C_{18} Dibenzocyclooctadiene Lignans from *Kadsura philippinensis*

Ya-Ching Shen,*,† Chia-Ching Liaw,† Yuan-Bin Cheng,† Atallah F. Ahmed,† Mei-Chou Lai,‡ Shorong-Shii Liou,‡ Tian-Shung Wu,§ Yao-Haur Kuo,§ and Yu-Chi Lin†

Department of Marine Resources, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, Republic of China, Department of Pharmacy, Tajen University, Yen-Pou, Ping Tung Shien, Taiwan, Republic of China, and National Research Institute of Chinese Medicine, Taipei 112, Taiwan, Republic of China

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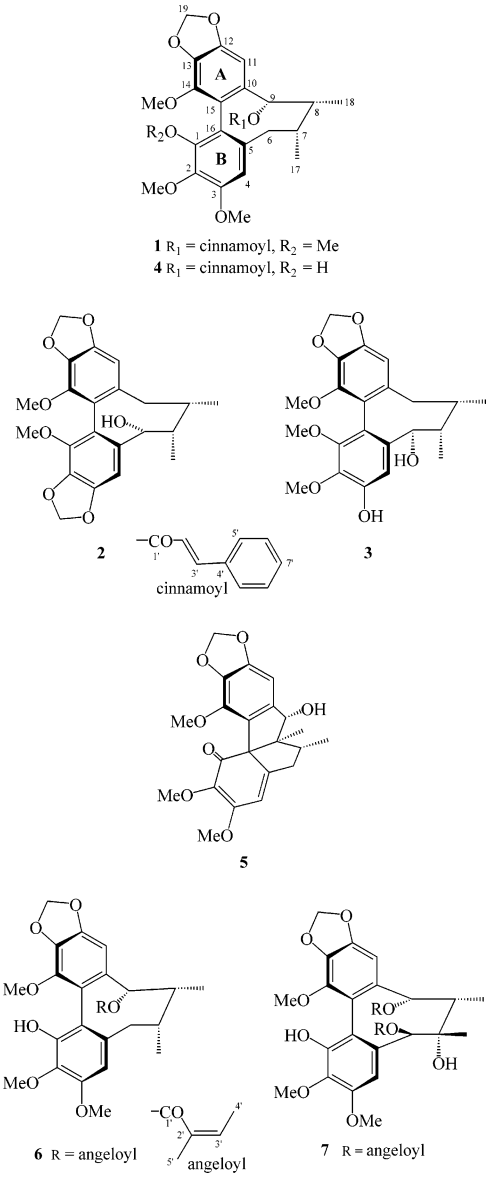
Four new C_{18} dibenzocyclooctadiene lignans, kadsuphilins A (**1**) and B (**3**), 6-*epi*-gomisin (**2**), and 1-demethylkadsuphilin A (**4**), along with eight known related metabolites, were isolated from an EtOAc fraction of an alcoholic extract of the aerial parts of *Kadsura philippinensis* growing in Taiwan. The structures of **1**−**4** were elucidated on the basis of spectroscopic analyses, including 2D NMR (HMQC, HMBC, and NOESY) experiments, and by comparison of their spectroscopic data with those of related metabolites. The configurations of the biphenyl and cyclooctadiene moieties were deduced from circular dichroism (CD) and NOESY NMR spectra, respectively. Some of the compounds showed radical-scavenging activity in a DPPH-HPLC method.

Plants belonging to the genus *Kadsura* (Schisandraceae) have been used for a long time in traditional Chinese medicine to treat several kinds of diseases.[1] Phytochemically, *Kadsura* species are also well known as a source of C_{18} dibenzocyclooctadiene lignans,[2] which have shown anti-HIV, antioxidant, antihepatotoxic, cytotoxic,[3] antitumor,[4] and anti-lipid peroxidative activities. Previously, we have reported two triterpene dilactones, kadsuphilactones A and B,[5] and three C_{19} homolignans, taiwankadsurins A, B, and C,[6] from the vine *K. philippinensis* Elmer, indigenous to the Philippines and Southern Taiwan. Further chemical analysis of this plant led to the isolation of four new C_{18} dibenzocyclooctadiene lignans, kadsuphilins A (**1**) and B (**3**), 6-*epi*-gomisin (**2**), and 1-demethylkadsuphilin A (**4**), in addition to eight known related metabolites from the medium-polarity fractions of the EtOAc partition of the alcoholic extract. This paper reports the isolation, structure elucidation, and biological activities of these compounds.

The alcoholic extract of the aerial parts of *K. philippinensis* was partitioned between EtOAc and H_2O (1:1). The EtOAc fraction obtained was subjected to flash column chromatography over silica gel. Medium-polarity fractions obtained were chosen for further purification using normal-phase HPLC, Sephadex LH-20, and preparative TLC chromatography to yield the new kadsuphilins A (**1**) and B (**3**), 6-*epi*-gomisin (**2**), and 1-demethylkadsuphilin A (**4**) and eight known lignans (see Experimental Section).

Kadsuraphilin A (**1**) was obtained as a yellowish-white powder and possesses a molecular formula of $C_{32}H_{34}O_8$, as derived from its HREIMS (*m*/*z* 546.2250, $[M]^+$) and NMR spectroscopic data (Tables 1 and 2). The UV spectrum showed λ_{max} (MeOH) values at 236, 260, and 283 nm, while its CD spectrum exhibited a strong negative Cotton effect at λ_{max} 254 nm, indicating that **1** is a C_{18} dibenzocyclooctadiene lignan[1,2] with a *S*-biphenyl configuration.[7] The IR spectrum of **1** indicated the presence of an ester (ν_{max} 1710 cm^{-1}) group and the absence of any hydroxyl groups. The NMR spectrum of **1** also showed the signals due to an octa-substituted biphenyl moiety [^{1}H NMR δ_H 6.66 and 6.54 (1H each, s); ^{13}C NMR δ_C 151.5, 151.4, 148.7, 141.5, 140.0, 136.2, 134.8, 133.1, 123.9, 120.9 (1C each, C); 110.5, 102.7 (1C each, CH)].[1,2] These NMR signals were found to be almost identical to those of kadsurin,[8] indicating the same substitution pattern on the biphenyl unit. Thus, one methylenedioxy group (δ_H 5.99 and 5.98, 1H each, s), four methoxy groups (δ_H 3.91, 3.81, 3.67, and 3.44, 3H each, s), a benzylic methylene group (δ_H 2.71, 2H, br d, J = 3.7 Hz), and a benzylic oxymethine (δ_H 5.93, 1H, s) were also found in the



* To whom correspondence should be addressed. Tel: 886-7-5252000, ext. 5058. Fax: 886-7-5255020. E-mail: ycshen@mail.nsysu.edu.tw.
† National Sun Yat-Sen University.
‡ Tajen University.
§ National Research Institute of Chinese Medicine.

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Table 1. ^{1}H NMR Chemical Shifts of Compounds **1**−**4**

position	**1**[a,c]	**2**[b]	**3**[b]	**4**[a]
H-4	6.66 s	6.91 s	7.04	6.46 s
H-6	2.71 2H, m	4.52 d (1.5)[c]	4.54 d (1.5)	2.69, br d (4.7)
H-7	2.10 m	2.00 m	2.00 m	2.12 m
H-8	2.10 m	1.91 m	1.98 m	2.12 m
H-9	5.93 s	2.12 dd (13.5, 10.0)	2.12 dd (13.5, 9.0)	5.73 s
		1.96 d (13.5)	1.96 d (13.5)	
H-11	6.54 s	6.45 s	6.46 s	6.56 s
H-17	1.00 3H, d (6.9)	0.70 3H, d (7.0)	0.70 3H, d (7.0)	1.01 3H, d (6.9)
H-18	1.11 3H, d (6.9)	1.00 3H, d (7.0)	1.00 3H, d (7.0)	1.13 3H, d (6.9)
H-19	5.98 s	5.94 2H, br s	5.95 2H, s	5.95 d (1.1)
	5.99 s			6.00 d (1.1)
H-20		5.98 d (1.0)		
		5.99 d (1.0)		
OMe-1	3.44 3H, s	3.85[d] 3H, s	3.52 3H, s	
OMe-2	3.67 3H, s		3.96 3H, s	3.56 3H, s
OMe-3	3.95 3H, s			3.94 3H, s
OMe-4	3.81 3H, s	3.87[d] 3H, s	3.83 3H, s	3.84 3H, s
H-2′	5.93 d (16.0)			5.87 (16.0)
H-3′	6.92 d (16.0)			7.07 (16.0)
H-5′−H-9′	7.36 5H, br s			7.35 5H, br s
OH-1			5.75 s	5.48 s

[a] Spectra recorded at 300 MHz in $CDCl_3$ at 25 °C. [b] 500 MHz in $CDCl_3$ at 25 °C. [c] *J* values are in Hz in parentheses. [d] Exchangeable values.

Table 2. ^{13}C NMR Chemical Shifts of Compounds **1**−**4**

#	**1**[a]	**2**[b]	**3**[b]	**4**[a]
1	151.4 (C)[c]	140.1 (C)*	150.0 (C)	146.9 (C)
2	140.0 (C)	135.5 (C)	138.2 (C)	133.5 (C)
3	151.5 (C)	148.3 (C)	148.1 (C)	150.3 (C)
4	110.5 (CH)	102.1 (CH)	109.1 (CH)	107.1 (CH)
5	133.1 (C)	135.2 (C)	137.3 (C)	134.5 C)
6	39.0 (CH_2)	73.3 (CH)	73.2 (CH)	38.8 (CH_2)
7	34.8 (CH)	42.4 (CH)	42.3 (CH)	34.9 (CH)
8	42.3 (CH)	39.1 (CH)	39.2 (CH)	41.8 (CH)
9	82.2 (CH)	34.6 (CH)	34.6 (CH)	82.8 (CH)
10	134.8 (C)	138.1 (C)	138.0 (C)	135.7 (C)
11	102.7 (CH)	102.9 (CH)	103.0 (CH)	102.8 (CH)
12	148.7 (C)	149.1 (C)	149.1 (C)	149.0 (C)
13	136.2 (C)	134.2 (C)	134.4 (C)	136.0 (C)
14	141.5 (C)	140.0 (C)[d]	140.7 (C)	141.4 (C)
15	120.9 (C)	119.3 (C)	119.5 (C)	119.4 (C)
16	123.9 (C)	120.3 (C)	120.5 (C)	117.2 (C)
17	15.0 (CH_3)	7.8 (CH_3)	7.6 (CH_3)	15.2 (CH_3)
18	19.6 (CH_3)	21.8 (CH_3)	22.0 (CH_3)	19.7 (CH_3)
19	101.3 (CH_2)	100.8 (CH_2)	100.8 (t)	101.3 (CH_2)
20		100.9 (CH_2)		
OMe-1	60.2 (CH_3)	59.6 (CH_3)	60.2 (CH_3)	
OMe-2	60.7 (CH_3)		61.0 (CH_3)	60.6 (CH_3)
OMe-3	56.0 (CH_3)			55.8 (CH_3)
OMe-14	59.8 (CH_3)	59.6 (CH_3)	59.6 (CH_3)	59.8 (CH_3)
1′	166.0 (C)			166.1 (C)
2′	118.1 (CH)			118.0 (CH)
3′	144.8 (CH)			144.2 (CH)
4′	134.4 (C)			134.5 (C)
5′, 9′	128.1 (CH)			128.1 (CH)
6′, 8′	128.9 (CH)			128.9 (CH)
7′	130.3 (CH)			130.1 (CH)

[a] 75 MHz in $CDCl_3$ at 25 °C. [b] 125 MHz in $CDCl_3$ at 25 °C. [c] Multiplicity determined from DEPT and indicated by usual symbols. The values are in ppm downfield from TMS. [d] Exchangeable values.

molecule of **1**. Similar to those of kadsurin, in the COSY and HMBC spectra (Figure 1), the two secondary methyl groups (δ_H 1.00 and 1.11, 3H each, d, J = 6.9 Hz) were placed at C-7 and C-8, respectively. Compound **1** differs from kadsurin only in the presence of a *trans*-cinnamoyl moiety [^{1}H NMR δ_H 5.93, 6.92 (1H each, d, J = 16.0 Hz), 7.36 (5H, br s)], instead of an acetyl moiety. This was further supported by the fragment ion peak that appeared at *m*/*z* 398 [M − cinnamic acid]$^+$ in the EIMS of **1**. The long-range ^{1}H−^{13}C correlations observed in the HMBC NMR spectrum from the benzylic H-9 at δ_H 5.93 (1H, s) to the ester carbonyl carbon (C-1′) at δ_C 166.0 (C) and from H-9 to the aromatic carbon C-11 at δ_C 102.7 (CH) were used to designate the C-9 location of the *trans*-cinnamoyl group. Moreover, after an extensive NMR study (HMQC and HMBC experiments), the molecular framework of **1** (Figure 1) was confirmed. The configuration of the cyclooctadiene

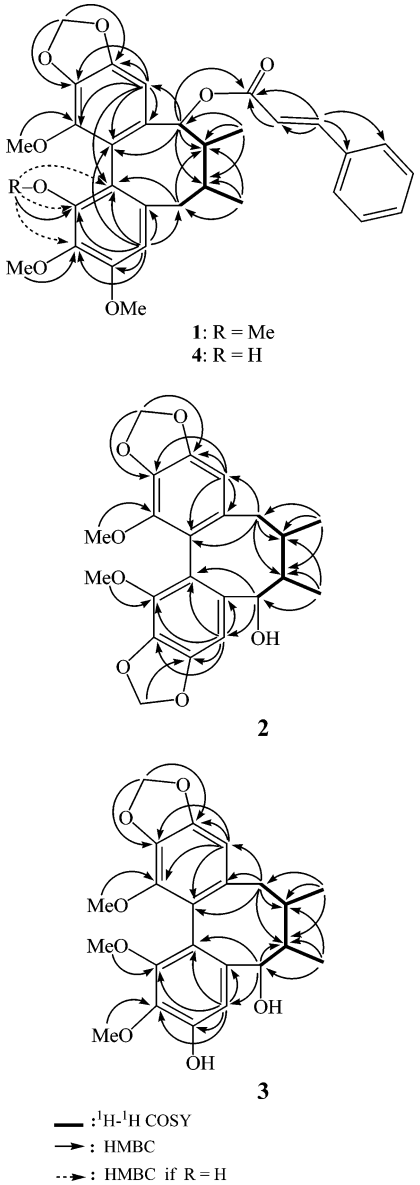

Figure 1. ^{1}H−^{1}H COSY and HMBC correlations for **1**−**4**.

moiety was evident from the NOESY experiments of **1** (Figure 2). The strong NOE correlation observed from the aromatic H-11 and

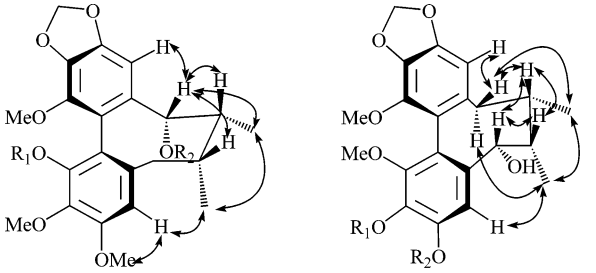

Figure 2. NOESY correlations of compounds **1**−**4**.

H-9 suggested H-9 and the cinnamoyl moiety to be positioned on the β- and α-face of the cyclooctadiene, respectively. The methine protons at C-7 and C-8 were also correlated with H-9 but not with the methyls at the same carbons, revealing the α-orientations of both CH_3-7 and CH_3-8. This was also apparent from the NOE correlations observed between the two methyls themselves and between the CH_3-7 and the aromatic H-4 signal. Therefore, the structure of kadsuaphilin A (**1**) was established unambiguously.

Compound **2** was obtained as a yellowish-white powder. It also showed absorption maxima in the UV spectrum similar to those of **1** and also a strong negative Cotton effect at λ_{max} 255 nm in the CD spectrum. The HREIMS (*m*/*z* 400.1523, $[M]^+$) was consistent with the molecular formula, $C_{22}H_{24}O_7$. The absorption band at 3400 cm^{-1} in the IR spectrum and the ion peak appearing at *m*/*z* 382 $[M - H_2O]^+$ in the EIMS suggested the presence of a hydroxyl group in **2**. The ^{13}C NMR spectrum showed the signals of 12 carbons of a biphenyl at δ_C 194.1−102.1 (Table 2). Besides the aromatic protons of biphenyl that appeared at δ_H 6.66 and 6.54 (1H each, s), the ^1H NMR spectrum of **2** also indicated the presence of two methylenedioxyl units at δ_H 5.99 and 5.98 (1H each, d, J = 1.5 Hz) and 5.94 (2H, br s), two methoxyls at δ_H 3.87 and 3.85 (3H each, s), and two secondary methyls at δ_H 1.00 and 0.70 (3H each, d, J = 7.0 Hz). From the HMBC spectrum of **2**, it was found that the single sp^3 oxymethine carbon resonating at δ_C 73.3 (d) correlated with a proton at δ_H 4.52 (1H, d, J = 1.5 Hz). A correlation exhibited from that proton to the aromatic C-4 and C-16 in the HMBC spectrum (Figure 1) was used to assign the oxymethine group at C-6. On the basis of the above findings and by the interpretation of its $^1H-^1H$ COSY, HMQC, and HMBC NMR spectra, the structure of **2** could be established (Figure 1). It was found that the ^{13}C NMR spectroscopic data (Table 2) of **2** were quite similar to those of gomisin R[19] except for the upfield shifts induced at C-4 and C-17 ($\Delta\delta_C$ −7.8 and −8.7, respectively) in **2** (Table 2). The structural assignment was further supported by the differences in chemical shift and J values of H-6 in **2** (δ_H 4.52, 1H, d, J = 1.5 Hz) and gomisin R (δ_H 4.27, 1H, d, J = 8.0 Hz). The α-orientation of the hydroxyl group at C-6 was confirmed by the NOESY correlations (Figure 2) of **2**. One of the C-9 protons (δ_H 1.96, d, J = 13.5 Hz) exhibited a NOE interaction with the aromatic H-11 and was thus assigned as H-9β. The NOE correlations found between H-9β and H-8 (δ_H 1.91, m) and between H-8 and H-6 confirmed the β-orientation of OH-6. The upfield shifted C-17 (δ_C 7.8, CH_3) in **2**, relative to that of gomisin R[9] (δ_C 16.5, CH_3) could be explained by the strong γ-effect arising from the steric compression of a *gauche* interaction between the methyl group attached at C-7 and the α-hydroxy group attached at C-6 in **2**. The above observations were used to establish the structure of **2** as 6-*epi*-gomisin.

Kadsuphilin B (**3**) possesses the molecular formula $C_{22}H_{26}O_7$, as determined by the HREIMS (*m*/*z* 402.1684, $[M]^+$) and NMR spectroscopic data. At least one hydroxyl exists in **3** (IR: ν_{max} 3419 cm^{-1}, EIMS: *m*/*z* 384 $[M - H_2O]^+$). However, its UV, CD, and IR data were very similar to that of **2**. Also, the ^{13}C NMR spectroscopic data of **3** were found to be quite similar to those of **2** (Table 2), except for the appearance of a methoxyl carbon signal at δ_C 61.0 (CH_3) in **3** instead of a methylenedioxy carbon resonance at δ_C 100.9 (CH_2) in **2**. Thus, the biphenyl ring B was substituted by two methoxyls and one hydroxyl. The location of the hydroxyl group at C-3 was determined by the strong HMBC correlations observed from H-4 (δ_H 1.96, d, J = 13.5 Hz) to C-3 at δ_C 148.1 (C) and C-2 at δ_C 138.2 (C), while the methoxyl protons at δ_H 3.96 (3H, s) correlated only with C-2 but not with C-3. Except for the above differences, the substitution pattern and configuration at the chiral centers C-6, C-7, and C-8 in the cyclooctadiene moiety of **3** were found to be identical to those of **2**, as indicated by the similarities in chemical shifts δ_H and J values of the corresponding ^1H NMR data (Table 1). Detailed analyses of 2D NMR (HMQC, HMBC, and NOESY) correlations (Figures 1 and 2) further established the structure of kadsuphilin B.

Table 3. Free Radical-Scavenging Activity of Compounds **1** and **5**−**7** at 100 μM

compound	radical-scavenging activity[a]
1	1.5 ± 0.65%
5	4.6 ± 0.64%
6	2.3 ± 0.28%
7	1.9 ± 0.52%
ascorbic acid[b]	12.5 ± 0.23%

[a] Radical-scavenging activity was measured by the DPPH-HPLC method. Each value is the mean ± SD of 8 samples. [b] Positive control substance.

Compound **4** was also defined as a C_{18} dibenzocyclooctadiene lignan with a *S*-biphenyl configuration, on the basis of its UV, CD, and NMR spectra. Its molecular formula, $C_{31}H_{32}O_8$, was deduced from HRESIMS (*m*/*z* 555.1997, $[M + Na]^+$) and NMR spectroscopic data (Tables 1 and 2). The presence of hydroxyl and ester functionalities in **4** was revealed from the IR bands at ν_{max} 3300 and 1707 cm^{-1}, respectively. As in the case of **1**, the ion peak shown at *m*/*z* 384 $[M - 148]^+$ in the EIMS together with the signals appearing at δ_H 5.87, 7.07 (1H each, d, J = 16 Hz), and 7.35 (5H, br s) in the ^1H NMR spectrum indicated a *trans*-cinnamoyl moiety in **4**. However, the appearance of three methoxyl signals in the ^1H and ^{13}C NMR spectra of **4**, instead of four, suggested this compound to be a demethylated kadsuphilin A derivative. The phenolic hydroxyl proton appeared at δ_H 5.48 (1H, s), which showed long-range $^1H/^{13}C$ correlation with C-1 (δ_C 146.9, C), C-2 (δ_C 133.5, C), and C-16 (δ_C 117.2, C) and implied a hydroxyl group at C-1. On the basis of the above findings with detailed analysis of the 2D NMR spectra, including NOESY (Figure 2), the structure of **4** was thus elucidated as 1-demethylkadsuphilin A.

Eight other known dibenzocyclooctadiene lignans, also isolated from *K. philippinensis*, were identified as the previously reported kadsurin isolated from *K. heteroclita*[8] and *K. japonica*,[10] schizanrin F isolated from *K. matsudai*,[11] kadsulignan K (**5**) isolated from *K. matsudai*,[12] kadsulignan D isolated from *K. longipedunculata*,[13] acetylbinankadsurin A isolated from *K. japonica*,[14] angeloylbinankadsurin A (**6**) isolated from *K. japonica*,[14] schizanrin J (**7**) isolated from *K matsudai*,[15] and kadsumarin A isolated from *K. matsudai*[15] by comparison of physical and spectroscopic ($[\alpha]_D$, MS, ^1H and ^{13}C NMR) data with literature values.

The isolation of C_{18} dibenzocyclooctadiene lignans from *K. philippinensis* is reported here for the first time. This class of compounds from *Kadsura*[1,2,8−13] and *Schisandra* species[16] represents a significant chemotaxonomic marker for the family Schisandraceae. We chose a limited panel of cancer cell lines including KB, Hepa59T/VGH, and Hela cells to test the in vitro cytotoxic potentialities of the compounds, but none of these lignans showed an ED_{50} value of <5 μg/mL. However, preliminary evaluation of the DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical-scavenging activity of these compounds revealed that compounds **1**, **5**, **6**, and **7** exhibit weak antioxidative activity, as shown in Table 3.[17]

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. CD was taken on a JASCO J-810 spectropolarimeter. IR spectra were recorded on a JASCO FT-5300 infrared spectrophotometer. The NMR spectra were recorded on a Bruker AVANCE DPX300 FT-NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Varian Unity INOVA 500 FT-NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, respectively, in $CDCl_3$ using TMS as internal standard. EIMS and FABMS were obtained with a VG Quattro 5022 spectrometer and JEOL JMS-SX 102 spectrometer, respectively. HRMS were recorded on a Finnigan MAT-95XL mass spectrometer.

Plant Material. *K. philippinensis* was collected at Green Island, Taiwan, in September 2002. A voucher sample (specimen code: TP 93-1) was deposited at the Department of Marine Resources, National Sun Yat-Sen University, Kaohsiung, Taiwan.

Extraction and Isolation. The aerial parts of *K. philippinensis* (1.1 kg, dry wt) were powdered and exhaustively extracted with EtOH, and the concentrated extract was subsequently partitioned between EtOAc and H_2O (1:1). The EtOAc-soluble portion (30 g) was subjected to flash chromatography on silica gel, using *n*-hexane−EtOAc (stepwise, 100:1 to 0:100), acetone, and finally MeOH to afford 18 fractions. Fraction 7, eluted with *n*-hexane−EtOAc (6:1), was purified over Sephadex LH-20, using CH_2Cl_2−MeOH (1:1), and then by normal-phase HPLC, using *n*-hexane−EtOAc (3:1), to yield **1** (7.4 mg, R_f 0.55, *n*-hexane−acetone, 2:1) and kadsurin (30 mg). Fraction 8, eluted with *n*-hexane−EtOAc (5:1), was purified on Sephadex LH-20, using MeOH, followed by preparative TLC developed with *n*-hexane−acetone (1:1), to afford **2** (2.0 mg, R_f 0.44, *n*-hexane−acetone, 2:1). Fraction 9, eluted with *n*-hexane−EtOAc (5:1) was initially fractionated over Sephadex LH-20, developed with MeOH, to provide three subfractions. The first and third subfractions were separately applied to silica gel columns using *n*-hexane−acetone (gradient, 8:1 to 1:1) followed by preparative TLC, developed with *n*-hexane−acetone (2:1), to afford kadsurin (31 mg), **5** (30 mg), and schizanrin F (8 mg) from the first subfraction and **3** (2 mg, R_f 0.35, *n*-hexane−acetone, 2:1) from the third subfraction, respectively. The second subfraction was rechromatographed on a silica gel column using *n*-hexane−acetone (gradient, 4:1 to 1:1) to yield kadsulignan D (34 mg). Fraction 10 eluted with *n*-hexane−EtOAc (4:1) was further purified on Sephadex LH-20, using MeOH, to afford kadsumarin (15 mg). Fraction 14, eluted with *n*-hexane−EtOAc (1:2), was purified with Sephadex LH-20, using MeOH, to give **4** (8 mg, R_f 0.44, *n*-hexane−acetone, 2:1) and a lignan mixture. This lignan mixture was isolated by normal-phase HPLC, using *n*-hexane−EtOAc (1:2), to yield **7** (3.5 mg), schizanrin F (3 mg), and an unresolved fraction, which was subsequently purified by preparative silica TLC, developed with *n*-hexane−CH_2Cl_2−MeOH (3:3:1), to afford binankadsurin (8 mg) and **6** (6 mg).

Kadsuphilin A (1): yellowish-white amorphous powder; $[\alpha]^{28}_D$ −12.0 (*c* 1.0, CH_2Cl_2); UV (MeOH) λ_{max} (log ϵ) 236 (4.92), 260 (4.25), 283 (3.64) nm; CD (*c* 0.1, MeOH) (ϵ) 254 (−0.15); IR (neat) ν_{max} 3053, 2984, 1710, 1425, 1264, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), Table 1; ^{13}C NMR ($CDCl_3$, 75 MHz), Table 2; EIMS *m*/*z* 546 (4, $[M]^+$), 398 (3, $[M - \text{cinnamic acid}]^+$), 300 (6), 131 (100), 103 (87); HREIMS *m*/*z* 546.2250 (calcd for $C_{32}H_{34}O_8$, 546.2254).

6-*epi*-Gomisin (2): yellowish-white amorphous powder; $[\alpha]^{28}_D$ +22 (*c* 1.0, CH_2Cl_2); UV (MeOH) λ_{max} (log ϵ) 237 (4.73), 261 (4.36), 281 (3.78) nm; CD (*c* 0.1, MeOH) (ϵ) 255 (−0.46); IR (neat) ν_{max} 3400, 3053, 2985, 1602, 1425, 1265, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz), Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz), Table 2; EIMS *m*/*z* 400 (18, $[M]^+$), 382 (6, $[M - H_2O]^+$), 344 (6), 285 (7), 220 (12), 208 (19), 165 (14); HREIMS *m*/*z* 400.1523 (calcd for $C_{22}H_{24}O_7$, 400.1528).

Kadsuphilin B (3): yellowish-white amorphous powder; $[\alpha]^{28}_D$ +51 (*c* 1.0, CH_2Cl_2); UV (MeOH) λ_{max} (log ϵ) 244 (4.46), 251 (4.12), 284 (3.54) nm; CD (*c* 0.1, MeOH) (ϵ) 254 (−0.27); IR (neat) ν_{max} 3419, 3053, 2936, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz), Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz), Table 2; EIMS *m*/*z* 402 (1, $[M]^+$), 384 (1, $[M - H_2O]^+$), 346 (1), 165 (5), 115 (13); HREIMS *m*/*z* 402.1684 (calcd for $C_{22}H_{26}O_7$, 402.1679).

1-Demethylkadsuphilin A (4): yellowish-white amorphous powder; $[\alpha]^{28}_D$ −49 (*c* 1.0, CH_2Cl_2); UV (MeOH) λ_{max} (log ϵ) 225 (4.93), 260 (4.46), 280 (3.75) nm; CD (*c* 0.1, MeOH) (ϵ) 256 (−0.095); IR (neat) ν_{max} 3300, 3054, 2976, 1707, 1616, 1459, 1265, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), Table 1; ^{13}C NMR ($CDCl_3$, 75 MHz), Table 2; EIMS *m*/*z* 532 (2, $[M]^+$), 384 (14, $[M - \text{cinnamic acid}]^+$), 131 (72), 103 (100); HRESIMS *m*/*z* 555.1997 (calcd for $C_{31}H_{32}O_8Na$, 555.1995).

Cytotoxicity Assays. Cell lines were purchased from the American Type Culture Collection (ATCC). Cytotoxicity assays of the test compounds were performed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[18,19]

Antioxidative Activity. The DPPH radical-scavenging activity was measured as previously published.[16] A solution of tested compound was mixed with 100 mM Tri-HCl buffer (pH 7.4, 800 μL) and added to 1 mL of 500 μM DPPH in ethanol. The mixture was shaken vigorously and left to stand for 20 min at room temperature in the dark. The absorbance at 517 nm by DPPH was measured by a UV−vis spectrophotometer.

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