Lignans from *Kadsura angustifolia*

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Phytochemical investigation of *Kadsura angustifolia* led to the isolation and identification of 26 lignans and two triterpenoids, including 11 new lignans named kadangustins A−K (**1**–**11**). The structures and stereochemistry of **1**–**11** were elucidated by analysis of spectroscopic data. Except for **11** and **20**, all the lignans were evaluated for their inhibitory activity against HIV-1. Binankadsurin A (**19**) showed anti-HIV activity with an EC_{50} value of 3.86 μM.

The family Schisandraceae, consisting of *Schisandra* and *Kadsura* genera, is medicinally important. Many plants of this family are commonly used in Traditional Chinese Medicine for their diverse beneficial bioactivities. Previous studies showed that the principal bioactive constituents of this family were lignans, especially the dibenzocyclooctadiene type,[1] some of which possessed anti-HIV,[2,3] antitumor,[4] cytotoxic,[5–9] antioxidant,[10,11] and antihepatotoxic[12,13] effects.

Recently, some new triterpenoids and lignans with unprecedented skeletons, such as kadlongilactones A and B,[6] longipedlactones A−I,[7] kadsuphilactone A,[8] and taiwankadsurins A−C,[9] have been isolated from the genus *Kadsura*. Some of them exihibited considerable bioactivities.[6–9] *Kadsura angustifolia* (Lem.) A. C. Smith is an evergreen liana, growing in the forests at elevations of 1280–2250 m in Yunnan Province, China.[14] Its stems are used as a folk medicine to promote blood circulation and treat fractures and menstrual irregularities. Some lignans and triterpenoids were isolated from this species in past decades.[15–17] Our present study led to the isolation of 26 lignans and two triterpenoids. The structures of the new compounds **1**–**11** were established by means of MS and extensive NMR spectra, and the absolute configurations of **1**–**7** were determined by CD and ROESY experiments. This paper deals with the isolation, structural characterization, and anti-HIV activity of these compounds.

Results and Discussion

A 70% aqueous acetone extract prepared from the stems of *K. angustifolia* was partitioned between EtOAc and H_2O. The EtOAc layer was subjected repeatedly to column chromatography on Si gel, Sephadex LH-20, RP-18, and HPLC to afford compounds **1**–**28**, including 11 new lignans named kadangustins A–K (**1**–**11**), together with 15 known lignans, kadsurarin (**12**),[18] schisantherin Q (**13**),[19] schisantherin L (**14**),[20] Gomisin R (**15**),[21] schisantherin P (**16**),[19] deangeloylschisantherin F (**17**),[22] schisantherin F (**18**),[23] binankadsurin A (**19**),[24] kadsulignan K (**20**),[25] kadsulignan L (**21**),[26] epoxide schisandrin C (**22**),[26] kadsulignan N (**23**),[26] *meso*-dihyroguaiaretic acid (**24**),[17] perseal F (**25**),[27] (2*S*,3*R*)-5-allyl-7-methoxy-3-hydroxymethyl-2-(3′-methoxy-4′-hydroxyphenyl)-2,3-dihydrobenzofuran (**26**),[28] and the known triterpenoids anwuweizic acid (**27**)[29] and (24*Z*)-3-oxo-12α-hydroxylanosta-8,24-dien-26-oic acid (**28**).[30]

Table 1. ^{13}C NMR Data of Compounds **1**–**7** (δ in ppm)

no.	**1**[a]	**2**[b]	**3**[a]	**4**[a]	**5**[a]	**6**[c]	**7**[c]
1	147.4 s	142.8 s	146.9 s	147.3 s	147.3 s	149.1 s	149.2 s
2	135.5 s	137.3 s	134.8 s	135.4 s	135.0 s	136.2 s	136.4 s
3	150.8 s	150.2 s	150.5 s	150.6 s	150.4 s	151.5 s	151.4 s
4	107.0 d	107.0 d	107.6 d	107.8 d	107.0 d	107.5 d	107.2 d
5	135.1 s	136.2 s	130.5 s	131.1 s	130.9 s	132.2 s	132.1 s
6	81.5 d	81.5 d	84.2 d	81.1 d	81.3 d	81.3 d	82.1 d
7	41.5 d	41.0 d	74.1 s	38.9 d	39.3 d	40.2 d	38.3 d
8	39.3 d	41.5 d	42.6 d	38.8 d	39.3 d	40.3 d	40.5 d
9	80.4 d	80.6 d	83.7 d	80.6 d	81.3 d	81.3 d	81.2 d
10	135.5 s	134.7 s	135.3 s	135.3 s	135.5 s	136.2 s	136.0 s
11	107.4 d	103.2 d	106.8 d	107.4 d	107.0 d	108.1 d	107.9 d
12	153.6 s	150.8 s	153.0 s	153.1 s	153.2 s	153.7 s	153.7 s
13	141.8 s	137.5 s	141.2 s	141.7 s	141.4 s	142.1 s	142.1 s
14	152.3 s	143.5 s	150.8 s	152.1 s	153.2 s	152.9 s	153.5 s
15	119.7 s	122.6 s	120.0 s	120.9 s	120.6 s	122.3 s	122.6 s
16	116.0 s	123.8 s	116.2 s	117.3 s	117.0 s	119.0 s	118.9 s
17	14.9 q	10.6 q	28.7 q	15.5 q	14.2 q	15.7 q	14.1 q
18	16.7 q	18.0 q	17.0 q	15.7 q	14.2 q	20.4 q	20.5 q
1′			165.1 s	165.6 s	165.4 s	166.6 s	166.6 s
2′			117.3 d	118.2 d	129.8 s	128.8 s	128.6 s
3′			145.0 d	144.5 d	128.1 d	138.6 d	137.9 d
4′			133.9 s	134.4 s	129.5 d	20.5 q	14.1 q
5′			128.0 d	127.9 d	133.0 d	15.7 q	11.8 q
6′			128.8 d	128.7 d	129.5 d		
7′			129.9 d	130.1 d	128.1 d		
8′			128.8 d	128.7 d			
9′			128.0 d	127.9 d			
1-OMe		59.6 q					
2-OMe	60.8 q		60.4 q	60.6 q	60.9 q	60.6 q	60.4 q
3-OMe	56.1 q		55.9 q	56.0 q	56.0 q	56.1 q	56.1 q
12-OMe	56.0 q		55.9 q	55.9 q	55.8 q	56.3 q	56.2 q
13-OMe	60.8 q		60.6 q	60.6 q	60.5 q	60.3 q	60.2 q
14-OMe	60.9 q	59.9 q	60.8 q	60.7 q	60.5 q	60.6 q	60.6 q
2,3-OCH_2O		102.5 t					
12,13-OCH_2O		102.3 t					
OAc	170.0 s	172.0 s	168.9 s	169.8 s	170.2 s	169.8 s	169.8 s
	20.2 q	20.5 q	20.1 q	20.2 q	20.4 q	20.5 q	20.5 q

[a] Data were recorded in $CDCl_3$. [b] Data were recorded in CD_3OD. [c] Data were recorded in $(CD_3)_2CO$.

The ^{13}C NMR spectroscopic data of the new lignans **1**–**11** are listed in Tables 1 and 2.

Kadangustin A (**1**), obtained as a white, amorphous powder, was assigned the molecular formula $C_{25}H_{32}O_9$ by HRESIMS *m/z* 499.1950 $[M + Na]^+$ (calcd 499.1944). The ^1H and ^{13}C NMR spectra of **1** indicated the presence of 12 aromatic carbons, two aromatic protons, one phenolic hydroxy group, and five methoxy groups, suggesting the presence of a biphenyl moiety.[31] HMBC correlations of H-11 with C-9, C-10, and C-15, and of H-4 with

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Table 2. ^{13}C NMR Data of Compounds **8–11** in $CDCl_3$ (δ in ppm)

no.	8	9	10	11
1	140.8 s	140.7 s	137.2 s	136.5 s
2	102.4 d	102.2 d	111.5 d	114.4 d
3	152.4 s	152.4 s	148.9 s	147.2 s
4	134.8 s	134.7 s	147.3 s	143.8 s
5	149.0 s	149.0 s	111.4 d	111.1 d
6	106.6 d	106.6 d	119.7 d	119.7 d
7	77.3 d	77.2 d	55.9 d	55.9 d
8	45.0 d	44.8 d	36.0 d	35.9 d
9	11.4 q	11.4 q	11.8 q	11.8 q
1′	134.8 s	136.8 s	137.7 s	137.7 s
2′	112.4 d	103.1 d	111.3 d	110.4 d
3′	147.1 s	148.6 s	149.0 s	148.8 s
4′	148.7 s	133.0 s	147.3 s	146.5 s
5′	111.1 d	143.3 s	111.3 d	111.1 d
6′	121.0 d	108.1 d	119.8 d	120.2 d
7′	37.0 t	37.5 t	67.0 t	67.0 t
8′	34.9 d	35.0 d	36.1 d	36.0 d
9′	17.9 q	17.8 q	9.6 q	9.6 q
3-OMe	55.9 q	55.8 q	55.9 q	55.8 q
4-OMe	60.9 q	60.9 q	55.8 q	
3′-OMe	55.8 q		55.9 q	55.9 q
4′-OMe	55.9 q		55.8 q	55.8 q
5′-OMe		56.5 q		
3′,4′-OCH_2O		101.1 t		

C-5, C-6, and C-16, together with $^1H-^1H$ COSY correlations of H-6/H-7/H-8/H-9 (Figure 1) and UV absorption bands at 360, 309, 284, and 210 nm, implied that **1** could be a dibenzocyclooctadiene lignan.[31] Further analysis of the HMBC spectrum showed that five methoxy groups were located at C-2, C-3, C-12, C-13, and C-14, respectively (Figure 1). In the cyclooctadiene ring, two secondary methyl groups (δ_H 0.98, d, J = 7.0 Hz; δ_H 1.02, d, J = 7.3 Hz) can be assigned to CH_3-17 and CH_3-18, respectively. The signals of two benzylic oxymethines were assigned to C-6 and C-9. The existence of an O-acetyl group at C-9 was deduced from the HMBC correlations of H-9 with C═O of OAc (Figure 1). According to the molecular formula, the quaternary carbon at C-1 and the benzylic oxymethine at C-6 should both be substituted by a hydroxy group.

Since the CD spectra of dibenzocyclooctadiene lignans are dominated by the axial chirality of the biphenyl chromophore, the absolute configuration of the biphenyl axis of compound **1** could be determined by CD. The CD curve showed a negative Cotton effect around 250 nm and a positive one around 220 nm, suggesting that **1** possessed an a*S*-biphenyl configuration.[31] With the axial chirality defined, a ROESY experiment was used to establish the relative configuration of the remaining stereocenters. The observed ROESY correlations of H-11 with H-8 and H-9, H-4 with H-6 and H_3-17, and H_3-18 with H-9 and H_3-17 were consistent with a cyclooctadiene lignan with a twisted boat/chair conformation and the relative configurations of C-6 (*R*), C-7 (*S*), C-8 (*R*), and C-9 (*R*) (Figure 3).[10] Furthermore, the proton–proton coupling constants of H-6 with H-7 (d, J = 7.2 Hz) and of H-9 with H-8 (d, J = 4.3 Hz) were in accordance with the outlined relative configuration. As a result, the structure of kadangustin A (**1**) was determined as shown.

Kadangustin B (**2**), obtained as a pale yellow, amorphous solid, had the molecular formula $C_{24}H_{26}O_9$ as revealed by its HRESIMS data *m/z* 481.1476 $[M + Na]^+$ (calcd 481.1474). The NMR spectra of **2** were similar to those of **1**, except for the substituents on the two aromatic rings. HMBC correlations of the protons at δ_H 5.88 (OCH_2O) with C-2 and C-3 and the protons at δ_H 5.98 (OCH_2O) with C-12 and C-13 suggested that one methylenedioxy group was connected with C-2 and C-3, and another was connected with C-12 and C-13. Furthermore, HMBC correlations of two methoxy groups (δ_H 3.83 and 3.90) with C-1 and C-14, respectively, showed their locations at C-1 and C-14. In addition, HMBC correlations of H-9 with C═O of OAc determined an acetyl group at C-9. In addition,

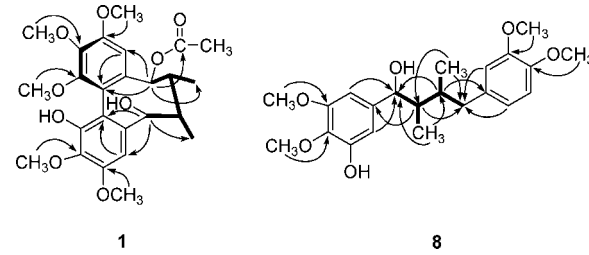

Figure 1. Selected HMBC (→) and $^1H-^1H$ COSY (—) correlations of **1** and **8**.

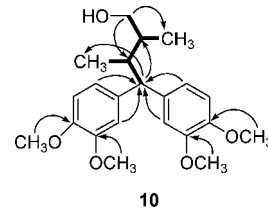

Figure 2. Selected HMBC (→) and $^1H-^1H$ COSY (—) correlations of **10**.

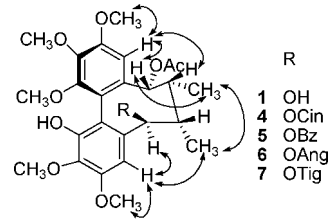

Figure 3. Key ROESY correlations of compounds **1** and **4**−**7**.

the presence of a hydroxy group was determined by the molecular formula and located at C-6 by deshielding of C-6 to δ_C 81.5 (d) (Table 1).

The biphenyl group in **2** was determined to have an a*S* configuration from its CD spectrum, which was similar to that of **1**. The observed ROESY correlations of H-11/H-8, H-9; H-4/H-6, H_3-17; and H_3-18/H-9, H_3-17, as well as the coupling constants of H-6 with H-7 (d, J = 7.2 Hz) and of H-8 with H-9 (d, J = 5.2 Hz), were in agreement with a cyclooctadiene lignan with a twisted boat/chair conformation having C-6 (*R*), C-7 (*S*), C-8 (*R*), and C-9 (*R*) relative configurations,[10] which were the same as those of **1**.

Kadangustin C (**3**), obtained as a white, amorphous powder, showed a quasi-molecular weight of 645.2311 $[M + Na]^+$ in the HRESIMS (calcd 645.2311) corresponding to the molecular formula $C_{34}H_{38}O_{11}$. The ^1H and ^{13}C NMR spectra, together with the CD, UV, and IR experiments, suggested that **3** was also an a*S*-biphenyl-configured dibenzocyclooctadiene lignan. The HMBC correlations of H-9 with C═O of OAc and of five methoxy groups with C-2, C-3, C-12, C-13, and C-14, respectively, suggested that the substitution patterns on the carbons of the aromatic rings and C-9 were the same as those of **1**. The carbon signals at δ_C 165.1 (C-1′), 117.3 (C-2′), 145.0 (C-3′), 133.9 (C-4′), 128.0 (C-5′ and C-9′), 128.8 (C-6′ and C-8′), and 129.9 (C-7′) (Table 1) suggested the presence of a cinnamate moiety, which was confirmed by analysis of HSQC, $^1H-^1H$ COSY, HMBC, and a characteristic ion peak at *m/z* 475 $[M - 147]^+$ in the FABMS. The *trans* configuration of the C-2′−C-3′ double bond was established by the coupling constant (J = 16.1 Hz) of H-2′ and H-3′. The HMBC correlation of H-6 with C-1′ positioned the *trans*-cinnamate at C-6. In addition, a hydroxy group at C-7 was deduced from the molecular formula and deshielding of C-7 to δ_C 74.1 (Table 1).

The ROESY correlations of H-9 with H-11, H-4 with H-6, H_3-18 with H-9, and H-8 with H-11 suggested that **3** possessed a twisted boat/chair conformation of the cyclooctadiene ring and C-6

(*S*), C-8 (*S*), and C-9 (*R*) relative configuration. However, the absence of correlation between H_3-17 and H-4 indicated a quasi-axial 7-OH and thus C-7 (*S*) relative configuration.[18]

Comparison of the NMR data of **1** with those of **4**–**7** disclosed that the main structural differences between these compounds were the substitutions at C-6. Kadangustin D (**4**) was obtained as a white, amorphous powder and possessed a molecular formula of $C_{34}H_{38}O_{10}$, as deduced from its HRESIMS *m/z* 629.2371 $[M + Na]^+$ (calcd 629.2362) and NMR data. The 1D and 2D NMR spectra of **4** showed the existence of a *trans*-cinnamate moiety identical to that of **3**. This was further supported by the ion peak at *m/z* 459 $[M - 147]^+$ in the FABMS. HMBC correlation of H-6 with C-1′ established the location of the *trans*-cinnamate group at C-6. Kadangustin E (**5**), obtained as a pale yellow, amorphous powder, had the molecular formula $C_{32}H_{36}O_{10}$ as revealed by its HRESIMS at *m/z* 603.2203 $[M + Na]^+$ (calcd 603.2206). The carbon signals at δ_C 165.4 (C-1′), 129.8 (C-2′), 128.1 (C-3′ and C-7′), 129.5 (C-4′ and C-6′), and 133.0 (C-5′) (Table 1) and the ion peak at *m/z* 459 $[M - 121]^+$ and 105 $[C_6H_5CO]^+$ in the FABMS suggested the presence of a benzoyloxy group in **5**. HMBC correlation of H-6 with C-1′ positioned the benzoyloxy group at C-6. Kadangustin F (**6**) was obtained as a pale yellow, amorphous powder. The positive HRESIMS showed a quasi-molecular ion at *m/z* 581.2362 (calcd 581.2362) corresponding to $[M + Na]^+$, indicating a molecular formula of $C_{30}H_{38}O_{10}$. The analysis of NMR data showed the presence of an angeloyloxy group substituted at C-6 by HMBC correlation of H-6 with C-1′. Kadangustin G (**7**) was obtained as a pale yellow, amorphous powder. The positive HRESIMS data of **7** at *m/z* 581.2360 $[M + Na]^+$ (calcd 581.2362) demonstrated that it had the molecular formula $C_{30}H_{38}O_{10}$, which was the same as that of **6**. The major difference constitutes replacement of an angeloyloxy group in **6** by a tigloyloxy group in **7**. The presence of a tigloyloxy group was deduced from the ^{13}C NMR spectrum, which showed two carbon signals at δ_C 14.1 (C-4′) and 11.8 (C-5′) in **7** instead of at δ_C 20.5 (C-4′) and 15.7 (C-5′) in **6** (Table 1).[32] This was further confirmed by correlations observed between the olefinic hydrogen (H-3′) and both methyls (H_3-4′ and H_3-5′) in the ROESY spectrum of **6**, while only the correlation of the olefinic hydrogen (H-3′) with the methyl (H_3-5′) was observed in the ROESY spectrum of **7**. Furthermore, HMBC correlation of H-6 with C-1′ positioned the tigloyloxy group at C-6 in **7**.

By comparison of ROESY, CD, and UV spectra with those of **1**, compounds **4**–**7** were also assigned a*S*-biphenyl-configured dibenzocyclooctadiene lignans with twisted boat/chair conformation of the cyclooctadiene ring and quasi-axial CH_3-17 and quasi-equatorial CH_3-18. Moreover, ROESY correlations of H-11/H-8, H-9; H-4/H-6, H_3-17; and H_3-18/H-9, H_3-17 suggested the relative configuration of C-6 (*R*), C-7 (*S*), C-8 (*R*), and C-9 (*R*), which were identical with those of **1** (Figure 3). The H-6/H-7 and H-8/H-9 coupling constants for compounds **4**–**7** also confirmed the above deduction.

Kadangustin H (**8**) was obtained as a pale yellow, amorphous solid. Its molecular formula was determined as $C_{22}H_{30}O_6$ by the HRESIMS at *m/z* 413.1946 $[M + Na]^+$ (calcd 413.1940). The functional groups appearing in the ^1H and ^{13}C NMR spectra included two aromatic rings, four methoxy groups, two methyl groups, one methylene group, and eight methine groups. The strong IR absorption bands indicated the presence of hydroxy groups (3432 cm^{-1}) and aromatic rings (1595, 1515, and 1464 cm^{-1}). In the HMBC spectrum, correlations were found from H-2 and H-6 to C-7 and from H-2′ and H-6′ to C-7′, which implied that the two substituted aromatic moieties were not linked directly (Figure 1). Moreover, the HMBC correlations of H-9 with C-7, C-8, and C-8′, of H-9′ with C-7′, C-8′, and C-8, of H-8 with C-1, C-7, and C-7′, and of H-8′ with C-1′, C-7, and C-7′, together with the spin system of H-7/H-8/H-8′/H-7′, H-8/H-9, and H-8′/H-9′ in the $^1H-^1H$ COSY spectrum, suggested that the skeleton of **8** was a substituted 1,4-bisphenyl-2,3-dimethylbutane-type lignan (Figure 1).[33] The chemical shift of C-7 (δ_C 77.3, d) (Table 1) and molecular formula of $C_{22}H_{30}O_6$ suggested a hydroxy group at C-7. The correlations from the protons of four methoxy groups to C-3′, C-4′, C-3, and C-4 located these groups at C-3′, C-4′, C-3, and C-4, respectively. Considering the presence of a quarternary carbon (C-5) in **8** and its molecular formula, a hydroxy group should be attached to C-5. On the basis of the above analysis, the structure of kadangustin H (**8**) was determined as shown.

Kadangustin I (**9**), obtained as a pale yellow, amorphous solid, had a molecular formula of $C_{22}H_{28}O_7$ deduced from its HRESIMS at *m/z* 427.1750 $[M + Na]^+$ (calcd 427.1732). The functional groups in the IR, UV, and NMR spectra were similar to those of compound **8**. The obvious difference was the replacement of two methoxy groups in **8** with a methylenedioxy group in **9**. In addition, HMBC correlations from the methylenedioxy proton (δ_H 5.93, s) to C-3′ and C-4′ implied that the methylenedioxy group was attached at C-3′ and C-4′.

Kadangustin J (**10**) was obtained as a pale yellow, amorphous solid. The molecular formula of **10** was determined as $C_{22}H_{30}O_5$ from its HRESIMS at *m/z* 397.1979 $[M + Na]^+$ (calcd 397.1990). The ^1H and ^{13}C NMR data indicated the presence of two aromatic rings and four methoxy and two methyl groups. Strong absorption bands accounting for hydroxy (3432 cm^{-1}) and aromatic groups (1606, 1592, 1515, 1464 cm^{-1}) could also be observed in its IR spectrum. The UV spectrum of **10** showed maximum absorption at 281 and 205 nm, which confirmed the existence of the aromatic functions. The most significant NMR differences of **10** and compounds **8** and **9** were the appearance of an oxygenated methylene group at δ_C 67.0 and a methine group at δ_C 55.9 (Table 1), which implied a different skeleton. By comparison, the skeleton of **10** was the same as that of the known 4,4-di(4-hydroxy-3-methoxyphenly)-2,3-dimethylbutanol.[34]

According to the HMBC correlations from H-2′, H-6′, H-2, and H-6 to C-7 (Figure 2), both aromatic groups were attached to C-7. The $^1H-^1H$ COSY correlations of H-7/H-8/H-8′/H-7′, H-8/H-9, and H-8′/H-9′, as well as the HMBC correlations from H-7 to C-8, C-8′, and C-9, indicated the presence of a 2,3-dimethylbutane moiety (Figure 2), which was further confirmed by a peak at *m/z* 287 $[M - C_5H_{10}OH]^+$ in the FABMS. According to the chemical shift of δ_C 67.0 and the molecular formula of **10**, a hydroxy group should be located at C-7′ (Table 1). Four methoxy groups located on C-3′, C-4′, C-3, and C-4, respectively, can be deduced from its HMBC spectrum (Figure 2). Thus, the structure of kadangustin J (**10**) was established as shown.

Kadangustin K (**11**) was obtained as a white, amorphous solid. It was assigned the molecular formula $C_{21}H_{28}O_5$ by its HRESIMS *m/z* 383.1828 $[M + Na]^+$ (calcd 383.1834). The UV, IR, and NMR spectral features were similar to those of **10**. The only difference between **11** and **10** was replacement of the methoxy group at C-4 in **10** by a hydroxy group in **11**.

Since the C−C bonds can rotate randomly, the relative configuration of compounds **8**–**11** could not be determined on the basis of ROESY spectra.

The lignans from *K. angustifolia* were tested for their ability to prevent the cytopathic effects of HIV-1 in C8166, and their cytotoxicity was measured in parallel with the determination of antiviral activity using AZT as a positive control (EC_{50} = 0.0161 μM and CC_{50} > 200 μM) (Table 3). Compounds **11** and **20** were not tested due to mass limitations. Among these lignans, binankadsurin A (**19**) showed potent anti-HIV activity with an EC_{50} of 3.86 μM, CC_{50} of 227.16 μM, and SI of 58.92, respectively. Other compounds showed weak or moderate anti-HIV activity (Table 3).

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. A Tenor 27 spectropho-

Table 3. Anti-HIV Activities of Lignans from *K. angustifolia*

compound	EC_{50} (μM)	CC_{50} (μM)	SI[a]
1	>200	>200	
2	149.65	>200	>2.92
3	38.34	190.27	4.96
4	25.43	97.54	3.84
5	60.84	138.26	2.27
6	72.62	159.52	2.20
7	25.73	72.24	2.81
8	27.00	30.72	1.14
9	21.48	35.10	1.63
10	44.68	246.84	5.52
12	168.31	>200	>2.14
13	45.89	211.59	4.61
14	137.97	>200	2.91
15	54.58	220.75	4.04
16	156.37	>200	>3.07
17	198.81	280.87	1.41
18	95.23	>200	4.32
19	3.86	227.16	58.92
21	26.21	360.84	13.77
22	9.35	220.40	23.58
23	43.56	381.91	8.77
24	15.61	49.15	3.15
25	40.86	269.81	6.60
26	13.07	38.07	2.91

[a] SI = EC_{50}/CC_{50}.

tometer was used for scanning IR spectroscopy with KBr pellets. CD spectra were measured on a JASCO J-810 spectropolarimeter. 1D and 2D NMR spectra were recorded on Bruker AM-400 and DRX-500 spectrometers with TMS as internal standard. Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to the solvent signals. HRESIMS and FABMS were performed on an API QSTAR time-of-flight spectrometer and a VG Autospec-3000 spectrometer, respectively. Semipreparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Zorbax SB-C_{18} (9.4 mm × 25 cm) column. Preparative HPLC was performed on a Shimadzu LC-8A preparative liquid chromatograph with a Shimadzu PRC-ODS (K) column (34 mm × 15 cm). Column chromatography was performed with Si gel (200–300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China), Lichroprep RP-18 gel (40–63 μM, Merck, Darmstadt, Germany), and MCI gel (75–150 μM, Mitsubishi Chemical Corporation, Tokyo, Japan). Fractions were monitored by TLC, and spots were visualized by heating Si gel plates sprayed with 5% H_2SO_4 in EtOH.

Plant Material. The stems of *K. angustifolia* were collected in Honghe Prefecture of Yunnan Province, China, in October 2005. The identity of plant material was verified by Prof. Xi-Wen Li. A voucher specimen (KIB 05-10-10) has been deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, China.

Extraction and Isolation. The air-dried and powdered stems of *K. angustifolia* (12 kg) were extracted four times with 70% aqueous Me_2CO (4 × 5 L) at room temperature and filtered to yield a filtrate, which was successively evaporated under reduced pressure and partitioned with EtOAc (3 × 4 L). The EtOAc partition (636 g) was applied to Si gel (200–300 mesh) column chromatography eluting with a $CHCl_3$−MeOH gradient system (20:1, 9:1, 8:2, 7:3, 6:4, 5:5) to give five fractions, A–E. The separation of fraction A by Si gel column chromatography eluted with petroleum ether−acetone (20:1–6:4) yielded mixtures A1−A7. Fraction A2 (170 g) was subjected to Si gel column chromatography using petroleum ether−acetone (20:1–6:4) for elution to afford fractions, A21−A29. Fraction A24 (106 mg) was purified by preparative HPLC (65% MeOH−H_2O, flow rate 25 mL/min) to give **15** (4 mg). Fraction A29 (62 mg) was purified by semipreparative HPLC (65% MeOH−H_2O, flow rate 3 mL/min) to give **25** (3 mg). Fraction A3 (54 g) was subjected to a reversed-phase column (RP-18) eluting with MeOH−H_2O (30%–90%) to afford fractions A31–A34 and compounds **27** (17 mg) and **21** (6.5 g). Part of fraction A32 (9.2 g) was subjected to RP-18 column chromatography (40%–90% MeOH−H_2O, gradient system) and then by preparative HPLC (65% MeOH−H_2O, flow rate 25 mL/min) to give **23** (4 mg). Fraction A4 (60 g) was subjected to Si gel column chromatography using petroleum ether−acetone (20:1–6:4) for elution followed by a reversed-phase column (RP-18) eluting with MeOH−H_2O (30%–90%) and then by Sephadex LH-20 using MeOH as eluant. Further purifications were performed by semipreparative HPLC and preparative HPLC separation (60% MeOH−H_2O, flow rate 3 mL/min, 25 mL/min) to give compounds **1** (12 mg), **2** (2 mg), **3** (10 mg), **4** (4 mg), **5** (2 mg), **6** (2 mg), **7** (5 mg), **8** (6 mg), **9** (5 mg), **10** (8 mg), **11** (1 mg), **12** (20 mg), **13** (6 mg), **14** (3 mg), **16** (18 mg), **17** (15 mg), **18** (3 mg), **19** (3 mg), **20** (2 mg), **22** (6 mg), **24** (8 mg), **26** (5 mg), and **28** (107 mg).

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}).[35]

Kadangustin A (1): $C_{25}H_{32}O_9$, white, amorphous powder; $[\alpha]^{23.4}_D$ +56.0 (*c* 0.950, MeOH); CD (*c* 0.0476, MeOH) λ_{max} nm ($\Delta\epsilon$) 250 (−55.86), 221 (+2.13); UV (MeOH) λ_{max} (log ϵ) 360 (2.75), 309 (2.62), 284 (3.90), 210 (5.01) nm; IR (KBr) ν_{max} 3521, 3407, 2965, 2942, 1713, 1602, 1578, 1491, 1454, 1427, 1408, 1374, 1329, 1271, 1191, 1156, 1128, 1104, 1025, 999 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.39 (1H, s, H-4), 4.48 (1H, d, J = 7.2 Hz, H-6), 1.94–1.96 (1H, m, H-7), 2.23–2.25 (1H, m, H-8), 5.72 (1H, d, J = 4.3 Hz, H-9), 6.56 (1H, s, H-11), 1.02 (3H, d, J = 7.3 Hz, H-17), 0.98 (3H, d, J = 7.0 Hz, H-18), 1.56 (3H, s, CH_3-Ac), 3.94, 3.92, 3.91, 3.89, 3.77 (each 3H, s, 5 × OMe), 5.56 (1H, s, OH); ^{13}C NMR data, Table 1; positive FABMS *m/z* 476 (37) $[M]^+$, 416 (71), 359 (100); HRESIMS (positive ion mode) *m/z* 499.1950 $[M + Na]^+$ (calcd 499.1944 for $C_{25}H_{32}O_9Na$).

Kadangustin B (2): $C_{24}H_{26}O_9$, pale yellow, amorphous solid; $[\alpha]^{22.8}_D$ +56.1 (*c* 0.272, MeOH); CD (*c* 0.0458, MeOH) λ_{max} nm ($\Delta\epsilon$) 258 (−36.10), 234 (+60.50), 219 (−2.58); UV (MeOH) λ_{max} (log ϵ) 369 (3.30), 217 (5.00) nm; IR (KBr) ν_{max} 3437, 2940, 2880, 1735, 1621, 1478, 1453, 1431, 1373, 1363, 1271, 1240, 1210, 1116, 1091, 1070, 1044 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 6.47 (1H, s, H-4), 4.39 (1H, d, J = 7.2 Hz, H-6), 1.85–1.86 (1H, m, H-7), 2.16 (1H, br s, H-8), 5.66 (1H, d, J = 5.2 Hz, H-9), 6.44 (1H, s, H-11), 0.92 (3H, d, J = 7.4 Hz, H-17), 0.98 (3H, d, J = 7.0 Hz, H-18), 1.61 (3H, s, CH_3-Ac), 3.83, 3.90 (each 3H, s, 2 × OMe), 5.88, 5.98 (each 2H, s, 2 × OCH_2O); ^{13}C NMR data, Table 1; positive FABMS *m/z* 458 (38) $[M]^+$, 441 (72), 416 (37), 341 (100); HRESIMS (positive ion mode) *m/z* 481.1476 $[M + Na]^+$ (calcd 481.1474 for $C_{24}H_{26}O_9Na$).

Kadangustin C (3): $C_{34}H_{38}O_{11}$, white, amorphous powder; $[\alpha]^{16.6}_D$ −53.7 (*c* 0.090, MeOH); CD (*c* 0.0622, MeOH) λ_{max} nm ($\Delta\epsilon$) 253 (−73.10), 224 (+13.46), 220 (−1.18); UV (MeOH) λ_{max} (log ϵ) 361 (3.13), 280 (4.62), 254 (4.57), 218 (5.01) nm; IR (KBr) ν_{max} 3567, 3431, 2938, 2850, 1746, 1712, 1637, 1611, 1600, 1587, 1498, 1459, 1427, 1410, 1376, 1367, 1335, 1233, 1198, 1158, 1131, 1037, 1007, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.67 (1H, s, H-4), 5.92 (1H, s, H-6), 2.25–2.28 (1H, m, H-8), 5.76 (1H, br, H-9), 6.64 (1H, s, H-11), 1.35 (3H, s, H-17), 1.32 (3H, d, J = 7.1 Hz, H-18), 1.57 (3H, s, CH_3-Ac), 5.85 (1H, d, J = 16.1 Hz, H-2′), 7.02 (1H, d, J = 16.1 Hz, H-3′), 7.35–7.37 (1H, overlap, H-5′), 7.35–7.37 (1H, overlap, H-6′), 7.35–7.37 (1H, overlap, H-7′), 7.35–7.37 (1H, overlap, H-8′), 7.35–7.37 (1H, overlap, H-9′), 3.93, 3.95, 3.95, 3.52, 3.61 (each 3H, s, 5 × OMe); ^{13}C NMR data, Table 1; positive FABMS *m/z* 622 (2) $[M]^+$, 475 (6), 415 (43), 131 (100); HRESIMS (positive ion mode) *m/z* 645.2311 $[M + Na]^+$ (calcd 645.2311 for $C_{34}H_{38}O_{11}Na$).

Kadangustin D (4): $C_{34}H_{38}O_{10}$, white, amorphous powder; $[\alpha]^{17.8}_D$ −110.1 (*c* 0.053, MeOH); CD (*c* 0.0606, MeOH) λ_{max} nm ($\Delta\epsilon$) 253 (−51.45), 249 (−46.53), 223 (+14.68), 219 (+9.64); UV (MeOH) λ_{max} (log ϵ) 347 (3.12), 280 (4.66), 254 (4.57), 217 (5.04) nm; IR (KBr) ν_{max} 3432, 2934, 2879, 1735, 1706, 1636, 1497, 1458, 1427, 1409, 1376, 1362, 1335, 1242, 1199, 1172, 1160, 1130, 1106, 1029, 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.58 (1H, s, H-4), 5.93 (1H, d, J = 8.1 Hz, H-6), 2.18–2.21 (1H, m, H-7), 2.25–2.29 (1H, m, H-8), 5.78 (1H, d, J = 3.8 Hz, H-9), 6.60 (1H, s, H-11), 0.95 (3H, d, J = 6.8 Hz, H-17), 1.07 (3H, d, J = 7.2 Hz, H-18), 1.58 (3H, s, CH_3-Ac), 6.03 (1H, d, J = 16.0 Hz, H-2′), 7.21 (1H, d, J = 16.0 Hz, H-3′), 7.38–7.39 (1H, overlap, H-5′), 7.33–7.34 (1H, overlap, H-6′), 7.26 (1H, br s, H-7′), 7.33–7.34 (1H, overlap, H-8′), 7.38–7.39 (1H, overlap, H-9′), 3.93, 3.92, 3.92, 3.83, 3.64 (each 3H, s, 5 × OMe); ^{13}C NMR data, Table 1; positive FABMS *m/z* 606 (5) $[M]^+$, 459 (100), 359 (73); HRESIMS (positive ion mode) *m/z* 629.2371 $[M + Na]^+$ (calcd 629.2362 for $C_{34}H_{38}O_{10}Na$).

Kadangustin E (5): $C_{32}H_{36}O_{10}$, pale yellow, amorphous powder; $[\alpha]^{17.6}_D$ 0.0 (*c* 0.073, MeOH); CD (*c* 0.0580, MeOH) λ_{max} nm ($\Delta\epsilon$) 237 (−27.94), 221 (+17.51); UV (MeOH) λ_{max} (log ϵ) 397 (2.60), 376 (2.76), 281 (3.98), 217 (4.96), 203 (5.01) nm; IR (KBr) ν_{max} 3432, 2936, 2880, 1716, 1619, 1497, 1455, 1427, 1409, 1375, 1362, 1335,

1240, 1197, 1179, 1158, 1129, 1108, 1027, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.59 (1H, s, H-4), 6.08 (1H, d, J = 6.6 Hz, H-6), 2.28–2.33 (1H, m, H-7), 2.34–2.38 (1H, m, H-8), 5.78 (1H, d, J = 2.2 Hz, H-9), 6.66 (1H, s, H-11), 0.97 (3H, d, J = 7.0 Hz, H-17), 1.13 (3H, d, J = 6.2 Hz, H-18), 1.60 (3H, s, CH_3-Ac), 7.26–7.29 (1H, overlap, H-3′), 7.44–7.46 (1H, overlap, H-4′), 7.44–7.46 (1H, overlap, H-5′), 7.44–7.46 (1H, overlap, H-6′), 7.26–7.29 (1H, overlap, H-7′), 3.96, 3.93, 3.92, 3.66, 3.40 (each 3H, s, 5 × OMe); ^{13}C NMR data, Table 1; positive FABMS m/z 580 (24) [M]$^+$, 459 (45), 105 (100); HRESIMS (positive ion mode) m/z 603.2203 [M + Na]$^+$ (calcd 603.2206 for $C_{32}H_{36}O_{10}Na$).

Kadangustin F (6): $C_{30}H_{38}O_{10}$, pale yellow, amorphous powder; $[\alpha]^{16.5}_D$ +92.0 (c 0.087, MeOH); CD (c 0.0558, MeOH) λ_{max} nm ($\Delta\epsilon$) 249 (−27.88), 224 (+27.75); UV (MeOH) λ_{max} (log ϵ) 380 (2.90), 344 (2.92), 214 (4.99) nm; IR (KBr) ν_{max} 3433, 2967, 2937, 1736, 1711, 1641, 1613, 1586, 1498, 1458, 1428, 1410, 1378, 1362, 1335, 1233, 1197, 1156, 1130, 1106, 1027, 1008 cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$, 500 MHz] δ 6.60 (1H, s, H-4), 5.83 (1H, d, J = 7.3 Hz, H-6), 2.33–2.35 (1H, m, H-7), 2.12–2.13 (1H, m, H-8), 5.73 (1H, d, J = 3.0 Hz, H-9), 6.70 (1H, s, H-11), 0.94 (3H, d, J = 7.4 Hz, H-17), 1.06 (3H, d, J = 6.6 Hz, H-18), 1.53 (3H, s, CH_3-Ac), 5.90–5.92 (1H, m, H-3′), 1.53 (3H, s, H-4′), 1.78–1.80 (3H, m, H-5′), 3.90, 3.85, 3.80, 3.74, 3.58 (each 3H, s, 5 × OMe); ^{13}C NMR data, Table 1; positive FABMS m/z 558 (18) [M]$^+$, 459 (100), 359 (98); HRESIMS (positive ion mode) m/z 581.2362 [M + Na]$^+$ (calcd 581.2362 for $C_{30}H_{38}O_{10}Na$).

Kadangustin G (7): $C_{30}H_{38}O_{10}$, pale yellow, amorphous powder; $[\alpha]^{25.5}_D$ +16.10 (c 0.207, MeOH); CD (c 0.0610, MeOH) λ_{max} nm ($\Delta\epsilon$) 238 (−51.45), 216 (+21.03); UV (MeOH) λ_{max} (log ϵ) 380 (2.89), 344 (2.93), 214 (4.96) nm; IR (KBr) ν_{max} 3433, 2967, 2937, 1736, 1711, 1641, 1613, 1586, 1498, 1458, 1428, 1410, 1378, 1362, 1335, 1233, 1197, 1156, 1130, 1106, 1027, 1008 cm^{-1}; ^{1}H NMR [$(CD_3)_2CO$, 400 MHz] δ 6.56 (1H, s, H-4), 5.86 (1H, d, J = 7.0 Hz, H-6), 2.30–2.34 (1H, m, H-7), 2.13 (1H, br s, H-8), 5.73 (1H, d, J = 2.0 Hz, H-9), 6.76 (1H, s, H-11), 0.92 (3H, d, J = 7.3 Hz, H-17), 1.08 (3H, d, J = 7.3 Hz, H-18), 1.54 (3H, s, CH_3-Ac), 5.97 (1H, br s, H-3′), 1.51 (3H, s, H-4′), 1.58 (3H, d, J = 7.3 Hz, H-5′), 3.89, 3.88, 3.79, 3.74, 3.46 (each 3H, s, 5 × OMe); ^{13}C NMR data, Table 1; positive FABMS m/z 558 (23) [M]$^+$, 459 (100), 399 (37); HRESIMS (positive ion mode) m/z 581.2360 [M + Na]$^+$ (calcd 581.2362 for $C_{30}H_{38}O_{10}Na$).

Kadangustin H (8): $C_{22}H_{30}O_6$, pale yellow, amorphous solid; $[\alpha]^{17.4}_D$ −4.8 (c 0.104, MeOH); UV (MeOH) λ_{max} (log ϵ) 370 (2.38), 349 (2.73), 278 (3.83), 205 (5.06) nm; IR (KBr) ν_{max} 3432, 2960, 2934, 2877, 2838, 1708, 1595, 1515, 1464, 1433, 1420, 1380, 1347, 1262, 1236, 1200, 1155, 1140, 1103, 1029, 1003 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.49 (1H, d, J = 1.8 Hz, H-2), 6.57 (1H, d, J = 1.8 Hz, H-6), 4.38–4.39 (1H, m, H-7), 1.82–1.86 (1H, m, H-8), 0.66 (3H, d, J = 7.0 Hz, H-9), 6.76 (1H, s, H-2′), 6.80 (1H, d, J = 8.4 Hz, H-5′), 6.74 (1H, d, J = 8.4 Hz, H-6′), 2.90 (1H, dd, J = 13.2, 3.6 Hz, H-7′a), 2.15–2.18 (1H, m, H-7′b), 2.34–2.39 (1H, m, H-8′), 0.88 (3H, d, J = 7.0 Hz, H-9′), 3.89, 3.88, 3.87, 3.86 (each 3H, s, 4 × OMe), 5.78 (1H, s, OH); ^{13}C NMR data, Table 2; positive FABMS m/z 390 (33) [M]$^+$, 373 (100), 151 (78); HRESIMS (positive ion mode) m/z 413.1946 [M + Na]$^+$ (calcd 413.1940 for $C_{22}H_{30}O_6Na$).

Kadangustin I (9): $C_{22}H_{28}O_7$, pale yellow, amorphous solid; $[\alpha]^{17.5}_D$ −3.8 (c 0.089, MeOH); UV (MeOH) λ_{max} (log ϵ) 276 (3.58), 207 (5.12) nm; IR (KBr) ν_{max} 3439, 2960, 2934, 2879, 1721, 1710, 1634, 1615, 1598, 1510, 1461, 1452, 1431, 1379, 1350, 1310, 1282, 1238, 1198, 1163, 1132, 1098, 1042, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.50 (1H, d, J = 1.1 Hz, H-2), 6.57 (1H, d, J = 1.1 Hz, H-6), 4.37 (1H, d, J = 9.2 Hz, H-7), 1.81–1.85 (1H, m, H-8), 0.63 (3H, d, J = 7.4 Hz, H-9), 6.42 (1H, s, H-2′), 6.38 (1H, s, H-6′), 2.85 (1H, dd, J = 13.2, 3.6 Hz, H-7′a), 2.11–2.16 (1H, m, H-7′b), 2.31–2.34 (1H, m, H-8′), 0.88 (3H, d, J = 7.0 Hz, H-9′), 3.89, 3.89, 3.87 (each 3H, s, 3 × OMe), 5.79 (1H, s, OH), 5.93 (2H, s, OCH_2O); ^{13}C NMR data, Table 2; positive FABMS m/z 404 (32) [M]$^+$, 387 (100), 165 (78); HRESIMS (positive ion mode) m/z 427.1750 [M + Na]$^+$ (calcd 427.1732 for $C_{22}H_{28}O_7Na$).

Kadangustin J (10): $C_{22}H_{30}O_5$, pale yellow, amorphous solid; $[\alpha]^{15.8}_D$ +4.9 (c 0.171, MeOH); UV (MeOH) λ_{max} (log ϵ) 281 (4.08), 205 (5.02) nm; IR (KBr) ν_{max} 3432, 2960, 2933, 2876, 2836, 1705, 1606, 1592, 1515, 1464, 1418, 1380, 1333, 1264, 1246, 1231, 1188, 1143, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80–6.83 (1H, overlap, H-2), 6.78–6.80 (1H, overlap, H-5), 6.76–6.78 (1H, overlap, H-6), 3.53 (1H, d, J = 11.8 Hz, H-7), 2.59–2.63 (1H, m, H-8), 0.68 (3H, d, J = 7.0 Hz, H-9), 6.80–6.83 (1H, overlap, H-2′), 6.78–6.80 (1H, overlap, H-5′), 6.76–6.78 (1H, overlap, H-6′), 3.46–3.50 (2H, m, H-7′), 1.74–1.78 (1H, m, H-8′), 0.75 (3H, d, J = 7.0 Hz, H-9′), 3.86, 3.86, 3.82, 3.82 (each 3H, s, 4 × OMe); ^{13}C NMR data, Table 2; positive FABMS m/z 375 (82) [M + H]$^+$, 287 (100), 151 (72); HRESIMS (positive ion mode) m/z 397.1979 [M + Na]$^+$ (calcd 397.1990 for $C_{22}H_{30}O_5Na$).

Kadangustin K (11): $C_{21}H_{28}O_5$, white, amorphous solid; $[\alpha]^{17.7}_D$ 0.0 (c 0.065, MeOH); UV (MeOH) λ_{max} (log ϵ) 362 (2.40), 321 (2.85), 281 (4.01), 205 (4.92) nm; IR (KBr) ν_{max} 3432, 2960, 2934, 2877, 2838, 1710, 1629, 1616, 1514, 1464, 1430, 1381, 1267, 1232, 1142, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78–6.79 (1H, overlap, H-2), 6.83–6.84 (1H, overlap, H-5), 6.75–6.79 (1H, overlap, H-6), 3.53 (1H, d, J = 11.8 Hz, H-7), 2.56–2.64 (1H, m, H-8), 0.68 (3H, d, J = 6.8 Hz, H-9), 6.83–6.84 (1H, overlap, H-2′), 6.83–6.84 (1H, overlap, H-5′), 6.75–6.79 (1H, overlap, H-6′), 3.47–3.50 (2H, overlap, H-7′), 1.74–1.80 (1H, m, H-8′), 0.76 (3H, d, J = 7.0 Hz, H-9′), 3.86, 3.86, 3.82 (each 3H, s, 3 × OMe), 5.44 (1H, s, OH); ^{13}C NMR data, Table 2; positive FABMS m/z 360 (30) [M]$^+$, 273 (100), 223 (40); HRESIMS (positive ion mode) m/z 383.1828 [M + Na]$^+$ (calcd 383.1834 for $C_{21}H_{28}O_5Na$).

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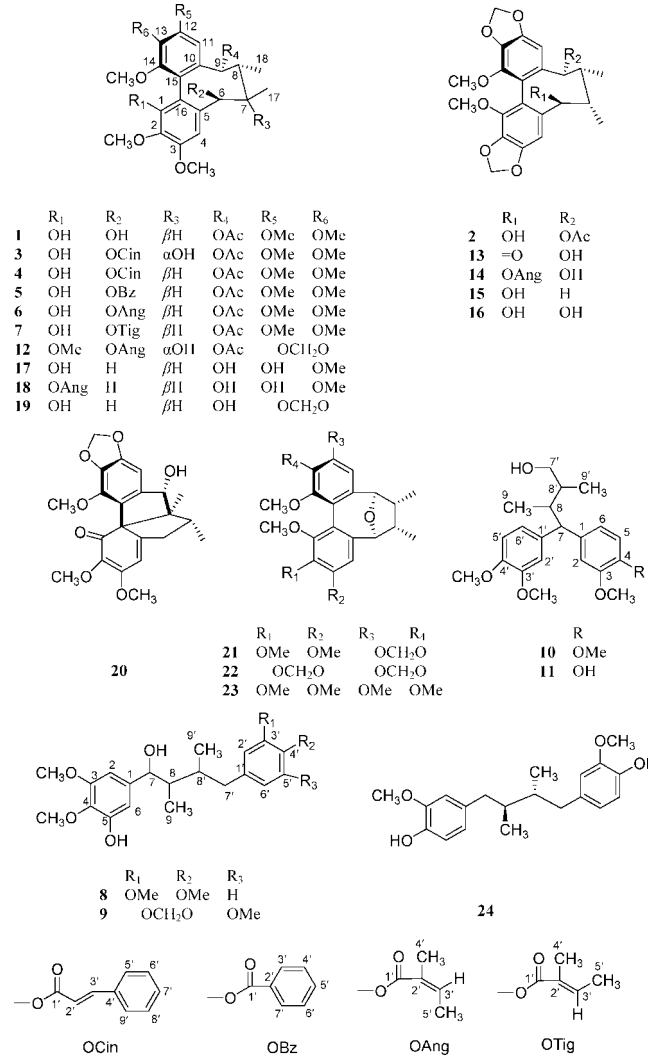
Supporting Information Available: ^{1}H and ^{13}C NMR spectra of kadangustins A–K (**1**–**11**), HMBC spectrum of kadangustin C (**3**), and CD spectra of kadangustins A–G (**1**–**7**). This material is available free of charge via the Internet at http://pubs.acs.org.

Chart 1



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