Seven New Lignan Esters from *Kadsura philippinensis*

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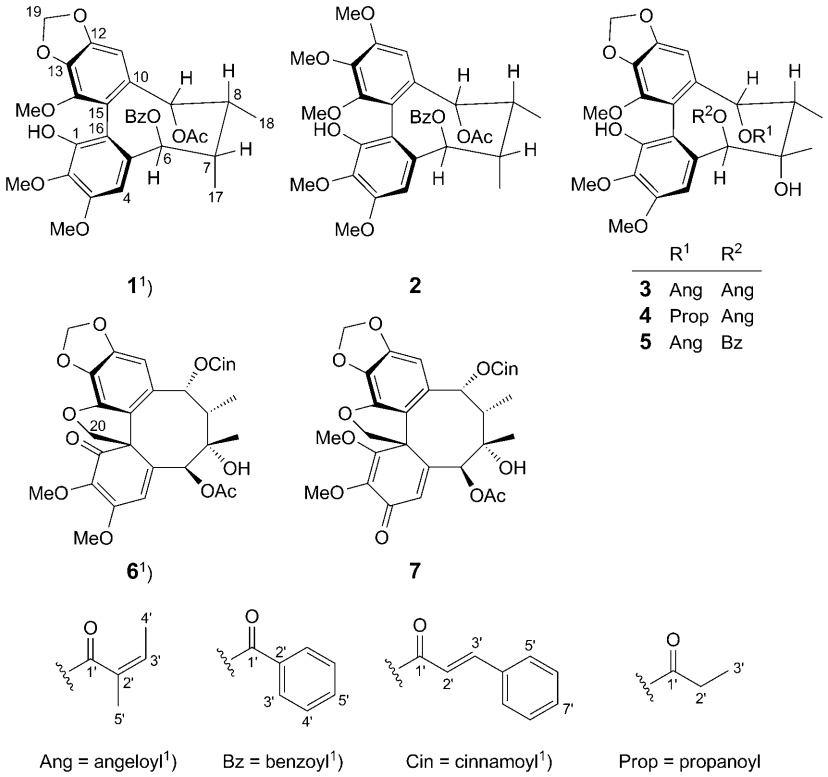
Five new oxygenated lignans with a dibenzocyclooctadiene skeleton, kadsuphilols P–T (**1**–**5**), and two new C_{19} homolignans, kadsuphilols U and V (**6** and **7**), were isolated by chromatographic fractionation of an AcOEt extract of the stems of *Kadsura philippinensis*. The structures of the isolated metabolites were elucidated through extensive spectroscopic analysis including HR-ESI-MS and 2D-NMR (HMQC, COSY, and HMBC). The configuration at the chiral centers and at the biphenyl moiety were determined by interpretation of NOESY and CD data, respectively.

Introduction. – Plants from Schisandraceae have yielded numerous lignans that demonstrated various beneficial pharmacological activities including antitumor [1], cytotoxic [2][3], antiviral [4][5], antihepatitis [6], hepatoprotective [7], and antioxidant [8] effects. Recently, some lignans revealed appreciable inhibitory activity against HIV-1 protease which is essential for maturation of the virus [9]. The genus *Kadsura* (Schisandraceae) is a rich source of lignans commonly used in Chinese and Japanese traditional medicine for their established healing properties, sometimes as a substitute for *Schisandra chinensis* BAILL [10–12]. These diverse biological activities were an incentive to re-investigate the lignan content of *K. philippinensis* ELMER (Schisandraceae) [13]. Herein, we report the results of a phytochemical study that led to the isolation of seven new oxygenated lignan esters, kadsuphilols P–V[1]) (**1**–**7**), in addition to benzoylbinankadsurin A [9]. Five of the isolated lignans **1**–**5** possessed a C_{18}-dibenzocyclooctadiene skeleton, while C_{19}-homolignans **6** and **7** possessed a 'spirobenzofuranoid' skeleton [14][15]. The structures of **1**–**7** were determined through detailed spectroscopic study of their HR-ESI-MS and NMR data, especially ^{1}H,^{1}H-COSY and HMBC data. The configuration at the chiral centers and at the biphenyl moiety were deduced from NOESY and CD spectra, respectively.

Results and Discussion. – Compound **1** possessed a molecular formula $C_{31}H_{32}O_{10}$, as deduced from its HR-ESI-MS (*m*/*z* 587.1891 ($[M + Na]^+$)) and NMR data, in agreement with 16 degrees of unsaturation. The UV data, with absorption maxima at λ_{max} 225, 259, and 284 nm, and IR absorption bands attributable to OH (3436 cm^{-1}),

[1]) Trivial atom numbering; for systematic names, see *Exper. Part*.



ester (1721 cm^{-1}), and aromatic (3058, 1611, 1510 cm^{-1}) functionalities, suggested the presence of a C_{18}-dibenzocyclooctadiene lignan ester [10][11]. The ^{1}H-NMR spectrum of **1** (*Table 1*) showed two aromatic *s*s of a biphenyl moiety at δ(H) 6.56 and 6.57 (H–C(4) and H–C(11)), three *s*s of MeO groups at δ(H) 3.55, 3.91, and 3.93, along with two *s*s of an OCH_2O group (δ(H) 5.89 and 5.86) and an OH group (δ(H) 5.63, D_2O-exchangeable). The cyclooctadiene ring was evident from two secondary-Me *d*s at δ(H) 0.99 (Me(17)) and 1.13 (Me(18)), two CH groups at δ(H) 2.30–2.35 (H–C(7)) and 2.38–2.44 (H–C(8)), two benzylic O-bearing CH groups at δ(H) 6.00 (*d*, J = 6.7 Hz, H–C(6)) and 5.67 (*d*, J = 2.1 Hz, H–C(9)), implying acylation at both positions. An AcO group was observed at δ(H) 1.58, and BzO signals resonated at δ(H) 7.55 (*d*, J = 7.6 Hz, H–C(3′), H–C(7′)), 7.32 (*t*, J = 7.6 Hz, H–C(4′), H–C(6′)), and 7.49 (*t*, J = 7.6 Hz, H–C(5′)), which were supported by EI-MS fragment ions at *m*/*z* 505 ([M – AcO]$^+$), and 443 ([M – BzO]$^+$). The ^{13}C-NMR spectrum (*Table 2*) revealed signals of ten quaternary aromatic C-atoms, two aromatic upfield CH groups adjacent to two O-bearing C-atoms (δ(C) 106.8 and 102.6), and three MeO groups (δ(C) 55.8, 59.3, and 60.8). AcO and BzO signals appeared at δ(C) 170.0 and 20.4, and δ(C) 165.3 (C(1′)), 130.1 (C(2′)), 129.5 (C(3′,7′)), 127.8 (C(4′,6′)), and 132.7 (C(5′)), respectively. The positions of the MeO, OH, BzO, and AcO groups were determined after comparison of NMR data with those of closely related compounds [9][11] as well as by a meticulous

Table 1. *^{1}H-NMR Data* ($CDCl_3$) *of Compounds* **1**–**7**[1])[a]). δ in ppm, J in Hz.

	1	**2**[b])	**3**	**4**	**5**	**6**	**7**[c])
H–C(4)	6.56 (*s*)	7.11 (*s*)	6.62 (*s*)	6.64 (*s*)	6.68 (*s*)	6.44 (*s*)	6.56 (*s*)
H–C(6)	6.00 (*d*, *J* = 6.7)	6.46 (*d*, *J* = 7.6)	5.65 (*s*)	5.64 (*d*, *J* = 4.4)	5.94 (*s*)	5.63 (*s*)	5.78 (*s*)
H–C(7)	2.30–2.35 (*m*)	2.44–2.50 (*m*)					
H–C(8)	2.38–2.44 (*m*)	2.52–2.57 (*m*)	2.26–2.32 (*m*)	2.12–2.18 (*m*)	2.41 (*q*, *J* = 7.2)	2.12 (*q*, *J* = 7.3)	2.04 (*q*, *J* = 7.4)
H–C(9)	5.67 (*d*, *J* = 2.1)	6.15 (*d*, *J* = 3.1)	5.61 (*s*)	5.62 (*s*)	5.69 (*s*)	5.90 (*s*)	5.77 (*s*)
H–C(11)	6.57 (*s*)	7.01 (*s*)	6.51 (*s*)	6.48 (*s*)	6.61 (*s*)	6.42 (*s*)	6.38 (*s*)
Me(17)	0.99 (*d*, *J* = 6.8)	1.10 (*d*, *J* = 6.8)	1.38 (*s*)	1.36 (*s*)	1.56 (*s*)	1.25 (br. *s*)	1.24 (*s*)
Me(18)	1.13 (*d*, *J* = 7.2)	1.15 (*d*, *J* = 7.2)	1.42 (*d*, *J* = 7.0)	1.28 (*d*, *J* = 7.1)	1.37 (*d*, *J* = 7.2)	1.32 (*d*, *J* = 7.2)	1.29 (*d*, *J* = 7.4)
CH_2(19)	5.89, 5.86 (2*s*)		5.92, 5.92 (2*s*)	5.91, 5.91 (2*s*)	5.86, 5.63 (2*s*)	6.01, 5.94 (2*s*)	6.02, 5.98 (2*s*)
CH_2(20)						4.76 (*d*, *J* = 9.2), 4.11 (*d*, *J* = 9.2)	4.53 (*d*, *J* = 9.0), 4.40 (*d*, *J* = 9.0)
OH–C(1)	5.63 (*s*)		5.49 (*s*)		5.48 (*s*)		
MeO–C(1)							3.82 (*s*)
MeO–C(2)	3.91 (*s*)	3.98 (*s*)	3.86 (*s*)	3.92 (*s*)	3.86 (*s*)	3.59 (*s*)	3.56 (*s*)
MeO–C(3)	3.93 (*s*)	3.91 (*s*)	3.91 (*s*)	3.94 (*s*)	3.94 (*s*)	4.00 (*s*)	
MeO–C(12)		3.86 (*s*)					
MeO–C(13)		3.83 (*s*)					
MeO–C(14)	3.55 (*s*)	3.56 (*s*)	3.74 (*s*)	3.76 (*s*)	3.39 (*s*)		
H–C(3′)	7.55 (*d*, *J* = 7.6)	7.84 (*d*, *J* = 7.2)	5.95 (*q*, *J* = 7.4)	5.97 (*q*, *J* = 7.2)	7.54 (*d*, *J* = 7.5)		
H–C(4′) or Me(4′)	7.32 (*t*, *J* = 7.6)	7.41 (*m*)	1.84 (*dd*, *J* = 7.2, 1.2)	1.89 (*d*, *J* = 7.2)	7.30 (*t*, *J* = 7.5)		
H–C(5′)	7.49 (*t*, *J* = 7.6)	7.41 (*m*)	1.34 (*d*, *J* = 1.2)	1.40 (*s*)	7.47 (*t*, *J* = 7.5)		
H–C(6′)	7.32 (*t*, *J* = 7.6)	7.41 (*m*)			7.30 (*t*, *J* = 7.5)		
H–C(7′)	7.55 (*d*, *J* = 7.6)	7.84 (*d*, *J* = 7.2)			7.54 (*d*, *J* = 7.5)		
CH_2(2″) or H–C(2″)				1.85 (*q*, *J* = 7.3), 1.68 (*m*)		6.06 (*d*, *J* = 15.9)	6.04 (*d*, *J* = 16.0)
H–C(3″) or Me(3″)			5.97 (*q*, *J* = 7.4)	0.86 (*t*, *J* = 7.5)	5.97 (*q*, *J* = 7.1)	7.58 (*d*, *J* = 15.9)	7.65 (*d*, *J* = 16.0)
Me(4″) or H–C(4″)			1.88 (*dd*, *J* = 7.2, 1.2)		1.90 (*d*, *J* = 7.1)		
Me(5″) or H–C(5″)			1.32 (*d*, *J* = 1.2)		1.43 (*s*)	7.49 (*m*)	7.56 (*m*)
H–C(6″,8″)						7.38 (*m*)	7.41 (*m*)
H–C(7″)						7.38 (*m*)	7.41 (*m*)
H–C(9″)						7.49 (*m*)	7.56 (*m*)
AcO–C(6)						1.81 (*s*)	1.81 (*s*)
AcO–C(9)	1.58 (*s*)	1.74 (*s*)					

[a]) Substituents at C(6) are numbered 1′, 2′, … *etc.*, while substituents at C(9) are numbered 1″, 2″, … *etc.* [b]) In (D_5)pyridine. [c]) At 500 MHz.

Table 2. *^{13}C-NMR Data* ($CDCl_3$) *of Compounds* **1**–**7**[a])

	1	**2**[b])	**3**	**4**	**5**	**6**	**7**[c])
C(1)	147.4 (*s*)	142.8 (*s*)	147.1 (*s*)	146.9 (*s*)	147.0 (*s*)	195.4 (*s*)	165.9 (*s*)
C(2)	134.6 (*s*)	131.1 (*s*)	134.9 (*s*)	134.7 (*s*)	135.1 (*s*)	132.0 (*s*)	134.2 (*s*)
C(3)	150.3 (*s*)	152.6 (*s*)	150.6 (*s*)	150.5 (*s*)	150.7 (*s*)	155.3 (*s*)	183.3 (*s*)
C(4)	106.8 (*d*)	112.3 (*d*)	107.3 (*d*)	107.1 (*d*)	107.4 (*d*)	123.4 (*d*)	130.9 (*d*)
C(5)	131.3 (*s*)	131.6 (*s*)	130.3 (*s*)	130.4 (*s*)	129.9 (*s*)	141.6 (*s*)	149.5 (*s*)
C(6)	81.6 (*d*)	82.0 (*d*)	85.0 (*d*)	85.0 (*d*)	85.5 (*d*)	82.3 (*d*)	81.3 (*d*)
C(7)	39.3 (*d*)	39.4 (*d*)	74.0 (*s*)	74.0 (*s*)	74.0 (*s*)	74.9 (*s*)	75.2 (*s*)
C(8)	37.8 (*d*)	39.9 (*d*)	43.1 (*d*)	42.9 (*d*)	43.3 (*d*)	44.1 (*d*)	44.5 (*d*)
C(9)	81.5 (*d*)	81.5 (*d*)	83.9 (*d*)	83.7 (*d*)	83.7 (*d*)	81.4 (*d*)	82.2 (*d*)
C(10)	134.4 (*s*)	135.9 (*s*)	133.7 (*s*)	133.5 (*s*)	134.5 (*s*)	129.3 (*s*)	129.9 (*s*)
C(11)	102.6 (*d*)	112.1 (*d*)	102.4 (*d*)	102.5 (*d*)	102.1 (*d*)	101.0 (*d*)	100.3 (*d*)
C(12)	148.9 (*s*)	151.7 (*s*)	149.1 (*s*)	148.9 (*s*)	149.2 (*s*)	150.1 (*s*)	150.3 (*s*)
C(13)	136.1 (*s*)	141.3 (*s*)	135.9 (*s*)	135.9 (*s*)	135.9 (*s*)	130.4 (*s*)	129.9 (*s*)
C(14)	141.3 (*s*)	152.5 (*s*)	140.7 (*s*)	140.7 (*s*)	141.4 (*s*)	143.3 (*s*)	143.9 (*s*)
C(15)	119.6 (*s*)	121.1 (*s*)	119.0 (*s*)	119.1 (*s*)	119.0 (*s*)	120.1 (*s*)	120.0 (*s*)
C(16)	116.2 (*s*)	124.7 (*s*)	115.5 (*s*)	115.5 (*s*)	115.6 (*s*)	63.0 (*s*)	56.0 (*s*)
C(17)	14.8 (*q*)	16.9 (*q*)	28.9 (*q*)	28.9 (*q*)	28.9 (*q*)	28.3 (*q*)	28.3 (*q*)
C(18)	17.9 (*q*)	15.4 (*q*)	17.4 (*q*)	17.2 (*q*)	17.4 (*q*)	17.6 (*q*)	17.6 (*q*)
C(19)	101.1 (*t*)		101.1 (*t*)	101.1 (*t*)	101.0 (*t*)	101.9 (*t*)	102.1 (*t*)
C(20)						79.1 (*t*)	83.9 (*t*)
C(1′)	165.3 (*s*)	165.7 (*s*)	165.8 (*s*)	165.8 (*s*)	164.8 (*s*)		
C(2′)	130.1 (*s*)	131.5 (*s*)	127.7 (*s*)	127.0 (*s*)	131.1 (*s*)		
C(3′)	129.5 (*d*)	128.6 (*d*)	141.3 (*d*)	139.6 (*d*)	129.4 (*d*)		
C(4′)	127.8 (*d*)	130.1 (*d*)	15.6 (*q*)	15.6 (*q*)	127.9 (*d*)		
C(5′)	132.7 (*d*)	133.1 (*d*)	19.9 (*q*)	19.8 (*q*)	132.9 (*d*)		
C(6′)	127.8 (*d*)	130.1 (*d*)			127.9 (*d*)		
C(7′)	129.5 (*d*)	128.6 (*d*)			129.4 (*d*)		
C(1″)			165.3 (*s*)	172.3 (*s*)	165.3 (*s*)	164.9 (*s*)	165.7 (*s*)
C(2″)			125.8 (*s*)	26.6 (*t*)	127.5 (*s*)	115.9 (*d*)	116.2 (*d*)
C(3″)			139.5 (*d*)	8.5 (*q*)	141.4 (*d*)	149.9 (*d*)	147.6 (*d*)
C(4″)			15.7 (*q*)		15.8 (*q*)	134.2 (*s*)	133.8 (*s*)
C(5″)			19.8 (*q*)		19.9 (*q*)	128.8 (*d*)	128.8 (*d*)
C(6″)						128.4 (*d*)	128.8 (*d*)
C(7″)						130.6 (*d*)	130.8 (*d*)
C(8″)						128.4 (*d*)	128.8 (*d*)
C(9″)						128.8 (*d*)	128.8 (*d*)
*Me*O–C(1)							61.4 (*q*)
*Me*O–C(2)	60.8 (*q*)	59.9 (*q*)	60.3 (*q*)	60.7 (*q*)	60.3 (*q*)	58.8 (*q*)	60.2 (*q*)
*Me*O–C(3)	55.8 (*q*)	60.3 (*q*)	55.8 (*q*)	55.8 (*q*)	55.9 (*q*)	59.0 (*q*)	
*Me*O–C(12)		56.9 (*q*)					
*Me*O–C(13)		60.5 (*q*)					
*Me*O–C(14)	59.3 (*q*)	60.4 (*q*)	59.2 (*q*)	59.3 (*q*)	59.0 (*q*)		
*Ac*O–C(6)						169.8 (*s*), 20.4 (*q*)	169.6 (*s*), 20.2 (*q*)
*Ac*O–C(9)	170.0 (*s*), 20.4 (*q*)	169.6 (*s*), 20.6 (*q*)					

[a]) Substituents at C(6) are numbered 1′, 2′, … *etc.*, while substituents at C(9) are numbered 1″, 2″, … *etc.* [b]) (D_5)pyridine. [c]) At 125 MHz.

inspection of the HMBC, COSY (*Fig. 1*), and NOESY data (*Fig. 2*). The aromatic H-atom at δ(H) 6.56 (H–C(4)) showed ^3J-correlations with C(2), C(16), and C(6), whereas the aromatic H-atom at δ(H) 6.57 (H–C(11)) correlated with C(13), C(15), and C(9). The three MeO groups were located at C(2), C(3), and C(14) as revealed by HMBCs of the signals of these C-atoms with the *s*s of the attached MeO groups. In turn, the OCH_2O group was attached to C(12)–C(13) (HMBC of CH_2(19) to C(12) (δ(C) 148.9) and C(13) (δ(C) 136.1)), and the OH group was linked to C(1) (HMBCs of OH *s* at δ(H) 5.63) to C(1) (δ(C) 147.4), C(2) (δ(C) 134.6), and C(16) (δ(C) 116.2)). The correlations of H–C(6) with C(4), C(16), and C(8) as well as with the BzO CO group, and the correlations of H–C(9) (δ(H) 5.67) with C(11), C(15), and the AcO CO group positioned the BzO and AcO groups at C(6) and C(9), respectively. The structure of the cyclooctadiene ring was also confirmed by the COSY connectivities H–C(6)/H–C(7)/H–C(8)/H–C(9), H–C(7)/Me(17), and H–C(8)/Me(18). The CD curve of **1** showed a negative *Cotton* effect around 252 nm and a positive one around 224 nm favoring the (*S*)-biphenyl configuration [10][11]. The relative configuration of **1** was determined by the NOESY data (*Fig. 2*), *i.e.*, the correlations H–C(4)/H–C(6), and Me(17), and H–C(6)/Me(17), indicating the α-configuration of H_{eq}–C(6) and Me_{ax}–C(17), and the correlations H_{eq}–C(9)/H–C(11) and H_{ax}–C(8) indicating the β-orientation of H–C(8) and H–C(9) [16]. Based on these findings, the structure **1** was established for kadsuphilol P.

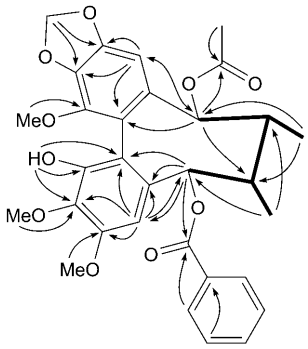


Fig. 1. *Selected HMBCs* (arrows) *and COSY results* (bold lines) *of* **1**

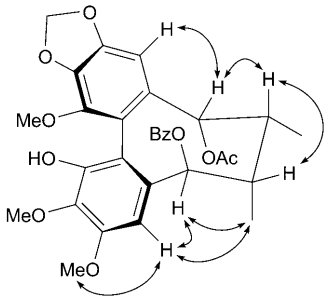


Fig. 2. *Key NOESY correlations of* **1**

The molecular formula of **2** was assigned $C_{32}H_{36}O_{10}$ by the HR-EI-MS (*m/z* 580.2313) and agreed with its NMR data (15 degrees of unsaturation). The UV, IR, and NMR spectra of **2** were quite similar to those of **1**, a significant difference between them being the presence of five MeO *s*s in **2** rather than three in **1**. Furthermore, no OCH_2O group was found in **2**. The ^{13}C-NMR data displayed the signals of two quaternary C-atoms (δ(C) 165.7 and 131.5) and three aromatic CH groups (δ(C) 130.1, 128.6, and 133.1) belonging to a BzO group, in addition to a CO (δ(C) 169.6) and a Me group (δ(C) 20.6) of an AcO group. The HMBC spectrum revealed correlations of H–C(6) with the BzO CO group, positioning the BzO group at C(6). The other O-bearing CH group resonating at δ(H) 6.15 (H–C(9)) correlated to the AcO CO group establishing the attachment of an AcO group to C(9). The MeO groups at δ(H) 3.98, 3.91, 3.86, 3.83, and 3.56 correlated to the quaternary C-atoms C(2), C(3), C(12), C(13), and C(14) locating a MeO group at each of these positions. The NOESY correlations H–C(4)/H–C(6), H–C(6)/Me(17), and H–C(9)/H–C(8) and H–C(11) suggested the α-orientation of H–C(6), Me(17), and Me(18) and the β-orientation of H–C(9). Thus, the structure of **2** was established for kadsuphilol Q.

The molecular formula of **3** was calculated as $C_{32}H_{38}O_{11}$ from its HR-EI-MS and NMR data (14 degrees of unsaturation). The UV (λ_{max} 249 and 293 nm) and IR spectra (3563, 1715, and 1618 cm^{-1}) of **3** suggested the presence of a dibenzocyclooctadiene lignan with OH groups and conjugated-ester groups. The ^{13}C-NMR data (*Table 2*) displayed aromatic signals of the biphenyl moiety, two CO groups (δ(C) 165.8 and 165.3), two benzylic O-bearing CH groups (δ(C) 85.0 and 83.9), a CH group (δ(C) 43.1), and a quaternary O-bearing C-atom (δ(C) 74.0) that suggested a disubstitution at C(6) and C(9) with two conjugated acyl groups and an OH substitution at either C(7) or C(8). Two sets of angelate (=(2*Z*)-2-methylbut-2-enoate) moieties were detected in the ^{1}H-NMR spectrum (*Table 1*) at δ(H) 5.95 and 5.97 (2*q*, H–C(3′), H–C(3″)), δ(H) 1.84 and 1.88 (2*dd*, Me(4′), Me(4″)), and δ(H) 1.34 and 1.32 (2*d*, Me(5′), Me(5″)), along with ^{13}C-NMR signals at δ(C) 165.8 and 165.3 (2 CO), δ(C) 127.7 and 125.8 (C(2′), C(2″)), δ(C) 141.3 and 139.5 (C(3′), C(3″)), δ(C) 15.6 and 15.7 (C(4′), C(4″)), and δ(C) 19.9 and 19.8 (C(5′), C(5″)) [11][17][18]. The EI-MS fragment ion at *m/z* 399 ($[M - 2\ AngOH]^+$) confirmed the presence of two angelate moieties. The CH group *s* at δ(H) 5.65 (H–C(6)) ^3J-correlated with the angeloyl CO group at δ(C) 165.8 (C(1′)), while H–C(9) (δ(H) 5.61) correlated with the O-bearing quaternary C-atom (δ(C) 74.0, C(7)) and the second angeloyl CO group (δ(C) 165.3, C(1″)). These data were compatible with two angeloyloxy substituents at C(6) and C(9) and an OH group at C(7). The OH substitution at C(7) was supported by the relatively low-field shift of C(17) (δ(C) 28.9) compared to δ(C) 14.8 in **1** and δ(C) 16.9 in **2** [19][20]. The HMBCs of the OCH_2O group (δ(H) 5.92 (*s*)) with C(12) (δ(C) 149.1) and C(13) (δ(C) 135.9), and of the three MeO signals at δ(H) 3.86, 3.91, and 3.74 with C(2) (δ(C) 134.9), C(3) (δ(C) 150.6), and C(14) (δ(C) 140.7) established substitution at these positions of the biphenyl moiety. The signal of the OH group at δ(H) 5.49 correlated with C(1) (δ(C) 147.1), C(2), and C(16) indicating OH substitution at C(1). The relative configuration was determined by the NOESY correlations H–C(4)/H–C(6), H–C(8)/H–C(9) and Me(17), and H–C(9)/H–C(11), consistent with the α-orientation of H–C(6), OH–C(7), Me–C(8), and the angeloyloxy group at C(9), along with the β-orientation

of the angeloyloxy at C(6), H–C(8), H–C(9), and Me(17). Accordingly, the structure of **3** was identified for kadsuphilol R.

The lignan **4** possessed a molecular formula $C_{30}H_{36}O_{11}$ (M^+ at m/z 572.2255 in the HR-EI-MS) (13 degrees of unsaturation). Its NMR data (*Tables 1* and *2*) revealed the presence of three MeO groups at C(2), C(3), and C(14) of the biphenyl moiety, in addition to an OCH_2O group (δ(C) 101.1) at C(12)–C(13), similar to those of **1**. The cyclooctadiene moiety demonstrated two O-bearing CH groups (δ(H) 5.64 and 5.62, and δ(C) 85.0 and 83.7), a quaternary O-bearing C-atom (δ(C) 74.0), an angeloyl moiety (δ(C) 165.8, 127.0, 139.6, 15.6, and 19.8), and an aliphatic ester (δ(C) 172.3, 26.6, and 8.5), suggesting substitutions with an OH, angeloyloxy and propanoyloxy group. The COSY cross-peaks of the geminal H-atoms at δ(H) 1.85 (q, $J = 7.3$ Hz) and 1.68 (m) with the upfield Me signal at δ(H) 0.86 (t, $J = 7.5$ Hz), and the HMBC of the latter Me group with the CO group at δ(C) 172.3 established the presence of a propanoyloxy moiety. The O-bearing CH group at δ(H) 5.64 (d, $J = 4.4$ Hz, H–C(6)) correlated with the aromatic CH group at δ(C) 107.1 (C(4)), the angeloyl CO group, the O-bearing quaternary C-atom (δ(C) 74.0, C(7)), and C(17) (δ(C) 28.9), indicating the attachment of the angeloyloxy group at C(6) and of the OH group at C(7). Furthermore, H–C(9) (δ(H) 5.62 (s)) correlated with the propanoyl CO group, thus locating the propanoyloxy group at C(9). A support of the proposed structure of **4** was provided by the NOESY correlations H–C(6)/H–C(4), Me(17)/H–C(8), and H–C(9)/H–C(8) and H–C(11) implying the same configuration as that of **3**. Based on these findings, the structure of **4** was assigned to kadsuphilol S.

The lignan **5** had a molecular formula $C_{34}H_{36}O_{11}$ (m/z 620.2253 in the HR-EI-MS; 17 degrees of unsaturation). Its spectral data indicated the presence of three MeO groups and one OCH_2O substitution at the biphenyl moiety. The HMBCs of three MeO at δ(H) 3.86, 3.94, and 3.39 to C(2), C(3), and C(14), respectively, together with correlations of the OCH_2O H-atoms at δ(H) 5.86 and 5.63 to C(12) and C(13) confirmed a substitution pattern at the biphenyl moiety similar to that of **1**, **3**, and **4**. The NMR data of the cyclooctadiene ring pointed to the presence of an OH group at C(7) (δ(C) 74.0), an angeloyloxy (δ(C) 165.3, 127.5, 141.4, 15.8, and 19.9) and a BzO group (δ(C) 164.8, 131.1, 129.4, 127.9, and 132.9). The O-bearing CH group at δ(H) 5.94 (H–C(6)) was ^2J-correlated with an O-bearing quaternary C-atom (δ(C) 74.0), and ^3J-correlated with the BzO CO group (δ(C) 164.8), thereby positioning the BzO at C(6). The other O-bearing CH group at δ(H) 5.69 was assigned to position C(9), to which the angeloyloxy group was attached (^3J-correlations of H–C(9) to C(1″), C(11), C(15), C(18), and NOESY correlation H–C(9)/H–C(11)). The NOESY correlations of **5** were the same as those of **3** and **4** implying the same configuration of the cyclooctadiene moiety. Based on these findings, the structure of **5** was assigned to kadsuphilol T.

The FAB-MS of **6** revealed a molecular-ion peak at m/z 627 ($[M + Na]^+$) corresponding to the molecular formula $C_{33}H_{32}O_{11}$ (18 degrees of unsaturation). In addition to two MeO (δ(C) 58.8 and 59.0) and an OCH_2O group (δ(C) 101.9), the ^{13}C-NMR spectrum of the biphenyl moiety of **6** displayed a CO signal at δ(C) 195.4 and a quaternary C-atom at δ(C) 63.0. This was associated with the absence of the usual chemical shift values for C(1) and C(16) (*cf.* **1** and **3**–**5**) and with a downfield shift of C(4) (δ(C) 123.4; directly attached to the H-atom at δ(H) 6.44 (s)). The HMBCs of the

OCH_2O moiety (δ(H) 6.01 and 5.94) and of the two MeO groups at δ(H) 3.59 and 4.00 suggested substitution by the two MeO groups at C(2) and C(3) and by the OCH_2O moiety at C(12)–C(13) (*Fig. 3*). Two H-atoms of a O-bearing CH_2 group resonating at δ(H) 4.76 and 4.11 (each *d*, $J = 9.2$ Hz, CH_2(20)) correlated with quaternary C-atoms at δ(C) 143.3 (C(14)), 63.0 (C(16)), and 141.6 (C(5)), and with the CO group at δ(C) 195.4. In addition, the CH group at δ(H) 6.44 (H–C(4)) correlated with the quaternary C-atom at δ(C) 63.0 (C(16)) as well as with C(2) (δ(C) 132.0) and C(6) (δ(C) 82.3). These data conformed to the presence of a CO group at C(1) and an O-bearing CH_2 group at C(16) forming a fused dihydrofuran ring that satisfied 14 degrees of unsaturation [15][19]. The NMR data of the cycooctadiene ring suggested the presence of an OH group at C(7) (δ(C) 74.9) and of a cinnamoyloxy and AcO group. A cinnamoyloxy group was evident from signals at δ(H) 6.06, 7.58 (2*d*, $J = 15.9$ Hz), 7.49 (*m*, 2 H), and 7.38 (*m*, 3 H), and C-atom signals at δ(C) 164.9 (C(1″)), 115.9 (C(2″)), 149.9 (C(3″)), 134.2 (C(4″)), 128.8 (C(5″,9″)), 128.4 (C(6″,8″)), and 130.6 (C(7″)). The O-bearing CH group at δ(H) 5.63 (H–C(6)) ^2J-correlated with C(7) (δ(C) 74.9), and ^3J-correlated with C(4) (δ(C) 123.4), C(8) (δ(C) 44.1), and C(17) (δ(C) 28.3), as well as with the AcO CO group (δ(C) 169.8), while H–C(9) (δ(H) 5.90) correlated with the cinnamoyl CO group (δ(C) 164.9), C(7), C(18) (δ(C) 17.6), and C(11) (δ(C) 101.0), thereby positioning an AcO at C(6) and a cinnamoyloxy at C(9). The NOESY correlations of **6** were similar to those of **3**, indicating the same relative configurations at C(6), C(7), C(8), and C(9). Thus, the structure **6** of a C_{19}-homolignan was unambiguously attributed to kadsuphilol U.

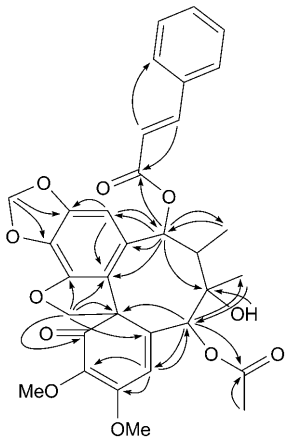


Fig. 3. *HMBCs of* **6**

Kadsuphilol V (**7**) possessed the same molecular formula $C_{33}H_{32}O_{11}$ as **6** (*m*/*z* 627.1844 in the HR-ESI-MS) implying a closely related structure. Comparison of the NMR data of **6** and **7** (*Tables 1* and *2*) unveiled a similar structure, having a CO group, an O-bearing CH_2 group at an sp^3 quaternary angular fusion atom, two MeO groups and an OCH_2O moiety, along with a cyclooctene ring substituted with a tertiary-alcohol, two Me, an AcO, and a cinnamoyloxy group. However, the CO resonance at δ(C) 195.4 of **6** was replaced by an upfield-shifted resonance at δ(C) 183.3 suggesting

the presence of an $\alpha,\beta,\alpha',\beta'$-dienone in **7** rather than of an $\alpha,\beta,\gamma,\delta$-dienone as in **6** [21]. This was associated by a relative downfield shift of C(1) (δ(C) 165.9, C(β) atom) and C(5) (δ(C) 149.5, C(β') atom) when compared with their counterparts in **6** (δ(C) 155.3 and 141.6). The O-bearing CH_2 group of the dihydrofuran moiety at δ(H) 4.53 and 4.40 (each *d*, $J = 9.0$ Hz) did not show HMBCs with the CO group (δ(C) 183.3) but, instead, correlated with the C(β) atom (δ(C) 165.9, C(1)), C(β') atom (δ(C) 149.5, C(5)), C(14) (δ(C) 143.9), and C(15) (δ(C) 120.0). The structure of **7** was supported by the HMBCs H–C(6) (δ(H) 5.78)/C(4), C(5), C(7) (δ(C) 75.2), C(8) (δ(C) 44.5), C(17) (δ(C) 28.3), and the AcO CO group (δ(C) 169.6), and H–C(9) (δ(H) 5.77)/C(7), C(10), C(11), C(15), C(18), and the cinnamoyl CO group (δ(C) 165.7). Furthermore, the HMBCs of the OCH_2O and the two MeO H-atoms to C(12), C(13), C(1), and C(2), respectively, verified the position of these groups. The NOESY correlations of **7** were similar to those of **6** indicating similar relative configurations of the substituents at the cyclooctene ring. Therefore, kadsuphilol V was assigned the structure **7**.

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Experimental Part

General. Column chromatography (CC): Silica gel *60* (SiO_2; *Merck*) or *Sephadex LH-20* (*Amersham Pharmacia Biotech AB*, Sweden). Prep. TLC: precoated silica gel plates (*Merck*, *Kieselgel 60 F-254*, 1 mm). HPLC: *Hitachi-L-6250* intelligent pump, *Hitachi-L-4000 H* UV detector, *Lichrosorb-Si-60* column (7 μm; 250 mm × 10 mm), *Lichrosorb-RP-18* column (7 μm; 250 mm × 10 mm). Optical rotations: *Jasco-DIP-1000* polarimeter. IR and UV Spectra: *Hitachi-T-2001* and *Hitachi-U-3210* spectrophotometer, resp. ^{1}H and ^{13}C-NMR, COSY, HMQC, HMBC, and NOESY Data: *Bruker-FT-300* or *Varian-Unity-INOVA-500* FT-NMR spectrometers; Me_4Si as internal standard; chemical shifts δ in ppm and coupling constants *J* in Hz. MS: Low-resolution EI- and FAB-MS, *VG-Quattro-5022* mass spectrometer; HR-MS *Jeol-HX-110* mass spectrometer; in *m*/*z*.

Plant Material. The aerial parts of *K. philippinensis* were collected at Green Island, Taiwan, in November, 2002. A voucher sample (specimen code: TP 93-2) was deposited at the School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan.

*Extraction and Isolation.*The dry leaves and stems (8.5 kg) were extracted three times with acetone, and the combined extract was concentrated and then partitioned between AcOEt/H_2O 1:1. The resulting AcOEt extract (250 g) was subjected to CC (SiO_2, hexane/AcOEt 100:1 → 0:1): *Fractions 1–24*. *Fr. 19* (4.9 g) was fractionated by CC (*Sephadex LH-20*, MeOH): *Frs. L_1–L_5*. *Fr. L_2* (3.1 g) was separated by flash column chromatography (SiO_2, hexane/AcOEt 20:1 → 0:1): *Frs. L_2-1–L_2-8*. *Fr. L_2-4* (200 mg) was subjected to CC (SiO_2, hexane/acetone 7:1 → 1:1): *Frs. L_2-4-a–L_2-4-d*. *Fr. L_2-4-b* was repeatedly subjected to normal-phase HPLC (hexane/CH_2Cl_2/MeOH 44:6:1): benzoylbinankadsurin A (35 mg), **3** (7.3 mg), and **5** (6 mg). *Fr. L_2-4-c* was fractionated by normal-phase HPLC (hexane/CH_2Cl_2/MeOH 20:6:1) followed by reversed-phase HPLC (MeOH/H_2O 7:3): **2** (7 mg) and **4** (11 mg). *Fr. L_2-5* was fractionated by CC (SiO_2, hexane/AcOEt 20:1 → 1:3): *Frs. L_2-5-a–L_2-5-c*. *Fr. L_2-5-a* was subjected to CC (*Sephadex LH-20*) followed by repeated separation by normal-phase prep. TLC (hexane/CH_2Cl_2/MeOH 20:6:1): **1** (38 mg) and a mixture that was further purified by reversed-phase HPLC (MeOH/H_2O 7:3): **6** (9.3 mg) and **7** (6 mg).

Kadsuphilol P (= rel-*(5*R,*6*S,*7*R,*8*R,*13a*S*)-5,6,7,8-Tetrahydro-2,3,13-trimethoxy-6,7-dimethylbenzo[3,4]cycloocta[1,2-f][1,3]benzodioxole-1,5,8-triol 8-Acetate 5-Benzoate*; **1**): Yellowish amorphous powder. $[\alpha]_D^{25} = -21$ (*c* = 0.1, MeOH). CD (*c* = 0.1, MeOH): 234 (+19.1), 254 (−18.2). UV (MeOH): 225 (3.64), 259 (3.40), 284 (3.18). IR (CH_2Cl_2): 3436 (OH), 3058, 2939, 1721 (ester), 1611, 1530 (arom.),

713. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. FAB-MS: 564 (M^+). EI-MS (70 eV): 564 (M^+), 505 ([M – AcO]$^+$), 443 ([M – BzO]$^+$). HR-ESI-MS: 587.1891 ([M + Na]$^+$, $C_{31}H_{32}NaO_{10}^+$; calc. 587.1893).

Kadsuphilol Q (= rel-*(5*R*,6*S*,7*R*,8*R*,12a*S*)-5,6,7,8-Tetrahydro-2,3,10,11,12-pentamethoxy-6,7-dimethyldibenzo[*a,c*]cyclooctene-1,5,8-triol 8-Acetate 5-Benzoate*; **2**): Yellowish amorphous powder. $[\alpha]_D^{25} = -31$ ($c = 0.4$, MeOH). CD ($c = 0.1$, MeOH): 224 (+8.4), 245 (−6.7). UV (MeOH): 229 (3.88), 258 (3.51), 282 (3.27). IR (CH_2Cl_2): 3412 (OH), 3058, 2940, 1715 (ester), 1265, 1109, 739. ^{1}H-NMR (300 MHz, (D_5)pyridine): *Table 1*. ^{13}C-NMR (75 MHz, (D_5)pyridine): *Table 2*. FAB-MS: 580 (M^+). EI-MS (70 eV): 580 (M^+), 505 ([M – AcO]$^+$), 443 ([M – BzO]$^+$). HR-ESI-MS: 580.2313 ([M + Na]$^+$, $C_{32}H_{36}NaO_{10}^+$; calc. 580.2319).

Kadsuphilol R (= rel-*(5*R*,6*R*,7*R*,8*S*,13a*R*)-5,6,7,8-Tetrahydro-1,6-dihydroxy-2,3,13-trimethoxy-6,7-dimethylbenzo[3,4]cycloocta[1,2-f][1,3]benzodioxole-5,8-diyl Bis[(2*Z*)-2-methylbut-2-enoate]*; **3**): Yellowish amorphous powder. $[\alpha]_D^{25} = -75$ ($c = 0.6$, MeOH). CD ($c = 0.1$, MeOH): 224 (+17.3), 245 (−16.7). UV (MeOH): 227 (3.98), 249 (3.77), 293 (3.68). IR (CH_2Cl_2): 3563 (OH), 3051, 2939, 1715 (ester), 1618, 1264, 1143, 738. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. FAB-MS: 598 (M^+). EI-MS (70 eV): 598 (M^+), 399 ([M – 2 AngOH]$^+$). HR-ESI-MS: 598.2411 (M^+, $C_{32}H_{38}O_{11}^+$; calc. 598.2408).

Kadsuphilol S (= rel-*(5*R*,6*R*,7*R*,8*S*,13a*R*)-5,6,7,8-Tetrahydro-1,6-dihydroxy-2,3,13-trimethoxy-6,7-dimethyl-8-(1-oxopropoxybenzo[3,4]cycloocta[1,2-f][1,3]benzodioxol-5-yl (2*Z*)-2-Methylbut-2-enoate*; **4**): Yellowish amorphous powder. $[\alpha]_D^{25} = -61$ ($c = 0.9$, MeOH). CD ($c = 0.1$, MeOH): 224 (+15.4), 245 (−11.8). UV (MeOH): 252 (3.79), 291 (3.48). IR (CH_2Cl_2): 3426 (OH), 2940, 1720 (ester), 1615, 1230, 1143, 1045, 734. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. FAB-MS: 572 (M^+). EI-MS (70 eV): 572 (M^+). HR-ESI-MS: 572.2255 (M^+, $C_{30}H_{36}O_{11}^+$; calc. 572.2245).

Kadsuphilol T (= rel-*(5*R*,6*R*,7*R*,8*S*,13a*R*)-8-(Benzoyloxy)-5,6,7,8-tetrahydro-1,6-dihydroxy-2,3,13-trimethoxy-6,7-dimethylbenzo[3,4]cycloocta[1,2-f][1,3]benzodioxol-5-yl (2*Z*)-2-Methylbut-2-enoate*; **5**): Yellowish amorphous powder. $[\alpha]_D^{25} = -26$ ($c = 0.3$, MeOH). CD ($c = 0.1$, MeOH): 224 (+14.5), 245 (−12.9). UV (MeOH): 238 (3.83), 252 (3.71), 292 (3.48). IR (CH_2Cl_2): 3565 (OH), 2939, 1719 (ester), 1614, 1257, 1111, 1040, 972, 843, 731. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. FAB-MS: 620 (M^+). EI-MS (70 eV): 620 (M^+). HR-ESI-MS: 620.2253 (M^+, $C_{34}H_{36}O_{11}^+$; calc. 620.2259).

Kadsuphilol U (= rel-*(5*R*,6*R*,7*R*,8*S*,14a*R*)-5-(Acetyloxy)-5,6,7,8-tetrahydro-6-hydroxy-2,3-dimethoxy-6,7-dimethyl-1-oxo-1*H*,14*H*-10,12,13-trioxabenzo[1,8]cyclooct[1,2,3-*cd*]-as-indacen-8-yl (2*E*)-3-Phenylprop-2-enoate*; **6**): Yellowish amorphous powder. $[\alpha]_D^{25} = -48$ ($c = 0.2$, MeOH). CD ($c = 0.1$, MeOH): 224 (+10.4), 245 (−9.8). UV (MeOH): 223 (4.02), 285 (3.85), 335 (3.69). IR (CH_2Cl_2): 3568 (OH), 3095, 2943, 1729 (ester), 1642 (C=C), 1580, 1228, 1142, 1067, 735. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. FAB-MS: 605 ([M + H]$^+$). EI-MS (70 eV): 604 (M^+), 456 ([M – CinOH]$^+$). HR-ESI-MS: 627.1846 ([M + Na]$^+$, $C_{33}H_{32}NaO_{11}^+$; calc. 627.1842).

Kadsuphilol V (= rel-*(5*R*,6*R*,7*R*,8*S*,14a*R*)-5-(Acetyloxy)-5,6,7,8-tetrahydro-6-hydroxy-1,2-dimethoxy-6,7-dimethyl-3-oxo-3*H*,14*H*-10,12,13-trioxabenzo[1,8]cyclooct[1,2,3-*cd*]-as-indacen-8-yl (2*E*)-3-Phenylprop-2-enoate*; **7**): Yellowish amorphous powder. $[\alpha]_D^{25} = -31$ ($c = 0.1$, MeOH). CD ($c = 0.1$, MeOH): 224 (+11.2), 245 (−8.7). UV (MeOH): 225 (3.94), 288 (3.63), 297 (3.28). IR (CH_2Cl_2): 3470 (OH), 1735 (ester), 1712 (dienone), 1640 (C=C), 1595, 1240, 742. ^{1}H-NMR (500 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (125 MHz, $CDCl_3$): *Table 2*. FAB-MS: 605 ([M + H]$^+$). EI-MS (70 eV): 604 (M^+), 456 ([M – CinOH]$^+$). HR-ESI-MS: 627.1844 ([M + Na]$^+$, $C_{33}H_{32}NaO_{11}^+$; calc. 627.1842).

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