by Si gel column chromatography eluted with petroleum ether–acetone (20 : 1—1 : 2) yielded mixtures A1—A7. Fraction A1 (11.5 g) was subjected to Si gel column chromatography using petroleum ether–acetone and preparative HPLC (72% MeOH–H_2O, flow rate 12 ml/min) to give compounds **9** (4.2 mg), **10** (7.4 mg), **11** (7.62 mg), and **16** (22.8 mg). Fraction A2 (8.2 g) was subjected to Si gel column chromatography eluting with petroleum ether–acetone and then run on preparative HPLC (68% MeOH–H_2O, flow rate 12 ml/min) to yield compounds **6** (15.8 mg), **7** (22.5 mg), **8** (12.6 mg), **14** (52.8 mg), and **15** (23 mg). Fraction A3 (8.0 g) was subjected to Si gel column chromatography eluting with petroleum ether–acetone and then run on preparative HPLC (60% MeOH–H_2O, flow rate 12 ml/min) to give compounds **1** (8.5 mg), **2** (11.8 mg), **3** (8.62 mg), **5** (9.24 mg), and **12** (13.8 mg). Fraction A4 (5.2 g) was run on Si gel open column chromatography using petroleum ether–acetone as eluent, following with preparative HPLC (55% MeOH–H_2O, flow rate 12 ml/min) to give compounds **4** (13.2 mg) and **13** (14.2 mg).

Anti-HIV-1 Assay The cytotoxicity assay against C8166 cells (CC_{50}) was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium (MTT) method and anti-HIV-1 activity was evaluated by the inhibition assay for the cytopathic effects of HIV-1 (EC_{50}).[31]

Schilancifolignan A (**1**): Yellow gum; $[\alpha]_D^{22.5}$ +22.5 (c=0.24, MeOH); CD (c=0.0506, MeOH) λ_{max} nm ($\Delta\varepsilon$): 251 (−68.2), 240 (−49.4), 224 (+11.5), 220 (−1.86); UV (MeOH) λ_{max} (log ε): 210 (5.06), 243 (3.51), 320 (0.58) nm; IR (KBr) ν_{max}: 3115, 2927, 2866, 1642, 1558, 1472, 1395, 1326, 1228, 1115, 1065, 1012, 976 cm^{-1}; ^{1}H-NMR (pyridine-d_5, 500 MHz) δ: 6.99 (1H, s, H-4), 2.79 (1H, dd, J=15.0, 6.3 Hz, H-6α), 2.45 (1H, d, J=11.0 Hz, H-6β), 1.99—2.06 (1H, overlap, H-7), 1.99—2.06 (1H, overlap, H-8), 4.09 (1H, d, J=8.2 Hz, H-9), 6.73 (1H, s, H-11), 0.82 (3H, d, J=6.9 Hz, H-17), 0.99 (3H, d, J=7.0 Hz, H-18), 5.89, 5.99 (2H, s, H-19), 3.09 (3H, s, H-1′), 3.79, 3.86, 3.89, 3.93 (each 3H, s, 4×OMe); ^{13}C-NMR data, Table 1; HR-ESI-MS m/z 453.1889 $[M+Na]^+$ (Calcd $C_{24}H_{30}NaO_7$ for 453.1886).

Schilancifolignan B (**2**): Yellow gum; $[\alpha]_D^{23.5}$ +18.5 (c=0.22, MeOH); CD (c=0.0480, MeOH) λ_{max} nm ($\Delta\varepsilon$): 252 (−65.4), 240 (−45.6), 222 (+10.5), 218 (−1.05); UV (MeOH) λ_{max} (log ε): 210 (5.02), 245 (3.42), 320 (0.61) nm; IR (KBr) ν_{max}: 3122, 2925, 2838, 1645, 1553, 1476, 1393, 1327, 1235, 1108, 1072, 1008, 973 cm^{-1}; ^{1}H-NMR (pyridine-d_5, 500 MHz) δ: 6.97 (1H, s, H-4), 2.53 (1H, dd, J=15.8, 6.6 Hz, H-6α), 2.38 (1H, d, J=11.5 Hz, H-6β), 2.02 (1H, m, H-7), 2.14 (1H, m, H-8), 4.22 (1H, d, J=8.3 Hz, H-9), 6.81 (1H, s, H-11), 0.93 (3H, d, J=6.7 Hz, H-17), 1.02 (3H, d, J=7.5 Hz, H-18), 6.09, 6.18 (2H, s, H-19), 3.02 (3H, s, H-1′), 3.83, 3.91, 3.98 (each 3H, s, 3×OMe); ^{13}C-NMR data, Table 1; HR-ESI-MS m/z 439.1735 $[M+Na]^+$ (Calcd $C_{23}H_{28}NaO_7$ for 439.1733).

Schilancifolignan C (**3**): Yellow gum; $[\alpha]_D^{23.6}$ +20.2 (c=0.20, MeOH); CD (c=0.0565, MeOH) λ_{max} nm ($\Delta\varepsilon$): 252 (−71.2), 240 (−49.5), 222 (+12.8), 218 (−1.26); UV (MeOH) λ_{max} (log ε): 210 (5.32), 248 (3.35), 320 (1.26) nm; IR (KBr) ν_{max}: 3122, 2936, 2838, 1728, 1647, 1549, 1481, 1382, 1327, 1396, 1138, 1059, 1024, 978 cm^{-1}; ^{1}H-NMR (pyridine-d_5, 500 MHz) δ: 7.02 (1H, s, H-4), 2.74 (1H, dd, J=15.1, 6.8 Hz, H-6α), 2.56 (1H, d, J=11.8 Hz, H-6β), 2.21—2.26 (1H, overlap, H-7), 2.21—2.26 (1H, overlap, H-8), 5.66 (1H, d, J=8.4 Hz, H-9), 6.73 (1H, s, H-11), 0.83 (3H, d, J=6.9 Hz, H-17), 0.93 (3H, d, J=7.7 Hz, H-18), 5.92, 5.99 (2H, s, H-19), 2.03 (3H, s, H-2′), 3.73, 3.82, 3.85 (each 3H, s, 3×OMe); ^{13}C-NMR data, Table 1; HR-ESI-MS m/z 467.1686 $[M+Na]^+$ (Calcd $C_{24}H_{28}NaO_8$ for 467.1682).

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