Kadsuphilols A−H, Oxygenated Lignans from *Kadsura philippinensis*

Ya-Ching Shen,*,† Yuan-Bin Cheng,‡ Ting-Wei Lan,§ Chia-Ching Liaw,‡ Shorong-Shii Liou,§ Yao-Haur Kuo,⊥ and Ashraf Taha Khalil†

School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan 100, Republic of China, Institute of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan 804, Republic of China, Department of Pharmacy, Tajen University, Yen-Pou, Ping Tung Shien, Taiwan, Republic of China, and National Research Institute of Chinese Medicine, Taipei, 112, Taiwan, Republic of China

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Eight new oxygenated lignans, kadsuphilols A−H (**1**−**8**), were isolated from the leaves and stems of *Kadsura philippinensis*. Four of the isolated lignans (**1**−**4**) possess the normal C_{18}-dibenzocyclooctadiene skeleton, while the other four lignans (**5**−**8**) are C_{19}-homolignans possessing a substituted cyclohexadienone ring with a *spiro*-benzofuranoid moiety. The structures of the isolated metabolites were elucidated through spectroscopic analyses, including 2D NMR experiments. Compounds **1** and **4** are the first report of an *R*-biphenyl configuration with a β-oxygenated substituent at the C-9 position. The in vitro radical-scavenging activities of these compounds using DPPH were tested and evaluated. Compound **3** exhibited more potent activity than vitamins C and E.

Cancer is associated in part with free radicals that accumulate in the human body, leading to the mutation of DNA. Many of natural antioxidants found in plants used in Traditional Chinese Medicine (TCM) have been shown to decrease the production of free radicals in the body. Thus, antioxidants such as lignans may be useful in preventing human cancers and other disease and are of interest for investigation. Plants from the Schisandraceae are used in TCM and have yielded numerous lignans that demonstrate desirable pharmacological effects, including antitumor,[1] cytotoxic,[2,3] antihepatitis,[4] anti-HIV,[5] hepatoprotective,[6] and antioxidant[7] activities. Plants of the genus *Kadsura* (Schisandraceae) are a rich source of lignans and are commonly used in oriental traditional medicine for their diverse healing properties.[8,9] The search for bioactive lignans with new skeletons prompted us to reinvestigate the lignan constituents of *Kadsura philippinensis* Elmer (Schisandraceae).[2,10,11] In this article, we report the results of a phytochemical study that led to the isolation of eight new oxygenated lignans, kadsuphilols A−H (**1**−**8**). Four of the isolated lignans (**1**−**4**) possess the normal C_{18}-dibenzocyclooctadiene skeleton, while compounds **5**−**8** are C_{19}-homolignans with a substituted cyclohexadienone ring and a *spiro*-benzofuranoid moiety.[12] The structures of **1**−**8** were determined through detailed spectroscopic analyses, involving 2D NMR experiments (^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, and ^{1}H−^{13}C HMBC). Their relative configurations were deduced from NOESY NMR spectra. The in vitro radical-scavenging activity of the new metabolites was tested and evaluated by reaction with 1,1-diphenyl-2-picryhydrazyl (DPPH) free radicals.

Results and Discussion

Compound **1** was assigned a molecular formula of $C_{22}H_{26}O_7$, according to its HREIMS (*m*/*z* 402.1676, $[M]^+$) and NMR spectroscopic data. The UV data, with absorption maxima at λ_{max} 216 and 254 nm, and its IR spectrum, with absorption bands at 3479 (OH) and 1613, 1503 cm^{-1}(aromatic moiety), suggested that **1** is a C_{18}-dibenzocyclooctadiene lignan with hydroxyl substitution.[8,9,13] The ^{1}H NMR spectrum of **1** (Table 1) exhibited two aromatic singlets for a biphenyl moiety (A and B) at δ 6.34 and 6.94 (H-4 and H-11), three singlets for methoxyl groups at δ 3.90 (6H) and 3.88, and two singlets characteristic of a methylenedioxy group. A cyclooctadiene ring was recognized by two secondary methyl doublets at δ 0.88 and 0.71 (H-17 and H-18), two methines at δ 2.01 and 1.98 (H-8 and H-7), a benzylic oxymethine at δ 4.50, and a methylene at δ 2.18 and 2.00 (H-6). This was confirmed by COSY NMR correlations between the methine at H-7 and H-6, H-17, and H-8 and between H-8 and H-18. The ^{13}C NMR spectrum (Table 2) revealed 10 quaternary aromatic signals, two aromatic upfield methines adjacent to two oxygenated carbons (δ_C 103.8 and 102.4), three methoxyl groups (δ_C 61.0, 59.8, and 55.7), and a methylenedioxy at δ_C 101.0.[13−16] The oxymethine carbon at δ_C 73.4 was ^3J-correlated with the aromatic singlet at δ_H 6.94 (H-11) as well as the methyl at δ_H 0.71 (H-18). In turn, the aromatic proton at δ 6.34, assigned to H-4, showed HMBC correlations to the quaternary carbons at δ_C 152.0 (C-3), 133.2 (C-2), 139.8 (C-5), and 114.1 (C-16) as well as a methylene carbon at δ_C 34.8. From the HMQC NMR data, the latter methylene carbon (δ_C 34.8) was directly attached to two protons at δ_H 2.18 and 2.00 that were ^3J-correlated to a methine at δ_C 42.4 (C-8) and quaternary at δ_C 114.1 (C-16), whereas the methyl proton at δ 0.88 (H-17) correlated with C-8 and the methylene at δ_C 34.8, confirming the assignment of the latter signal at C-6. The methylenedioxy protons (δ_H 5.99 and 5.97) correlated with the quaternary carbon signals at δ_C 135.4 and 148.5 (C-12 and C-13), while the three methoxyls could be located at C-2, C-3, and C-14, respectively, as a result of an HMBC NMR correlation of the each of the afore-mentioned carbons and the attached methoxyl singlet. A hydroxyl proton was observed at δ_H 5.80 and showed ^3J-correlations to signals at δ_C 133.2 (C-2) and 114.1 (C-16) as well as a ^2J-correlation to a resonance at δ_C 146.5 (C-1), confirming the substitution of OH at C-1. It was concluded that **1** is a dibenzocyclooctadiene lignan with hydroxyl substitution at C-1 and C-9 and methoxyl substitution at C-2, C-3, and C-14, as well as having a methylenedioxy group at C-12/C-13. The relative configuration of **1** was determined through inspection of a molecular model as well as the NOESY NMR spectrum (Figure 1), which revealed a chair form of the cyclooctadiene ring, with NOE correlations between H-4/H-6α, H-17 and H-18eq/H-17ax, indicating the α-configuration for H-17 and H-18. The absence of a NOE interaction between H-9eq/H-11 and H-18eq indicated the β-orientation of H-8 and α-disposition of H-9.[16] The CD spectrum of **1** exhibited a strong positive Cotton effect at λ_{max} 253 nm, indicating that **1** is in a *R*-biphenyl configuration with a β-hydroxy at the C-9 position rather than a *S*-biphenyl configuration with an α-hydroxy at the C-9 position as in binankadsurin A.[17,18] On the

* Author to whom correspondence should be addressed. Tel: 886-02-3123456, ext. 2226. Fax: 886-02-23919098. E-mail: ycshen@ntu.edu.tw.
† National Taiwan University.
‡ National Sun Yat-Sen University.
§ Tajen University.
⊥ National Research Institute of Chinese Medicine.

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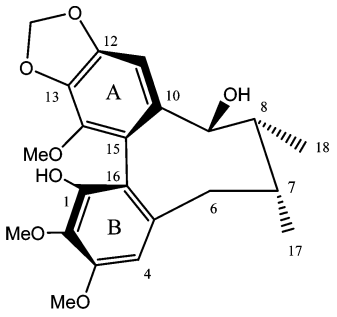

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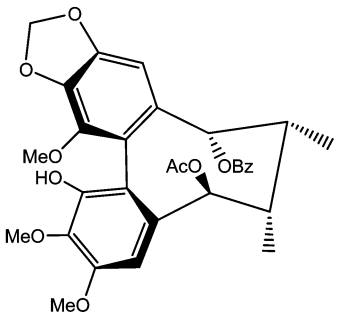

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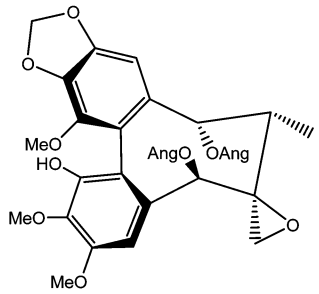

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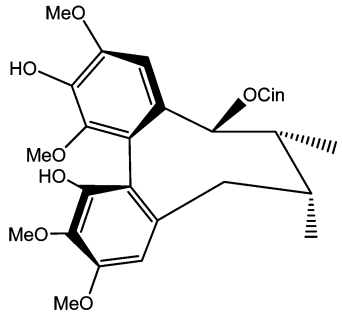

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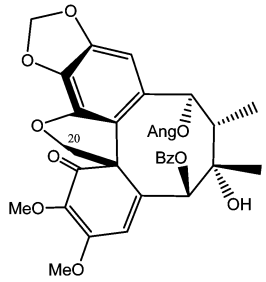

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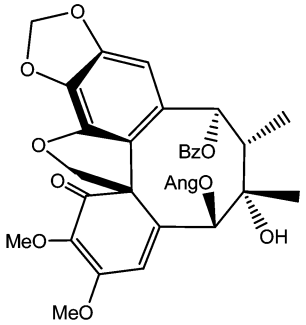

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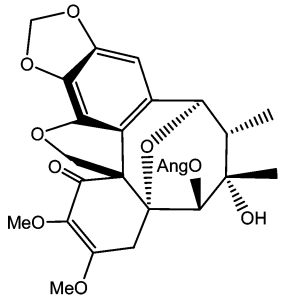

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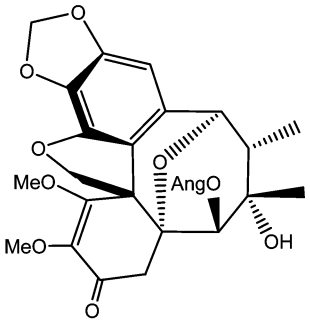

8

basis of these observations, structure **1** was established for kadsuphilol A.

The molecular formula of **2** was assigned as $C_{31}H_{32}O_{10}$, deduced from the HRMS (*m*/*z* 564.1993, $[M]^+$) and in accordance with its NMR data. The UV and IR spectra of **2** suggested the presence of a dibenzocyclooctadiene lignan as in the case of **1**. The ^1H and ^{13}C NMR signals assignable to the biphenyl ring (Tables 1 and 2) were almost identical to the corresponding values in **1**, indicating a similar substitution pattern. However, the signals attributable to the cyclooctadiene moiety were different. A benzoyl ester was evident from signals for a carbonyl at δ_C 165.7, a quaternary carbon at δ_C 129.8, and aromatic methines at δ_C 128.0, 129.4, and 132.6, in addition to aromatic protons at δ_H 7.44 (2H, d, J = 7.5 Hz) and 7.26 (3H, m). An acetate moiety was indicated by a methyl singlet at δ_H 1.81 (δ_C 20.9, 170.2). The aromatic singlet at δ_H 6.61 (H-11) was ^3J-correlated to the oxymethine at δ_C 81.0 (C-9), which was directly attached to the proton at δ_H 5.89 (H-9). The latter was ^3J-correlated to carbon signals at δ_C 38.0 (C-7), 102.9 (C-11), 120.2 (C-15), and 14.3 (C-18) as well as the benzoyl carbonyl at δ_C 165.7, confirming the attachment of a benzoyloxy group at C-9. The

Table 1. ^{1}H NMR Spectroscopic Data (300 MHz, $CDCl_3$) for Compounds **1**−**8**[a]

position[b]	1	2	3	4	5	6	7	8
4	6.34 s	6.62s	6.41 s	6.70 s	6.55 s	6.52 s	3.08 s (2H)	2.88 d (17.3) 3.12 d (17.3)
6	2.18 m 2.00 m	5.82 d (8.5)	5.27 s	2.39 m 2.06 m	5.92 s	5.79 s	5.26 s	5.24 s
7	1.98 m	2.18 m		2.06 m				
8	2.01 m	2.32 m	2.88 m	2.06 m	2.29 q (7.2)	2.23 q (7.2)	1.84 q (7.3)	1.76 q (7.3)
9	4.50 s	5.89 d (4.8)	5.62 s	4.58 s	5.71 s	5.84 s	4.73 s	4.76 s
11	6.94 s	6.61 s	6.60 s	7.02 s	6.56 s	6.49 s	6.16 s	6.15 s
17	0.88 d (6.9)	1.03 d (7.0)	2.88 m (2H)	1.06 d (6.6)	1.29 s	1.32	0.94 s	0.91 s
18	0.71 d (6.8)	1.12 d (7.4)	0.99 d (7.2)	0.71 d (6.6)	1.36 d (7.2)	1.29 d (7.2)	1.31 d (7.3)	1.29 d (7.3)
19	5.99 s 5.97 s	6.02 s 5.97 s	5.95 s 5.94 s		5.97 s 5.92 s	5.98 s 5.93 s	5.94 s 5.91 s	5.94 s 5.91 s
20					4.62 d (9.0) 4.02 d (9.0)	4.63 d (9.0) 4.06 d (9.0)	4.58 d (9.6) 4.51 d (9.6)	4.58 d (9.6) 4.51 d (9.6)
OCH_3-1								4.02 s
OCH_3-2	3.90 s	3.40 s	3.85 s	3.85 s	3.71 s	3.16 s	3.66 s	3.65 s
OCH_3-3	3.90 s	3.97 s	3.89 s	3.94s	4.05 s	3.89s	4.06 s	
OCH_3-12				3.81 s				
OCH_3-14	3.88 s	3.85 s	3.71 s	3.55 s				
OH-1	5.80 s							
2′		1.81 s						
3′			5.96 q (7.4)		7.54 t (7.0)	6.10 q (7.4)	6.09 q (7.0)	7.07 q (7.1)
4′			1.85 d (7.4)		7.32 m	1.90 d (7.4)	1.90 d (7.0)	1.90 d (7.1)
5′			1.43 s		7.32 m	1.35 s	1.39 s	1.39 m
6′					7.32 m			
7′					7.54 t (7.0)			
2″				6.35 d (16.0)				
3″		7.44 d (7.5)	5.96 q (7.4)	7.61 d (16.0)	6.03 q (7.1)	7.70 d (7.5)		
4″		7.26 m	1.85 d (8.6)		1.87 d (7.1)	7.37 t (7.5)		
5″		7.26 m	1.29 s	7.37 br s	1.29 s	7.54 t (7.5)		
6″		7.26 m		7.37 brs		7.37 t (7.5)		
7″		7.44 d (7.5)		7.37 br s		7.70 d (7.5)		
8″,9″				7.37 br s				

[a] Assignments were aided by HMQC and HMBC techniques. [b] The ester substituent at C-6 is assigned with a prime symbol and that at C-9 with a double prime symbol.

acetate carbonyl at δ_C 170.2 was ^3J-correlated to the oxymethine proton at δ_H 5.82, which, in turn, was ^3J-correlated to two methines at δ_C 107.3 (C-4) and 38.0 (C-8) and a quaternary carbon at δ_C 116.5 (C-16), indicating the substitution of an acetoxy group at C-6. The NOESY spectrum exhibited correlations between H-4/H-6, H-17; H-17/H-18; and H-9/H-8, H-11, in good agreement with the α-orientation of H-6, H-17, and H-18 and the *β*-orientation of H-9. Accordingly, the structure **2** was deduced for kadsuphilol B.

The molecular formula of **3** was assigned as $C_{32}H_{36}O_{11}$, as derived from its HRMS (*m*/*z* 596.2255, $[M]^+$) and in agreement with the NMR data. The UV and IR spectra of **2** were supportive of a dibenzocyclooctadiene lignan as for **1** and **2**. The ^{1}H and ^{13}C NMR signals due to the biphenyl ring (Tables 1 and 2) were almost identical to the corresponding values in **1** and **2**, suggesting the same substitution pattern. Two sets of angeloyl esters were detected in the ^{1}H NMR spectrum by a quartet at δ_H 5.96 (2H) and, in the ^{13}C NMR spectrum, by two sets of signals at δ_C 165.6, 127.0, 140.0, 15.7, and 19.6 and δ_C 166.1, 126.8, 140.1, 15.6, and 19.8. The aromatic singlet at δ_H 6.41 (H-4) was ^3J-correlated to the oxymethine at δ_C 84.0 (C-6), which was directly attached to the proton at δ_H 5.27. The latter was ^3J-correlated to the carbon signals at δ_C 105.1 (C-4), 115.2 (C-16), and 37.4 (C-8), as well as the angeloyl carbonyl at δ_C 165.6. The carbonyl of the second angeloyl at δ_C 166.1 was ^3J-correlated to the oxymethine at δ_H 5.62, which in turn correlated with signals at δ_C 102.6 (C-11) and 118.6 (C-15), as well as an oxygenated quaternary signal at δ_C 60.4. The latter carbon was correlated to proton signals at δ_H 5.27 (H-6), 5.62 (H-9), and 0.99 (H-18) along with the CH_2 signal at δ_H 2.88 (2H, m), suggesting the presence of an exo-epoxy ring at C-7. This was supported by the ^3J-correlation of the C*H*$_2$ at δ_H 2.88 to C-6 and C-8 as well as its NOESY correlation with δ_H 0.99 (H-18) and 5.27 (H-6) together with correlations between H-6 and *C*H$_2$ at δ_C 47.4 (C-17). The NOESY spectrum (Figure 1) also exhibited correlations between H-4/H-6; H-17/H-6, H-18; and H-9/H-8, H-11, reflecting the α-orientation of H-6, H-17, and H-18 as well as the *β*-orientation of H-9. From all of these data, structure **3** was assigned unambiguously to kadsuphilol C.

The NMR data of lignan **4**, of molecular formula $C_{31}H_{34}O_8$ ($[M]^+$ 534.2244), revealed a similar substitution in ring B of the biphenyl moiety but a different substitution pattern in ring A, when compared to **1**−**3** (Tables 1 and 2). The signals characteristic of a methylenedioxy group were absent, and four methoxyl groups were observed at δ_C 61.0, 56.0, 60.9 and 60.3 and δ_H 3.85, 3.94, 3.81, and 3.55, which were assigned to positions C-2, C-3, C-12, and C-14, respectively. This was achieved through analysis of HMBC correlations of the methoxyl protons to their respective attached carbons. The carbon signal assignable to C-14 resonated at a significantly lower field (δ_C 149.5) when compared to the corresponding values in **1**−**3** (δ_C 140.5, 141.8, and 141.2, respectively) and could be justified by the substitution of a hydroxyl group at C-13 rather than a methoxyl or a methylenedioxy group. This was confirmed by the presence of a hydroxyl proton signal at δ_H 5.66 that exhibited a ^2J-correlation to a carbon signal at δ_C 148.3 (C-13) and its ^3J-correlation to a quaternary carbon signal at δ_C 137.8 (C-12). A *trans*-cinnamoyl moiety was detected via proton signals at δ_H 6.35 and 7.61 (each d, $J = 16$ Hz) and carbon signals at δ_C 164.4, 117.0, 145.8, 134.1, 128.9, 128.1, and 130.5. In addition, a EIMS fragment ion at *m*/*z* 386 was observed due to the loss of a cinnamic acid unit. The oxymethine at δ_H 4.58 (H-9) displayed a HMQC correlation to a signal at δ_C 72.9 as well as ^3J-correlations to signals at δ_C 26.2 (C-7), 109.4 (C-11), 119.3 (C-15), and 7.9 (C-18), which validated the substitution of a cinnamoyloxy group at C-9. The methylene protons at δ_H 2.39 and 2.06 were assigned to H-6 as a result of their ^3J-correlations to carbon signals at δ_C

Table 2. ^{13}C NMR Spectroscopic Data (75 MHz, $CDCl_3$) for Compounds **1**−**8**[a]

position[b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	146.5 s	147.5 s	147.6 s	141.8 s	194.7 s	194.9 s	192.7 s	165.1 s
2	133.2 s	135.0 s	135.1 s	139.2 s	132.3 s	132.1 s	132.2 s	134.0 s
3	152.0 s	150.7 s	151.2 s	153.2 s	155.0 s	154.7 s	157.5 s	190.3 s
4	103.8 d	107.3 d	105.1 d	109.8 d	122.9 d	124.0 d	40.6 t	49.2 t
5	139.8 s	131.5 s	131.2 s	130.5 s	141.3 s	140.5 s	75.5 s	76.1 s
6	34.8 t	81.0 d	84.0 d	34.8 t	82.4 d	82.0 d	76.9 d	75.8 d
7	39.2 d	38.0 d	60.4 s	36.2 d	75.4 s	75.5 s	72.3 s	72.5 s
8	42.4 d	38.0 d	37.4 d	42.1 d	44.2 d	44.2 d	43.7 d	43.8 d
9	73.4 d	81.0 d	80.3 d	72.9 d	83.5 d	83.8 d	77.4 d	77.4 d
10	135.9 s	133.7 s	133.6 s	138.6 s	129.7 s	128.7 s	127.4 s	129.1 s
11	102.4 d	102.9 d	102.6 d	109.4 d	101.0 d	101.3 d	95.9 d	95.9 d
12	135.4 s	136.5 s	136.4 s	137.8 s	150.3 s	150.2 s	151.3 s	151.5 s
13	148.5 s	148.9 s	149.1 s	148.3 s	130.3 s	130.2 s	128.9 s	128.8 s
14	140.5 s	141.8 s	141.2 s	149.5 s	143.4 s	143.9 s	141.0 s	141.9 s
15	119.5 s	120.2 s	118.6 s	119.3 s	120.1 s	119.8 s	120.9 s	120.6 s
16	114.1 s	116.5 s	115.2 s	121.0 s	63.1 s	63.0 s	56.9 s	52.9 s
17	20.0 q	16.4 q	47.4 t	22.0 q	28.3 q	28.6 q	23.1 q	22.9 q
18	7.8 q	14.3 q	15.1 q	7.9 q	18.0 q	18.1 q	15.3 q	15.3 q
19	101.0 t	101.3 t	101.2 t		101.9 t	101.9 t	101.2 t	101.3 t
20					79.0 t	78.9 t	78.2 t	80.3 t
OCH_3-1								62.1 q
OCH_3-2	61.0 q	60.1 q	60.2 q	61.0 q	58.7 q	58.5 q	60.7 q	60.7 q
OCH_3-3	55.7 q	55.8 q	55.9 q	56.0 q	58.5 q	58.6 q	58.8 q	
OCH_3-12				60.9 q				
OCH_3-14	59.8 q	59.7 q	59.4 q	60.3 q				
1′		170.2 s	165.6 s		165.1 s	166.2 s	166.5 s	166.5 s
2′		20.9 q	127.0 s		132.3 s	126.0 s	125.9 s	126.0 s
3′			140.0 d		129.7 d	142.1 d	141.8 d	141.3 d
4′			15.7 q		128.3 d	15.7 q	15.6 q	15.6 d
5′			19.6 q		133.8 d	19.2 q	19.2 q	19.1 q
6′					128.3 d			
7′					129.7 d			
1″		165.7 s	166.1 s	164.4 s	165.8 s	165.4 s		
2″		129.8 s	126.8 s	117.0 d	124.7 s	129.3 s		
3″		128.0 d	140.1 d	145.8 d	141.8 d	129.4 d		
4″		129.4 d	15.6 q	134.1 s	15.9 q	128.3 d		
5″		132.6 d	19.8 q	128.9 d	20.5 q	133.2 d		
6″		129.4 d		128.1 d		128.3 d		
7″		128.0 d		130.5 d		129.4 d		
8″				128.1 d				
9″				128.9 d				

[a] Assignments were aided by DEPT, HMQC, and HMBC. [b] The ester substituent at C-6 is assigned with a prime symbol and that at C-9 with a double prime symbol.

109.8 (C-4), 42.1 (C-8), and 121.0 (C-16). An upfield shift was observed for C-18 (δ_C 7.9), similar to the corresponding value in **1** (δ_C 7.8). The NOESY spectrum of **4** was similar to that of **1**, indicating the same relative stereochemistry with a β-oxygenated substituent at the C-9 position. The CD spectrum of **4**, exhibiting a positive Cotton effect at λ_{max} 251 nm, agreed with an *R*-biphenyl configuration similar to **1**.[17,18] Consequently, **4** was assigned for the structure of kadsuphilol D.

Compound **5** was assigned a molecular formula of $C_{34}H_{34}O_{11}$, corresponding to 18 degrees of unsaturation, through analysis of its HRMS and NMR data. The ^{13}C NMR spectrum of **5** displayed signals for a ketone at δ_C 194.7, two ester carbonyls at δ_C 165.8 and 165.0, two oxymethines at δ_C 82.4, and 82.5, a methine at δ_C 44.2, two methyls at δ_C 28.3 and 18.0, and a quaternary oxygenated carbon at δ_C 75.4. The NMR spectroscopic data also revealed the presence of benzoyl and angeloyl ester units (Tables 1 and 2). The oxymethine at δ_C 82.5 was directly attached to the proton at δ_H 5.71 (H-9), which in turn was ^3J-correlated to the aromatic carbons at δ_C 101.0 (C-11), 120.1 (C-15), and 18.0 (C-18) as well as the quaternary carbon at δ_C 75.4 and the angeloyl carbonyl at δ_C 165.8. The other oxymethine carbon at δ_C 82.4 was directly attached to the proton that resonated at δ_H 5.92, showing ^3J-correlations to the methine carbon at δ_C 44.2 (C-8), a methyl at δ_C 28.3 (C-17), a methine at δ_C 122.9 (C-4), and a benzoyl carbonyl at δ_C 165.1. Both the C-17 (δ_C 28.3) and C-4 (δ_C 122.9) signals resonated at relatively downfield values when compared to the corresponding chemical shifts in **1**−**4**.[19] It could be proposed that a hydroxyl group is linked to C-7, while a benzoyloxy and an angeloyloxy group were attached to positions 6 and 9, respectively. Two methoxy groups (δ_C 58.7, 58.5 and δ_H 3.71, 4.05) and a methylenedioxy (δ_C 101.9 and δ_H 5.97, 5.92) were positioned at C-2, C-3, C-12, and C-13, respectively, by HMBC NMR spectroscopic analysis. The oxymethylene carbon at δ_C 79.0 was directly attached to protons resonating at δ_H 4.62 and 4.02 (each d, J = 9 Hz), suggestive of the presence of a furanoid ring.[20,21] The latter protons revealed ^2J-correlations to the quaternary carbon at δ_C 63.1 (C-16) along with ^3J-correlations to quaternary carbon signals at δ_C 141.3 (C-5) and 143.4 (C-14), as well as the carbonyl at δ_C 194.7 (C-1). These data clearly confirmed that **5** is a C_{19}-homolignan possessing a substituted cyclohexadienone ring with a *spiro*-dihydrobenzofuran ring as in kadsulignans C and D.[22] The NOESY cross-peaks between H-4/H-6; H-8/H-9, H-17; and H-9/H-11 were in accordance with the α-orientation of H-6 and H-18 as well as the β-orientation of H-8, H-9, and H-17. On the basis of these results, structure **5** was elucidated for kadsuphilol E.

The EIMS data of **6** revealed the molecular formula $C_{34}H_{34}O_{11}$, the same as that of **5**. Moreover, the ^{13}C NMR data of **6** and **5** (Table 2) were almost identical, suggesting the same lignan skeleton and the same substitution pattern. Nevertheless, the proton assigned to H-6 in **6** (δ_H 5.79) was slightly upfield-shifted when compared to the corresponding value in **5** (δ_H 5.92) and was ^3J-correlated to C-4 (δ_C 124.0) and C-16 (δ_C 63.0), as well as the angeloyl carbonyl at δ_C 166.2. The latter carbonyl was, in turn, correlated to the methyl at δ_C 19.2 (C-5′); therefore the angeloyloxy group was located at

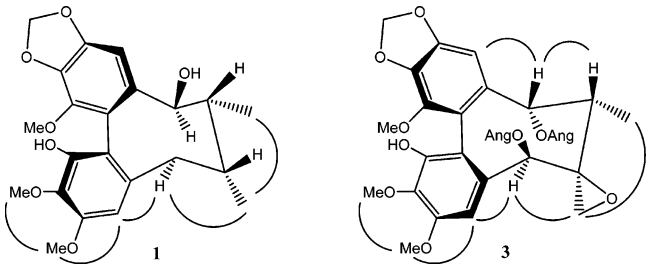

Figure 1. Selected NOESY correlations of **1** and **3**.

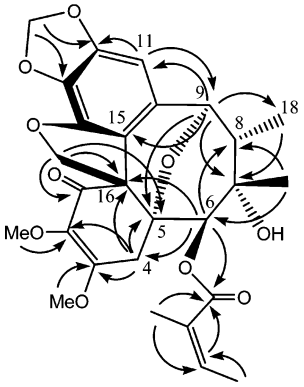

Figure 2. Selected HMBC correlations of **7**.

C-6 rather than C-9 in the case of compound **5**. In addition, the oxymethine at δ_H 5.84 (H-9) was slightly downfield-shifted when compared to the corresponding value in **5** (δ_H 5.71). The H-9 signal was ^3J-correlated to C-11 (δ_C 101.3) and C-15 (δ_C 119.8), in addition to the benzoyl carbonyl at δ_C 165.4. Moreover, the aromatic signal appeared at δ_H 7.70 (2H, d, J = 7.5 Hz, H-3″,7″), confirming the substitution of a benzoyloxy group at C-9. Consequently, **6** was assigned for the structure of kadsuphilol F.

The HRMS of **7** revealed an exact mass at *m*/*z* 514.1832, corresponding to a molecular formula of $C_{27}H_{30}O_{10}$ and 13 degrees of unsaturation. The NMR data (Tables 1 and 2) indicated a homolignan skeleton similar to **5** and **6** with two methoxy groups at C-1 and C-2, a methylenedioxy at C-11/C-12, an angeloyloxy substituent at either C-6 or C-9, and a hydroxyl group, most likely at C-7 (δ_C 72.3). In addition to the proton signals at δ_H 6.16 (s, H-11) and 6.09 (q, J = 7 Hz, H-3′), the ^{1}H NMR spectrum of **7** did not show any aromatic or olefinic proton resonance that could be assigned to H-4. A two-proton singlet was observed at δ_H 3.08 that was ^3J-correlated to carbons at δ_C 132.2 (C-2), 76.9 (C-6), and 56.9 (C-16) and ^2J-correlated to an oxygenated quaternary carbon at δ_C 75.5. In addition, the HMBC spectrum (Figure 2) showed correlations between H-6 (δ_H 5.26) and C-8 (δ_C 43.7), C-16 (δ_C 56.9), the angeloyl carbonyl (δ_C 166.5), and the CH_2 at δ_C 40.6, proving the saturation at C-4 and C-5 and the attachment of an angeloyl ester at C-6. In turn, the oxymethine signal at δ_H 4.73 was assigned to H-9 as a result of being ^3J-correlated to C-7, C-11, C-15, and C-18, proving the substitution by a hydroxyl at C-7. The downfield shift of both C-9 at δ_C 77.4 and the quaternary carbon at δ_C 75.5 indicated their oxygenation with probable formation of an ether linkage between C-5 and C-9. This was confirmed by the MS data and the calculated 13 degrees of unsaturation and was in accordance with the observed HMBC correlations between C-5 (δ_C 75.5) and H-4, H-20 and in particular with H-9. The relative stereochemistry of **7** was determined by comparison of NMR data with related compounds as well as the NOE interactions between H-17/H-8 and H-9/H-8, H-11 (Figure 3), which were in agreement with the α-orientation of H-6 and H-18, as well as the β-orientation of H-17, H-8, and H-9.[20] Therefore, structure **7** was established for kadsuphilol G.

The molecular formula of **8** was identical to that of **7**, suggesting these compounds to be closely related structurally. Although they

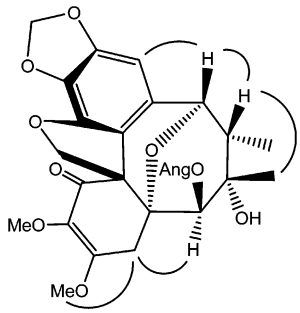

Figure 3. Key NOESY correlations of **7**.

Table 3. Free-Radical-Scavenging Activities of Compounds **1**−**8** at Various Concentrations[a]

compound	100 μM	50 μM	25 μM	12.5 μM	6.25 μM
1	−4.2	−1.6	−10.7	−18.5	−38.9
2	−23.1	−30.8	−32.2	−33.8	−35.6
3	54.7[b]	51.4	48.1	46.2	47.4
4	38.1	34.4	32.2	28.1	10.0
5	35.6	33.9	32.0	13.8	20.2
6	12.9	12.8	11.4	10.3	8.6
7	8.4	6.6	6.1	3.9	3.9
8	−2.8	−3.7	−3.2	−4.7	−5.3
vitamin C[c]	39.0	36.7	24.9	20.7	19.2
vitamin E[c]	17.6	12.9	12.6	4.9	1.3

[a] Radical-scavenging activities were measured by the DPPH method. [b] Data are shown as % inhibition. [c] Positive control substances.

gave almost the same ^{1}H NMR data (Table 1), their ^{13}C NMR data revealed some differences. The CH_2 carbon assignable to C-4 was shifted from δ_C 40.6 in **7** to δ_C 49.2 in **8**, and this was associated with a slight upfield shift of C-16 from δ_C 56.9 in **7** to δ_C 52.9 in **8**. The furanoid methylene at δ_H 4.58 and 4.51 (each d, J = 9.6 Hz, H-20) did not show a HMBC correlation with the carbonyl at δ_C 190.3, but instead they were correlated to a downfield aromatic signal at δ_C 165.1. The latter carbon was ^3J-correlated to a methoxyl proton at δ_H 4.02, suggesting its assignment to C-1. The second methoxy group was located at C-2 from a correlation between signals appearing at δ_H 3.65 and δ_C 134.0. The methylene protons at δ_H 3.12, 2.88 (each d, J = 17.3 Hz) revealed ^2J-correlations to the carbonyl at δ_C 190.3 and the quaternary carbon at δ_C 76.1 (C-5), as well as ^3J-correlation to oxymethines at C-6 (δ_C 75.8), C-2 (δ_C 134.0), and C-16 (δ_C 52.9). These results indicated that the carbonyl at δ_C 190.3 is located at C-3 rather than C-1 in **7**, and at the same time, a CH_2 was retained at position C-4. Other HMBC and NOESY correlations of **8** were identical to those in **7**. Accordingly, **8** was assigned for the structure of kadsuphilol H.

The new lignans **1**−**8** were tested and evaluated for antioxidative activity by application of the DPPH (1,1-diphenyl-2-picrylhydrazyl) free-radical test. Among these compounds, kadsuphilols C (**3**), D (**4**), and E (**5**) showed significant DPPH free-radical-scavenging activity (Table 3). It is notable that kadsuphilol C (**3**) exhibited more potent activity than vitamins C and E at several concentrations (6.25, 12.5, 25, 50, and 100 μM). Thus, the data were 47.4% and 51.4% for **3** compared with 19.2% and 36.7% for vitamin C and 1.3% and 12.9% for vitamin E at 6.25 and 50 μM, respectively (Table 3).

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a JASCO DIP-1000 polarimeter. IR and UV spectra were measured on a Hitachi T-2001 and a Hitachi U-2001 spectrophotometer, respectively. CD spectra were taken on a JASCO J-720 circular dichroism spectrophotometer. The ^{1}H and ^{13}C NMR, COSY, HMQC, HMBC, and NOESY spectra were recorded on a Bruker FT-300 NMR spectrometer or on a Varian Unity INOVA 500 FT-NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, respectively, using TMS as internal standard. Chemical shifts are given in δ (ppm) and coupling

constants in Hz. Low-resolution EIMS and FABMS were recorded on a VG Quattro 5022 mass spectrometer, and HRMS were measured on a JEOL HX 110 mass spectrometer. Silica gel 60 (Merck) was used for column chromatography, and precoated silica gel plates (Merck, Kieselgel 60 F-254, 1 mm) were used for preparative TLC. Sephadex LH-20 (Amersham Pharmacia Biotech AB, Sweden) was used for compound purification.

Plant Material. The aerial parts of *K. philippinensis* were collected at Green Island, Taiwan, in November, 2004. This plant was identified by one of the authors (Y.-C.S.) A voucher sample (specimen code: TP 93-2) was deposited in the School of Pharmacy, 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 evaporated under vacuum, then partitioned between EtOAc and water (1:1). The resulting EtOAc extract (250 g) was subjected to column chromatography on silica gel using a *n*-hexane−EtOAc gradient (100:1 to 0:1) for elution, to furnish 24 fractions. Fraction 19 (8.7 g) was separated on a column of Sephadex LH-20 using MeOH for elution to produce three fractions (L_1−L_3). Fraction L_1 (4.9 g) was further purified on a flash column using silica gel and a gradient of *n*-hexane−EtOAc (20:1 to 1:3) for elution to produce seven subfractions (L_1-1 to L_1-7). Subfraction L_1-4 was chromatographed on a silica gel column using *n*-hexane−acetone (7:1 to 1:1) to give three fractions (L_1-4-a to L_1-4-c). Fraction L_1-4-b was separated by preparative TLC [silica gel GF_{254}, *n*-hexane−CH_2Cl_2−MeOH (5:3:0.5)]. The band with R_f 0.67 was scraped, eluted with acetone, and further separated by NP-HPLC using *n*-hexane−CH_2Cl_2−MeOH (22:3:0.5) to yield **3** (3.5 mg). Fraction L_2 (3.3 g) underwent separation by flash column chromatography to yield eight fractions (L_2-1 to L_2-8). L_2-3 was fractionated over Sephadex LH-20 (MeOH) to give three fractions (a−c). Fraction L_2-3-b (966 mg) was chromatographed on a silica gel column using a gradient of *n*-hexane−EtOAc to yield five fractions (1−5). Fraction L_2-3-b-1 (62 mg) was fractionated by NP-HPLC using *n*-hexane−CH_2Cl_2−MeOH (22:3:0.5) to produce a mixture (22 mg) that was purified by RP-HPLC [MeOH−H_2O, 7:3] to yield **5** (8.4 mg). Fraction L_2-4 (1.3 g) was fractionated over Sephadex LH-20 (MeOH) to give three fractions (a−c). Fraction L_2-4-a (550 mg) was subjected to NP-HPLC using *n*-hexane−CH_2Cl_2−MeOH (10:3:0.5) to give five fractions (1−5). Fraction L_2-4-a-4 was purified by RP-HPLC [MeOH−H_2O, 7:3] to yield **8** (17.4 mg). Fraction L_2-4-a-5 was separated by NP-HPLC using *n*-hexane−CH_2Cl_2−MeOH (22:3:0.5) to furnish **7** (14.2 mg) and **4** (4.5 mg). Fraction L_2-4-b (698 mg) was chromatographed on a silica gel column using *n*-hexane−CH_2Cl_2−MeOH (100:6:1 to 20:6:1) to give three fractions (1−3). Fraction L_2-4-b-2 was separated by NP-HPLC using *n*-hexane−CH_2Cl_2−MeOH (22:6:1) to give six fractions (A−F). Fraction L_2-4-b-2-A (7.5 mg) was purified by RP-HPLC [MeOH−H_2O, 7:3] to yield **2** (2.7 mg). Fraction L_2-4-b-2-B (182 mg) was further chromatographed by NP-HPLC using *n*-hexane−CH_2Cl_2−MeOH (20:3:0.5) to yield **6** (10.9 mg). Fraction L_3 (370 mg) was separated on a silica gel column using *n*-hexane−CH_2Cl_2−MeOH (10:3:0.5) to give three fractions (a−c). Fraction L_3-a (179 mg) was purified by NP-HPLC using *n*-hexane−CH_2Cl_2−MeOH (10:3:0.5) to yield **1** (17.7 mg).

Kadsuphilol A (1): colorless, amorphous powder; $[\alpha]_D^{25}$ +15 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 216 (3.86), 254 (3.25) nm; CD (*c* 0.1, MeOH) 208 (−47.8), 230 (+20.6), 253 (+29.2) nm; IR (CH_2Cl_2) 3479 (OH), 2956 (CH), 1613 (C═C), 1503, 1112, 936, 853, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 403 $[M + H]^+$; EIMS *m/z* 402 $[M]^+$ (100), 384 $[M - H_2O]^+$ (72); HRMS *m/z* 402.1676 (calcd for 402.1679, $C_{22}H_{26}O_7$).

Kadsuphilol B (2): colorless, amorphous powder; $[\alpha]_D^{25}$ +11 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 220 (3.60) nm; IR (CH_2Cl_2) 3444 (OH), 3060 (CH), 2937 (CH), 1715 (br, ester), 1613 (C═C), 1514, 1249 (acetate C−O st), 1108, 935, 829, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 565 $[M + H]^+$; EIMS *m/z* 564 $[M]^+$ (18), 505 $[M -$ acetoxy$]^+$ (16), 443 $[M -$ benzoyloxy$]^+$ (20); HRMS *m/z* 564.1993 (calcd for 564.1996, $C_{31}H_{32}O_{10}$).

Kadsuphilol C (3): colorless, amorphous powder; $[\alpha]_D^{25}$ +52 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 219 (3.68) nm; IR (CH_2Cl_2) 3437 (OH), 2934 (CH), 1711 (br, ester), 1616 (C═C), 1515, 1231, 1146, 1046, 937, 844, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 597 $[M + H]^+$; EIMS *m/z* 596 $[M]^+$ (7), 496 $[M -$ angelic acid$]^+$ (0.8); 397 $[M - 2 \times$ angelic acid$]^+$ (1), 83 [angeloyl] (100); HRMS *m/z* 596.2255 (calcd for 596.2258, $C_{32}H_{36}O_{11}$).

Kadsuphilol D (4): colorless, amorphous powder; $[\alpha]_D^{25}$ +89 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 213 (3.35), 280 (3.01) nm; CD (*c* 0.1, MeOH) 213 (−51.0), 238 (+28.6), 251 (+24.7) nm; IR (CH_2Cl_2) 3422 (OH), 2936 (CH), 1720 (br., ester), 1634 (C═C), 1608 (C═C), 1493, 1269, 1139, 1083, 859, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 535 $[M + H]^+$; EIMS *m/z* 534 $[M]^+$ (10), 386 $[M -$ cinnamic acid$]^+$ (25), 131 [cinnamoyl] (100); HRMS *m/z* 534.2244 (calcd for 534.2254, $C_{31}H_{34}O_8$).

Kadsuphilol E (5): yellow, amorphous powder; $[\alpha]_D^{25}$ −120 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 219 (3.65) nm; IR (CH_2Cl_2) 3571 (OH), 3008 (C−H), 2944 (CH), 1722 (br, ester), 1660, 1645 (C═C), 1599 (C═C), 1504, 1257, 1124, 1069, 956, 848, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 619 $[M + H]^+$ (8), 154 [$C_8H_{10}O_3$, ring B] (100); EIMS *m/z* 618 $[M]^+$ (1), 519 $[M -$ angeloyloxy$]^+$ (2.4), 496 $[M -$ benzoic acid$]^+$ (1.3), 105 [benzoyl]$^+$ (100); HRMS *m/z* 618.2093 (calcd for 618.2101, $C_{34}H_{34}O_{11}$).

Kadsuphilol F (6): yellow, amorphous powder; $[\alpha]_D^{25}$ −29 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 219 (3.47) nm; IR (CH_2Cl_2) 3500 (OH), 3061 (ar C−H), 2978, 2944 (CH), 1714 (br, ester), 1644 (C═C), 1582 and 1486 (C═C), 1502, 1258, 1140, 1067, 936, 845, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 619 $[M + H]^+$ (8), 154 [$C_8H_{10}O_3$, ring B] (100); EIMS *m/z* 618 $[M]^+$ (0.5), 518 $[M -$ angelic acid$]^+$ (0.4), 496 $[M -$ benzoic acid$]^+$ (0.5), 105 [benzoyl]$^+$ (82), 83 [angeloyl]$^+$ (100); HRMS *m/z* 618.2092 (calcd for 618.2101, $C_{34}H_{34}O_{11}$).

Kadsuphilol G (7): yellow, amorphous powder; $[\alpha]_D^{25}$ +150 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 216 (3.66), 274 (3.18) nm; IR (CH_2Cl_2) 3487 (OH), 2966, 1714 (br, ester), 1627 (C═C), 1460 (C═C), 1257, 1141, 1048, 929, 849, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 515 $[M + H]^+$ (35), 154 [$C_8H_{10}O_3$, ring B] (100); EIMS *m/z* 514 $[M]^+$ (11), 431 $[M -$ angeloyl$]^+$ (21), 414 $[M -$ angelic acid$]^+$ (8), 371 $[M -$ angelic acid $- CO - OH]^+$ (12), 83 [angeloyl]$^+$ (90), 55 $[C_4H_7]^+$ (100); HRMS *m/z* 514.1832 (calcd for 514.1839, $C_{27}H_{30}O_{10}$).

Kadsuphilol H (8): yellow, amorphous powder; $[\alpha]_D^{25}$ +98 (*c* 0.01, CH_2Cl_2); UV (MeOH) (log ϵ) λ_{max} 219 (3.86) nm; IR (CH_2Cl_2) 3484 (OH), 2934 (CH), 1714 (ester), 1660 (C═C), 1612, 1456, 1259, 1139, 1049, 932, 835, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), see Table 1; ^{13}C NMR (75 MHz, $CDCl_3$), see Table 2; FABMS *m/z* 515 $[M + H]^+$ (17), 154 [$C_8H_{10}O_3$, ring B] (100); EIMS *m/z* 514 $[M]^+$ (14), 431 $[M -$ angeloyl$]^+$ (0.2), 414 $[M -$ angelic acid$]^+$ (3), 83 [angeloyl]$^+$ (100), 55 $[C_4H_7]^+$ (100); HRMS *m/z* 514.1831 (calcd for 514.1839, $C_{27}H_{30}O_{10}$).

Antioxidative Activity. DPPH radical-scavenging activity was measured according to a published protocol.[23] Dilutions of compounds **1**−**8** (in 100% DMSO) were treated with a solution of 100 μM DPPH in ethanol at 37 °C. The mixtures were shaken vigorously and stood for 30 min. The absorbances at 517 nm were measured using a UV−vis spectrophotometer. Vitamins C and E were used as standard compounds.

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