Schisanartane Nortriterpenoids with Diverse Post-modifications from *Schisandra propinqua*

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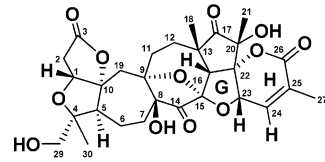
Twenty-one highly oxygenated nortriterpenoids with a schisanartane skeleton were isolated from the stems of *Schisandra propinqua* var. *propinqua*. These nortriterpenoids featured a polycyclic framework composed of 7/8/5 consecutive carbocycles, which were organized by similar 5/5/7/5/7/5 rings A−F and varied oxygen-containing rings G and H. A biosynthetic classification of these compounds is proposed on the basis of their diverse post-modifications.

Micrandilactone A (**14**) was the first natural highly oxygenated nortriterpenoid with a schisanartane skeleton and was isolated from the stems of *Schisandra micrantha* in 2003.[1] Since then, our group has isolated a series of structurally interesting and novel nortriterpenoids with C_{29},[2−13] C_{28},[14,15] C_{27},[16,17] C_{25},[18] and C_{22}[19] backbones from more than 10 species of the *Schisandra* genus under the Schisandraceae family. Schisanartane-type nortriterpenoids are a unique family derived from the cycloartane triterpenoid. They feature a polycyclic backbone with 7/8/5 consecutive carbocycles and more than 12 stereogenic centers. These carbocycles are organized with similar 5/5/7/5/7/5 rings A−F and varied oxygen-containing rings G and H. Varied oxygen-containing ring systems and diverse post-modifications on the backbone have afforded a vast structural diversity of compounds in the schisanartane family, accounting for the majority of C_{29} *Schisandra* nortriterpenoids. The unique ring assembly and the highly oxygenated structural features of the schisanartane-type nortriterpenoids are distinct from normal cycloartane triterpenoids and are of great interest and have presented great challenges among phytochemists, synthetic chemists, and pharmacologists.

Schisandra propinqua var. *propinqua* is an indigenous climbing plant found in Yunnan Province. In traditional Chinese medicine, the aerial parts of this species are used for the treatment of rheumatic lumbago, traumatic injury, and related diseases. Previous phytochemical investigations of the plant collected from the same region in Yunnan Province have led to the identification of several *Schisandra* nortriterpenoids,[2,7,8,13] including eight schisanartanes.[2] Further studies led to the isolation of 21 schisanartane nortriterpenoids, including the 10 new compounds schisandilactones A−J (**1**−**10**) and 11 known analogues: propindilactones A−C (**11**−**13**),[2] micrandilactones A (**14**), D (**15**), and E (**16**),[3] henridilactone D (**17**),[4] lancifodilactone C (**18**),[5] propindilactone D (**19**),[2] and henridilactones A and B (**20** and **21**).[4] These compounds are biogenetically related and consist of varied oxygen-containing rings G and H, including the 5/6, 5/5, and 0/5 type, which are structurally unique compared to the normal 6/5 type. Herein, we describe the structure, biosynthetic relations, and cytotoxicity of the new schisanartane nortriterpenoids.



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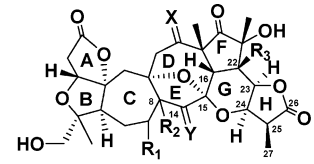
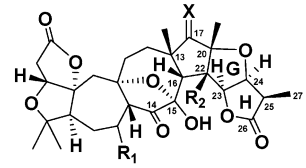
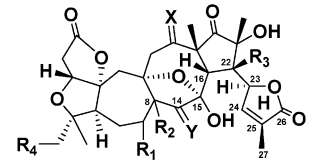


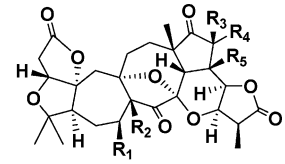
	R_1	R_2	X	Y	R_3
7	H	β-H	O	α-OH	H
8	H	α-H	O	α-OH	OH
9	H	β-H	H_2	O	H
10	β-O-		H_2	O	OH
11	H	β-H	O	α-OH	OH
12	H	β-OH	H_2	O	OH
13	H	β-H	H_2	O	OH



	R_1	X	R_2
2	β-OH	α-OH	H
3	β-OH	O	OH
4	α-OH	O	OH



	R_1	R_2	X	Y	R_3	R_4
5	H	α-H	O	α-OH	H	OH
6	α-OH	β-H	H_2	O	OH	H



	R_1	R_2	R_3	R_4	R_5
14	OH	H	CH_3	OH	OH
15	OH	H	CH_3	OH	H
16	OH	H	OH	CH_3	H
17	OH	H	H	CH_3	H
18	OH	H	CH_3	H	H
19	-O-		OH	CH_3	H
20	=		CH_3	OH	H
21	=		CH_3	OH	OH

Results and Discussion

The powdered, dry stems of *S. propinqua* var. *propinqua* were extracted with 70% aqueous acetone and subsequently partitioned with petroleum ether and EtOAc. The EtOAc fraction was evaporated and subjected to successive chromatographic fractionation and purification steps to yield compounds **1**−**10** and the 11 known compounds. The known compounds were identified to be schisanartane members by comparing their spectroscopic and physical data with reported data.[2−5]

Schisandilactone A (**1**) was obtained as an amorphous powder. Its molecular formula ($C_{29}H_{34}O_{12}$) was determined by HRESIMS (*m*/*z* 573.1944 $[M - H]^-$; calcd 573.1972), which suggested 13 degrees of unsaturation. The IR spectrum indicated hydroxy (3437 cm^{-1}), lactone (1732 cm^{-1}), carbonyl (1777 cm^{-1}), and double-bond (1679 cm^{-1}) functionalities. The ^{13}C and DEPT NMR spectra of **1** (Table 1) revealed 29 carbon signals, including four methyl, seven methylene (one oxygenated), four methine (two oxygenated), one trisubstituted double bond, and 12 nonprotonated (two esters, two carbonyls, and seven oxygenated) carbons. These data suggested that **1** was a highly oxygenated C_{29} nortriterpenoid possessing

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Table 1. ^{13}C NMR Data of Compounds **1**−**6**[a]

carbon	1	2	3	4	5	6
1	82.1, CH	81.8, CH	81.8, CH	82.0, CH	80.8, CH	82.0, CH
2	35.3, CH_2	35.6, CH_2	35.4, CH_2	35.3, CH_2	35.7, CH_2	35.3, CH_2
3	175.2, C	176.0, C	176.0, C	176.0, C	174.6, C	175.5, C
4	87.3, C	84.6, C	84.3, C	84.2, C	87.7, C	84.2, C
5	55.7, CH	57.1, CH	57.5, CH	52.6, CH	51.9, CH	53.2, CH
6	20.1, CH_2	37.6, CH_2	37.2, CH_2	31.1, CH_2	23.2, CH_2	31.0, CH_2
7	32.5, CH_2	69.4, CH_2	69.4, CH_2	67.9, CH_2	23.1, CH_2	68.3, CH
8	79.5, C	67.0, CH	60.2, CH	57.3, CH	47.2, CH	57.4, CH
9	83.0, C	78.1, C	79.7, C	80.3, C	80.7, C	82.0, C
10	97.0, C	97.0, C	96.4, C	96.7, C	97.2, C	96.2, C
11	35.0, CH_2	39.2, CH_2	42.4, CH_2	42.6, CH_2	52.1, CH_2	42.6, CH_2
12	32.1, CH_2	25.2, CH_2	31.9, CH_2	31.6, CH_2	207.4, C	34.4, CH_2
13	47.5, C	44.6, C	51.5, C	52.2, C	64.9, C	50.0, C
14	213.7, C	212.1, C	213.5, C	214.4, C	78.4, CH	213.4, C
15	103.4, C	100.2, C	100.1, C	100.1, C	105.3, C	99.7, C
16	67.2, CH	50.5, CH	63.6, CH	62.5, CH	55.9, CH	60.2, CH
17	218.9, C	87.4, CH	218.8, C	218.0, C	219.1, C	220.5, C
18	26.9, CH_3	26.9, CH_3	30.9, CH_3	30.9, CH_3	21.5, CH_3	18.4, CH_3
19	41.7, CH_2	42.5, CH_2	41.8, CH_2	41.5, CH_2	44.6, CH_2	41.8, CH_2
20	79.9, C	92.1, C	89.6, C	89.2, C	76.2, C	80.4, C
21	21.6, CH_3	26.5, CH_3	20.8, CH_3	21.0, CH_3	25.5, CH_3	32.5, CH_3
22	93.5, C	54.4, CH	88.3, C	88.3, C	54.4, CH	83.0, C
23	71.3, CH	89.4, CH	86.5, CH	86.6, CH	80.7, CH	83.7, CH
24	136.7, CH	83.4, CH	80.8, CH	80.8, CH	152.2, CH	150.7, CH
25	128.9, C	41.7, CH	42.4, CH	42.6, CH	129.6, C	130.5, C
26	161.4, C	179.3, C	178.7, C	178.7, C	174.1, C	174.8, C
27	17.4, CH_3	9.8, CH_3	9.4, CH_3	9.4, CH_3	10.7, CH_3	10.8, CH_3
29	67.7, CH_2	21.7, CH_3	21.4, CH_3	21.6, CH_3	67.7, CH_2	21.8, CH_3
30	17.7, CH_3	28.3, CH_3	28.2, CH_3	28.1, CH_3	17.0, CH_3	28.0, CH_3

[a] Data were determined at 125 MHz in pyridine-d_5 with δ in ppm.

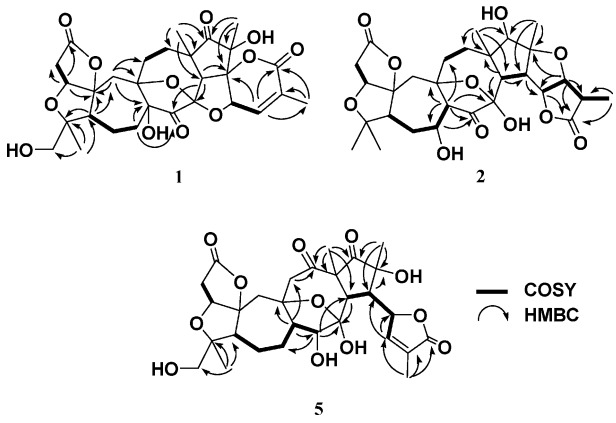


Figure 1. $^1H-^1H$ COSY and selected HMBC correlations of **1**, **2**, and **5**.

eight rings and three hydroxy groups, which is comparable to micrandilactone A (**14**).

The planar structure of **1** is shown in Figure 1 and was established by analysis of its 1D and 2D NMR spectra (including $^1H-^1H$ COSY, HSQC, and HMBC) in comparison to the spectra of compound **14**. The ^1H NMR spectrum of **1** (Table 2) exhibited a typical ABX spin system (δ_H 4.34, d, J = 6.0 Hz; 2.65, d, J = 18.0 Hz; and 2.85, dd, J = 6.0, 18.0 Hz) and a pair of characteristic signals of two AB-type doublets (δ_H 2.65 and 2.26, d, J = 15.5 Hz), which indicated that **1** had similar 5/5/7 rings A−C to all the other C_{29} nortriterpenoids.[2−13] However, HMBC correlations of a methylene group (δ_H 3.68 and 3.84, d, J = 12.0 Hz) with C-4 (δ_C 87.3), C-5 (δ_C 55.7), and C-30 (δ_C 17.7) indicated the C-29 methyl group was oxygenated in **1**. Furthermore, the $^1H-^1H$ COSY spectrum showed the spin system of H-5/H_2-6/H_2-7. This finding, together with the HMBC correlations of H-7 (δ_H 2.02, dd, J = 9.0, 14.5 Hz) with C-8, C-9, and C-14, confirmed that C-8 carried a hydroxy group. The other four groups of selected HMBC correlations from H_2-11 to C-9, from CH_3-18 to C-12, C-13, C-16, and C-17, from H-16 to C-13, C-14, C-15, and C-22, and from CH_3-21 to C-17, C-20, and C-21 corroborate the $^1H-^1H$ COSY correlations of H_2-11/H_2-12 and built up the rings D, E, and F. Thus, compound **1** was established to be a schisanartane-type nortriterpenoid possessing consecutive 7/8/5 carbon rings and an oxygen bridge between C-9 and C-15, similar to those found in **14**.

The trisubstituted double bond and the other ester group were present as an α-methyl-α,β-unsaturated ester group, which was confirmed by two key HMBC correlations, from H-24 to C-22, C-23, C-25, C-26, and C-27 and from CH_3-27 to C-24, C-25, and C-26. As mentioned above, compound **1** should have eight rings and three hydroxy groups. Thus, there should be another lactone ring and oxygen-containing ring in compound **1**. Comparison of the spectroscopic data of **1** and **14** showed that the chemical shifts of the F ring carbons change considerably: C-13, $\Delta\delta_C$ −1.8; C-17, −1.9; C-18, −3.1; C-21, −2.6. These changes were especially pronounced for C-16 and C-22, which were notably deshielded and shifted 13.0 and 18.0 ppm, respectively. On the basis of these findings, the remaining two rings should have cyclized between the hydroxy groups of C-15, C-22, C-23, and C-26 by oxygen bridges. There were two possibilities: either between C-15/C-22 and C-23/C-26, which would form a four-membered ring G and a five-membered lactone ring H, or between C-15/C-23 and C-22/C-26, which would form a five-membered ring G and a six-membered lactone ring H. The chemical shift of C-26 in **1** was δ_C 161.4. This position was remarkably shielded and shifted 16.1 ppm more than **14**, which suggested that C-26 should be in a comparatively flexible six-membered lactone ring as shown, rather than a relatively rigid five-membered lactone ring. Thus, the gross structure of **1** was established to be a schisanartane type and possessed a five-membered furan ring G and a six-membered lactone ring H (5/6 type). These structures were distinct from the six-membered pyran ring G and five-membered lactone ring H (6/5 type) of compound **14**.

The relative configuration of compound **1** was established using information from the ROESY spectrum, by comparing its spectroscopic data to those of **14**, and through molecular modeling studies as shown in the computer-generated 3D drawing (Figure 2). On the basis of biogenetic considerations, H-5 was assigned with an

Table 2. ^{1}H NMR Data of Compounds **1**−**6**[a]

position	1	2	3	4	5	6
1β	4.34, d, (6.0)	4.28, d, (5.5)	4.24, d, (5.5)	4.28, d, (5.5)	4.20, d, (6.5)	4.32, d, (5.5)
2α	2.65, d, (18.0)	2.76, d, (18.0)	2.75, d, (18.0)	2.80, d, (15.5)	2.57, d, (18.0)	2.77, d, (18.5)
2β	2.85, dd, (6.0, 18.0)	3.09, dd, (5.5, 18.0)	3.16, dd, (5.5, 18.0)	3.17−3.24[b]	2.85, dd, (6.5, 18.0)	3.10, dd, (5.5, 18.5)
5α	3.10, dd, (4.5, 13.5)	2.49, m	2.34, m	3.15−3.22[b]	2.78−2.83[b]	3.15−3.70[b]
6α	2.28−2.34[b]	2.08, m	2.07−2.10[b] (2 H)	1.93−2.03[b]	1.59, m	2.03, m, (2 H)
6β	1.70, m	2.15, m		1.86, m	1.43, m	
7α	2.49, dd, (10.0, 14.5)	4.92, dd, (9.5, 11.5)	4.78, m		2.01, m	5.03, br. s
7β	2.02, dd, (9.0, 14.5)			4.92, m	1.77, m	
8		2.89, d, (9.5)	2.86, d, (10.0)	2.87, d, (5.5)	3.24, m	3.13−3.16[b]
11α	2.30−2.34[b]	1.85, m	1.97, m	1.95−2.03[b]	3.40, ABd, (14.0)	1.80−1.94[b] (2 H)
11β	2.10, m	1.77, m	1.70, m	1.56−1.66[b]	2.96, ABd, (14.0)	
12α	2.17, m	2.38−2.46[b]	2.10−2.15[b]	2.09, m		2.16, d, (13.5)
12β	1.78, m	1.66, dd, (5.5, 14.5)	1.78, m	1.66−1.75[b]		1.82−1.92[b]
14					4.22, d, (10.5)	
16	3.49, s	3.03, d, (11.0)	3.66, s	3.68, s	2.78−2.82[b]	3.54, s
17		3.65, s				
18β	1.26, s, (3 H)	1.23, s, (3 H)	1.37, s, (3 H)	1.46, s, (3 H)	1.48, s, (3 H)	2.09, s, (3 H)
19α	2.65, ABd, (16.0)	2.44, ABd, (16.0)	2.22, ABd, (16.0)	2.30, ABd, (16.0)	2.54, ABd, (16.5)	2.65, ABd, (16.0)
19β	2.26, ABd, (16.0)	2.37, ABd, (16.0)	2.43, ABd, (16.0)	2.43, ABd, (16.0)	1.92, ABd, (16.5)	2.36, ABd, (16.0)
21	1.66, s, (3 H)	1.53, s, (3 H)	1.65, s, (3 H)	1.73, s, (3 H)	1.83, s, (3 H)	1.59, s, (3 H)
22		3.27, d, (11.5)			2.58−2.61[b]	
23	5.94, d, (3.0)	6.86, br d, (3.0)	6.85, br s	6.62, br s	6.37, br d, (10.0)	6.28, br. s
24	6.59, br d, (3.0)	5.39, br t like, (4.2)	5.74, br s	5.93, br s	7.74, s	7.50, br s
25		3.55, m	3.33, m	3.41, m		
27	1.88, s, (3 H)	1.46, d, (7.5, 3 H)	1.50, d, (7.5, 3 H)	1.59, d, (7.0, 3 H)	1.72, s, (3 H)	1.68, s, (3 H)
29	3.84, ABd, (12.0)	1.10, s, (3 H)	1.07, s, (3 H)	1.12, s, (3 H)	3.75, ABd, (11.5)	1.14, s, (3 H)
	3.68, ABd, (12.0)				3.61, ABd, (11.5)	
30	1.23, s, (3 H)	1.17, s, (3 H)	1.16, s, (3 H)	1.22, s, (3 H)	1.14, s, (3 H)	1.18, s, (3 H)

[a] Data were determined at 500 MHz in pyridine-d_5 with δ in ppm and J in Hz. [b] Overlapped.

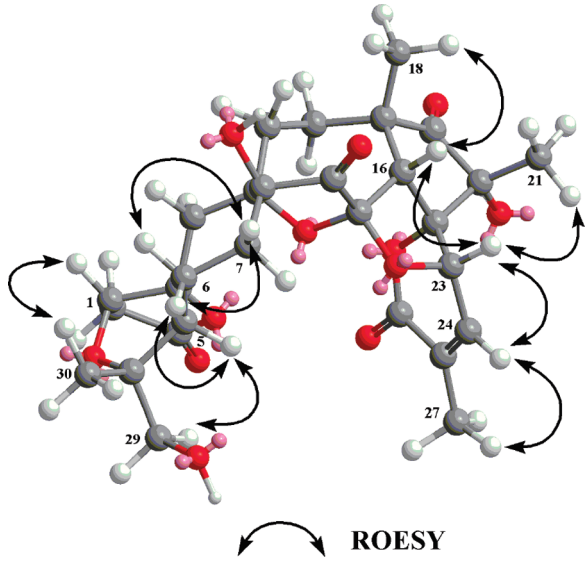


Figure 2. Selected ROESY correlations of **1**.

α-orientation and CH_3-18 with a β-orientation. The observed correlation of H_2-29 with H-5 indicated H_2-29 had an α-orientation. If 8-OH was α-orientated, the geometries generated by the MM2 force field in the CHEM3D software should have shown close proximity between H-7β and H-11β. However, the ROESY spectrum of **1** did not display this correlation. Accordingly, 8-OH was deduced to have a β-orientation. The strong ROESY correlation of CH_3-18 with H-16 indicated a β-orientation for H-16. The cross-peaks of H-23/H-16 and CH_3-21/H-16 suggested that both H-23 and CH_3-21 were in β-orientations. Thus, ring H was below the F ring, and the relative configuration of C-22 was determined as *S**. The relative configurations of the other stereogenic centers in **1** were the same as those in **14**, which could be deduced from the similar proton chemical shifts and ROESY correlations (Tables 1 and 2, Figure 2).

Schisandilactone B (**2**) was obtained as a colorless solid. The HRESIMS gave an $[M - H]^-$ ion at *m/z* 561.2349, corresponding to a molecular formula of $C_{29}H_{38}O_{11}$ (calcd. 561.2341) and indicating 11 degrees of unsaturation. The 1D NMR spectroscopic data (Tables 1 and 2), along with the HSQC spectrum (Table S1), showed the presence of four methyl singlets at δ_H 1.53, 1.23, 1.17, and 1.10, one methyl doublet at δ_H 1.46 (d, J = 7.5 Hz) and five methylene, 10 methine (five oxygenated ones), and nine nonprotonated carbons. Two carboxylic carbons at δ_C 176.0 and 179.3 and one carbonyl group at δ_C 212.1 accounted for three of the 11 degrees of unsaturation. The remaining eight degrees of unsaturation were, therefore, indicative of the octacyclic skeleton for **2**. The above analysis implied that **2** was a highly oxygenated C_{29} nortriterpenoid with eight rings and three hydroxy groups.

The spectroscopic data of compound **2** (Table S1) showed similar 5/5/7 A/B/C ring signals to those of micrandilactone D (**15**), while the signals of the other rings were different (Tables 1 and 2). The notable difference was found in the carbonyl group of compound **15**, which was reduced to an oxygenated methine at δ_C 87.4 in **2**. The HMBC cross-peaks from the two methyl groups at δ_H 1.23 (s, CH_3-18) and 1.53 (s, CH_3-21) to this methine and two protons at δ_H 2.89 (d, J = 9.5, H-8) and 4.92 (dd, J = 9.5, 11.5 Hz, H-7) to the carbonyl group at δ_C 212.1 indicated that the carbonyl group at C-14 remained unchanged, while the C-17 was reduced. This speculation was confirmed by two proton spin systems of H_2-11/H_2-12 and H-16/H-22 in the ^{1}H−^{1}H COSY spectrum and four groups of cross-peaks of H-8 with C-7, C-9, C-11, C-14, and C-15, of CH_3-18 with C-12, C-13, C-16, and C-17, of H-16 with C-13, C-15, and C-22, and of CH_3-21 with C-17, C-20, and C-22 in the HMBC spectrum (Figure 1, Table S1). Thus, compound **2** was elucidated to be a schisanartane nortriterpenoid possessing a 7/8/5 carbocyclic ring system.

The five-membered lactone ring H present in compound **2** was confirmed from the spin system of H-23/H-24/H-25/CH_3-27 in the ^{1}H−^{1}H COSY spectrum and the key HMBC correlations from H-23 to C-26, from H-24 to C-25 and C-26, and from CH_3-27 to C-25 and C-26 (Figure 1). The formation of the oxygen-containing ring G remains unanswered. Because the hydroxy group may be attached at C-15 or C-20, the oxygen-containing ring G may cyclize between

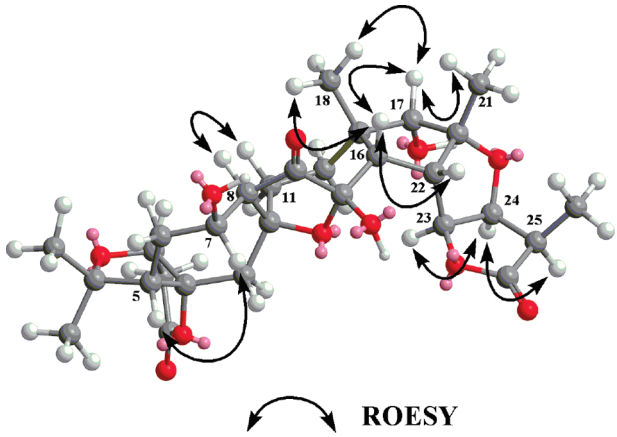


Figure 3. Selected ROESY correlations of **2**.

C-15 and C-23 as a pyran ring or between C-20 and C-23 as a furan ring. When compared with **15**, which contains a pyran ring G and a methine C-22,[15,16] the chemical shifts of C-20 (δ_C 92.1), C-22 (δ_C 54.4), C-23 (δ_C 89.4), and C-24 (δ_C 83.4) in **2** were dramatically deshielded by 17.4, 12.8, 15.7, and 11.0 ppm, respectively. Their protons, especially H-23 (δ_H 6.86), were deshielded by about 2.0 ppm in the ^{1}H NMR spectrum. These differences indicated that ring G of **2** should be present as a comparatively rigid five-membered furan ring, which was confirmed by the HMBC cross-peak of H-24 with C-20. Thus, compound **2** was established as another variety of schisanartane-type nortriterpenoid with a five-membered furan ring G and a five-membered lactone ring H (5/5 type).

When compared to rubrifloradilactone C,[20] the only member with 5/5 G/H-type rings, compound **2** had the same relative configurations for rings A and B. These configurations could be established with the ROESY experiment and by comparing their NMR data (Figure 3). Because H-5 was assigned with an α-orientation (vide supra) and CH_3-18 had a *β*-orientation, H-7 showed a strong ROESY cross-peak with H-5, which indicated its α-orientation; H-8 showed a ROESY correlation with H-11*β*, suggesting its *β*-orientation; H-16 and H-17 showed ROESY cross-peaks with CH_3-18, CH_3-21, and H-22, which indicated that they were cofacial and *β*-orientated. Because the ^{1}H and ^{13}C NMR data, as well as the ROESY correlations of the H-ring substituents in **2**, were almost identical to those of the X-ray-characterized rubrifloradilactone C, H-23, H-24, and H-25 of **2** were all assigned in an α-orientation. When the carbonyl group at C-17 in rubrifloradilactone C changed into an α-hydroxy group in **2**, the deshielding effect from the C-17 carbonyl group disappeared and the planar ring F became distorted. These changes caused distortions of the relatively strained rings D and E. Thus, the chemical shifts of the carbon atoms of rings D and E changed considerably ($\Delta\delta_C$: C-8, -6; C-9, +1.4; C-11, +2.8; C-12, +6.1; C-13, +5.9; C-14, +1.5; C-16, +1.3). Compound **2** was therefore determined as shown.

Schisandilactone C (**3**) had the same molecular formula ($C_{29}H_{36}O_{12}$) as micrandilactone A (**14**), as established by HRESIMS with *m/z* 575.2152 $[M - H]^-$ (calcd 575.2134). ^{1}H and ^{13}C NMR data (Tables 1 and 2), in combination with ^{1}H−^{1}H COSY and HMBC experiments, suggested **3** was an isomer of **14**. Spectroscopic comparison of **3** and **14** revealed that the data of rings A/B/C were similar, while the signals of C-14 ($\Delta\delta_C$ +6.1) and C-16 ($\Delta\delta_C$ +9.5) in rings D/E, C-20 ($\Delta\delta_C$ +9.4) and C-22 ($\Delta\delta_C$ +12.8) in ring F, and C-23 ($\Delta\delta_C$ +9.7) and C-24 ($\Delta\delta_C$ +5.6) in ring G were all dramatically deshielded in **3**. All of these features resembled those from rubrifloradilactone C. ^{1}H−^{1}H COSY, HMBC, and ROESY experiments further suggested compound **3** was a C-22 hydroxy derivative of rubrifloradilactone C.

Schisandilactone D (**4**) was established to be a C-7 epimer of compound **3**, because their molecular formulas were the same and

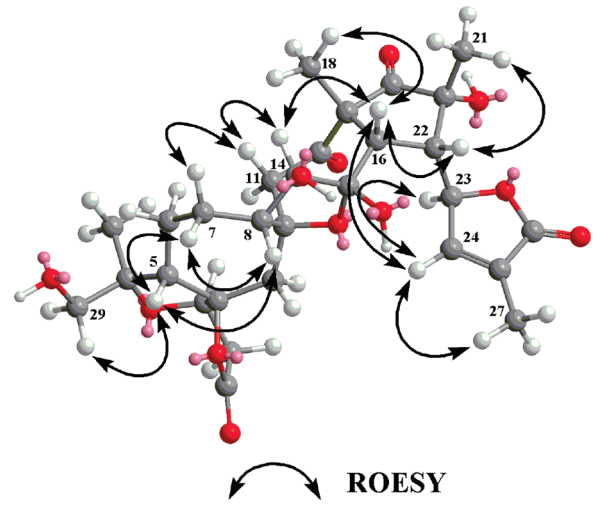


Figure 4. Selected ROESY correlations of **5**.

they had similar spectroscopic data. The minor differences were restricted to C-5, C-6, C-7, and C-8 of ring C. The ROESY correlation of H-7 with H-8, rather than with H-5α as in compound **3**, confirmed the α-orientation of 7-OH in compound **4**.

Schisandilactone E (**5**), a colorless solid, presented a molecular formula of $C_{29}H_{36}O_{12}$ as determined by HRESIMS at *m/z* 575.2143 $[M - H]^-$ (calcd 575.2129) with 12 double-bond equivalents. Its ^{13}C NMR (Table 1) spectrum with DEPT experiments resolved 29 carbon resonances that came from four methyl groups, six methylene units, seven methine groups (three oxygenated), one trisubstituted double bond, and 10 nonprotonated carbon atoms (five oxygenated, two eaters, and two carbonyls), which indicated that **5** contained seven rings. The ^{1}H NMR (Table 2) spectrum showed four methyl groups, three AB spin systems at δ_H 3.40, 2.96 (d, J = 14.0 Hz, each 1 H), δ_H 2.54, 1.92 (d, J = 16.5 Hz, each 1 H), and δ_H 3.75, 3.61 (d, J = 11.5 Hz, each 1 H), and one typical ABX spin system at δ_H 4.20 (d, J = 6.5 Hz), 2.57 (d, J = 18.0 Hz), and 2.85 (dd, J = 6.5, 18.0 Hz). The spectroscopic analysis and the HMBC spectrum (Figure 1) revealed that compound **5** featured a schisanartane backbone. The HMBC correlations from CH_3-30 (δ_H 1.14, s, 3 H) to C-29 (δ_C 67.7) rationalized the existence of an oxygenated methylene at C-29. The carbonyl carbon at δ_C 207.4 was placed at C-12, on the basis of the HMBC correlations from H_2-11 (the AB spin system at δ_H 3.40, 2.96) to C-8 and C-12. The carbonyl carbon at δ_C 219.1 was placed at C-17, which was determined by the HMBC correlations from CH_3-21 (δ_H 1.83, s, 3 H) to C-17. Accordingly, the carbonyl carbon at C-14 in compound **14** was reduced to a secondary alcohol functionality, which was confirmed by the HMBC correlations from H-14 (δ_H 4.22, d, J = 10.5 Hz) to C-7, C-8 (δ_C 47.2), C-15 (δ_C 105.3), and C-16 (δ_C 55.9). The existence of the α-methyl-α,*β*-unsaturated five-membered lactone ring H was determined by the HMBC cross-peaks of CH_3-27 (δ_H 1.72, s, 3 H) to C-24 (δ_C 152.2), C-25 (δ_C 129.6), and C-26 (δ_C 174.1), in combination with ^{1}H−^{1}H COSY correlations of H-22/H-23/H-24 (Figure 1). Thus, compound **5** was established to be another variety of the schisanartane skeleton and possessed an α-methyl-α,*β*-unsaturated five-membered lactone H ring, but without the pyran G ring (0/5 type).

The ROESY spectrum of compound **5** (Figure 4), showing correlations of H-5α with H-7α, H-7*β* with H-11*β*, and H-8 with H-7α, indicated that H-8 had an α-orientation. H-14 showed correlations with both H-11*β* and H-16, which suggested that 14-OH had an α-orientation. The remaining carbons had the same configurations as **14**.

Schisandilactone F (**6**) was assigned the same molecular formula of $C_{29}H_{36}O_{12}$ as schisandilactones C (**3**) and E (**5**) and micrandilactone A (**14**) by HRESIMS at *m/z* 575.2114 $[M - H]^-$ (calcd

575.2129). Comparison of their ^{13}C NMR (Table 1) and DEPT data revealed that **6** possessed the same planar A−F rings as **3** and **14**, as well as the same α-methyl-α,β-unsaturated five-membered lactone ring H as **5**. This was confirmed by the $^1H-^1H$ COSY and HMBC correlations of **6**. ^{13}C NMR signals of C-5, C-6, C-7, and C-8 of **6** had minor shift differences compared to **14**, which indicated that the configuration of C-7 may be reversed. Because H-5 was α-orientated and H-8 was in a β-orientation in **14**, the presence of an H-8/H-7 correlation and the absence of an H-7/H-5 correlation in the ROESY spectrum of **6** confirmed that the 7-OH was α-orientated in **6**. This orientation was opposite the β-orientation in **14**. The other relative configurations of rings A−F resembled **14**, and the configuration of C-23 was the same as **5**, which could be deduced by their similar ^1H NMR signals (Table 2) and ROESY experiments. Accordingly, compound **6** represents a further schisanartane member with 0/5-type rings G and H.

Schisandilactone G (**7**) was obtained as a colorless solid in MeOH. The HRESIMS at *m/z* 575.2124 $[M - H]^-$ (calcd 575.2129) indicated the same molecular formula, $C_{29}H_{36}O_{12}$, as schisandilactones C (**3**), E (**5**), and F (**6**) and micrandilactone A (**14**). 1D NMR signals, including ^1H (Table S2), ^{13}C NMR (Table S3), and DEPT, indicated that **7** was a schisanartane nortriterpenoid with 6/5-type rings G and H. These features were similar to **14**, which was confirmed by $^1H-^1H$ COSY and HMBC experiments. Besides the differences on rings G and H, the main differences between **5** and **7** were the carbon signals for C-8, C-9, and C-11, which were deshielded and shifted 4.3, 2.5, and 5.2 ppm in **7**, respectively. These differences indicated a reversed configuration of C-8 in **7**. A ROESY correlation of H-8 with H-11β was observed to confirm the β-orientation of H-8 in **7**. The configuration of the stereocenters of rings G and H in **7** was the same as those in **14**, and the configurations of the remaining carbon in **7** were the same as **5**.

Schisandilactone H (**8**) was isolated as an amorphous powder. The molecular formula $C_{29}H_{36}O_{13}$ was established by HRESIMS (*m/z* 591.2087 $[M - H]^-$, calcd 591.2078). ^{13}C NMR (Table S2) and DEPT displayed similar signals for rings A−E to those of **5** and rings F−H to those of **14**. ^1H, HSQC, $^1H-^1H$ COSY, HMBC, and ROESY experiments all confirmed compound **8** was another schisanartane derivative with 6/5-type rings G and H, as shown.

Schisandilactone I (**9**), a white gum, had a molecular formula of $C_{29}H_{36}O_{11}$ on the basis of HRESIMS (*m/z* 559.2191 $[M - H]^-$, calcd 559.2179). ^{13}C NMR (Table S2) data analysis with the known schisanartane nortriterpenoids revealed that compound **9** was an analogue of propindilactone C (**13**) with a quaternary carbon containing a hydroxy group replaced by an aliphatic methine in **9**. The aliphatic methine at δ_C 41.8 was assigned to C-22 because all the carbon signals were identical except those around C-22, most of which were minimally shielded. These findings were confirmed by HMBC correlations. The relative configuration of **9** was identical to **13** by comparing their ^1H NMR and ROESY data.

Schisandilactone J (**10**) was isolated as a white gum. HRESIMS gave an ion peak at *m/z* 589.1923 ($[M - H]^-$, calcd 589.1921), establishing the molecular formula as $C_{29}H_{34}O_{13}$ with 13 degrees of unsaturation. ^1H (Table S2) and ^{13}C NMR (Table S3) and DEPT spectra displayed four methyl singlets and similar signals to micrandilactone A (**14**), which suggested that **10** was oxygenated at CH_3-29, just as the schisandilactones G−I (**7**−**9**). HMBC and ROESY experiments confirmed the existence of an oxygenated α-methylene at C-29. Analysis of the molecular formula of **10** and **14** indicated that one H_2O unit was absent in **10** compared to **14** to build up another oxygen ring. The carbon signal differences in the ^{13}C NMR data (Table S3) were restricted to C-7 and C-8. In compound **10**, the oxygenated methine C-7 (δ_C 64.1) was shielded. The corresponding proton showed $^1H-^1H$ COSY correlations with H_2-6 and HMBC correlations with the oxygenated and shielded quaternary C-8 (δ_C 61.3). These correlations confirmed that an epoxy ring was formed between C-7 and C-8. ROESY correlation of H-7 with H-5 indicated a β-orientation for the epoxy ring. The other relative configurations were similar to **14**.

The schisanartane nortriterpenoids are commonly found in the *Schisandra* genus. From a biosynthetic point of view, their unusual arrangement of the 7/8/5 consecutive carbocyclic rings and varied oxygen atom containing rings with diverse post-modifications are of great research interest. According to the different oxygen-containing rings, schisanartane nortriterpenoids can be classified into five groups: five-membered furan ring G between C-15 and C-23 and six-membered lactone ring H between C-22 and C-26 (5/6 rings G and H), exemplified by compound **1**; five-membered furan ring G between C-20 and C-24 and five-membered lactone ring H between C-23 and C-26 (5/5 rings G and H), such as compounds **2**−**4**; missing ring G and five-membered lactone ring H between C-23 and C-26 (0/5 rings G and H), such as compounds **5** and **6**; six-membered pyran ring G between C-15 and C-24 and five-membered lactone ring H between C-23 and C-26 (6/5 rings G and H), which is the most common group among all schisanartane nortriterpenoids (compounds **7**−**21** as examples). In addition, spirocyclic five-membered rings G and H also exist.[9,10] Other post-modifications, including oxidization, reduction, hydration, or dehydration, occurred widely, especially the formation of C-8 and C-20 epimeric pairs and the keto or enol isomers of C-14.

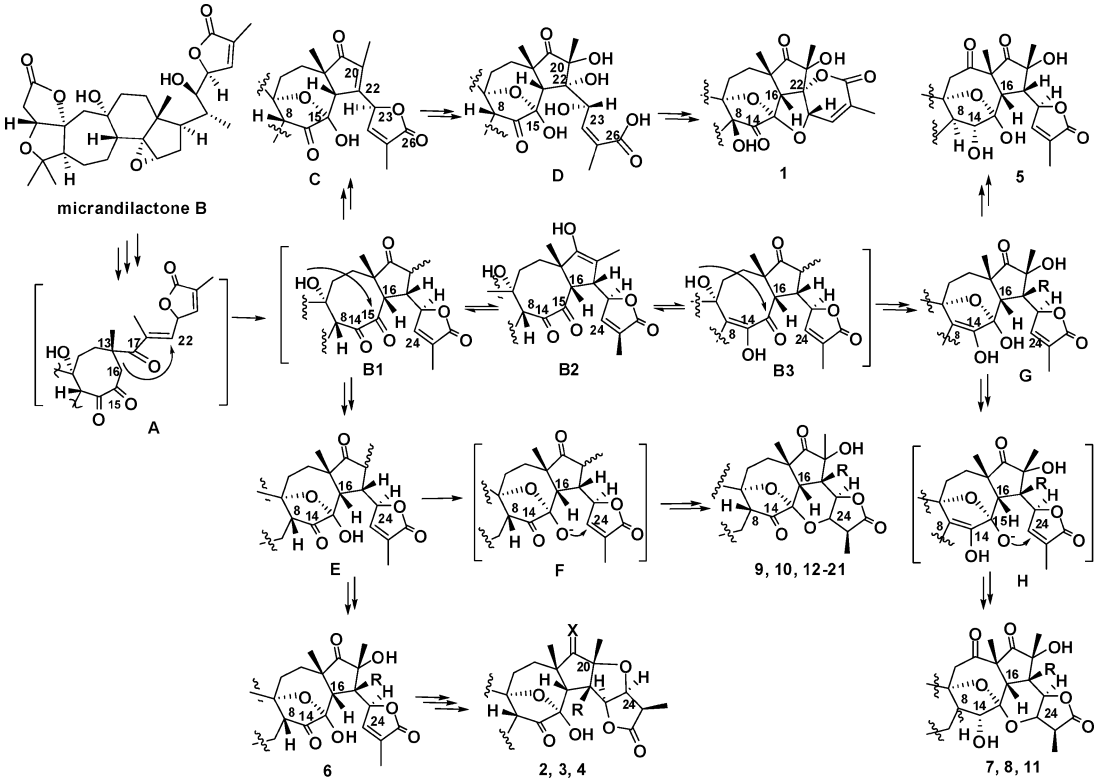
The schisanartane type of compounds are proposed to be modified from the schiartane type (i.e., micrandilactone B[7,11]) through the preschisanartane type.[3,6] As all three types of nortriterpenoids coexist in *S. propinqua* var. *propinqua*,[2,7,8] the diverse schisanartane nortriterpenoids isolated in this paper can be biogenetically linked together (Scheme 1). Cleavage and oxidation of the three-membered ring in the preschisanartane skeleton give intermediate **A**, followed by Michael addition between C-16 and C-22, which constructs the 8/5 consecutive carbocyclic schisanartane framework (intermediate **B2**). While the enolic C-17 in **B2** converts into the more stable keto isomer in **B1**, the epimeric C-20 would be generated. HO-9 and the carbonyl group at C-15 usually close the eight-membered ring to form rings D and E. Compound **1** may have then formed through dehydrogenation (intermediate **C**), hydration, and opening of ring H (intermediate **D**), followed by two cyclizations between C-15 and C-23, and C-22 and C-26. The hemiketal C-15 intermediate **E** may have gone through further Michael addition at C-24 to afford the 6/5 rings G- and H-type compounds **9**, **10**, and **12**−**21** with other post-modifications. Alternatively, hydration at C-20 would give the 0/5 rings G and H in compound **6**. Then, HO-20 cyclizes at C-24 by an enzymatically controlled process to give the 5/5 rings G and H in compounds **2**−**4**. Moreover, intermediate **B1** or **B2** may readily convert to its C-14 enol isomer **B3**. The C-15 hemiketal intermediate **G** from **B3** could be reduced to form the C-8 or C-14 epimer, which upon further ring closure and oxidation would afford compounds **5**, or **7**, **8**, and **11** (Scheme 1).

Compounds **1**−**10** were tested for cytotoxicity against A549, HT-29, and K562 cells according to the method described previously.[21] All were inactive, with IC_{50} values greater than 100 μM.

Experimental Section

General Experimental Procedures. Melting points were obtained on an XRC-1 micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were obtained on a Bio-Rad FtS-135 spectrophotometer with KBr pellets. 1D and 2D NMR spectra were recorded on a Bruker DRX-500 NMR spectrometer with TMS as the internal standard. HRESIMS spectra were acquired on an API QSTAR TOF mass spectrometer or on a Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS. FABMS spectra were acquired on a VG Autospec-3000 mass spectrometer. Semipreparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Zorbax SB-C_{18}, 9.4 mm × 25 cm column at 30 °C. Column chromatography (CC) was performed on silica gel (200−300 mesh; Qingdao Marine Chemical Inc., Qingdao, People's Republic of China), Lichroprep RP-18 gel (40−63 μm, Merck,

Scheme 1. Putative Biosynthetic Relations of the Schisanartane Nortriterpenoids



Darmstadt, Germany), and Sephadex LH-20 (Pharmacia). All solvents including petroleum ether (60−90 °C) were distilled prior to use. Precoated silica gel GF_{254} plates (Qingdao Haiyang Chemical Plant, Qingdao, People's Republic of China) were used for TLC, which was guided by spots heated after spraying with 15% H_2SO_4 in EtOH.

Plant Material. Stems of *S. propinqua* var. *propinqua* were collected in July 2008 from Tengchong County, Yunnan Province, People's Republic of China, and identified by Prof. Xi-Wen Li, Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (No. 20080813) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, People's Republic of China.

Extraction and Isolation. The air-dried stems of *S. propinqua* (10 kg) were extracted with 70% aqueous acetone (4 × 15 L, 3 days each) at room temperature. The solvent was removed in vacuo to afford a crude extract (600 g), which was dissolved in H_2O and extracted successively with petroleum ether and EtOAc. The EtOAc-soluble part (280 g) was separated by CC (on SiO_2 with $CHCl_3$/acetone, 1:0, 9:1, 8:2, 2:1, 1:1, 0:1) to afford six main fractions (A−F). Fraction C ($CHCl_3$/acetone, 9:1−8:2, 35 g) was subjected to repeated CC, first on RP-18 in 30−60% aqueous MeOH to afford five fractions (C1−5) and then on Sephadex LH-20. The samples were eluted with MeOH to screen out parts without spots, as guided by TLC. Fraction C3 (50% aqueous MeOH, 15 g) was purified on silica gel eluted with $CHCl_3$/MeOH in a gradient system (15:1−5:1), guided by TLC, to afford 10 fractions (C3-1−10). Fraction C3-3 (1.5 g) was further purified on silica gel by PE/i-PrOH (5:1) and was then crystallized in MeOH, which yielded **17** (100 mg) and **21** (17 mg). Fractions C3-8 (0.8 g), C3-9 (0.3 g), and C3-10 (0.5 g) were purified on silica gel with PE/i-PrOH (5:1) to give nine (C3-8-1−9), five (C3-9-1−5), and six fractions (C3-10-1−6), respectively. Fraction C3-8-5 (138 mg) was crystallized from MeOH to give **14** (100 mg). Fractions C3-8-9 (42 mg), C3-9-5 (35 mg), and C-3-10-3 (45 mg) were prepared in 50% aqueous MeOH to afford **20** (15 mg), **4** (3 mg), and **16** (10 mg), respectively. Fraction D ($CHCl_3$/acetone, 8:2−2:1, 50 g) was separated by CC on silica gel with $CHCl_3$/acetone (4:1) to obtain fractions D1, D2, and D3. Fraction D2 was subjected to RP-18 in 30−60% aqueous MeOH to afford five fractions (D2-1−5), which were separated on Sephadex LH-20 and eluted with MeOH to screen out parts without spots, as guided by TLC. Fraction D2-2 (40% aqueous MeOH, 8 g) was chromatographed on silica gel with PE/i-PrOH (5:1) to obtain five fractions (D2-2-1−5). Fractions D-2-2-1 (0.5 g), D2-2-2 (1.3 g), and D2-2-3 (2.3 g) were purified on silica gel by $CHCl_3$/MeOH (5:1) to give five (D2-2-1-1−5), five (D2-2-2-1−5), and six fractions (D2-2-3-1−6), respectively. Fraction D2-2-1-3 (112 mg) was crystallized from MeOH to give **12** (50 mg). The mother liquor was purified by semipreparatory HPLC (35% aqueous MeOH) to yield **2** (5 mg), **8** (10 mg), **10** (6 mg), and **11** (7 mg). Fraction D2-2-2-2 (105 mg) was prepared in 35% aqueous MeOH to yield **3** (30 mg), **13** (10 mg), and **19** (3 mg). Fraction D2-2-3-2 (146 mg) was crystallized from MeOH to give **15** (80 mg). Fraction D3 was subjected to the same procedures as D2 to obtain five fractions (D3-1−5), which were further subjected to silica gel CC (PE/i-PrOH, 5:1) to give five fractions. D3-1-4 (50 mg) and D3-5-1 (96 mg) were purified by preparative HPLC (55% aqueous MeOH) to yield **6** (15 mg) and **9** (46 mg). D3-3-3 (36 mg) and D3-4-1 (78 mg) were subjected to recrystallization from MeOH to obtain **18** (20 mg) and **7** (30 mg). The mother liquor of D3-4-1 was purified by preparative HPLC (55% aqueous MeOH) to yield **1** (10 mg) and **5** (3 mg).

Schisandilactone A (1): amorphous powder; $[\alpha]^{20.2}_D$ +4.3 (*c* 0.05, MeOH); IR (KBr) ν_{max} 3437, 2936, 1777, 1732, 1679, 1454, 1383, 1367, 1025, 1139, 1072, 1009, 920 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 1; negative FABMS *m/z* 573 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 573.1944 (calcd for $C_{29}H_{33}O_{12}$, 573.1972).

Schisandilactone B (2): colorless solid; $[\alpha]^{25.7}_D$ +24.0 (*c* 0.25, MeOH); IR (KBr) ν_{max} 3342, 2978, 2942, 1762, 1680, 1455, 1382, 1203, 1138, 1062, 982 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 1; negative FABMS *m/z* 561 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 561.2349 (calcd for $C_{29}H_{37}O_{11}$, 561.2341).

Schisandilactone C (3): white powder; $[\alpha]^{25.8}_D$ +13.9 (*c* 0.56, MeOH); IR (KBr) ν_{max} 3485, 2978, 2940, 1765, 1636, 1458, 1379, 1323, 1235, 1201, 1103, 1028, 983, 923, 865, 682, 594 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 1; negative FABMS *m/z* 575 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 575.2152 (calcd for $C_{29}H_{37}O_{12}$, 575.2134).

Schisandilactone D (4): colorless powder; $[\alpha]^{22.6}_D$ +50.0 (*c* 0.05, MeOH); IR (KBr) ν_{max} 3422, 2936, 1765, 1745, 1453, 1243, 1177, 1104 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 1; negative FABMS *m/z* 575 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 575.2117 (calcd for $C_{29}H_{35}O_{12}$, 575.2129).

Schisandilactone E (5): colorless solid; $[\alpha]^{20.0}_D$ +2.2 (*c* 0.15, MeOH); IR (KBr) ν_{max} 3435, 2927, 1748, 1692, 1204, 1136, 1059 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 1; negative

FABMS *m/z* 575 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 575.2143 (calcd for $C_{29}H_{35}O_{12}$, 575.2129).

Schisandilactone F (6): white powder; $[\alpha]^{22.2}_D$ +39.3 (*c* 0.75, MeOH); IR (KBr) ν_{max} 3383, 2974, 2936, 1748, 1637, 1230, 1106, 1064 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 1; negative FABMS *m/z* 575 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 575.2114 (calcd for $C_{29}H_{35}O_{12}$, 575.2129).

Schisandilactone G (7): colorless solid; $[\alpha]^{23.0}_D$ +13.5 (*c* 0.33, MeOH); IR (KBr) ν_{max} 3466, 2924, 1777, 1743, 1696, 1203, 1185, 1171, 1059, 1008 cm^{-1}; ^1H NMR data, see Table S1, ^{13}C NMR data, see Table S2; negative FABMS *m/z* 575 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 575.2124 (calcd for $C_{29}H_{35}O_{12}$, 575.2129).

Schisandilactone H (8): amorphous powder; $[\alpha]^{24.8}_D$ +69.6 (*c* 0.40, MeOH); IR (KBr) ν_{max} 3425, 2941, 1779, 1741, 1692, 1188, 1074, 1011 cm^{-1}; ^1H NMR data, see Table S1, ^{13}C NMR data, see Table S2; negative FABMS *m/z* 591 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 591.2087 (calcd for $C_{29}H_{35}O_{13}$, 591.2078).

Schisandilactone I (9): white gum; $[\alpha]^{22.4}_D$ +30.0 (*c* 2.5, MeOH); IR (KBr) ν_{max} 3444, 2973, 1775, 1746, 1456, 1381, 1172, 1069, 1005 cm^{-1}; ^1H NMR data, see Table S1, ^{13}C NMR data, see Table S2; negative FABMS *m/z* 559 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 559.2191 (calcd for $C_{29}H_{35}O_{11}$, 559.2179).

Schisandilactone J (10): white gum; $[\alpha]^{22.4}_D$ +91.7 (*c* 0.30, MeOH); IR (KBr) ν_{max} 3440, 2936, 1782, 1635, 1456, 1167, 1041 cm^{-1}; ^1H NMR data, see Table S1, ^{13}C NMR data, see Table S2; negative FABMS *m/z* 589 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 589.1923 (calcd for $C_{29}H_{33}O_{13}$, 589.1921).

Cytotoxicity Assay. The cytotoxicity of compounds **1**−**10** against suspended tumor cells was determined by the trypan blue exclusion method. For adherent cells, cytotoxicity was measured by the sulforhodamine B (SRB) assay. Cells were plated in a 96-well plate 24 h before treatment and continuously exposed to different concentrations (100, 10, 1, and 0.1 μM) of compounds for 72 h. After compound treatment, cells were counted (suspended cells) or fixed and stained with SRB (adherent cells) as described.[21] Amrubicin hydrochloride was used as a positive control, with IC_{50} values of 0.94 (A549), 4.57 (HT-29), and 1.20 μM (K562), respectively.

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Supporting Information Available: Detailed NMR assignment of compound **2**; ^1H and ^{13}C NMR data tables of compounds **7**−**10**; HRESIMS, 1D and 2D NMR spectra of **1**−**7**; ^1H and ^{13}C NMR spectra of **8**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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