Dibenzocyclooctadiene Lignans from *Schisandra wilsoniana* and Their Anti-HIV-1 Activities

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Twelve new dibenzocyclooctadiene lignans, marlignans A−L (**1**−**12**), together with 16 known compounds, were isolated from the leaves and stems of *Schisandra wilsoniana*. The structures of **1**−**12** were elucidated by spectroscopic methods including 1D- and 2D-NMR techniques. Compounds **1**−**12** were evaluated for their anti-HIV activities, of which compounds **3**, **6**, **8**, and **12** showed modest activities with therapeutic index values of 13.2, 15.6, 17.6, and 16.4, respectively.

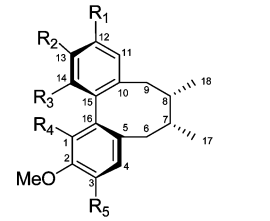
The plant family Schisandraceae, consisting of the genera *Schisandra* and *Kadsura*, is important medicinally. Many plants of this family are used commonly in Traditional Chinese Medicine for their diverse beneficial bioactivities.[1] Previous studies have shown that plants of the Schisandraceae are rich sources of dibenzocyclooctadiene lignans, which have been found to exhibit anti-HIV,[2−4] antitumor,[5] cytotoxic,[6,7] antioxidant,[8,9] and antihepatotoxic[10,11] effects.

Schisandra wilsoniana A. C. Smith (Schisandraceae) is a climbing plant mainly distributed in Heqing, Dali, and Yulong Prefectures of Yunnan Province in mainland China.[12,13] In previous work, a number of bioactive compounds, such as highly oxygenated nortriterpenoids, carotane sesquiterpenoids, and lignans, were isolated from this plant.[13−15] Some of these compounds showed anti-HIV-1 and anti-HBV activities in in vitro test systems. Motivated by a search for new bioactive metabolites from this plant, our group has investigated the chemical constituents of the leaves and stems of *S. wilsoniana*, which led to the isolation and characterization of 12 new dibenzocyclooctadiene lignans, marlignans A−L (**1**−**12**), along with 16 known substances. Compounds **1**−**12** were evaluated for their anti-HIV-1 activities, and the results are described herein.

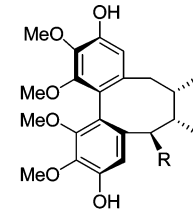
Results and Discussion

A 70% aqueous acetone extract prepared from the leaves and stems of *S. wilsoniana* was partitioned between EtOAc and H_2O. The EtOAc layer was subjected repeatedly to column chromatography on silica gel, Sephadex LH-20, RP-18, and semipreparative RP-HPLC to afford 12 new lignans, named marlignans A−L (**1**−**12**), together with 16 known lignans, which were identified as rubrisandrin A,[16] rubrisandrin B,[16] gomisin J,[17] gomisin N,[18] epigomisin O,[18] gomisin O,[18] gomisin S,[19] schisandrin C,[20] (−)-gomisin L_2,[21] angeloylisogomisin O,[22] gomisin N,[23] gomisin T,[19] schizandrin,[24] (+)-gomisin K,[25] angeloygomisin Q,[26] and benzoylgomisin Q.[25]

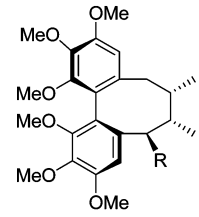
Compound **1** was obtained as a yellow gum, and the molecular formula was determined as $C_{21}H_{26}O_6$ by HRESIMS at *m*/z 397.1629 $[M + Na]^+$ (calcd *m*/z 397.1627). Its ^1H and ^{13}C NMR spectra showed signals for 26 hydrogens and 21 carbons, respectively,



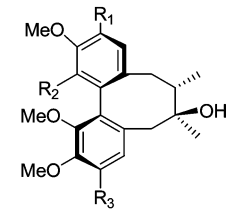
1 $R_1 = R_3 = R_5 = OH$; $R_2 = R_4 = OMe$
2 $R_1 = R_2 = OMe$; $R_3 = R_4 = R_5 = OH$
3 $R_1 = R_5 = OMe$; $R_2 = R_3 = R_4 = OH$



4 R = OH **5** R = OAc
6 R = OMe **7** R = OBz
8 R = =O



9 R = OAc
10 R = OEt



11 $R_1 = R_2 = OH$; $R_3 = OMe$
12 $R_1 = R_3 = OH$; $R_2 = OMe$

corresponding to two aromatic rings with two aromatic protons (δ_H 7.02 and 6.34), two methylene carbons (δ_C 35.9 and 39.6), two methine carbons (δ_C 34.3 and 41.7), two methyl groups (δ_C 13.0 and 21.9; δ_H 0.77, d, $J = 6.8$ Hz; δ_H 0.89, d, $J = 6.8$ Hz), three phenolic hydroxy groups (δ_H 10.43, 10.61, and 11.16), and three methoxy groups (δ_C 60.1, 60.6, and 60.5; δ_H 3.84, 3.90, and 3.89), suggesting the presence of a biphenyl moiety.[27] UV absorption bands at 210 and 241 nm and $^1H-^1H$ COSY correlations of H-6/H-7/H-8/H-9, H-7/H-17, and H-8/H-18 (Figure 1), together with the HMBC correlations (Figure 1) of H-11 (δ_H 6.34) with C-9 (δ_C 35.9), C-10 (δ_C 134.7), and C-15 (δ_C 119.5) and of H-4 (δ_H 7.02) with C-5 (δ_C 135.2), C-6 (δ_C 39.6), and C-16 (δ_C 121.7), implied that **1** is a dibenzocyclooctadiene lignan possessing three phenolic hydroxy groups and three methoxy groups. The ^1H and ^{13}C NMR spectra of **1** were found to be similar to those of rubrisandrin A.[16] Analysis of the ^1H and ^{13}C NMR data of **1** suggested that the only difference was due to a methoxy group in rubrisandrin A on an aromatic ring being replaced by a hydroxy group in **1**. In dibenzocyclooctadiene lignans, the chemical shifts of C-3 and C-12 methoxy groups occur at δ_C 55−56, whereas the C-1, C-2, C-13, and C-14 methoxy groups are found at δ_C 60−61.[2,17] The disappearance of the ^{13}C NMR signal at δ_C 55−56 in **1** suggested that two hydroxy groups are located at C-3 and C-12, which was also supported by HMBC correlations of the hydroxy proton signal at δ_H 10.61 with C-2, C-3, and C-4 and the hydroxy proton signal

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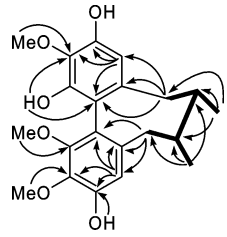

Figure 1. Selected HMBC (→) and ^{1}H−^{1}H COSY (−) correlations of **1**.

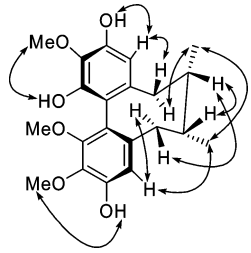

Figure 2. Key ROESY correlations of compound **1**.

at δ_H 10.44 with C-12. The HMBC correlations of another hydroxy proton signal at δ_H 11.16 with C-13, C-14, and C-15 indicated that this hydroxy group is located at C-14. The HMBC correlations of three methoxy groups (δ_C 60.1, 60.6, 60.5) with C-1, C-2, and C-13 suggested that these methoxy groups could be positioned at C-1, C-2, and C-13, respectively. In the cyclooctadiene ring, the signals for two methines were assigned to C-7 and C-8 with two benzylic methylenes attributed to C-6 and C-9 and two methyl groups located at C-17 and C-18, respectively, based on the analysis of its ^{1}H−^{1}H COSY and HMBC spectra. Thus, the planar structure of **1** was established.

The CD spectrum of **1** gave a negative Cotton effect at 253 nm and a positive Cotton effect at 220 nm, indicating that **1** has a *S*-biphenyl configuration.[27] The ROESY correlations between H-4/CH_3-17, H-11/H-9, and H-11/H-8 in **1** suggested a twist-boat-chair (TBC) conformation for the cyclooctadiene ring[28] (Figure 2). The substituent positions and stereochemical assignments in the cyclooctadiene ring of **1** were supported by the ROESY correlations of H-4/H-6α, H-4/CH_3-17, H-7/H-8, CH_3-17/CH_3-18, H-11/H-9β, H-8/H-6β, and H-9α/CH_3-18. Thus, the structure of **1** was determined as shown, and this compound has been given the trivial name marlignan A.

Compounds **2** and **3** were obtained as yellow gums and showed sodiated molecular ions at *m*/*z* 397.1629 and 397.1624 in the HRESIMS (both calcd *m*/*z* 397.1627), respectively, corresponding to the same molecular formula, $C_{21}H_{26}O_6$, for both compounds. The ^{1}H and ^{13}C NMR spectra of **2** and **3** were very similar to those of **1**. The obvious chemical shift differences resulted from the substituent group variations in the aromatic rings. Analysis of the HSQC, HMBC, and ROESY spectra of **2** and **3** showed that the methoxy groups are located at C-2, C-12, and C-13, and the phenolic hydroxy groups at C-1, C-3, and C-14 for **2**. In turn, methoxy groups could be located at C-2, C-3, and C-12, and the phenolic hydroxy groups at C-1, C-13, and C-14 for **3**. Thus, the structures of **2** and **3** were established, and they have been accorded the trivial name marlignan B and C, respectively.

Compound **4**, obtained as a yellow gum, was assigned the molecular formula $C_{22}H_{28}O_7$ from its HRESIMS at *m*/z 427.1730 $[M + Na]^+$ (calcd *m*/*z* 427.1733). Its ^{13}C and DEPT NMR spectra showed signals for 22 carbons, corresponding to two aromatic rings with two aromatic protons (δ_H 6.71 and 6.52), one methylene (δ_C 36.5), one oxygenated methine (δ_C 80.9), two methyl groups (δ_C 37.8 and 36.9), and four methoxy groups (δ_C 60.3, 60.8, 60.7, and 60.9), again suggesting the presence of a biphenyl moiety.[27] The HMBC correlations of H-11 (δ_H 6.52) with C-9 (δ_C 36.9), C-10 (δ_C 137.7), and C-15 (δ_C 122.6) and of H-4 (δ_H 6.71) with C-5 (δ_C 136.5), C-6 (δ_C 80.9), and C-16 (δ_C 123.7), together with ^{1}H−^{1}H COSY correlations of H-6/H-7/H-8/H-9, H-7/H-17, and H-8/H-18 and UV absorption bands at 210 and 241 nm, implied that **4** is also a dibenzocyclooctadiene lignan. The chemical shifts of the methoxy groups (δ_C 60.3, 60.8, 60.7, and 60.9) suggested that these are located at C-1, C-2, C-13, and C-14,[17] which was confirmed by analysis of its HMBC spectrum. In the cyclooctadiene ring, the oxygenated methine carbon was assigned to C-6 on the basis of the HMBC correlation from H-4 (δ_H 6.71) to C-6 (δ_C 80.9). The CD spectrum of **4** (negative Cotton effect at 252 nm and a positive Cotton effect at 223 nm) indicated that **4** has an *S*-biphenyl configuration.[27] The ROESY correlations between H-4/CH_3-17 and H-11/H-7 in **4** suggested a TBC conformation for the cyclooctadiene ring. The configuration of the hydroxy group attached to C-6 was deduced as being β-oriented by the chemical shift (δ_C 80.9), which was similar to β-oriented derivatives of the gomisins.[25] This was confirmed by the ROESY correlation between H-4/H-6α and H-6α/CH_3-18. Thus, the structure of **4** (marlignan D) was established, as shown.

Compounds **5**−**8** (marlignans E−H) were all obtained as yellow gums. By comparison of their IR, UV, ^{1}H and ^{13}C NMR, and ROESY spectra with those of **4**, compounds **5**−**8** were also assigned as *S*-biphenyl-configured dibenzocyclooctadiene lignans with a twisted boat/chair conformation of the cyclooctadiene ring, a quasi-axial CH_3-17, and a quasi-equatorial CH_3-18. Obvious differences between these compounds resulted from the substituent group at C-6. A β-oriented acetoxy group (δ_H 1.80; δ_C 169.9 and 21.0) was placed at C-6 for **5**, a β-oriented methoxy group (δ_H 3.01; δ_C 55.7) for **6**, and a β-oriented benzoyloxy group (δ_H 7.92, 7.32, 7.39; δ_C 165.6, 131.1, 130.1, 128.7, 133.1) for **7**. For compound **8**, C-6 was assigned as a carbonyl group (δ_C 201.1). Thus, the structures of **5**−**8** were established, as shown.

Compounds **9** and **10** (marlignans I and J) were both obtained as yellow gums. Comparison of ^{1}H and ^{13}C NMR spectra of **9** with those of **5** disclosed that the main structural differences between two compounds refer to the substituents in the aromatic rings. Two phenolic hydroxy groups were located at C-3 and C-12 for **5**, whereas two methoxy groups could be located at C-3 and C-12 for **9**. By comparison of the ^{1}H and ^{13}C NMR spectra of **10** with those of **9**, a difference was evident for the substituent group at C-6; that is, a β-oriented ethoxy group (δ_H 0.95, t, $J = 7.0$ Hz, and 3.14−3.23, m; δ_C 15.5, 63.7) could be located at C-6 for **10**. Thus, the structures of **9** and **10** were established, as shown.

Compounds **11** and **12** (marlignans K and L) were obtained as yellow gums, and both were assigned the molecular formula $C_{22}H_{28}O_7$ by HRESIMS at *m*/*z* 427.1735 and 427.1737 $[M + Na]^+$ (both calcd *m*/*z* 427.1733). The ^{1}H and ^{13}C NMR spectra of compound **11** showed signals for 28 protons and 22 carbons, respectively, corresponding to two aromatic rings with two aromatic protons (δ_H 7.02, 6.36), two methylene carbons (δ_C 39.2, 34.2), one methine carbon (δ_C 41.9), one oxygenated quaternary carbon (δ_C 73.0), two methyl groups, and four methoxy groups. The HMBC correlations of H-11 (δ_H 6.36) with C-9 (δ_C 34.2), C-10 (δ_C 135.4), and C-15 (δ_C 119.3) and of H-4 (δ_H 6.36) with C-5 (δ_C 134.7), C-6 (δ_C 39.2), and C-16 (δ_C 121.9), together with ^{1}H−^{1}H COSY correlations of H-9/H-8/H-18 and the UV absorptions at 212 and 240 nm, implied that **11** is a dibenzocyclooctadiene lignan possessing two phenolic hydroxy groups and four methoxy groups. The ^{1}H and ^{13}C NMR spectra of **11** were very similar to those of gomisin T.[19] The differences resulted from the appearance of a phenolic hydroxy group and the lack of a methoxy group in **11** on one of the aromatic rings, which was supported by the absence of a methoxy group singal when compared with gomisin T. Further analysis of the HMBC spectrum showed that four methoxy groups could be located at C-1, C-2, C-3, and C-13, and two phenolic

Table 1. ^{13}C NMR Data of Compounds **1**−**6** (δ in ppm)

position	**1**[a]	**2**[a]	**3**[a]	**4**[b]	**5**[a]	**6**[b]
1	151.8 s	146.1 s	147.6 s	152.7 s	152.6 s	151.9 s
2	140.5 s	140.0 s	136.2 s	141.8 s	142.1 s	141.3 s
3	150.3 s	148.2 s	150.2 s	151.7 s	151.2 s	150.5 s
4	112.5 d	115.6 d	107.4 d	116.1 d	116.8 d	116.1 d
5	135.2 s	135.1 s	134.5 s	136.5 s	137.2 s	136.8 s
6	39.6 t	39.3 t	39.7 t	80.9 d	81.4 d	90.1 d
7	34.3 d	34.4 d	34.3 d	37.8 d	38.0 d	38.8 d
8	41.7 d	41.4 d	41.5 d	36.9 d	37.2 d	36.5 d
9	35.9 t	36.2 t	36.3 t	36.5 t	39.2 t	37.9 t
10	134.7 s	134.4 s	132.1 s	137.7 s	134.3 s	137.6 s
11	106.9 d	103.6 d	104.0 d	110.7 d	111.5 d	111.1 d
12	148.7 s	150.7 s	151.3 s	151.6 s	149.2 s	149.6 s
13	139.8 s	138.2 s	134.9 s	139.9 s	139.9 s	139.3 s
14	146.4 s	142.5 s	144.1 s	151.9 s	152.1 s	151.3 s
15	119.5 s	118.6 s	119.5 s	122.6 s	121.8 s	121.7 s
16	121.7 s	122.7 s	118.5 s	123.7 s	123.1 s	123.7 s
17	13.0 q	13.1 q	13.1 q	17.5 q	16.8 q	17.2 q
18	21.9 q	21.9 q	21.9 q	17.5 q	16.8 q	17.4 q
1′					169.9 s	55.7 q
2′					21.0 q	
OMe-1	60.1 q			60.3 q	60.5 q	60.6 q
OMe-2	60.6 q	60.5 q	60.5 q	60.8 q	60.2 q	60.2 q
OMe-3			55.9 q			
OMe-12		55.9 q	56.0 q			
OMe-13	60.5 q	60.6 q		60.7 q	60.4 q	60.5 q
OMe-14				60.9 q	60.6 q	60.9 q

[a] Data were recorded in C_5D_5N. [b] Data were recorded in $CDCl_3$.

hydroxy groups occurred at C-12 and C-14, respectively. In the cyclooctadiene ring, the signal of a methine group (δ_C 41.9 d) was assigned at C-8, for an oxygenated quaternary carbon (δ_C 73.0) at C-7, and for two benzylic methylenes (δ_C 39.2, 34.2) at C-6 and C-9, by analysis of the 2D NMR spectra of **11**. Two methyl groups, Me-17 (δ_C 30.1; δ_H 1.39, s) and Me-18 (δ_C 16.6; δ_H 0.72, d, J = 8.8 Hz), were assigned at C-7 and C-8, respectively, by analysis of its HMBC spectrum. Thus, the planar structure of **11** was determined.

The CD spectrum of **11** (positive Cotton effect at 250 nm and a negative Cotton effect at 220 nm) indicated that **11** has an *R*-biphenyl configuration.[19,24] The ROESY correlations between H-4/H-6 and H-11/CH_3-18 in **11** suggested a TBC conformation for the cyclooctadiene ring. The substituent positions and stereochemical assignments in the cyclooctadiene ring of **11** were supported by the ROESY correlations between the protons H-11/H-9α, H-9α/CH_3-18, CH_3-17/CH_3-18, H-4/H-6β, H-8/H-9β, and H-6α/CH_3-17. Thus, the structure of **11** was determined, as shown.

The ^1H and ^{13}C NMR spectra of **12** were very close to those of **11**. The obvious chemical shift differences resulted from the different substituent groups in the aromatic rings. Analysis of the HMBC spectra showed that four methoxy groups could be located at C-1, C-2, C-13, and C-14, with two phenolic hydroxy groups positioned at C-3 and C-12. Thus, the structure of **12** was established, as shown.

Since certain dibenzocyclooctadiene lignans from *Schisandra* genus species exhibit potential anti-HIV activities, the new compounds **1**−**12** were tested for their potencies in preventing the cytopathic effects of HIV-1 in C8166 cells. Cytotoxicity was measured in parallel with the determination of antiviral activity, using AZT as a positive control (0.0043 μg/mL and CC_{50} >200 μg/mL).[29] The results are shown in Table 3. Of the substances tested, compounds **3**, **6**, **8**, and **12** showed therapeutic index (TI) values of 13.2, 15.6, 17.6, and 16.4, respectively.

Table 2. ^{13}C NMR Data of Compounds **7**−**12** (δ in ppm)

position	**7**[a]	**8**[a]	**9**[b]	**10**[b]	**11**[a]	**12**[a]
1	152.8 s	152.8 s	151.4 s	151.3 s	152.5 s	152.4 s
2	139.9 s	142.5 s	142.6 s	142.2 s	140.4 s	140.3 s
3	149.2 s	149.1 s	153.0 s	153.3 s	152.9 s	149.2 s
4	116.6 d	113.4 d	111.4 d	111.1 d	111.4 d	112.4 d
5	136.0 s	135.0 s	134.2 s	135.6 s	132.5 s	136.9 s
6	81.9 d	201.1 s	81.0 d	88.5 d	39.2 t	39.1 t
7	37.5 d	41.4 d	36.8 d	37.2 d	73.0 s	72.2 s
8	38.2 d	45.6 d	37.1 d	38.1 d	41.9 d	41.5 d
9	37.9 t	40.1 t	38.4 t	40.7 t	34.2 t	34.2 t
10	135.8 s	136.7 s	136.3 s	137.2 s	134.4 s	134.9 s
11	111.8 d	111.3 d	106.5 d	106.2 d	112.6 d	115.5 d
12	149.0 s	148.5 s	151.9 s	152.8 s	148.2 s	148.6 s
13	137.6 s	139.8 s	140.4 s	140.1 s	137.9 s	139.7 s
14	152.1 s	151.7 s	150.8 s	150.4 s	148.2 s	152.3 s
15	121.9 s	121.2 s	122.4 s	122.5 s	122.6 s	121.6 s
16	123.0 s	123.0 s	123.2 s	123.6 s	123.7 s	122.5 s
17	13.0 q	15.6 q	16.8 q	16.5 q	30.1 q	29.8 q
18	17.9 q	15.7 q	16.8 q	16.5 q	16.6 q	16.9 q
1′	165.6 s		170.0 s	63.7 t		
2′	131.1 s		21.1 q	15.5 q		
3′, 7′	130.1 d					
4′, 6′	128.7 d					
5′	133.1 d					
OMe-1	60.4 q	60.6 q	60.0 q	60.3 q	60.7 q	60.5 q
OMe-2	60.2 q	60.8 q	59.7 q	60.9 q	60.8 q	60.7 q
OMe-3			55.7 q	55.8 q	55.7 q	
OMe-12			55.8 q	56.0 q		
OMe-13	60.3 q	60.9 q	60.9 q	60.5 q	61.0 q	60.5 q
OMe-14	60.5 q	60.7 q	60.4 q	60.7 q		60.8 q

[a] Data were recorded in C_5D_5N. [b] Data were recorded in $CDCl_3$.

Table 3. Anti-HIV Activities of Compounds **1**−**12**

compound	CC_{50} (μg/mL)	EC_{50} (μg/mL)	TI
1	15.8	2.6	6.0
2	43.4	5.1	8.4
3	65.6	5.0	13.2
4	14.2	2.5	5.7
5	13.7	1.6	8.7
6	21.4	1.4	15.6
7	14.2	2.1	6.7
8	46.5	2.6	17.6
9	13.5	2.9	4.6
10	17.2	1.9	9.3
11	14.8	1.9	7.7
12	22.6	1.4	16.4

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. CD spectra were measured on a JASCO J-810 spectropolarimeter. A Tenor 27 spectrophotometer was used for scanning IR spectrometry. 1D and 2D NMR spectra were recorded on a DRX-500 NMR spectrometer with TMS as internal standard. Unless otherwise specified, chemical shifts (δ) are expressed in ppm with reference to the solvent signals. HRESIMS was performed on a VG Autospec-3000 spectrometer. Semipreparative HPLC was performed on a Shimadzu LC-8A preparative liquid chromatograph with Zorbax PrepHT GF (21.2 mm ×25 cm) or Venusil MP C_{18} (20 mm ×25 cm) columns. Column chromatography was performed using silica gel (200−300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, People's Republic of 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 silica gel plates sprayed with 5% H_2SO_4 in EtOH.

Plant Material. The leaves and stems of *S. wilsoniana* were collected on Marer Mountain in Dali Prefecture, Yunnan Province, People's Republic of China, in July 2005. The identification of the plant material was verified by Prof. Xi-Wen Li of Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (KIB 05-7-12) has been deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The air-dried and powdered leaves and stems of *S. wilsoniana* (8.0 kg) were extracted four times with 70% aqueous Me_2CO (4 × 10 L) at room temperature and filtered, with the filtrate evaporated under reduced pressure and partitioned with EtOAc (3 × 4 L). The EtOAc partition (636 g) was applied to silica 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 further separation of fraction A (150 g) by silica gel column chromatography, eluted with petroleum ether−acetone (20:1−1:2), yielded mixtures A1−A7. Fraction A1 (35 g) was subjected to silica gel column chromatography using petroleum ether−acetone and semipreparative HPLC (75% MeOH−H_2O, flow rate 12 mL/min) to give **9** (4.2 mg), **10** (7.4 mg), gomisin J (15.8 mg), gomisin N (22.6 mg), angeloylisogomisin O (58.4 mg), and gomisin N (158 mg). Fraction A2 (8.2 g) was subjected to silica gel column chromatography using petroleum ether−acetone and semipreparative HPLC (65% MeOH−H_2O, flow rate 12 mL/min) to give **5** (2.8 mg), **6** (3.9 mg), **7** (1.8 mg), epigomisin O (123 mg), gomisin O (28.5 mg), schisandrin C (19.2 mg), schizandrin (9.26 mg), (+)-gomisin K (12.9 mg), angeloygomisin Q (11.8 mg), and benzoylgomisin Q (23.4 mg). Fraction A3 (6.5 g) was subjected to silica gel column chromatography using petroleum ether−acetone and semipreparative HPLC (60% MeOH−H_2O, flow rate 12 mL/min) to afford **4** (7.5 mg), **8** (2.1 mg), rubrisandrin A (35.4 mg), rubrisandrins B (16.6 mg), gomisin S (11.9 mg), and (−)-gomisins L_2 (24.8 mg). Fraction A4 (4.6 g) was subjected to silica gel column chromatography using petroleum ether−acetone and semipreparative HPLC (55% MeOH−H_2O, flow rate 12 mL/min) to give **1** (13.2 mg), **2** (11.5 mg), **3** (16.2 mg), **11** (16.2 mg) **12** (20.1 mg), and gomisin T (18.2 mg).

Marlignan A (1): yellow gum; $[\alpha]_D^{24}$ +42.3 (*c* 0.21, MeOH); UV (MeOH) λ_{max} (log ε) 210 (5.22), 241 (3.28), 326 (0.45) nm; CD (*c* 0.02, MeOH), nm ($\Delta\varepsilon$) 253 (−17.2), 224 (+7.62), 220 (+5.02); IR (KBr) ν_{max} 3450, 2938, 2875, 2830, 1640, 1595, 1489, 1396, 1328, 1278, 1238, 1195, 1130, 1108, 1065, 1007, 982 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 7.02 (1H, s, H-4), 2.63 (1H, dd, J = 13.4, 7.0 Hz, H-6α), 2.67 (1H, d, J = 13.3 Hz, H-6β), 1.82−1.87 (1H, overlapping, H-7), 1.82−1.87 (1H, overlapping, H-8), 2.07 (1H, d, J = 13.0 Hz, H-9α), 2.48 (1H, dd, J = 9.2, 13.2 Hz, H-9β), 6.34 (1H, s, H-11), 0.77 (3H, d, J = 6.8 Hz, H-17), 0.89 (3H, d, J = 6.8 Hz, H-18), 3.84, 3.89, 3.90 (3H each, s, 3 × OMe), 10.43, 10.61, 11.16 (1H each, s, 3 × OH); ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 397 $[M + Na]^+$; HRESIMS *m/z* 397.1629 $[M + Na]^+$ (calcd for $C_{21}H_{26}NaO_6$, 397.1627).

Marlignan B (2): yellow gum; $[\alpha]_D^{24}$ +38.5 (*c* 0.28, MeOH); UV (MeOH) λ_{max} (log ε) 210 (5.16), 240 (3.31), 325 (0.29) nm; IR (KBr) ν_{max} 3468, 2941, 2871, 1638, 1585, 1486, 1468, 1398, 1332, 1280, 1235, 1198, 1072, 1015, 988, 959 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 6.96 (1H, s, H-4), 2.51 (1H, overlapping, H-6α), 2.66 (1H, d, J = 13.4 Hz, H-6β), 1.81 (1H, m, H-7), 1.87 (1H, m, H-8), 2.14 (1H, d, J = 13.0 Hz, H-9α), 2.51 (1H, overlapping, H-9β), 6.62 (1H, s, H-11), 0.74 (3H, d, J = 7.0 Hz, H-17), 0.92 (3H, d, J = 7.0 Hz, H-18), 3.84, 3.88, 3.90 (3H each, s, 3 × OMe), 10.13, 10.46, 11.11 (1H each, s, 3 × OH); ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 397 $[M + Na]^+$; positive HRESIMS *m/z* 397.1629 $[M + Na]^+$ (calcd for $C_{21}H_{26}NaO_6$, 397.1627).

Marlignan C (3): yellow gum; $[\alpha]_D^{25}$ +35.8 (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ε) 210 (5.33), 240 (3.30), 328 (0.43) nm; IR (KBr) ν_{max} 3448, 2943, 2881, 2815, 1642, 1586, 1482, 1458, 1392, 1325, 1283, 1235, 1198, 1135, 1102, 1068, 1014, 982, 967 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 6.59 (1H, s, H-4), 2.56 (dd, J = 13.5, 7.0 Hz, H-6α), 2.70 (1H, d, J = 13.5 Hz, H-6β), 1.86−1.88 (1H, overlapping, H-7), 1.86−1.88 (1H, overlapping, H-8), 1.86 (1H, d, J = 13.0 Hz, H-9α), 2.52 (1H, dd, J = 9.2, 13.3 Hz, H-9β), 6.50 (1H, s, H-11), 0.77 (3H, d, J = 6.8 Hz, H-17), 0.92 (3H, d, J = 6.8 Hz, H-18), 3.69, 3.76, 3.80 (3H each, s, 3 × OMe), 9.87, 10.08, 10.63 (1H each, s, 3 × OH); ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 397 $[M + Na]^+$; HRESIMS *m/z* 397.1624 $[M + Na]^+$ (calcd $C_{21}H_{26}NaO_6$ for 397.1627).

Marlignan D (4): yellow gum; $[\alpha]_D^{25}$ +42.8 (*c* 0.28, MeOH); UV (MeOH) λ_{max} (log ε) 210 (5.84), 241 (3.52), 326 (0.52), 345 (0.32) nm; CD (*c* 0.03, MeOH), nm ($\Delta\varepsilon$) 252 (−36.5), 247 (−22.8), 223 (+6.2), 215 (+2.22); IR (KBr) ν_{max} 3480, 3452, 2938, 2865, 2822, 1622, 1546, 1471, 1447, 1387, 1323, 1277, 1233, 1187, 1128, 1118, 1065, 1022, 978, 951 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.71 (1H, s, H-4), 5.82 (1H, d, J = 7.6 Hz, H-6), 1.95 (1H, overlapping, H-7), 2.19 (1H, m, H-8), 1.94 (1H, overlapping, H-9α), 2.26 (1H, m, H-9β), 6.52 (1H, s, H-11), 0.78 (3H, d, J = 6.6 Hz, H-17), 0.97 (3H, d, J = 6.7 Hz, H-18), 3.65, 3.66, 3.87, 3.89 (3H each, s, 4 × OMe); ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 427 $[M + Na]^+$; HRESIMS *m/z* $[M + Na]^+$ *m/z* 427.1730 $[M + Na]^+$ (calcd for $C_{22}H_{28}NaO_7$, 427.1733).

Marlignan E (5): yellow gum; $[\alpha]_D^{23}$ +52.0 (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ε) 205 (5.22), 242 (4.28), 285 (2.90), 309 (1.18), 360 (1.85) nm; IR (KBr) ν_{max} 3485, 2970, 2946, 1715, 1622, 1565, 1494, 1450, 1424, 1405, 1362, 1268, 1184, 1145, 1124, 1112, 1023, 876 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 7.42 (1H, s, H-4), 5.94 (d, J = 9.8 Hz, H-6), 2.04−2.07 (1H, overlapping, H-7), 2.04−2.07 (1H, overlapping, H-8), 2.20 (1H, dd, J = 16.1, 6.9 Hz, H-9α), 2.47 (1H, m, H-9β), 6.98 (1H, s, H-11), 0.84 (3H, overlapping, H-17), 0.84 (3H, overlapping, H-18), 3.72, 3.88, 3.92, 3.93 (3H each, s, 4 × OMe), 11.8, 11.68 (1H each, s, 2 × OH), 1.80 (3H, s, H-2′); ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 469 $[M + Na]^+$; HRESIMS *m/z* 469.1842 $[M + Na]^+$ (calcd for $C_{24}H_{30}NaO_8$, 469.1838).

Marlignan F (6): yellow gum; $[\alpha]_D^{22}$ +33.2; UV (MeOH) λ_{max} (log ε) 205 (5.64), 245 (3.28), 329 (0.64), 348 (0.48) nm; IR (KBr) ν_{max} 2948, 2932, 2870, 1622, 1575, 1491, 1456, 1412, 1326, 1272, 1150, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.74 (1H, s, H-4), 3.94 (d, J = 8.5 Hz, H-6), 1.64 (1H, brs, H-7), 1.96 (1H, m, H-8), 2.00 (1H, dd, J = 7.9, 15.0 Hz, H-9α), 2.39 (1H, m, H-9β), 6.50 (1H, s, H-11), 0.88 (3H, overlapping, H-17), 0.88 (3H, overlapping, H-18), 3.76, 3.87, 3.88, 3.89 (3H each, s, 4 × OMe), 3.01 (3H, s, H-1′); ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 441 $[M + Na]^+$; HRESIMS *m/z* 441.1892 $[M + Na]^+$ (calcd for $C_{24}H_{30}NaO_7$, 441.1889).

Marlignan G (7): yellow gum; $[\alpha]_D^{24}$ +35.2 (*c* 0.21, MeOH); UV (MeOH) λ_{max} (log ε) 203 (5.22), 243 (4.22), 281 (2.18), 374 (2.42), 395 (1.87) nm; CD (*c* 0.04, MeOH), nm ($\Delta\varepsilon$) 252 (−56.5), 247 (−42.8), 223 (+11.2), 215 (+7.22); IR (KBr) ν_{max} 3456, 2932, 2878, 1726, 1618, 1552, 1524, 1496, 1452, 1415, 1372, 1365, 1338, 1246, 1196, 1175, 1155, 1132, 1105, 1029, 1014 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 7.32 (1H, s, H-4), 6.28 (1H, d, J = 8.1 Hz, H-6), 2.09 (1H, m, H-7), 1.89 (1H, m, H-8), 2.23 (1H, m, H-9α), 2.41 (1H, m, H-9β), 7.08 (1H, s, H-11), 0.83 (3H, d, J = 6.8 Hz, H-17), 0.91 (3H, d, J = 6.8 Hz, H-18), 3.72, 3.74, 3.87, 3.89 (3H each, s, 4 × OMe), 10.63, 10.32 (1H each, s, 2 × OH), 7.92 (2H, d, J = 8.3 Hz, H-3′), 7.92 (2H, d, J = 8.3 Hz, H-3′, H-7′), 7.32 (2H, m, H-4′, H-6′), 7.39 (2H, m, H-4′, H-6′); ^{13}C NMR data, see Table 2; positive ESIMS *m/z* 531 $[M + Na]^+$; HRESIMS *m/z* 531.1999 $[M + Na]^+$ (calcd for $C_{29}H_{32}NaO_8$, 531.1995).

Marlignan H (8): yellow gum; $[\alpha]_D^{25}$ +26.5 (*c* 0.28, MeOH); UV (MeOH) λ_{max} (log ε) 203 (5.48) 240 (4.15), 280 (2.25), 370 (2.26) nm; CD (*c* 0.08, MeOH), nm ($\Delta\varepsilon$) 252 (−45.8), 230 (+38.6), 212 (−2.17); IR (KBr) ν_{max} 3468, 2936, 2842, 1732, 1680, 1642, 1588, 1485, 1438, 1402, 1325, 1264, 1230, 1192, 1160, 1122, 1038, 1015 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 8.20 (1H, s, H-4), 1.82 (1H, m, H-7), 3.04 (1H, m, H-8), 2.68 (1H, m, H-9α), 2.38 (1H, dd, J = 12.4, 11.2 Hz, H-9β), 7.05 (1H, s, H-11), 0.81 (3H, d, J = 6.6 Hz, H-17), 1.02 (3H, d, J = 6.5 Hz, H-18), 3.70, 3.91, 3.93, 4.00 (3H each, s, 4 × OMe); ^{13}C NMR data, see Table 2; positive ESIMS *m/z* 425 $[M + Na]^+$; HRESIMS *m/z* $[M + Na]^+$ 425.1571 (calcd for $C_{22}H_{26}NaO_7$, 425.1576).

Marlignan I (9): yellow gum; $[\alpha]_D^{23}$ +38.4 (*c* 0.32, MeOH); UV (MeOH) λ_{max} (log ε) 206 (5.88), 242 (3.62), 328 (0.61), 346 (0.47) nm; IR (KBr) ν_{max} 2947, 2862, 1721, 1638, 1582, 1471, 1408, 1381, 1285, 1211, 1130, 1102, 1042, 1014, 852 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.70 (1H, s, H-4), 5.64 (1H, d, J = 8.2 Hz, H-6), 1.85−1.87 (1H, overlapping, H-7), 1.85−1.87 (1H, overlapping, H-8), 2.43 (1H, m, H-9α), 2.12 (1H, dd, J = 8.0, 15.2 Hz, H-9β), 6.52 (1H, s, H-11), 0.85 (3H, d, J = 6.8 Hz, H-17), 0.96 (3H, d, J = 7.0 Hz, H-18), 3.75, 3.78, 3.84, 3.86, 3.91, 3.93 (3H each, s, 6 × OMe); ^{13}C NMR data, see Table 2; positive ESIMS *m/z* 497 $[M + Na]^+$; HRESIMS *m/z* 497.2154 $[M + Na]^+$ (calcd for $C_{26}H_{34}NaO_8$, 497.2151).

Marlignan J (10): yellow gum; $[\alpha]_D^{24}$ +35.5 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ε) 205 (5.64), 240 (3.60), 329 (0.64), 348 (0.48) nm; CD (*c* 0.07, MeOH), nm ($\Delta\varepsilon$) 249 (−62.4), 240 (−38.5), 220 (+22.6), 210 (+5.4); IR (KBr) ν_{max} 2948, 2932, 2870, 1622, 1575, 1491, 1456, 1412, 1326, 1272, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.74 (1H, s, H-4), 4.06 (1H, d, J = 8.2 Hz, H-6), 1.99−2.02 (1H, m, H-7), 1.85−1.88 (1H, m, H-8), 2.56 (1H, dd, J = 13.6, 8.1 Hz, H-9α), 2.23 (1H, d, J = 13.0 Hz, H-9β), 6.34 (1H, s, H-11), 0.76 (3H, d, J = 6.9 Hz, H-17), 0.84 (3H, d, J = 7.6 Hz, H-18), 3.79, 3.81, 3.82, 3.86, 3.87, 3.90 (3H each, s, 6 × OMe), 3.14−3.23 (2H, m, H-1′), 0.95 (3H, t, J = 7.0 Hz, H-2′); ^{13}C NMR data, see Table 2; positive ESIMS *m/z* 483 $[M + Na]^+$; HRESIMS *m/z* 483.2356 $[M + Na]^+$ (calcd for $C_{26}H_{36}NaO_7$, 483.2359).

Marlignan K (11): yellow gum; $[\alpha]_D^{25}$ +42.2 (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ε) 208 (5.48), 240 (3.22), 325 (0.52), 345 (0.31) nm; CD (*c* 0.02, MeOH), nm ($\Delta\varepsilon$) 250 (+18.6), 240 (+10.2), 222 (+18.6), 222 (−6.8); IR (KBr) ν_{max} 3452, 2938, 2868, 1610, 1562,

1482, 1463, 1395, 1330, 1276, 1186, 1065, 1025, 976, 948 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 7.02 (1H, s, H-4), 2.83 (1H, d, J = 13.8 Hz, H-6α), 3.22 (1H, d, J = 13.1 Hz, H-6β), 2.17 (1H, m, H-8), 2.62 (1H, d, J = 10.8 Hz, H-9α), 2.51 (1H, dd, J = 14.6, 6.6 Hz, H-9β), 6.77 (1H, s, H-11), 1.39 (3H, s, H-17), 0.72 (3H, d, J = 8.8 Hz, H-18), 3.70, 3.88, 3.89, 3.90 (3H each, s, 4 × OMe), 5.01, 10.26, 11.05 (1H each, s, 3 × OH); ^{13}C NMR data, see Table 2; positive ESIMS *m/z* 427 $[M + Na]^+$; HRESIMS *m/z* 427.1735 $[M + Na]^+$ (calcd for $C_{22}H_{28}NaO_7$, 427.1733).

Marlignan L (12): yellow gum; $[\alpha]_D^{25}$ +35.2 (*c* 0.24, MeOH); UV (MeOH) λ_{max} (log ε) 210 (5.06), 239 (3.48), 330 (0.58), 348 (0.27) nm; IR (KBr) ν_{max} 3449, 2942, 2865, 1622, 1541, 1460, 1392, 1326, 1279, 1189, 1061, 1018, 978, 942 cm^{-1}; ^1H NMR (C_5D_5N, 500 MHz) δ 7.04 (1H, s, H-4), 2.56 (1H, d, J = 13.8 Hz, H-6α), 3.03 (1H, d, J = 13.1 Hz, H-6β), 1.82 (1H, m, H-8), 2.09 (1H, d J = 11.1 Hz, H-9α), 2.45 (1H, dd, J = 14.0, 6.4 Hz, H-9β), 6.79 (1H, s, H-11), 1.05 (3H, s, H-17), 0.73 (3H, d, J = 8.4 Hz, H-18), 3.75, 3.83, 3.85, 3.95 (3H each, s, 4 × OMe), 5.18, 11.22, 11.40 (1H each, s, 3 × OH); ^{13}C NMR data, see Table 2; positive ESIMS *m/z* 427 $[M + Na]^+$; HRESIMS *m/z* 427.1737 $[M + Na]^+$ (calcd for $C_{22}H_{28}NaO_7$, 427.1733).

Anti-HIV-1 Assay. The cytotoxicity assay against C8166 cells (CC_{50}) was assessed using the MTT method, and anti-HIV-1 activity was evaluated by the inhibition assay for the cytopathic effects of HIV-1 (EC_{50}).[29]

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Supporting Information Available: ^1H and ^{13}C NMR, HSQC, HMBC COSY, ROESY, and HRESIMS spectra of **1**, ^1H and ^{13}C NMR, HSQC, and HMBC of **2**−**4**, **9**, and **11**, H and ^{13}C NMR spectra of **5**−**8**, **10**, and **12**, and CD spectra of **1** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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