New Oxygenated Lignans from *Kadsura philippinensis*

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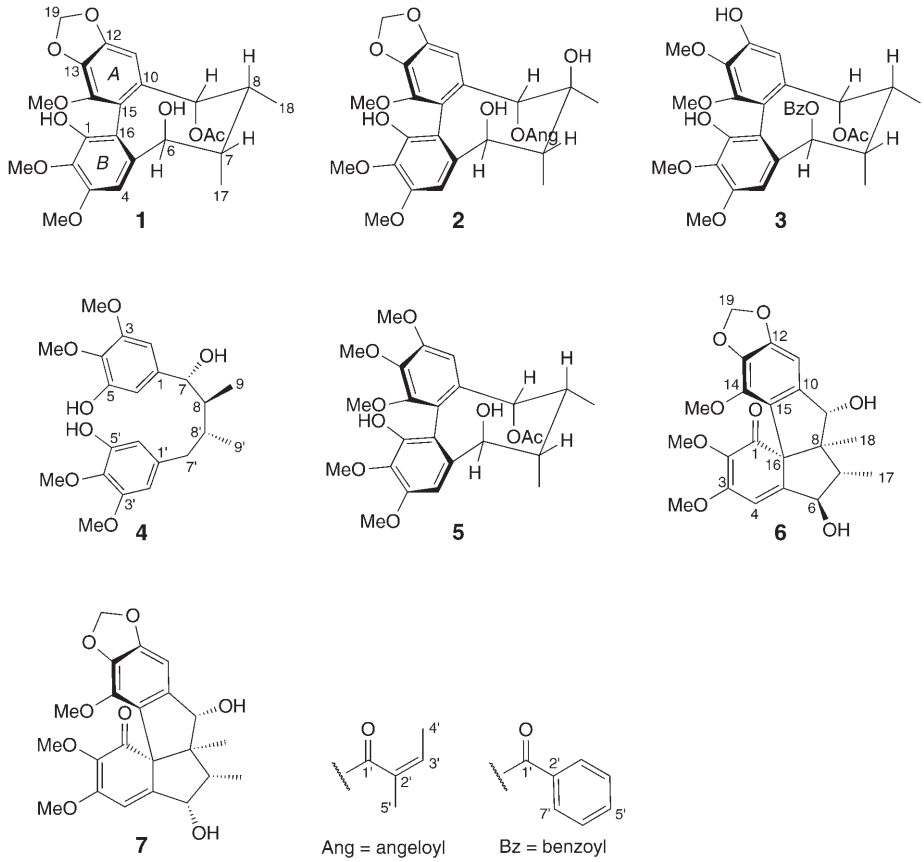
Seven new oxygenated lignans, kadsuphilins G–M (**1**–**7**, resp.), were isolated by chromatographic fractionation of an AcOEt extract of the aerial part of *Kadsura philippinensis* including four compounds with a dibenzocyclooctadiene skeleton, two with a bicyclooctane ring system, and one of 1,4-biphenyldimethylbutane type. The structures of the isolated compounds were elucidated through extensive spectroscopic analyses, particularly 2D-NMR experiments (HMQC, HMBC, and NOESY). The configuration of the chiral centers and the biphenyl moiety were determined by NOESY as well as CD spectroscopy, respectively.

Introduction. – Lignans constitute a large group of natural products derived from dimerization of two phenylpropanoid units at the central C-atoms of their side chains [1]. They possess numerous biological properties such as cancer protective [2], cytotoxic [3], antiviral [4], anti-HIV [5], hepatoprotective [6], antioxidative [7], antiulcerogenic [8], and antiplatelet aggregation [9] activities. Being a member of the family Schisandraceae and closely related to the genus *Schisandra* [10][11], the genus *Kadsura* is a rich source of lignans with common use in Chinese and Japanese traditional medicine for cure of various ailments [12][13]. It was deemed interesting to conduct a phytochemical investigation of the lignan content of the leaves and stems of *Kadsura philippinensis* ELMER (Schisandraceae) [14][15] that resulted in the isolation of seven new oxygenated lignans, kadsuphilins G–M (**1**–**7**). Four of the isolated lignans possess a dibenzocyclooctadiene skeleton (**1**–**3**, and **5**), two a bicyclooctane ring system (**6** and **7**), and one is a 1,4-biphenyldimethylbutane derivative (**4**). The structures of these compounds were elucidated through extensive spectroscopic analyses, particularly 2D-NMR experiments (HMQC, HMBC and NOESY). The configuration of the chiral centers and the biphenyl moiety were determined by NOESY as well as CD spectroscopy, respectively.

Results and Discussion. – *Structure Elucidation*. Compound **1** was obtained as a yellowish powder and possessed a molecular formula $C_{24}H_{28}O_9$, as revealed from its HR-ESI-MS (*m*/*z* 483.1631, $[M + Na]^+$), and NMR spectral data (*Tables 1* and *2*). The

UV spectrum with absorption maxima at λ_{max} 222, 257, and 288 nm [16][17], and the IR spectrum with absorption bands at 3520 (OH), 1732 (ester), 1614 and 1500 (aromatic nucleus), and 732 cm^{-1} (substituted benzene) [18][19] suggested that **1** was a C_{18} dibenzocyclooctadiene lignan with a OH group and ester substitution. In the NMR spectrum, ^1H and ^{13}C chemical shift assignments were guided by DEPT, HMQC, COSY as well as HMBC experiments.

The ^1H-NMR spectrum of **1** (*Table 1*) showed two aromatic *singlets* of a biphenyl moiety at 6.38 and 6.49 ppm (H–C(4)[1]) and H–C(11)), three *singlets* of MeO groups at 3.92 (6 H) and 3.91 ppm (3 H), in addition to two signals at 5.98 and 6.00 ppm, diagnostic of a OCH_2O group. The cyclooctadiene ring was manifested in two secondary Me *doublets* at 0.98 and 0.99 ppm, two CH groups at 1.90–1.94 and 2.19–2.24 ppm, and two benzylic O–CH groups at 4.44 and 5.64 ppm. In the COSY spectrum (*Fig. 1*), the CH group at δ 1.90–1.94 ppm (H–C(7)) was correlated to the Me group at 0.98 ppm (Me(17)), and the two CH groups at 4.44 (H–C(6)) and 2.19–



[1]) Arbitrary numbering, see also *Formulae*. For systematic names, see *Exper. Part*.

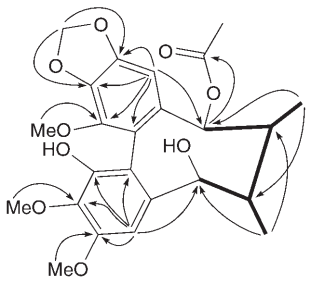


Fig. 1. *HMBC* (arrow) *and* $^1H,^1H$*-COSY* (bold line) *correlations of* **1**

2.24 ppm (H–C(8)), and the latter was correlated to the Me at 0.99 ppm (Me(18)) and the CH group at 5.64 ppm (H–C(9)). It was assumed that the CH group at 4.44 ppm (H–C(6)) was attached to a OH group, while the more low field-shifted CH group at 5.64 ppm (H–C(9)) was attached to an ester moiety. An Ac group was observed at δ(H) 1.54 ppm, and its presence was supported by the fragment ions at *m*/*z* 60 ([MeCOOH]$^+$) and 400 ([*M* – AcOH]$^+$) in the EI-MS spectrum.

The ^{13}C-NMR spectrum (*Table 2*) revealed ten quaternary aromatic signals, two aromatic upfield CH groups at 106.5 and 102.9 ppm, apparently adjacent to two oxygenated carbons. The OCH_2O group appeared at 101.3 ppm, whereas the three MeO groups resonated at 60.8, 55.8 and 59.7 ppm. The positions of the three MeO groups, the OCH_2O group, the OH group, and the AcO group were determined after comparison of the NMR data with those of closely related compounds [19–22], as well as a meticulous inspection of the HMBC spectrum (*Fig. 1*). The aromatic H-atom at 6.38 ppm, assigned to H–C(4)[1]), showed HMBC correlations to C(3), C(2), C(16), C(1), and C(6), whereas the aromatic H-atom at 6.49 ppm, assigned to H–C(11), had correlations with C(12), C(13), C(15), C(14), and C(9). The OCH_2O H-atoms were correlated to C(12) and C(13), while the three MeO *singlets* at 3.92 and 3.91 ppm were correlated with C(2), C(14), and C(3), respectively. In the cyclooctadiene ring, the Me *doublet* at 0.98 ppm (Me(17)) showed correlations with the OH-bearing C-atom at 81.4 ppm (C(6)) and the CH group at 39.2 ppm (C(8)), and the other Me *doublet* at 0.99 ppm (Me(18)) was correlated with the CH group at 41.2 ppm (C(7)), as well as with the acylated CH group at 79.9 ppm (C(9)), indicating the attachment of the OH group to C(6) and the AcO group to C(9). This was further evidenced by the correlation between H–C(9) and the acetate CO group at 170.0 ppm. From these data, it was concluded that **1** is a dibenzocyclooctadiene lignan with OH substituents at C(1) and C(6), MeO substituents at C(2), C(3), and C(14), an OCH_2O group at C(12)/C(13) and an AcO group at C(9). The CD curve of **1** showed a positive *Cotton* effect at 234 nm and a negative *Cotton* effect at 254 nm favoring the (a*S*)-biphenyl configuration [14]. The relative configuration of **1** was determined through inspection of a molecular model as well as the NOESY spectrum (*Fig. 2*) which revealed correlations between H–C(4) and H–C(6) and H–C(17), and between H–C(6) and Me(17), indicating the α-configuration of H_{eq}–C(6) and Me(17_{ax}). The NOE interaction between H_{eq}–C(9) and H–C(11) and H_{ax}–C(8) indicated the β-orientation of H–C(8) and H–C(9) [22][23]. Based on the fore-mentioned discussion, the name *kadsuphilin G* was assigned to compound **1**.

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

Position[1])	**1**	**2**	**3**	**4**	**5**	**6**	**7**
H–C(2)	–	–	–	6.49 (*d*, *J* = 1.5)	–	–	–
H–C(4)	6.38 (*s*)	6.26 (*s*)	6.58 (*s*)	–	6.37 (*s*)	6.54 (*d*, *J* = 1.0)	6.62 (*d*, *J* = 1.0)
H–C(6)	4.44 (br. *s*)	4.91 (*d*, *J* = 7.0)	6.06 (*d*, *J* = 7.2)	6.57 (*d*, *J* = 1.5)	4.51 (br. *d*, *J* = 7.0)	4.16 (*d*, *J* = 7.0)	4.59 (*d*, *J* = 9.3)
H–C(7)	1.90–1.94 (*m*)	2.41 (*dq*, *J* = 7.0)	2.27–2.33 (*m*)	4.38 (*d*, *J* = 9.6)	2.21–2.26 (*m*)	1.80 (*dq*, *J* = 7.0)	2.10–2.16 (*m*)
H–C(8)	2.19–2.24 (*m*)	–	2.38–2.43 (*m*)	1.70–1.83 (*m*)	1.94–1.98 (*m*)	–	–
H–C(9)	5.64 (*d*, *J* = 5.5)	5.58 (*s*)	5.71 (*t*, *J* = 1.9)	0.65 (*d*, *J* = 6.9)	5.70 (br. *s*)	4.42 (*d*, *J* = 12.0)	4.40 (*d*, *J* = 11.9)
H–C(11)	6.49 (*s*)	6.73 (*s*)	6.76 (*s*)		6.56 (*s*)	6.75 (*s*)	6.72 (*s*)
Me(17)	0.98 (*d*, *J* = 7.5)	0.97 (*d*, *J* = 8.0)	0.96 (*d*, *J* = 7.2)		1.03 (*d*, *J* = 7.4)	1.09 (*d*, *J* = 7.0)	0.98 (*d*, *J* = 7.5)
Me(18)	0.99 (*d*, *J* = 7.5)	1.33 (*s*)	1.08 (*d*, *J* = 7.2)		0.97 (*d*, *J* = 7.1)	0.86 (*s*)	0.88 (*s*)
CH_2(19)	5.98 (*d*, *J* = 1.5), 6.00 (*d*, *J* = 1.5)	5.97 (*d*, *J* = 1.5), 6.01 (*d*, *J* = 1.5)				5.93 (*d*, *J* = 1.5), 5.91 (*d*, *J* = 1.5)	5.92, 5.89 (2*s*)
H–C(2′)				6.33 (*d*, *J* = 1.5)			
H–C(3′)		5.90 (*q*, *J* = 7.0)	7.45 (*d*, *J* = 7.5)				
H–C(4′)		1.90 (*dd*, *J* = 7.0, 1.5)	7.28 (*t*, *J* = 7.5)				
H–C(5′)		1.28 (*d*, *J* = 1.5)	7.41–7.45 (*m*)				
H–C(6′)				6.48 (*d*, *J* = 1.5)			
H_α–C(7′)				2.11 (*dd*, *J* = 12.9, 10.5)			
H_β–C(7′)				2.84 (*dd*, *J* = 12.9, 3.6)			
H–C(8′)				2.32–2.37 (*m*)			
H–C(9′)				0.89 (*d*, *J* = 7.0)			
2-MeO	3.92 (*s*)	3.89 (*s*)	3.91 (*s*)		3.93 (*s*)	3.68 (*s*)	3.68 (*s*)
3-MeO	3.91 (*s*)	3.87 (*s*)	3.93 (*s*)	3.87 (*s*)	3.91 (*s*)	4.10 (*s*)	4.11 (*s*)
4-MeO				3.87 (*s*)			
12-MeO					3.90 (*s*)		
13-MeO			3.33 (*s*)		3.89 (*s*)		
14-MeO	3.92 (*s*)	3.89 (*s*)	3.56 (*s*)		3.78 (*s*)	3.84 (*s*)	3.82 (*s*)
3′-MeO				3.89 (*s*)			
4′-MeO				3.85 (*s*)			
MeCO	1.54 (*s*)		1.59 (*s*)		1.56 (*s*)		
1-OH	5.66 (*s*)	5.55 (*s*)	5.73 (*s*)		5.66 (*s*)		
9-OH						4.85 (*d*, *J* = 12.0)	4.82 (*d*, *J* = 11.9)

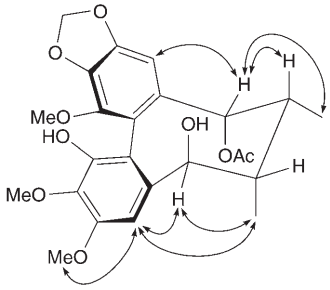


Fig. 2. *Key NOESY correlations of compound* **1**

The molecular formula of **2** was assigned $C_{27}H_{32}O_{10}$ as deduced from its HR-ESI-MS and in accordance with its NMR data. The UV and IR spectra of **2** suggested a dibenzocyclooctadiene lignan as in case of **1**. The ^{1}H-NMR spectrum (*Table 1*) showed two aromatic *singlets* (6.26 and 6.73 ppm, H–C(4)[1]) and H–C(11)), an OCH_2O group (5.97 and 6.01 ppm), and three MeO *singlets* (3.87 (3 H) and 3.89 ppm (6 H)). The ^{13}C-NMR data (*Table 2*) revealed twelve aromatic signals including two upfield CH groups (106.0, C(4) and 107.5 ppm, C(11)) in addition to OCH_2O (101.3 ppm) and three MeO groups (60.4, 55.9 and 59.7 ppm). The previous data were almost identical to the corresponding values in **1**, suggesting the same substitution pattern in the biphenyl ring. The cyclooctadiene ring was evident by two O–CH groups at 4.91 (*d*, $J=7$) and 5.58 ppm (*s*), two Me groups, a *doublet* at 0.97 ppm and a *singlet* at 1.33 ppm, suggesting a tri-substituted ring. The ^{13}C-NMR data showed signals for a quaternary C-atom (74.8 ppm), three CH (82.8, 47.2, 85.1 ppm) and two Me groups (15.5, 29.5 ppm). An angeloyl ester was evident from the ^{13}C-NMR quaternary C-atom signals (166.0, 126.7 ppm), one olefinic CH (140.0 ppm), and two Me groups (15.7 and 20.4 ppm), as well as the ^{1}H-NMR CH signal at 5.90 (*q*, $J=7.0$ Hz, H–C(3′)), and two Me (1.90 (*dd*, $J=7.0$, 1.5 Hz), 1.28 (*d*, $J=1.5$ Hz, H–C(5′))) [18][20]. The O–CH H-atom at 5.58 ppm revealed HMBC correlations to the CO group at 166.0 ppm and to the two CH groups at 107.5 (C(11)) and 47.2 ppm (C(7)), locating the angeloyloxy group at C(9). The other O–CH H-atom resonating at 4.91 ppm, H–C(6), was ^3J-correlated to the ^{13}C signals at 106.0 (C(4)), 15.5 (C(17)), and the oxygenated quaternary C-atom at 74.8 ppm (C(8)), verifying the attachment of a OH group to each of C(6) and C(8). In addition, the Me group at 0.97 ppm (Me(17)) had correlations with C(6) and C(8), while the Me group at 1.33 ppm (Me(18)) was correlated to the C-atom signals at 47.2 (C(7)) and 85.1 ppm (C(9)). The HMBC correlations in the aromatic moiety were similar to those observed in **1** (*Fig. 1*), confirming a similar substitution pattern. The NOESY spectrum (*Fig. 3*) exhibited correlations between H–C(4) and H–C(6) and Me(17), H–C(17) and H–C(6) and Me(18), and H–C(9) and H–C(11) in good agreement with the α-orientation of H–C(6), Me(17), and Me(18) and β-orientation of H–C(9) and OH–C(8). The CD spectrum of **2** revealed a positive *Cotton* effect at 221 nm and a negative one at 245 nm indicating the (a*S*)-biphenyl configuration. Structure **2** was established as *Kadsuphilin H*.

The molecular formula of **3** was found to be $C_{31}H_{34}O_{10}$ from its HR-ESI-MS and NMR data. The UV and IR spectra of **3** suggested a dibenzocyclooctadiene lignan as in

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

Position[1])	**1**	**2**	**3**	**4**	**5**	**6**	**7**
C(1)	147.7 (*s*)	147.6 (*s*)	147.3 (*s*)	140.2 (*s*)	147.3 (*s*)	196.9 (*s*)	197.1 (*s*)
C(2)	134.4 (*s*)	134.6 (*s*)	135.0 (*s*)	122.4 (*d*)	134.6 (*s*)	136.8 (*s*)	139.8 (*s*)
C(3)	150.7 (*s*)	150.3 (*s*)	150.4 (*s*)	152.4 (*s*)	150.6 (*s*)	162.0 (*s*)	162.5 (*s*)
C(4)	106.5 (*d*)	106.0 (*d*)	107.1 (*d*)	134.9 (*s*)	106.5 (*d*)	117.0 (*d*)	113.6 (*d*)
C(5)	135.6 (*s*)	133.7 (*s*)	131.2 (*s*)	149.1 (*s*)	135.2 (*s*)	155.4 (*s*)	160.1 (*s*)
C(6)	81.4 (*d*)	82.8 (*d*)	81.3 (*d*)	106.7 (*d*)	80.1 (*d*)	79.2 (*d*)	72.7 (*d*)
C(7)	41.2 (*d*)	47.2 (*d*)	39.5 (*d*)	77.3 (*d*)	41.4 (*d*)	49.5 (*d*)	44.5 (*d*)
C(8)	39.2 (*d*)	74.8 (*s*)	37.9 (*d*)	44.9 (*d*)	38.2 (*d*)	58.6 (*s*)	61.7 (*s*)
C(9)	79.9 (*d*)	85.1 (*d*)	81.3 (*d*)	11.4 (*q*)	81.4 (*d*)	79.9 (*d*)	80.4 (*d*)
C(10)	134.1 (*s*)	132.7 (*s*)	136.3 (*s*)		135.4 (*s*)	134.7 (*s*)	136.4 (*s*)
C(11)	102.9 (*d*)	107.5 (*d*)	110.2 (*d*)		107.0 (*d*)	102.4 (*d*)	101.9 (*d*)
C(12)	149.3 (*s*)	148.2 (*s*)	149.3 (*s*)		153.5 (*s*)	150.5 (*s*)	150.5 (*s*)
C(13)	136.3 (*s*)	136.4 (*s*)	139.0 (*s*)		141.5 (*s*)	136.6 (*s*)	136.5 (*s*)
C(14)	141.7 (*s*)	142.1 (*s*)	150.4 (*s*)		152.1 (*s*)	141.6 (*s*)	141.9 (*s*)
C(15)	118.6 (*s*)	119.5 (*s*)	119.5 (*s*)		119.3 (*s*)	128.1 (*s*)	128.4 (*s*)
C(16)	115.4 (*s*)	115.3 (*s*)	116.5 (*s*)		115.2 (*s*)	73.3 (*s*)	77.3 (*s*)
C(17)	17.5 (*q*)	15.5 (*q*)	14.5 (*q*)		14.2 (*q*)	13.6 (*q*)	9.4 (*q*)
C(18)	21.0 (*q*)	29.5 (*q*)	17.4 (*q*)		17.0 (*q*)	11.1 (*q*)	11.9 (*q*)
C(19)	101.3 (*t*)	101.3 (*t*)				101.5 (*t*)	101.5 (*t*)
C(1′)		166.0 (*s*)	165.3 (*s*)	138.6 (*s*)			
C(2′)		126.7 (*s*)	129.9 (*s*)	105.0 (*d*)			
C(3′)		140.0 (*d*)	129.4 (*d*)	152.1 (*s*)			
C(4′)		15.7 (*q*)	128.1 (*d*)	133.5 (*s*)			
C(5′)		20.4 (*q*)	133.0 (*d*)	148.9 (*s*)			
C(6′)			128.1 (*d*)	108.7 (*d*)			
C(7′)			129.4 (*d*)	37.6 (*t*)			
C(8′)				34.8 (*d*)			
C(9′)				17.9 (*q*)			
2-MeO	60.8 (*q*)	60.4 (*q*)	60.9 (*q*)		60.9 (*q*)	60.0 (*q*)	60.2 (*q*)
3-MeO	55.8 (*q*)	55.9 (*q*)	55.9 (*q*)	55.9 (*q*)	55.9 (*q*)	58.0 (*q*)	58.0 (*q*)
4-MeO				61.0 (*q*)			
12-MeO					55.9 (*q*)		
13-MeO			60.3 (*q*)		60.8 (*q*)		
14-MeO	59.7 (*q*)	59.7 (*q*)	60.0 (*q*)		61.0 (*q*)	59.6 (*q*)	59.6 (*q*)
3′-MeO				55.8 (*q*)			
4′-MeO				61.0 (*q*)			
Ac	170.0 (*s*), 20.2 (*q*)		170.1 (*s*), 20.5 (*q*)		170.2 (*s*), 20.3 (*q*)		

[a]) Assignments were made by HMQC and HMBC experiments.

case of **1**. The ^{1}H-NMR spectrum (*Table 1*) showed two aromatic *singlets* at 6.58 and 6.76 ppm (H–C(4)[1]), H–C(11)), and four MeO *singlets* (3.91, 3.93, 3.33, and 3.56 ppm). Two O–CH H-atom signals were observed at 6.06 (*d*, $J = 7.2$ Hz) and 5.71 ppm (*t*, $J = 1.9$ Hz) in addition to two CH group *multiplets* at 2.27–2.33 and 2.38–2.43 ppm, two secondary Me *doublets* at 0.96 and 1.08 ppm suggesting substitution at C(6) and C(9) with an ester group. The ^{13}C-NMR data (*Table 2*) displayed 10

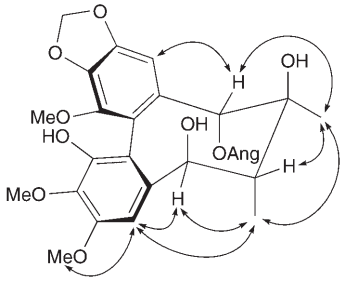


Fig. 3. *Key NOESY correlations of compound* **2**

quaternary aromatic signals in addition to two upfield CH groups at 107.1 (C(4)) and 110.2 ppm (C(11)), along with four MeO signals at 60.9, 60.3, 60.0, and 55.9 ppm. The Me *singlet* at 1.59 ppm (δ(C) 20.5 ppm) and a CO group at 170.1 ppm were attributed to an AcO moiety, while the aromatic H-atom signals at 7.45, 7.28 and 7.41–7.45 ppm (δ(C) 165.3, 129.9, 129.4, 128.1, and 133.0 ppm) were assignable to a benzoyl group. The CH signal at 81.3 ppm was correlated in the HMQC spectrum to two H-atoms at 6.06 and 5.71 ppm [21], whereas the latter H-atom had ^3J correlations to C(11), C(7), C(15), and the acetate CO group at 170.1 ppm, leading to the assignment of the signal at 5.71 ppm to H–C(9), to which an AcO group was attached. On the other hand, the H-atom at 6.06 ppm was assigned to H–C(6), based on its HMBC correlations to C(4), C(5), C(8), C(16), and the benzoyl CO group at 165.3 ppm, locating the benzoyloxy substituent at the C(6) position. The proposed cyclooctadiene substitution was further supported by the correlations between Me(17) and C(6), and Me(18) and C(7), and the COSY correlations between H–C(8) and H–C(9) and Me(18), and of H–C(7) with H–C(6) and Me(17). The substitution pattern in the biphenyl ring was determined as a result of HMBC correlations between H–C(11) and C(10), C(12), C(13), and C(15), and between H–C(4) and C(5), C(3), C(2), and C(16), in addition to the correlations of the OH signal at 5.73 ppm with the signals of C(1) and C(16). In addition, the MeO groups at 3.91, 3.93, 3.33, and 3.56 ppm were correlated with C(2), C(3), C(13), and C(14), respectively. The relative configuration was determined by the aid of NOESY correlations between H–C(4) and H–C(6) and Me(17), and of H–C(17) with Me(18), along with the correlations between H–C(9) and H–C(11) and H–C(8), reflecting the α-orientation of H–C(6), Me(17), Me(18), and the AcO group, as well as the β-orientation of H–C(8), H–C(9), and the benzoyloxy group at C(6). The CD spectrum proved the (a*S*)-biphenyl configuration due to a positive *Cotton* effect at 224 nm and a negative *Cotton* effect at 245 nm. Accordingly, **3** was identified as *Kadsuphilin I*.

The molecular formula of **4** was calculated as $C_{22}H_{30}O_7$ from its HR-ESI-MS at *m*/*z* 429.1891 ($[M+Na]^+$). Although **4** gave a green coloration with $FeCl_3$ like the previously discussed lignans, yet its UV data were somewhat different (215, 274 nm). The molecular formula was in agreement with eight degrees of unsaturation that can be accounted for by just two benzene rings, implying the absence of any other rings. The ^{13}C-NMR of **4** (*Table 2*) displayed 8 quaternary aromatic C-atom signals, as well as four aromatic CH signals in two rings, in addition to two secondary Me groups, one

methylene and three aliphatic CH groups, indicating a lignan with a biphenyldimethylbutane skeleton. Unlike the other discussed lignans, the ^{1}H-NMR spectrum of **4** (*Table 1*) revealed four upfield aromatic H-atom signals at 6.49, 6.57, 6.33 and 6.48 ppm, implying their proximity to phenolic C-atoms. Four MeO substituents were detected, two at 3.87 ppm (6 H) with ^3J correlations to the signals at 152.4 and 134.9 ppm, attributed to C(3)[1]) and C(4), respectively, and two MeO groups at 3.89 and 3.85 ppm, correlated to the signals at 152.1 and 133.5 ppm, assigned to C(3′) and C(4′). Each of C(4) and C(4′) should be flanked by two other phenolic C-atoms to account for their relative upfield shift, suggesting OH substitution at C(5) and C(5′).

The O–CH H-atom at 4.38 ppm was correlated to an O–CH C-atom at 77.3 ppm in the HMQC spectrum, and ^3J correlated to the C-atom signals at 122.4 (C(2)), 106.7 (C(6)) and 34.8 ppm (C(8′)), confirming the location of the OH at C(7), and that the aromatic CH groups (C(2) and C(6)) were *ortho* to the dimethylbutyl moiety linkage. In addition, the HMBC spectrum also showed correlations between the Me group at 0.65 ppm (Me(9)) and C-atoms at 77.3 (C(7)) and 34.8 ppm (C(8′)), while the Me group at 0.89 ppm (Me(9′)) was correlated to the CH signal at 44.9 (C(8)) and the CH_2 signal at 37.6 ppm (C(7′)). Furthermore, H–C(2) showed ^3J correlations with C(4), C(6), and C(7), H–C(6) with C(2), C(4), and C(7), and similarly H–C(2′) with C(4′), C(6′), and C(7′), and H–C(6′) with C(2′), C(4′), and C(7′) confirmed the proposed lignan structure. The NOESY correlations between H–C(7) and H–C(2), H–C(6), and Me(9), Me(9) and H–C(7), H–C(8) and Me(9′), H_α–C(7′) and H–C(2′), H–C(6′), and H–C(8), were in accordance with the β-orientation of H–C(7) and Me(9), and showed that the two secondary Me groups were *trans*-disposed with an α-orientation of Me(9′). A final confirmation was obtained by comparison of the NMR data of the dimethylbutyl moiety of **4** with the published values for a closely related synthetic hexamethoxy derivative [24]. Compound **4** was elucidated as *kadsuphilin J*. The absolute configuration of **4** remains to be established.

The EI-MS spectral data of **5** revealed a molecular ion peak M^+ at m/z 476, determining its molecular formula $C_{25}H_{32}O_9$. The UV, IR, and NMR (*Tables 1* and *2*) spectral data of **5** were closely related to **1**, disclosing a dibenzocyclooctadiene lignan having a OH and AcO substitution. Nevertheless, the substitution pattern of the phenyl ring *A* was different, lacking NMR signals of a OCH_2O group. The ^{1}H-NMR spectrum of **5** revealed five MeO signals, two at 3.93 and 3.91 ppm with ^3J correlations to 134.6 and 150.6 ppm, assigned to C(2)[1]) and C(3), respectively. The three other MeO signals at 3.90, 3.89 and 3.78 ppm were ^3J correlated with 153.5, 141.5, and 152.1 ppm, assigned to C(12), C(13), and C(14), respectively. The proposed substitution pattern of the biphenyl ring was supported by HMBC correlations between H–C(4) and C(2), C(3), and C(16), between H–C(11) and C(12), C(13), and C(15), and between OH–C(1) (5.66 ppm, D_2O-exchangeable) and C(1) and C(16). HMBC and NOESY correlations involving the cyclooctadiene ring were similar to those of **1**, proving the same substitution and/or configuration at C(6), C(7), C(8), and C(9). The CD curve of **5** showed a similar curse as that of **1** (positive *Cotton* effect at 217 nm, a negative one at 252 nm) indicating the (a*S*)-biphenyl configuration as **1**. Thus, **5** was identified as *Kadsuphilin K*.

The EI-MS analysis of **6** supported a molecular ion peak at m/z 416 corresponding to a molecular formula $C_{22}H_{24}O_8$, in agreement with NMR data. The IR spectrum

revealed the presence of OH (3420), a conjugated CO group (1660) and aromatic rings (1605). The UV spectrum displayed absorption maxima at 225 and 285, which suggested a $\alpha,\beta,\gamma,\delta$-dienone lignan [25]. The ^{1}H-NMR spectrum (*Table 1*) showed one aromatic H-atom *singlet* (6.75 ppm), one olefinic H-atom (6.54 ppm), as well as signals for two Me groups (1.09, 0.86 ppm, one secondary and one tertiary), two O–CH groups (4.16 and 4.42 ppm), and one CH group (1.80 ppm). Three MeO groups resonated at 3.68, 4.10, and 3.84 ppm, and a OCH_2O group was observed with signals at 5.91 and 5.93 ppm. The ^{13}C-NMR of **6** (*Table 2*) displayed six aromatic signals (134.7, 102.4, 150.5, 136.6, 141.6, 128.1 ppm), a CO group (196.9 ppm), an olefinic CH at 117.0 ppm and three olefinic quaternary C-atoms (136.8, 162.0, 155.4 ppm). Two O–CH groups (79.2 and 79.9 ppm), a CH group (49.5), two Me (13.6, 11.1 ppm), and a quaternary C-atom at (58.6 ppm) were also assigned to the cyclooctane ring. The CH_2 signal at 101.5 ppm was assigned to a OCH_2O group, while the three Me signals at 60.0, 58.0, and 59.6 ppm were ascribed to three MeO groups. The O–CH H-atom at 4.42 ppm was assigned to H–C(9)[1]), as it showed a COSY correlation with a OH H-atom at 4.85 ppm, and a NOESY correlation to the aromatic H-atom at 6.75 ppm (H–C(11)). The latter showed HMBC correlations with C(12), C(13), C(15), and C(9), the OCH_2O H-atoms with C(12) and C(13), while the MeO at 3.84 ppm was correlated with C(14), thus defining the substitution at the benzene ring *A*. The NOESY and COSY correlations between the second O–CH (4.16 ppm) and the olefinic H-atom at 6.54 ppm helped to assign these two signals to H–C(6) and H–C(4), respectively. The latter H-atom (H–C(4)) had a NOESY correlation to the MeO at 4.10 ppm (*Fig. 4*), which in turn was ^3J correlated to a C-atom at 162.0 ppm (C(3)). The relative downfield shift of the latter C-atom was due to its β-position in an $\alpha,\beta,\gamma,\delta$ dienone (ring *B*), which was supported by the HMBC correlation of H–C(4) with C(2) (136.8 ppm, α-position), C(6), and C(16). Similarly, the MeO group at 3.68 ppm was located at C(2) due to their ^3J correlation. These data were closely related to those of the previously discussed lignans, but with the probable presence of a cyclohexadienone instead of the phenyl ring *B*, having two MeO substituents at C(2) and C(3). The proposed structure of **6** was supported by COSY correlations between H–C(7) and H–C(6) and Me(17), as well as ^3J correlations between Me(18) and C(7), C(9), and C(16), between H–C(7) and C(5), C(9), and Me(18), between Me(17) and C(6) and C(8), and between H–C(6) and C(4), C(8), and C(16). The significant correlation between the tertiary Me group Me(18) and C(16) strongly suggested that the quaternary C(8) and C(16) were connected through a single bond, thus forming a bicyclooctane ring [25]. The two rings *A* and *B* contributed by 9 degrees of unsaturation to **6**, leaving two additional degrees, that could be fulfilled by the formation of a bicyclooctane ring, confirming the deduced skeleton. The relative stereochemistry of **6** was determined through inspection of a molecular model and its NOESY spectrum (*Fig. 4*) which revealed correlations between H–C(6) and H–C(4) and Me(17), between H–C(9) and H–C(7) and H–C(11), between Me(18) and Me(17) and OH–C(9). This proved the α-orientation of the two Me groups at C(7) and C(8), and OH–C(9), as well as the β-orientation of H–C(7) and H–C(9). The CD curve of **6** showed a positive *Cotton* effect at 232 and 379 nm, and a negative *Cotton* effect at 316 nm, indicating the same configuration as kadsulignan K [25]. Compound **6** was established as *Kadsuphilin L*.

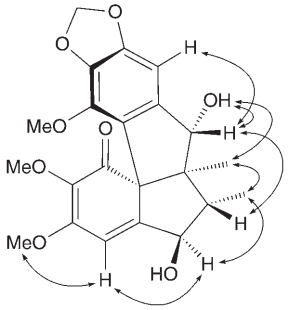


Fig. 4. *Key NOESY correlations of compound* **6**

The ^{13}C-NMR and EI-MS data of **7** disclosed a molecular formula $C_{22}H_{24}O_8$, the same as that of **6**. The UV, IR, ^{1}H-NMR, and ^{13}C-NMR data of the two compounds were closely similar. The ^{1}H- and ^{13}C-NMR data (*Tables 1* and *2*), as well as the COSY and HMBC spectra of **7** confirmed the presence of the same benzobicyclooctane ring with a dienone ring *B* and the same substitution pattern as in case of **6**. In comparison with **6**, the ^{1}H-NMR data of **7** (*Table 1*) revealed significant downfield shifts of H–C(6)[1]) (+0.43 ppm) and H–C(7) (+0.33 ppm), associated with an increase of the coupling constant *J*(6,7) from 7.0 to 9.3 Hz. The ^{13}C-NMR data (*Table 2*) were also closely similar to those of **6** except for the significant relative upfield chemical shifts of C(6) (–6.5 ppm), C(7) (–5.0) along with a relative downfield shift of C(5) (+4.7 ppm) and C(16) (+4.0 ppm). These results reflect a different configuration, most probably at C(6). The NOESY spectrum of **7** outlined correlations between H–C(6) and H–C(7), between H–C(9) and H–C(7) and H–C(11), and between Me(18) and Me(17) and OH–C(9). A NOESY correlation between H–C(6) and Me(17) was completely absent, indicating that **7** has the same configuration of **6** except a reversal of the configuration at C(6). The CD curves of **7** were similar to those of **6**, indicating the same configuration as **6**. Therefore, compound **7** was determined as *Kadsuphilin M*.

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Experimental Part

General. Silica gel *60* (*Merck*) was used for column chromatography (CC), and pre-coated silica gel plates (*Merck*, *Kieselgel 60 F-254*, 1 mm) were used for prep. TLC. *LiChrospher® Si 60* (5 μm, *250-10*, *Merck*) and *LiChrospher®* 100 *RP-18e* (5 μm, *250-10*, *Merck*) were used for NP-HPLC and RP-HPLC (*Hitachi, L-6250*, flow rate 2 ml/min, UV detection at 254 nm), resp. Optical rotation: *JASCO* model *DIP-1000* polarimeter. UV spectra: *Hitachi U-3210* spectrophotometer; λ_{max} in nm. CD spectra: *JASCO J-720* circular dichroism spectrophotometer. IR spectra: *Hitachi T-2001* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker FT-300* spectrometer, 300 and 75 MHz, resp., or *Varian Unity INOVA 500 FT-NMR* spectrometer, 500 and 125 MHz, resp.; δ in ppm, *J* in Hz. MS: *VG Quattro 5022* (EI) and *Bruker Daltonics ApexII* (ESI) mass spectrometers.

Plant Material. The aerial parts of *K. philippinensis* were collected at Green Island, Taiwan, in September, 2002. A voucher sample (specimen code: TP 93-1) was deposited in the School of Pharmacy, National Taiwan University, Taipei, Taiwan.

Extraction and Isolation. The dry leaves and stems (1.1 kg) were extracted three times with EtOH (5 l, r.t., 3 d each time) and the combined extract was evaporated in vacuum then partitioned between AcOEt/H_2O (1:1, each 500 ml). The resulting AcOEt extract (30 g) was subjected to a flash column on silica gel using hexane/AcOEt (gradient 100:1 to 0:1, each 500 ml), acetone (1 l) and finally MeOH (1 l) for elution to furnish 18 fractions. *Fr. 13* (eluted with hexane/AcOEt 1:1, 1.3 g) was purified on *Sephadex LH-20* using MeOH (2 l) for elution to produce five fractions (L_1–L_5). *Fr. L_3* (570 mg) was re-fractionated on a flash column using silica gel and a gradient of hexane/AcOEt/MeOH to produce 10 subfractions (*L_3-1* to *L_3-10*). *Subfr. L_3-8* (65 mg) was repeatedly subjected to NP-HPLC using hexane/CH_2Cl_2/MeOH 40:60:1 and then 45:55:1 to yield **1** (3 mg). *Subfr. L_3-9* (77 mg) was separated on prep. TLC using hexane/acetone 3:1 for development to yield a mixture (40 mg) that was further separated on NP-HPLC using hexane/AcOEt 4:3 followed by hexane/CH_2Cl_2/MeOH 40:60:1 to give **2** (2 mg) and **3** (2 mg). *Subfr. L_3-10* (66 mg) was separated on prep. TLC using hexane/acetone 2:1 followed by purification on RP-HPLC using MeOH/H_2O 3:2 to yield **4** (6 mg). Likewise, *Fr. 14* (eluted with hexane/AcOEt 1:2, 1.2 g) was purified on *Sephadex LH-20* using MeOH for elution to produce five fractions (F_1–F_5). *Fr. F_2* (145 mg) was subjected to NP-HPLC using hexane/AcOEt 1:2 for elution to yield **5** (3 mg). *Fr. F_4* (118 mg) was subjected to NP-HPLC using hexane/AcOEt 1:2 for elution to give a mixture that was separated on NP-PTLC using hexane/CH_2Cl_2/MeOH 3:3:1 for development to give **6** (1.8 mg) and **7** (1.5 mg).

Kadsuphilin G (=*(a*S*)-(5*R*,6*S*,7*R*,8*R*)-5,6,7,8-Tetrahydro-1,5-dihydroxy-2,3,13-trimethoxy-6,7-dimethylbenzo[3′,4′]cycloocta[1′,2′:4,5]benzo[1,2-*d*][1,3]dioxol-8-yl Acetate*; **1**). Amorphous yellowish powder. $[\alpha]_D^{25} = -10$ ($c = 0.8$, CH_2Cl_2). UV (MeOH): 222 (4.61), 257 (3.96), 288 (3.63). CD: λ_{ex} 234 nm (+19.2); λ_{ex} 254 nm (−18.9). IR: 3520 (OH), 1732 (ester), 1614, 1500, 1240, 732. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. EI-MS: 400 (6, $[M - AcOH]^+$), 60 (85, $[MeCOOH]^+$). HR-ESI-MS: 483.1631 ($[M + Na]^+$, $C_{24}H_{28}NaO_9$; calc. 483.1631).

Kadsuphilin H (=*(a*S*)-(5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-1,5,7-trihydroxy-2,3,13-trimethoxy-6,7-dimethylbenzo[3′,4′]cycloocta[1′,2′:4,5]benzo[1,2-*d*][1,3]dioxol-8-yl (2*E*)-2-Methylbut-2-enoate*; **2**). Amorphous colorless powder. $[\alpha]_D^{25} = -12$ ($c = 0.3$, CH_2Cl_2). UV (MeOH): 215 (4.31). CD: λ_{ex} 234 nm (+19.2); λ_{ex} 254 nm (−18.9). IR: 3565, 1721, 1645, 1582, 1451, 1258, 1027, 736, 713. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. HR-ESI-MS: 539.1892 ($[M + Na]^+$, $C_{27}H_{32}NaO_{10}$; calc. 539.1893).

Kadsuphilin I (=*(a*S*)-(5*R*,6*S*,7*R*,8*R*)-8-(Benzyloxy)-5,6,7,8-tetrahydro-3,12-dihydroxy-1,2,10,11-tetramethoxy-6,7-dimethyldibenzo[a,c]cycloocten-5-yl Acetate*; **3**). Amorphous colorless powder. $[\alpha]_D^{25} = -1.0$ ($c = 5.0$, CH_2Cl_2). UV (MeOH): 231 (4.63), 283 (3.91). CD: λ_{ex} 224 nm (+6.06); λ_{ex} 245 nm (−8.59). IR: 3562, 1718, 1645, 1455, 1227, 1135, 736. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. FAB-MS: 461 ($[M + H]^+$). HR-ESI-MS: 589.2048 ($[M + Na]^+$, $C_{31}H_{34}NaO_{10}$; calc. 589.2050).

Kadsuphilin J (=*5-[(1*R**,2*S**,3*R**)-1-Hydroxy-4-(3-hydroxy-4,5-dimethoxyphenyl)-2,3-dimethylbutyl]-2,3-dimethoxyphenol*; **4**). Amorphous colorless powder. $[\alpha]_D^{25} = -8.8$ ($c = 0.5$, CH_2Cl_2). UV (MeOH): 215 (4.44), 274 (3.52). CD: λ_{ex} 211 nm (+14.3); λ_{ex} 215 nm (−24.8). IR: 3444, 1715, 1614, 1463, 1263, 1108, 738, 713. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. HR-ESI-MS: 429.1891 ($[M + Na]^+$, $C_{22}H_{30}NaO_7$; calc. 429.1889).

Kadsuphilin K (=*(a*S*)-(5*R*,6*S*,7*R*,8*R*)-5,6,7,8-Tetrahydro-8,12-dihydroxy-1,2,3,10,11-pentamethoxy-6,7-dimethyldibenzo[a,c]cycloocten-5-yl Acetate*; **5**). Amorphous colorless powder. $[\alpha]_D^{25} = -19$ ($c = 0.1$, CH_2Cl_2). UV (MeOH): 228 (4.52), 256 (3.85), 287 (3.42). CD: λ_{ex} 217 nm (+7.4); λ_{ex} 252 nm (−4.3). IR: 3420 (OH), 3054, 2984, 1729, 1603, 1265, 1108, 896, 738. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. EI-MS (70 eV, rel. int.): 476 (8, M^+), 416 (9, $[M - AcOH]^+$), 385 (14, $[M - AcOH - OMe]^+$). HR-EI-MS: 476.2053 ($C_{25}H_{32}O_9$; calc. 476.2051).

Kadsuphilin L (=*(a*S*)-(5*R*,6*S*,6*a*S*,7*S*,12*b*S*)-5,6,6a,7-Tetrahydro-5,7-dihydroxy-2,3,12-trimethoxy-6,6a-dimethyl-1*H*-indeno[1′,7a′:2,3]indeno[5,6-*d*][1,3]dioxol-1-one*; **6**). Amorphous colorless powder. $[\alpha]_D^{25} = +17$ ($c = 0.1$, CH_2Cl_2). UV (MeOH): 225 (4.38), 285 (3.37). CD: λ_{ex} 232 nm (+13.6); λ_{ex} 316 nm (−6.1); λ_{ex} 379 nm (+2.7). IR: 3420 (OH), 3054, 2984, 1660, 1605, 895, 738. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. EI-MS (70 eV, rel. int.): 416 (3, M^+; $C_{22}H_{24}O_8$), 398 (2, $[M - H_2O]^+$).

Kadsuphilin M (=*(a*S*)-(5*S*,6*S*,6a*S*,7*S*,12b*S*)-5,6,6a,7-Tetrahydro-5,7-dihydroxy-2,3,12-trimethoxy-6,6a-dimethyl-1*H*-indeno[1′,7a′:2,3]indeno[5,6-*d*][1,3]dioxol-1-one*; **7**). Amorphous colorless powder. $[\alpha]_D^{25} = -15$ ($c = 0.1$, CH_2Cl_2). UV (MeOH): 231 (4.30), 287 (3.25). CD: λ_{ex} 230 nm (+9.4); λ_{ex} 306 nm (−3.9); λ_{ex} 378 nm (+2.3). IR: 3380 br (OH), 3054, 2984, 1658, 1603, 896,739. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. EI-MS (70 eV, rel. int.): 416 (7, M^+; $C_{22}H_{24}O_8$).

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