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# C<sub>18</sub> Dibenzocyclooctadiene Lignans from *Kadsura philippinensis*

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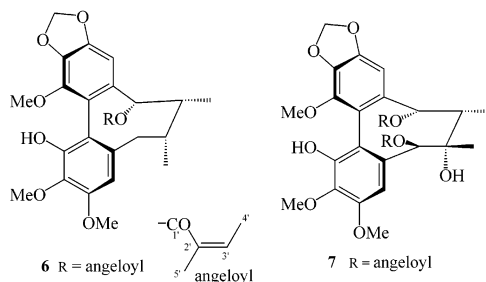
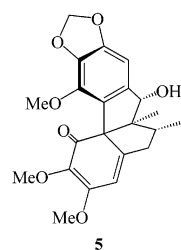
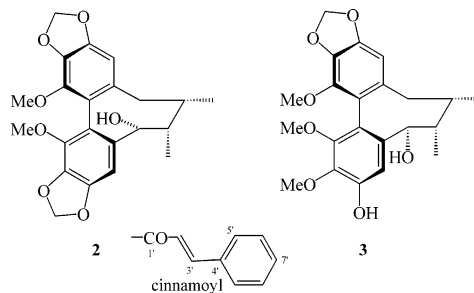
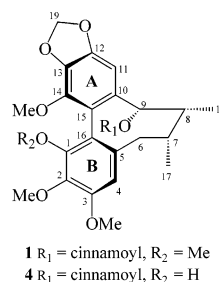
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Four new C<sub>18</sub> dibenzocyclooctadiene lignans, kadsuphilins A (**1**) and B (**3**), 6-*epi*-gomisin (**2**), and 1-demethylkadsuphilin A (**4**), along with eight known related metabolites, were isolated from an EtOAc fraction of an alcoholic 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.<sup>1</sup> Phytochemically, *Kadsura* species are also well known as a source of C<sub>18</sub> dibenzocyclooctadiene lignans,<sup>2</sup> which have shown anti-HIV, antioxidant, antiepatotoxic, cytotoxic,<sup>3</sup> antitumor,<sup>4</sup> and anti-lipid peroxidative activities. Previously, we have reported two triterpene dilactones, kadsuphilactones A and B,<sup>5</sup> and three C<sub>19</sub> homolignans, taiwankadsurins A, B, and C,<sup>6</sup> 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<sub>18</sub> 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<sub>2</sub>O (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<sub>32</sub>H<sub>34</sub>O<sub>8</sub>, as derived from its HREIMS (*m/z* 546.2250, [M]<sup>+</sup>) and NMR spectroscopic data (Tables 1 and 2). The UV spectrum showed  $\lambda_{\max}$  (MeOH) values at 236, 260, and 283 nm, while its CD spectrum exhibited a strong negative Cotton effect at  $\lambda_{\max}$  254 nm, indicating that **1** is a C<sub>18</sub> dibenzocyclooctadiene lignan<sup>1,2</sup> with a *S*-biphenyl configuration.<sup>7</sup> The IR spectrum of **1** indicated the presence of an ester ( $\nu_{\max}$  1710 cm<sup>-1</sup>) group and the absence of any hydroxyl groups. The NMR spectrum of **1** also showed the signals due to an octa-substituted biphenyl moiety [<sup>1</sup>H NMR  $\delta_{\text{H}}$  6.66 and 6.54 (1H each, s); <sup>13</sup>C NMR  $\delta_{\text{C}}$  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)].<sup>1,2</sup> These NMR signals were found to be almost identical to those of kadsurin,<sup>8</sup> indicating the same substitution pattern on the biphenyl unit. Thus, one methylenedioxy group ( $\delta_{\text{H}}$  5.99 and 5.98, 1H each, s), four



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methoxy groups ( $\delta_{\text{H}}$  3.91, 3.81, 3.67, and 3.44, 3H each, s), a benzylic methylene group ( $\delta_{\text{H}}$  2.71, 2H, br d, *J* = 3.7 Hz), and a benzylic oxymethine ( $\delta_{\text{H}}$  5.93, 1H, s) were also found in the

**Table 1.**  $^1\text{H}$  NMR Chemical Shifts of Compounds 1–4

position	1 <sup>a,c</sup>	2 <sup>b</sup>	3 <sup>b</sup>	4 <sup>a</sup>
H-4	6.66 s	6.91 s	7.04	6.46 s
H-6	2.71 2H, m	4.52 d (1.5) <sup>c</sup>	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 <sup>d</sup> 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 <sup>d</sup> 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

<sup>a</sup> Spectra recorded at 300 MHz in  $\text{CDCl}_3$  at 25 °C. <sup>b</sup> 500 MHz in  $\text{CDCl}_3$  at 25 °C. <sup>c</sup>  $J$  values are in Hz in parentheses. <sup>d</sup> Exchangeable values.

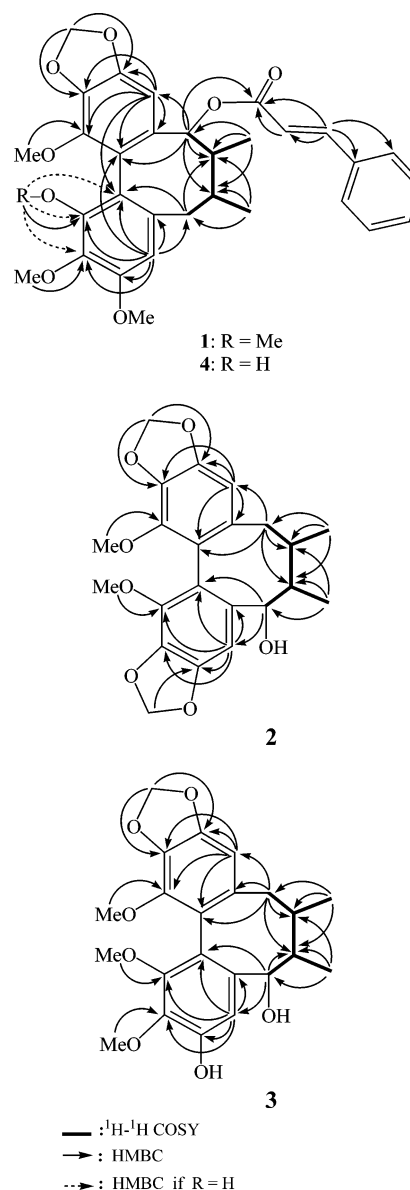
**Table 2.**  $^{13}\text{C}$  NMR Chemical Shifts of Compounds 1–4

#	1 <sup>a</sup>	2 <sup>b</sup>	3 <sup>b</sup>	4 <sup>a</sup>
1	151.4 (C) <sup>c</sup>	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 <sub>2</sub> )	73.3 (CH)	73.2 (CH)	38.8 (CH <sub>2</sub> )
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) <sup>d</sup>	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 <sub>3</sub> )	7.8 (CH <sub>3</sub> )	7.6 (CH <sub>3</sub> )	15.2 (CH <sub>3</sub> )
18	19.6 (CH <sub>3</sub> )	21.8 (CH <sub>3</sub> )	22.0 (CH <sub>3</sub> )	19.7 (CH <sub>3</sub> )
19	101.3 (CH <sub>2</sub> )	100.8 (CH <sub>2</sub> )	100.8 (t)	101.3 (CH <sub>2</sub> )
20		100.9 (CH <sub>2</sub> )		
OMe-1	60.2 (CH <sub>3</sub> )	59.6 (CH <sub>3</sub> )	60.2 (CH <sub>3</sub> )	
OMe-2	60.7 (CH <sub>3</sub> )		61.0 (CH <sub>3</sub> )	60.6 (CH <sub>3</sub> )
OMe-3	56.0 (CH <sub>3</sub> )			55.8 (CH <sub>3</sub> )
OMe-14	59.8 (CH <sub>3</sub> )	59.6 (CH <sub>3</sub> )	59.6 (CH <sub>3</sub> )	59.8 (CH <sub>3</sub> )
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)

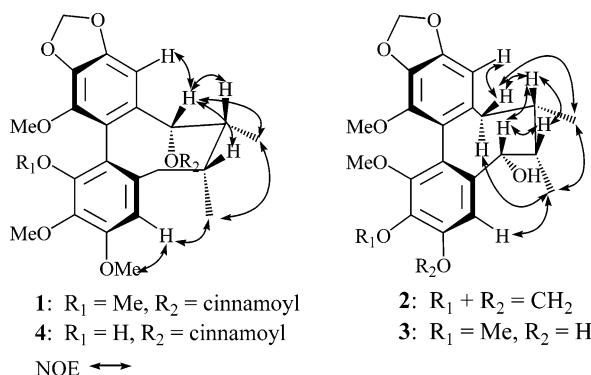
<sup>a</sup> 75 MHz in  $\text{CDCl}_3$  at 25 °C. <sup>b</sup> 125 MHz in  $\text{CDCl}_3$  at 25 °C.

<sup>c</sup> Multiplicity determined from DEPT and indicated by usual symbols. The values are in ppm downfield from TMS. <sup>d</sup> Exchangeable values.

molecule of **1**. Similar to those of kadsurin, in the COSY and HMBC spectra (Figure 1), the two secondary methyl groups ( $\delta_{\text{H}}$  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 [ $^1\text{H}$  NMR  $\delta_{\text{H}}$  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 [ $\text{M} - \text{cinnamic acid}$ ]<sup>+</sup> in the EIMS of **1**. The long-range  $^1\text{H}$ – $^{13}\text{C}$  correlations observed in the HMBC NMR spectrum from the benzylic H-9 at  $\delta_{\text{H}}$  5.93 (1H, s) to the ester carbonyl carbon (C-1') at  $\delta_{\text{C}}$  166.0 (C) and from H-9 to the aromatic carbon C-11 at  $\delta_{\text{C}}$  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.**  $^1\text{H}$ – $^1\text{H}$  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  $\beta$ - and  $\alpha$ -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  $\alpha$ -orientations of both  $\text{CH}_3$ -7 and  $\text{CH}_3$ -8. This was also apparent from the NOE correlations observed between the two methyls themselves and between the  $\text{CH}_3$ -7 and the aromatic H-4 signal. Therefore, the structure of kadsuphilin 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  $\lambda_{\text{max}}$  255 nm in the CD spectrum. The HREIMS ( $m/z$  400.1523,  $[\text{M}]^+$ ) was consistent with the molecular formula,  $\text{C}_{22}\text{H}_{24}\text{O}_7$ . The absorption band at  $3400\text{ cm}^{-1}$  in the IR spectrum and the ion peak appearing at  $m/z$  382  $[\text{M} - \text{H}_2\text{O}]^+$  in the EIMS suggested the presence of a hydroxyl group in **2**. The  $^{13}\text{C}$  NMR spectrum showed the signals of 12 carbons of a biphenyl at  $\delta_{\text{C}}$  194.1–102.1 (Table 2). Besides the aromatic protons of biphenyl that appeared at  $\delta_{\text{H}}$  6.66 and 6.54 (1H each, s), the  $^1\text{H}$  NMR spectrum of **2** also indicated the presence of two methylenedioxy units at  $\delta_{\text{H}}$  5.99 and 5.98 (1H each, d,  $J = 1.5$  Hz) and 5.94 (2H, br s), two methoxys at  $\delta_{\text{H}}$  3.87 and 3.85 (3H each, s), and two secondary methyls at  $\delta_{\text{H}}$  1.00 and 0.70 (3H each, d,  $J = 7.0$  Hz). From the HMBC spectrum of **2**, it was found that the single  $\text{sp}^3$  oxymethine carbon resonating at  $\delta_{\text{C}}$  73.3 (d) correlated with a proton at  $\delta_{\text{H}}$  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  $^1\text{H}$ – $^1\text{H}$  COSY, HMQC, and HMBC NMR spectra, the structure of **2** could be established (Figure 1). It was found that the  $^{13}\text{C}$  NMR spectroscopic data (Table 2) of **2** were quite similar to those of gomisin R<sup>19</sup> except for the upfield shifts induced at C-4 and C-17 ( $\Delta\delta_{\text{C}}$   $-7.8$  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** ( $\delta_{\text{H}}$  4.52, 1H, d,  $J = 1.5$  Hz) and gomisin R ( $\delta_{\text{H}}$  4.27, 1H, d,  $J = 8.0$  Hz). The  $\alpha$ -orientation of the hydroxyl group at C-6 was confirmed by the NOESY correlations (Figure 2) of **2**. One of the C-9 protons ( $\delta_{\text{H}}$  1.96, d,  $J = 13.5$  Hz) exhibited a NOE interaction with the aromatic H-11 and was thus assigned as H-9 $\beta$ . The NOE correlations found between H-9 $\beta$  and H-8 ( $\delta_{\text{H}}$  1.91, m) and between H-8 and H-6 confirmed the  $\beta$ -orientation of OH-6. The upfield shifted C-17 ( $\delta_{\text{C}}$  7.8,  $\text{CH}_3$ ) in **2**, relative to that of gomisin R<sup>9</sup> ( $\delta_{\text{C}}$  16.5,  $\text{CH}_3$ ) could be explained by the strong  $\gamma$ -effect arising from the steric compression of a *gauche* interaction between the methyl group attached at C-7 and the  $\alpha$ -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  $\text{C}_{22}\text{H}_{26}\text{O}_7$ , as determined by the HREIMS ( $m/z$  402.1684,  $[\text{M}]^+$ ) and NMR spectroscopic data. At least one hydroxyl exists in **3** (IR:  $\nu_{\text{max}}$   $3419\text{ cm}^{-1}$ , EIMS:  $m/z$  384  $[\text{M} - \text{H}_2\text{O}]^+$ ). However, its UV, CD, and IR data were very similar to that of **2**. Also, the  $^{13}\text{C}$  NMR

**Table 3.** Free Radical-Scavenging Activity of Compounds **1** and **5–7** at  $100\text{ }\mu\text{M}$

compound	radical-scavenging activity <sup>a</sup>
<b>1</b>	$1.5 \pm 0.65\%$
<b>5</b>	$4.6 \pm 0.64\%$
<b>6</b>	$2.3 \pm 0.28\%$
<b>7</b>	$1.9 \pm 0.52\%$
ascorbic acid <sup>b</sup>	$12.5 \pm 0.23\%$

<sup>a</sup> Radical-scavenging activity was measured by the DPPH-HPLC method. Each value is the mean  $\pm$  SD of 8 samples. <sup>b</sup> Positive control substance.

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  $\delta_{\text{C}}$  61.0 ( $\text{CH}_3$ ) in **3** instead of a methylenedioxy carbon resonance at  $\delta_{\text{C}}$  100.9 ( $\text{CH}_2$ ) in **2**. Thus, the biphenyl ring B was substituted by two methoxys and one hydroxyl. The location of the hydroxyl group at C-3 was determined by the strong HMBC correlations observed from H-4 ( $\delta_{\text{H}}$  1.96, d,  $J = 13.5$  Hz) to C-3 at  $\delta_{\text{C}}$  148.1 (C) and C-2 at  $\delta_{\text{C}}$  138.2 (C), while the methoxyl protons at  $\delta_{\text{H}}$  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  $\delta_{\text{H}}$  and  $J$  values of the corresponding  $^1\text{H}$  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.

Compound **4** was also defined as a  $\text{C}_{18}$  dibenzocyclooctadiene lignan with a *S*-biphenyl configuration, on the basis of its UV, CD, and NMR spectra. Its molecular formula,  $\text{C}_{31}\text{H}_{32}\text{O}_8$ , was deduced from HRESIMS ( $m/z$  555.1997,  $[\text{M} + \text{Na}]^+$ ) and NMR spectroscopic data (Tables 1 and 2). The presence of hydroxyl and ester functionalities in **4** was revealed from the IR bands at  $\nu_{\text{max}}$   $3300$  and  $1707\text{ cm}^{-1}$ , respectively. As in the case of **1**, the ion peak shown at  $m/z$  384  $[\text{M} - 148]^+$  in the EIMS together with the signals appearing at  $\delta_{\text{H}}$  5.87, 7.07 (1H each, d,  $J = 16$  Hz), and 7.35 (5H, br s) in the  $^1\text{H}$  NMR spectrum indicated a *trans*-cinnamoyl moiety in **4**. However, the appearance of three methoxyl signals in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **4**, instead of four, suggested this compound to be a demethylated kadsuphilin A derivative. The phenolic hydroxyl proton appeared at  $\delta_{\text{H}}$  5.48 (1H, s), which showed long-range  $^1\text{H}/^{13}\text{C}$  correlation with C-1 ( $\delta_{\text{C}}$  146.9, C), C-2 ( $\delta_{\text{C}}$  133.5, C), and C-16 ( $\delta_{\text{C}}$  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. heteroclitia*<sup>8</sup> and *K. japonica*,<sup>10</sup> schizanrin F isolated from *K. matsudai*,<sup>11</sup> kadsulignan K (**5**) isolated from *K. matsudai*,<sup>12</sup> kadsulignan D isolated from *K. longipedunculata*,<sup>13</sup> acetylbinankadsurin A isolated from *K. japonica*,<sup>14</sup> angeloylbinankadsurin A (**6**) isolated from *K. japonica*,<sup>14</sup> schizanrin J (**7**) isolated from *K. matsudai*,<sup>15</sup> and kadsurin A isolated from *K. matsudai*<sup>15</sup> by comparison of physical and spectroscopic ( $[\alpha]_{\text{D}}$ , MS,  $^1\text{H}$  and  $^{13}\text{C}$  NMR) data with literature values.

The isolation of  $\text{C}_{18}$  dibenzocyclooctadiene lignans from *K. philippinensis* is reported here for the first time. This class of compounds from *Kadsura*<sup>1,2,8–13</sup> and *Schisandra* species<sup>16</sup> 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  $\text{ED}_{50}$  value of  $<5\text{ }\mu\text{g/mL}$ . 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.<sup>17</sup>



## 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  $^1\text{H}$  and 75 MHz for  $^{13}\text{C}$  or on a Varian Unity INOVA 500 FT-NMR spectrometer at 500 MHz for  $^1\text{H}$  and 125 MHz for  $^{13}\text{C}$ , respectively, in  $\text{CDCl}_3$  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  $\text{H}_2\text{O}$  (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  $\text{CH}_2\text{Cl}_2$ –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– $\text{CH}_2\text{Cl}_2$ –MeOH (3:3:1), to afford binakadsurin (8 mg) and **6** (6 mg).

**Kadsuphilin A (1):** yellowish-white amorphous powder;  $[\alpha]_D^{28}$   $-12.0$  (*c* 1.0,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 236 (4.92), 260 (4.25), 283 (3.64) nm; CD (*c* 0.1, MeOH) ( $\epsilon$ ) 254 ( $-0.15$ ); IR (neat)  $\nu_{\text{max}}$  3053, 2984, 1710, 1425, 1264, 738  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz), Table 1;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz), Table 2; EIMS  $m/z$  546 (4,  $[\text{M}]^+$ ), 398 (3,  $[\text{M} - \text{cinnamic acid}]^+$ ), 300 (6), 131 (100), 103 (87); HREIMS  $m/z$  546.2250 (calcd for  $\text{C}_{32}\text{H}_{34}\text{O}_8$ , 546.2254).

**6-epi-Gomisin (2):** yellowish-white amorphous powder;  $[\alpha]_D^{28}$   $+22$  (*c* 1.0,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 237 (4.73), 261 (4.36), 281 (3.78) nm; CD (*c* 0.1, MeOH) ( $\epsilon$ ) 255 ( $-0.46$ ); IR (neat)  $\nu_{\text{max}}$  3400, 3053, 2985, 1602, 1425, 1265, 739  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz), Table 1;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz), Table 2; EIMS  $m/z$  400 (18,  $[\text{M}]^+$ ), 382 (6,  $[\text{M} - \text{H}_2\text{O}]^+$ ), 344 (6), 285 (7), 220 (12), 208 (19), 165 (14); HREIMS  $m/z$  400.1523 (calcd for  $\text{C}_{22}\text{H}_{24}\text{O}_7$ , 400.1528).

**Kadsuphilin B (3):** yellowish-white amorphous powder;  $[\alpha]_D^{28}$   $+51$  (*c* 1.0,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 244 (4.46), 251 (4.12), 284 (3.54) nm; CD (*c* 0.1, MeOH) ( $\epsilon$ ) 254 ( $-0.27$ ); IR (neat)  $\nu_{\text{max}}$  3419,

3053, 2936, 1610  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz), Table 1;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz), Table 2; EIMS  $m/z$  402 (1,  $[\text{M}]^+$ ), 384 (1,  $[\text{M} - \text{H}_2\text{O}]^+$ ), 346 (1), 165 (5), 115 (13); HREIMS  $m/z$  402.1684 (calcd for  $\text{C}_{22}\text{H}_{26}\text{O}_7$ , 402.1679).

**1-Demethylkadsuphilin A (4):** yellowish-white amorphous powder;  $[\alpha]_D^{28}$   $-49$  (*c* 1.0,  $\text{CH}_2\text{Cl}_2$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 225 (4.93), 260 (4.46), 280 (3.75) nm; CD (*c* 0.1, MeOH) ( $\epsilon$ ) 256 ( $-0.095$ ); IR (neat)  $\nu_{\text{max}}$  3300, 3054, 2976, 1707, 1616, 1459, 1265, 739  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz), Table 1;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz), Table 2; EIMS  $m/z$  532 (2,  $[\text{M}]^+$ ), 384 (14,  $[\text{M} - \text{cinnamic acid}]^+$ ), 131 (72), 103 (100); HRESIMS  $m/z$  555.1997 (calcd for  $\text{C}_{31}\text{H}_{32}\text{O}_8\text{Na}$ , 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.<sup>18,19</sup>

**Antioxidative Activity.** The DPPH radical-scavenging activity was measured as previously published.<sup>16</sup> A solution of tested compound was mixed with 100 mM Tri-HCl buffer (pH 7.4, 800  $\mu\text{L}$ ) and added to 1 mL of 500  $\mu\text{M}$  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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