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Propindilactones E−J, Schiartane Nortriterpenoids from *Schisandra propinqua* var. *propinqua*

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Six new nortriterpenoids, propindilatones E−J (**1**−**6**), and two known (**7**, **8**) schiartane-type nortriterpenoids were isolated from the stems of *Schisandra propinqua* var. *propinqua*. Their structures were elucidated by extensive spectroscopic analyses, and the structure of compound **4** was confirmed through single-crystal X-ray diffraction. The absolute configuration of compounds **1**−**3** was established using CD methods. Compounds **4**−**6** were noncytotoxic against K562, A549, and HT-29 human cancer cells.

Plants belonging to the medicinally important genus *Schisandra* produce some structurally intriguing nortriterpenoids. Systematic phytochemical investigations on stems of 10 species have resulted in a series of complex *Schisandra* nortriterpenoids with C_{29},[1−12] C_{28},[13,14] C_{27},[15,16] C_{25},[17] and C_{22}[18] skeletons, some of which showed promising bioactivities. The C_{29} type is the most common and can be divided into five classes including schiartane,[9] 18(13→14)-*abeo*-schiartane,[10] schisanartane,[1−8] preschisanartane,[11] and wuweiziartane.[12] Except for those having the schisanartane skeleton, reports of compounds with the other four classes, together with C_{27}, C_{25}, and C_{22} skeletons, are relatively rare. Therefore, our studies were expanded to include *Schisandra propinqua* var. *propinqua* (Schisandrea), which is indigenous in Yunnan Province. Six new nortriterpenoids, propindilactones E−J (**1**−**6**), together with micrandilactones B (**7**) and C (**8**),[9] all of which possessed the schiartane skeleton, were discovered to coexist with eight schisanartane-type C_{29} triterpenoids,[19] a 2,3-*seco*-lanostane triterpenoid,[20] and typical dibenzocyclooctadien lignans[21] reported previously. *S. propinqua* var. *propinqua* is the second plant reported in the genus *Schisandra* that can produce schiartane nortriterpenoids besides *S. micrantha*.[9] In this paper, we discuss the isolation, structure elucidation, and biological evaluation of the new compounds.

Results and Discussion

A 70% aqueous acetone extract of the stems of *S. propinqua* var. *propinqua* was partitioned successively with petroleum ether and EtOAc. The EtOAc-soluble fraction was dried and subjected to several chromatographic procedures to yield compounds **1**−**8**. Two of the compounds were identified as micrandilactones B (**7**) and C (**8**) by comparison of their spectroscopic and physical data with those reported in the literature.[9] These two compounds are C_{29} triterpenoids with the schiartane (3,4:9,10-*seco*-28-norcycloartane) skeleton featuring 5/5/7/6/5-membered consecutive rings and a β-Me located at C-13.

Propindilactone E (**1**) showed a HRESIMS pseudomolecular ion peak $[M - H]^-$ at *m/z* 517.2780, corresponding to the molecular formula $C_{29}H_{42}O_8$. This was corroborated by the ^{13}C (Table 1) and DEPT NMR spectra, which displayed 29 signals for the carbons including five methyls, eight methylenes, seven methines (involving four aliphatic and three oxygenated ones), five sp^3 quaternary carbon atoms (comprising one aliphatic and four oxygenated ones), two ester groups, and one trisubstituted double bond. This information, together with the typical ABX spin system at δ_H 4.30 (d, J = 4.5 Hz), 2.73 (d, J = 17.5 Hz), and 2.96 (dd, J = 4.5, 17.5 Hz) in the ^1H NMR spectrum (Table 2), assigned to H-1, H-2α, and H-2β, respectively, indicated that compound **1** was a C_{29} nortriterpenoid dilactone with six rings similar to micrandilactone C (**8**).

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

no.	1	2	3	4	5	6
1	82.1 (d)	82.0 (d)	81.8 (d)	82.1 (d)	82.2 (d)	82.0 (d)
2	36.9 (t)	36.8 (t)	36.1 (t)	36.8 (t)	37.2 (t)	36.6 (t)
3	175.6 (s)	175.6 (s)	175.3 (s)	175.7 (s)	175.9 (s)	175.3 (s)
4	85.1 (s)	85.0 (s)	85.7 (s)	85.1 (s)	85.2 (s)	84.9 (s)
5	59.0 (d)	59.3 (d)	60.1 (d)	59.2 (d)	58.8 (d)	59.1 (d)
6	27.9 (t)	27.7 (t)	26.5 (t)	28.7 (t)	28.8 (t)	27.0 (t)
7	25.2 (t)	24.6 (t)	26.8 (t)	25.0 (t)	24.5 (t)	23.6 (t)
8	49.8 (d)	49.6 (d)	50.1 (d)	56.7 (d)	56.7 (d)	44.4 (d)
9	74.8 (s)	75.5 (s)	75.7 (s)	72.1 (s)	72.3 (s)	74.7 (s)
10	99.7 (s)	99.7 (s)	99.4 (s)	99.8 (s)	99.9 (s)	99.2 (s)
11	38.6 (t)	38.5 (t)	38.0 (t)	37.9 (t)	38.4 (t)	44.5 (t)
12	29.7 (t)	30.2 (t)	28.4 (t)	40.2 (t)	39.0 (t)	75.1 (d)
13	48.0 (s)	48.3 (s)	45.7 (s)	46.3 (s)	46.1 (s)	46.2 (s)
14	86.4 (s)	85.1 (s)	191.1 (s)	87.2 (s)	87.2 (s)	73.4 (s)
15	33.1 (t)	73.9 (d)	127.2 (d)	79.7 (d)	77.0 (d)	54.0 (d)
16	27.3 (t)	40.2 (t)	211.2 (s)	79.7 (d)	35.8 (t)	31.4 (t)
17	47.8 (d)	46.4 (d)	57.8 (d)	60.7 (d)	54.5 (d)	45.8 (d)
18	16.3 (q)	15.6 (q)	27.9 (q)	18.8 (q)	18.6 (q)	11.3 (q)
19	46.9 (t)	46.7 (t)	45.6 (t)	46.9 (t)	47.5 (t)	46.0 (t)
20	42.3 (d)	42.1 (d)	36.5 (d)	35.8 (d)	37.0 (d)	36.8 (d)
21	15.2 (q)	15.2 (q)	14.1 (q)	17.4 (q)	18.9 (q)	15.1 (q)
22	73.2 (d)	73.0 (d)	72.2 (d)	76.7 (d)	76.5 (d)	80.0 (d)
23	82.3 (d)	82.2 (d)	82.3 (d)	78.1 (d)	78.3 (d)	24.1 (t)
24	148.9 (d)	149.0 (d)	149.3 (d)	33.9 (t)	34.0 (t)	140.1 (d)
25	130.1 (s)	130.1 (s)	130.1 (s)	34.7 (d)	34.7 (d)	127.8 (s)
26	174.9 (s)	175.0 (s)	175.3 (s)	181.0 (s)	181.1 (s)	166.0 (s)
27	10.6 (q)	10.6 (q)	10.8 (q)	16.8 (q)	16.8 (q)	17.1 (q)
29	23.5 (q)	23.4 (q)	22.5 (q)	23.4 (q)	23.7 (q)	23.0 (q)
30	29.9 (q)	29.8 (q)	29.0 (q)	29.8 (q)	30.2 (q)	30.0 (q)

[a] Data were determined at 125 MHz in C_5D_5N with δ in ppm.

Comparison of the ^{13}C NMR data between **1** and **8** (Table 1) indicated that the A, B, and F rings of **1** were identical with those of **8**, and the major difference was that an oxymethine at δ_C 77.2 in **8** was replaced by a methylene at δ_C 33.1 in **1**. Three proton spin systems involving H-5/H_2-6/H_2-7/H-8, H_2-11/H_2-12, and H_2-15/H_2-16/H-17 in the $^1H-^1H$ COSY spectrum (Figure 1) of **1** indicated that C-15 was a methylene carbon. HMBC correlations (Figure 1) of one OH at δ_H 6.15 (brs, 14-OH) with δ_C 49.8 (C-8),

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

no.	1	2	3	4	5	6
1β	4.30 (d, 4.5)	4.31 (d, 4.5)	4.33 (d, 4.5)	4.27 (d, 4.5)	4.28 (d, 4.5)	4.28 (d, 4.5)
2α	2.73 (d, 17.5)	2.74 (d, 17.5)	2.79 (d, 17.5)	2.72 (d, 15.5)	2.68−2.76[b]	2.75 (d, 17.5)
2β	2.96 (dd, 4.5, 17.5)	2.98 (dd, 4.5, 17.5)	3.09 (dd, 4.5, 17.5)	2.95 (dd, 4.5, 15.5)	2.95 (dd, 4.5, 18.0)	3.02 (dd, 4.5, 17.5)
5α	2.66 (dd, 3.5, 13.5)	2.59−2.61[b]	2.49 (dd, 4.0, 13.5)	2.62 (dd, 3.5, 13.0)	2.67−2.73[b]	2.52 (dd, 3.0, 13.5)
6α	1.66−1.71[b]	1.60 (m)	1.63−1.71[b]	1.73 (m)	1.76 (m)	2.01−2.05[b]
6β	1.35 (m)	1.32 (m)	1.40 (m)	1.32−1.39[b]	1.33 (m)	1.30 (m)
7α	2.29 (m)	2.09−2.16[b]	2.00 (m)	2.11−2.16[b]	2.14−2.25[b]	1.88−1.94 (m)
7β	1.87−1.91[b]	2.70−2.76[b]	1.90 (m)	2.78 (m)	2.67−2.74[b]	1.41 (m)
8β	1.71−1.73[b]	1.85−1.89[b]	2.54−2.59[b]	1.85−1.92[b]	2.00 (m)	2.16[b]
11α	1.87−1.91[b]	1.85−1.91[b]	1.91−1.99[b]	1.81−1.88[b]	1.82−1.92[b]	2.16[b]
11β	1.76 (m)	1.79−1.82[b]	1.68−1.74[b]	1.60 (m)	1.58−1.64[b]	1.88−1.94[b]
12α	2.44 (dt, 4.5, 13.5)	2.46 (dt, 3.5, 13.0)	2.42 (m)	2.50−2.58[b]	2.71−2.79[b]	5.76 (dd, 4.5, 11.0)
12β	1.69−1.72[b]	1.67 (brd, 11.5)	1.67−1.72[b]	1.84−1.91[b]	1.62−1.68[b]	
15α	1.49−1.56[b]		6.11 (s)			3.36 (brs)
15β	1.83−1.89[b]	4.21 (dd,4.0,9.0)		4.64 (brs)	4.48 (brs)	
16α	2.11 (m)	2.03 (m)		4.44 (brs)	2.45−2.52[b]	2.00−2.03[b]
16β	1.49−1.56[b]	2.21 (m)			2.14−2.23[b]	1.54 (m)
17	2.60 (m)	2.59−2.65[b]	3.40 (brs)	2.43(dd, 4.5, 11.5)	2.46−2.55[b]	1.52−1.57[b]
18	0.92 (s)	0.93 (s)	1.28 (s)	1.37 (s)	1.45 (s)	1.12 (s)
19α	2.06 (2H, brs)	2.12 (ABd, 15.5)	2.32 (ABd, 15.5)	2.16 (ABd, 16.5)	2.12 (ABd, 16.0)	2.14 (ABd, 15.5)
19β		2.07 (ABd, 15.5)	2.16 (ABd, 15.5)	2.07 (ABd, 16.5)	2.04 (ABd, 16.0)	2.06 (ABd, 15.5)
20	2.23 (m)	2.10−2.16[b]	2.60 (m)	2.57−2.64[b]	2.49−2.56[b]	1.98 (m)
21	1.42 (d, 7.0)	1.37 (d, 6.5)	1.27 (d, 7.5)	1.33 (d, 6.5)	1.21 (d, 6.0)	0.94 (d, 6.5)
22	4.14 (brd, 3.5)	4.10 (brs)	4.74 (d, 9.0)	4.03 (d, 6.5)	3.76 (d, 7.0)	4.40 (brd, 13.0)
23	5.26 (brs)	5.23 (brs)	5.29 (brs)	4.88 (brd, 7.5)	4.79 (brd, 7.0)	2.01−2.05[b]
						1.79 (m)
24	7.20 (brs)	7.16 (brs)	7.17 (brs)	2.46−2.54[b]	2.49−2.57[b]	6.43 (d, 5.5)
				1.87−1.94[b]	1.87−1.96[b]	
25				3.10 (m)	3.05 (m)	
27	1.79 (s)	1.79 (s)	1.86 (s)	1.18 (d, 7.5)	1.18 (d, 7.5)	1.91 (s)
29	1.15 (s)	1.12 (s)	1.14 (s)	1.08 (s)	1.01 (s)	1.10 (s)
30	1.30 (s)	1.29 (s)	1.31 (s)	1.28 (s)	1.28 (s)	1.25 (s)

[a] Data were determined at 500 MHz in C_5D_5N with δ in ppm and J in Hz. [b] Overlapped.

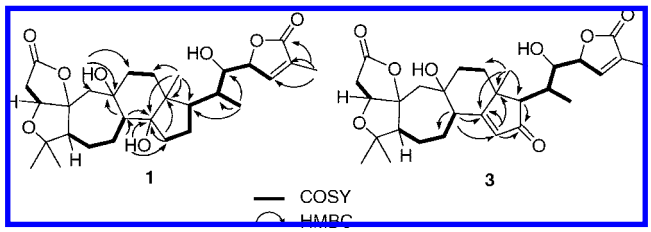
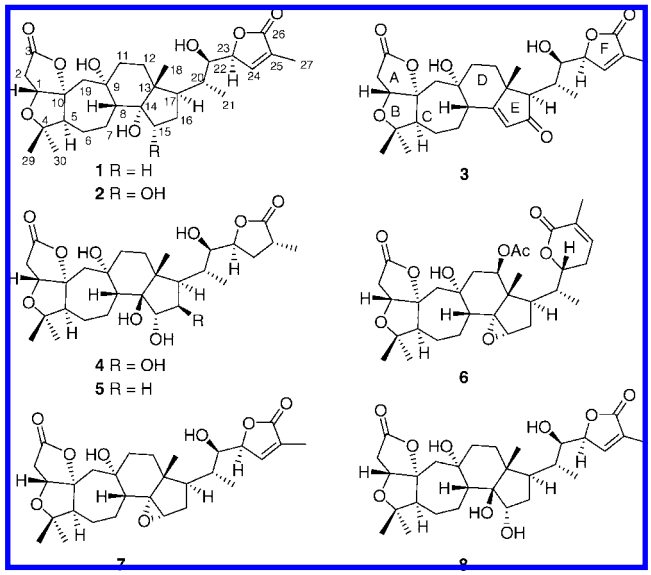


Figure 1. ^{1}H−^{1}H COSY and selected HMBC correlations of **1** and **3**.



86.4 (C-14), and 33.1 (C-15) and of a methyl at δ_H 0.92 (s, H_3-18) with δ_C 29.7 (C-12), 48.0 (C-13), 86.4 (C-14), and 47.8 (C-17) suggested that compound **1** possessed a schiartane skeleton featuring an OH at C-14 and a methyl substituent at C-13. Thus, the structure of **1** was established as shown.

The relative configuration of **1** was determined by means of ROESY experiments and comparison with that of **8** and was confirmed by X-ray analysis. Biogenetically, H-5 and H-17 were tentatively assigned to be α-oriented and Me-18 to be β-oriented, as schiartane-type triterpenoids are thought to be derived from cycloartane triterpenes.[4] Therefore, the cross-peaks in the ROESY spectrum from H-7α to H-5 and 14-OH and from 14-OH to H-17 indicated that 14-OH was cofacial with H-5 and H-17 and was α-oriented, while ROESY correlations of H-8 with both H-7β and Me-18 suggested that H-8 was β-oriented. The relative configurations of other chiral centers in compound **1**, except those on the side chain, which will be further determined below, were identical to those of **8**.

Propindilactone F (**2**) had the molecular formula $C_{29}H_{42}O_9$, as established from HRESIMS ([M − H]$^-$ at m/z 533.2739), the same as compound **8**, and **2** had one more oxygen atom than compound **1**. Comparison of ^{13}C NMR data between **2** and **1** (Table 1) suggested that **2** was identical to **1** except for an additional OH at C-15. This was supported by a methylene at δ_C 33.1 (t) in **1** rather than an oxymethine at δ_C 73.9 (d) in **2**. However, further comparison of the ^{13}C NMR data (Table 1) of **2** and **8** revealed major differences between signals of C-8, C-12, C-17, and C-20. This information indicated that the orientation of one or both OH groups at C-14 or C-15 in **8** may differ in the case of **2**. ROESY cross-peaks of H-8 with Me-18 and H-7β and of H-15 with H-7β, H-8, H_2-16, and Me-18 for compound **2** revealed that 15-OH in **2** was α-directed, the same as that of **8** (Figure 2). Thus, the OH at C-14 was α-oriented rather than β-oriented as in **8**, which resulted in upfield shifts of C-12 (−Δ 9.4 ppm) and C-17 (−Δ 8.3 ppm) because of the γ-gauche effect from 14-OH to both H-12α and H-17 of compound **2** (Figure 2). Otherwise, the structure of **2** was

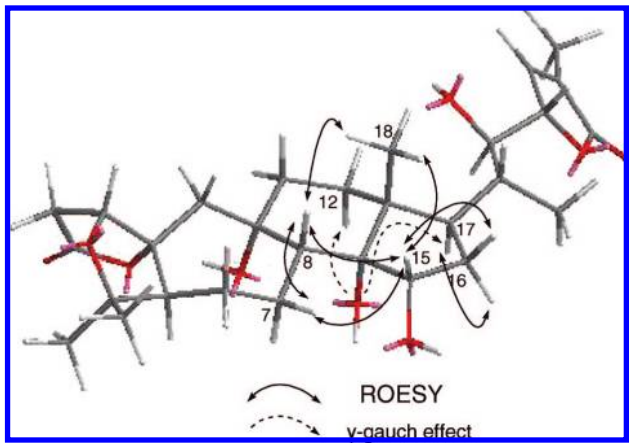


Figure 2. Selected ROESY correlations and γ-gauche effect from 14-OH to H-12α and H-17 of compound **2**.

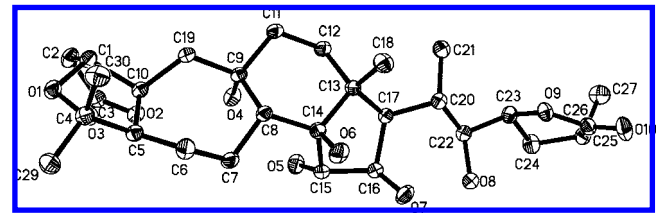


Figure 3. ORTEP view, X-ray crystal structure of **4**.

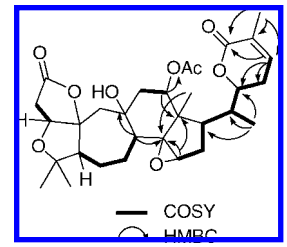


Figure 4. COSY and key HMBC correlations of **6**.

identical to that of **8** by comparison of their ^{1}H NMR coupling constants and ROESY data.

Propindilactone G (**3**) gave the molecular formula $C_{29}H_{38}O_8$ by HRESIMS, requiring 11 degrees of unsaturation. Four singlet and one doublet methyl groups, two trisubstituted double bonds, two esters, and one ketone group in the ^{13}C NMR spectrum of **3** (Table 1), together with the characteristic signals of ABX and AB systems in the ^{1}H spectrum (Table 2), indicated that compound **3** was also a C_{29} nortriterpenoid with the typical 5/5/7-membered A/B/C rings and a five-membered α-methyl-α,β-unsaturated-γ-lactone ring. This conclusion was supported by ^{1}H−^{1}H COSY correlations of H-1/H-2β and H-5/H_2-6/H_2-7/H-8 and by HMBC cross-peaks from H_3-27 to C-24, C-25, and C-26 (Figure 1). Proton spin systems in the ^{1}H−^{1}H COSY spectra of H_2-11/H_2-12 and H-17/H-20/H_3-21(H-22)/H-23/H-24, in combination with key HMBC cross-peaks from H_3-18 to C-12, C-13, C-14, and C-17 and from H-8 to C-14 and C-15 (Figure 1), proved that compound **3** also possessed the schiartane skeleton with a six-membered D ring, a five-membered E ring, and Me-18 located at C-13. The other trisubstituted double bond and the ketone group were present as an α,β-unsaturated ketone group in ring E, which was confirmed by two key HMBC correlations from H-15 to C-13, C-14, and C-16 and from H-17 to C-16 (Figure 1).

Propindilactones E−G (**1**−**3**) should have similar configurations (excluding those of ring E) to those of micrandilactone B (**7**), not only because most stereogenic centers of micrandilactones B (**7**) and C (**8**) are the same as determined by their single-crystal X-ray analysis[9] but also because **1**−**3** and **8** are derivatives of **7** with a few simple modifications of ring E. This deduction was confirmed by analysis of ^{1}H NMR coupling constants and ROESY correlations between **1**−**3** and **7**, in combination with their CD spectra, whose Cotton effects occurred around 220 nm, corresponding to the α,β-unsaturated-γ-lactone moiety (C-24, C-25, and C-26, λ_{max} around 213 nm in their UV spectra, Woodward's rules showed ca. 227 nm),[22] which were similar (**1**: $\Delta\epsilon$ −9.6 at 221 nm, **2**: $\Delta\epsilon$ −13.9 at 220 nm, **3**: $\Delta\epsilon$ −28.9 at 211 nm, **7**: $\Delta\epsilon$ −26.8 at 218 nm). The absolute configuration of **7** had been established by a modified Mosher method and by an X-ray study and then applied to establish the absolute configuration of related nortriterpenoids.[10,11] Thus, the CD spectrum similarity between **1**−**3** and **7** determined the absolute configuration of **1**−**3** as depicted.

Propindilactone H (**4**) was obtained as colorless crystals. Signals of three tertiary methyl and two secondary methyl groups in the ^{1}H NMR data (Table 2), in combination with the molecular formula $C_{29}H_{44}O_{10}$ deduced from HRESIMS, revealed that compound **4** was a C_{29} nortriterpenoid closely related to compound **8**. Analysis of the ^{13}C NMR data of **4** (Table 1) showed signals of the A/B/C/D rings identical to those of **8**. Except for ring F, the main difference was in the signals of ring E, including a methylene replaced by an oxymethine at δ_C 79.7 (d, C-16) and two methine (one oxymethine and one aliphatic methine) carbons downshifted Δ 2.5 ppm and Δ 6.0 ppm accordingly, which indicated an OH at C-16. The proton spin system in the ^{1}H−^{1}H COSY spectrum, H-15/H-16/H-17/H-20/H_3-21(H-22)/H-23/H_2-24/H-25/H_3-27, further confirmed the substructures of rings E and F.

There are three continuous OH's substituted at carbon atoms on ring E in compound **4**, and their relative configurations could not be established by means of ROESY correlations. Thus, the relative configuration of **4** was determined through X-ray diffraction, as shown in Figure 4. Both 14-OH and 16-OH were β-oriented, while 15-OH was α-oriented, and C-23 had an *S** configuration, while C-25 had an *R** configuration (Figure 3).

Propindilactone I (**5**) had ^{13}C NMR (Table 1) signals of the A−E rings identical to those of compound **8**, and those of the C-17 side chain and ring F were identical to those of compound **4**, which indicated that **5** was an analogue of **8** with no double bond in ring F. This assumption was confirmed by the molecular formula $C_{29}H_{44}O_9$ assigned by HRESIMS, together with ^{1}H and 2D NMR including ^{1}H−^{1}H COSY, HMBC, and ROESY correlations.

Propindilactone J (**6**) was assigned the molecular formula $C_{31}H_{42}O_9$ by HRESIMS. 1D NMR spectra (Tables 1 and 2) of **6** gave signals of an acetyl group (δ_C 170.0, s; 21.5, q; δ_H1.91, s) and a C_{29} nortriterpenoid skeleton with rings A−C identical to those of micrandilatone C (**8**). The acetyl group was at C-12, as evidenced by the ^{1}H−^{1}H COSY spin system of H_2-11/H-12 and HMBC correlations from H-12 to C═O of OAc, C-13, and Me-18 (Figure 4).^{13}C NMR signals at δ_C 73.4 (s, C-14) and 54.0 (d, C-15) indicated the existence of an epoxide group between C-14 and C-15, similar to that of micrandilactone B (**7**), which was supported by correlations from H-8 to C-14 and from H-15 to C-13 and C-14 in the HMBC spectrum. Major changes occurred in the F ring, where the typical ^{13}C NMR signals at δ_C 10.6 (q), 72.8 (d), 82.0 (d), 130.2 (s), 148.8 (d), and 175.4 (s) for the five-membered α-methyl-α,β-unsaturated-γ-lactone ring of **7** were replaced by signals at δ_C 17.1 (q), 24.1 (t), 80.0 (d), 127.8 (s), 140.1 (d), and 166.0 (s) for the six-membered α-methyl-α,β-unsaturated-δ-lactone ring of **6**. This structure was further supported by the ^{1}H−^{1}H COSY spin system of H-15/H_2-16/H-17/H-20/H_3-21(H-22)/H_2-23/H-24 and by HMBC cross-peaks from H_3-27 to C-24, C-25, and C-26, from H-24 to C-22 and C-23, and from H_3-21 to C-17, C-20, and C-22 (Figure 4). Correlations of H-7β with H-8 and H-15 indicated that H-15 was α-oriented, and the cross-peak of H-12 with H-17 indicated

that 12-OAc was β-oriented. The CD spectrum of compound **6** showed a positive Cotton effect near 260 nm ($\Delta\epsilon$ +6.6), similar to those kadsulactone and kadsudilactone,[23] which possess similar lactone moieties in the side chain; thus C-22 was assigned an *R* configuration. The other substituents had the same orientations as those reported for **7**.

Compounds **4**−**6** were tested for cytotoxicity against A549, HT-29, and K562 cells according to the method described previously.[24] 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 carried out on a JASCO DIP-370 digital polarimeter. IR spectra were obtained on a Bio-Rad FtS-135 spectrophotometer with KBr pellets, and UV data were obtained using a UV-210A spectrometer. CD spectra were measured on a JASCO J-810 spectropolarimeter. High-resolution electrospray-ionization (HRESIMS) and fast atom bombardment (FABMS) mass spectra were acquired on an API QSTAR time-of-flight mass spectrometer and a VG Autospec-3000 mass spectrometer, respectively. 1D and 2D NMR spectra were taken on a Bruker DRX-500 NMR spectrometer with TMS as internal standard. Semipreparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Zorbax SB-C_{18}, 9.4 mm × 25 cm column. 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, Darmstadt, Germany), and Sephadex LH-20 (Pharmacia). All solvents including petroleum ether (60−90 °C) were distilled prior to use.

Plant Material. Stems of *S. propinqua* var. *propinqua* were collected in Tengchong County, Yunnan Province, P. R. China, in July 2006, and identified by Prof. Xi-Wen Li, Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (No. 20050823) was deposited at 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 stems of *S. propinqua* var. *propinqua* (8 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 (560 g), which was dissolved in H_2O and then extracted successively with petroleum ether and EtOAc. The EtOAc-soluble part (250 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, 29 g) was subjected to repeated CC, first on Sephadex LH-20 eluted with MeOH, then on silica gel eluted by PE/i-PrOH in a gradient system, followed by crystallization, which yielded **6** (30 mg) and **7** (50 mg). Fraction D ($CHCl_3$/acetone, 8:2−2:1, 45 g) was separated by CC on silica gel with $CHCl_3$/acetone (4:1) to obtain fractions D1, D2, and D3. Fraction D2 was then subjected to RP-18 in CC using a 30−60% aqueous MeOH gradient system, then separated further on Sephadex LH-20 eluted with MeOH to afford five fractions (D2.1−D2.5). Fraction D2.2 (40% aqueous MeOH) was chromatographed on silica gel with PE/i-PrOH (5:1) followed by semipreparative HPLC (35% MeOH in H_2O) to yield **1** (3 mg) and **5** (65 mg). Fraction D3 was subjected to the same procedures as D2 to obtain five fractions (D3.1−D3.5). Fraction D3.4 (60% MeOH in H_2O) was subjected to silica gel CC (PE/i-PrOH, 5:1) followed by recrystallization to obtain **4** (30 mg) and **8** (120 mg). The mother liquor after removing the crystals was further purified by semipreparative HPLC (55% MeOH in H_2O) to yield **2** (2 mg) and **3** (3 mg).

Propindilactone E (1): white solid; mp 151−152 °C; $[\alpha]^{25.5}_D$ +41.1 (*c* 0.15 MeOH); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 221.0 (−9.61), 197.0 (+13.8); UV (MeOH) λ_{max} (log ε) 213 (3.88) nm; IR (KBr) ν_{max} 3433, 2971, 2936, 1755, 1630, 1452, 1384, 1200, 1063, 918 cm^{-1}; ^{13}C NMR, see Table 1; ^1H NMR, see Table 2, 9-OH: δ_H 6.76 (brs), 14-OH: δ_H 6.15 (brs); negative FABMS *m/z* 517 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 517.2780 (calcd for $C_{29}H_{41}O_8$, 517.2801).

Propindilactone F (2): white solid; $[\alpha]^{20.0}_D$ +23.3 (*c* 0.15 MeOH); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 220.2 (−13.95), 205.4 (−0.85), 199.2 (−13.2); UV (MeOH) λ_{max} (log ε) 212.6 (3.67) nm; IR (KBr) ν_{max} 3386, 2927, 2936, 1755, 1455, 1408, 1384, 1249, 1203, 1087, 1066, 912 cm^{-1}; ^{13}C and ^1H NMR, see Tables 1 and 2; negative FABMS *m/z* 533 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$*m/z* 533.2739 (calcd for $C_{29}H_{41}O_9$, 533.2750).

Propindilactone G (3): white solid; $[\alpha]^{25.6}_D$ +41.1 (*c* 0.15 MeOH); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 237.4 (+20.97), 211.8 (−28.90); UV (MeOH) λ_{max} (log ε), 213.2 (3.96) nm; IR (KBr) ν_{max} 3441, 2971, 2932, 1756, 1665, 1613, 1384, 1063 cm^{-1}; ^{13}C and ^1H NMR, see Tables 1 and 2; negative FABMS *m/z* 513 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 513.2455 (calcd for $C_{29}H_{37}O_8$, 513.2488).

Propindilactone H (4): colorless crystals; mp 188−189 °C; $[\alpha]^{25.7}_D$ +36.9 (*c* 0.13 MeOH); UV (MeOH) λ_{max} (log ε) 205.4 (3.92) nm; IR (KBr) ν_{max} 3426, 2971, 2934, 1767, 1630, 1204 cm^{-1}; ^{13}C and ^1H NMR, see Tables 1 and 2; negative FABMS *m/z* 551 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 551.2859 (calcd for $C_{29}H_{43}O_{10}$, 551.2856).

Propindilactone I (5): amorphous powder; mp 225−226 °C; $[\alpha]^{21.5}_D$ +25.0 (*c* 0.29 MeOH); UV (MeOH) λ_{max} (log ε) 202.6 (3.09) nm; IR (KBr) ν_{max} 3385, 2959, 2926, 1768, 1459, 1380, 1199, 1067, 1030, 1013, 919 cm^{-1}; ^{13}C and ^1H NMR, see Tables 1 and 2; negative FABMS *m/z* 535 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 535.2896 (calcd for $C_{29}H_{43}O_9$, 535.2907).

Propindilactone J (6): colorless crystals; mp 280−281 °C; $[\alpha]^{21.5}_D$ +51.3 (*c* 0.08 MeOH); CD (MeOH) λ_{max} nm ($\Delta\varepsilon$) 260.0 (+6.60), 250.4 (+7.20), 240.8 (+3.45), 204.8 (+27.85), 198.8 (+13.26), 196.4 (+20.90); UV (MeOH) λ_{max} (log ε) 209.4 (3.80), 194.8 (3.46) nm; IR (KBr) ν_{max} 3422, 2926, 1784, 1717, 1461, 1374, 1241, 1137, 1037 cm^{-1}; ^1H NMR, see Table 2, acetyl: δ_H 1.91 (s); ^{13}C NMR data, see Table 1; acetyl: δ_C 170.0 (s), 21.5 (q); negative FABMS *m/z* 557 $[M - H]^-$; HRESIMS (neg) $[M - H]^-$ *m/z* 557.2740 (calcd for $C_{31}H_{41}O_9$, 557.2751).

X-ray Crystallographic Analysis of 4. Formula: $C_{29}H_{44}O_{10}$; M_r = 552.64; triclinic crystalline system; space group: *P*1; a = 7.464(1) Å, b = 9.449(1) Å, c = 10.763(1) Å; V = 678.29(14) Å^3; Z = 1; α = 78.65(1)°, β = 84.64(1)°, γ = 65.71(1)°; crystal dimensions 0.40 × 0.60 × 0.80 mm. The total number of independent reflections measured was 1975, of which 1963 were observed ($|F|^2 \geq 2\sigma|F|^2$). The final indices were R_1 = 0.0387, wR_2 = 0.1059, S = 1.055. Crystal structure measurements were made by using a MAC DIP-2030 K diffractometer with graphite-monochromated Mo Kα radiation. The data were collected by using the $\omega-2\theta$ scan technique to a maximum 2θ value of 50.0°. The crystal structures were solved by direct methods using Shelxs-97 expanded by using difference Fourier techniques and refined by the program and method NOMCSDP and full-matrix least-squares calculations. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included at their calculated positions. Drawing of the molecule was achieved with ORTEP. Crystallographic data for the structure of **4** have been deposited in the Cambridge Crystallographic Data Centre (deposition number CCDC 680974). Copies of the data can be obtained free of charge via www.ccdc.acm.ac.Uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk]).

Cytotoxicity Assay. Cytotoxicity of compounds **4**−**6** against suspended tumor cells was determined by the trypan blue exclusion method and against adherent cells 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 in the literature.[24] Amrubicin hydrochloride was used as a positive control with IC_{50} values of 0.82 (A549), 4.36 (HT-29), and 1.26 μM (K562), respectively.

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Supporting Information Available: ^1H, ^{13}C, and DEPT NMR spectra of propindilactones E−J (**1**−**6**), UV, HRESIMS, HSQC, $^1H-^1H$ COSY, HMBC, and ROESY spectra of propindilactone E (**1**), and CD spectra of micrandilatone B (**7**) and propindilactones E−G (**1**−**3**) and J (**6**). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Li, R. T.; Zhao, Q. S.; Li, S. H.; Han, Q. B.; Sun, H. D.; Lu, Y.; Zhang, L. L.; Zheng, Q. T. *Org. Lett.* **2003**, *5*, 1023–1026.

(2) Li, R. T.; Shen, Y. H.; Xiang, W.; Sun, H. D. *Eur. J. Org. Chem.* **2004**, *4*, 807–811.
(3) Li, R. T.; Xiang, W.; Li, S. H.; Lin, Z. W.; Sun, H. D. *J. Nat. Prod.* **2004**, *67*, 94–97.
(4) Li, R. T.; Xiao, W. L.; Shen, Y. H.; Zhao, Q. S.; Sun, H. D. *Chem.−Eur. J.* **2005**, *11*, 2989–2996.
(5) Xiao, W. L.; Zhu, H. J.; Shen, Y. H.; Li, R. T.; Li, S. H.; Sun, H. D.; Zheng, Y. T.; Wang, R. R.; Lu, Y.; Wang, C.; Zheng, Q. T. *Org. Lett.* **2005**, *7*, 2145–2148.
(6) Xiao, W. L.; Pu, J. X.; Chang, Y.; Li, X. L.; Huang, S. X.; Yang, L. M.; Li, L. M.; Lu, Y.; Zheng, Y. T.; Li, R, T.; Zheng, Q. T.; Sun, H. D. *Org. Lett.* **2006**, *8*, 1475–1478.
(7) Xiao, W. L.; Huang, S. X.; Zhang, L.; Tian, R. R.; Wu, L.; Li, X. L.; Pu, J. X.; Zheng, Y. T.; Lu, Y.; Li, R. T.; Zheng, Q. T.; Sun, H. D. *J. Nat. Prod.* **2006**, *69*, 650–653.
(8) Xiao, W. L.; Li, X. L.; Wang, R. R.; Yang, L. M.; Li, L. M.; Huang, S. X.; Pu, J. X.; Zheng, Y. T.; Li, R. T.; Sun, H. D. *J. Nat. Prod.* **2007**, *70*, 1056–1059.
(9) Li, R. T.; Han, Q. B.; Zheng, Y. T.; Wang, R. R.; Yang, L. M.; Lu, Y.; Sang, S. Q.; Zheng, Q. T.; Zhao, Q. S.; Sun, H. D. *Chem. Commun.* **2005**, *23*, 2936–2938.
(10) Huang, S. X.; Yang, L. B.; Xiao, W. L.; Lei, C.; Liu, J. P.; Lu, Y.; Weng, Z. Y.; Li, L. M.; Li, R. T.; Yu, J. L.; Zheng, Q. T.; Sun, H. D. *Chem.−Eur. J.* **2007**, *13*, 4816–4822.
(11) Huang, S. X.; Li, R. T.; Liu, J. P.; Lu, Y.; Chang, Y.; Lei, C.; Xiao, W. L.; Yang, L. B.; Zheng, Q. T.; Sun, H. D. *Org. Lett.* **2007**, *9*, 2079–2082.
(12) Huang, S. X.; Yang, J.; Huang, H.; Li, L. M.; Xiao, W. L.; Li, R. T.; Sun, H. D. *Org. Lett.* **2007**, *9*, 4175–4178.
(13) Li, R. T.; Li, S. H.; Zhao, Q. S.; Lin, Z. W.; Sun, H. D.; Lu, Y.; Wang, C.; Zheng, Q. T. *Tetrahedron Lett.* **2003**, *44*, 3531–3534.
(14) Xiao, W. L.; Yang, L. M.; Gong, N. Bo.; Wu, L.; Wang, R. R.; Pu, J. X.; Li, X. L.; Huang, S. X.; Zheng, Y. T.; Li, R. T.; Lu, Yang.; Zheng, Q. T.; Sun, H. D. *Org. Lett.* **2006**, *8*, 991–994.
(15) Xiao, W. L.; Tian, R. R.; Pu, J. X.; Li, X.; Wu, L.; Lu, Y.; Li, S. H.; Li, R. T.; Zheng, Y. T.; Zheng, Q. T.; Sun, H. D. *J. Nat. Prod.* **2006**, *69*, 277–279.
(16) Xiao, W. L.; Yang, L. M.; Li, L. M.; Pu, J. X.; Huang, S. X.; Weng, Z. Y.; Lei, C.; Liu, J. P.; Wang, R. R.; Zheng, Y. T.; Li, R. T.; Sun, H. D. *Tetrahedron Lett.* **2007**, *48*, 5543–5546.
(17) Xiao, W. L.; Li, R. T.; Li, S. H.; Li, X. L.; Sun, H. D.; Zheng, Y. T.; Wang, R. R.; Lu, Y.; Wang, C.; Zheng, Q. T. *Org. Lett.* **2005**, *7*, 1263–1266.
(18) Li, R. T.; Han, Q. B.; Zhao, A. H.; Sun, H. D. *Chem. Pharm. Bull.* **2003**, *51*, 1174–1176.
(19) Lei, C.; Huang, S. X.; Chen, J. J.; Pu, J. X.; Li, L. M.; Xiao, W. L.; Liu, J. P.; Yang, L. B.; Sun, H. D. *Helv. Chim. Acta* **2007**, *90*, 1399–1405.
(20) Lei, C.; Huang, S. X.; Pu, J. X.; Liu, J. P.; Yang, G. Y.; Yang, L. B.; Lu, Y.; Chen, J. J.; Lu, Y.; Xiao, W. L. *Planta Med.* **2008**, *74*, 1–3.
(21) Lei, C.; Huang, S. X.; Chen, J. J.; Pu, J. X.; Yang, L. B.; Zhao, Y.; Liu, J. P.; Gao, X. M.; Xiao, W. L. *Chem. Pharm. Bull.* **2007**, *55*, 1281–1283.
(22) Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds: Tables of Spectral Data*; Chinese Version, Translated by Rong, G. B., Zhu, S. Z.; East China University of Science and Technology: Shanghai, 2002; pp 388−389.
(23) Tan, R.; Xue, H.; Li, L. N. *Planta Med.* **1991**, *57*, 87–88.
(24) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A. *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.

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