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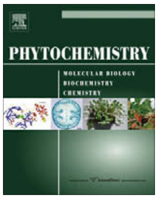

Dibenzocyclooctadiene lignans from *Kadsura philippinensis*

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ABSTRACT

Lignans with the dibenzocyclooctadiene skeleton, kadsuphilols I–L, and one C_{19}-homolignan, kadsuphilol M, were isolated by chromatographic fractionation of an ethyl acetate extract of the aerial parts of *Kadsura philippinensis.* Their structures were elucidated through extensive spectroscopic methods, including HRESIMS and 2D NMR experiments (HMQC, COSY and HMBC). The stereochemistry at the chiral centers and the biphenyl moist, were determined using NOESY, as well as analysis of CD spectra, respectively. The relative configuration of heteroclitin J was confirmed by single crystal X-ray crystallographic analysis. The *in vitro* radical-scavenging activities of these compounds by using DPPH were evaluated.

1. Introduction

Plants from the Schisandraceae have yielded numerous lignans of various pharmacological activities, including those having antitumor (Hausott et al., 2003), cytotoxic (Kuo et al., 1997; Wu et al., 2004), anti-HIV (Chen et al., 1997), antihepatitis (Kuo et al., 2001), hepatoprotective (Tang et al., 2003) and antioxidative (Chiu et al., 2002) effects. The genus *Kadsura* (Schisandraceae) is a rich source of lignans commonly used in traditional Chinese medicine for their healing properties, sometimes as a substitute for *Schisandra chinensis* Baill (Liu and Li, 1993; Ookawa et al., 1995; Li, 1998). Motivated by the search for bioactive metabolites from *Kadsura* (Shen et al., 2006; Shen et al., 2007), a re-investigation of the lignan content of *Kadsura philippinensis* Elmer (Schisandraceae) was carried out. Herein, we report the results of a phytochemical study that led to isolation of five new lignans, kadsuphilols I–M (**1**–**5**). Four of the isolated lignans **1**–**4** possessed a C_{18}-dibenzocyclooctadiene skeleton, while lignan **5** was a C_{19}-homolignan with a spirobenzofuranoid skeleton (Ayres and Loike, 1990; Li and Xue, 1990). Three known lignans, kadsulignan E (**6**) (Gao et al, 2008), heteroclitin J (**7**) (Xu et al, 2007), kadsuphilin K (**8**) (Shen et al., 2008) were also isolated and their structures determined. These lignans were tested for the antioxidative activity using the DPPH radical-scavenging method.

2. Results and discussion

2.1. Isolation, structure determinations

Kadsuphilols I–M (**1–5**) and compounds **6–8** were obtained from the ethyl acetate extract of the aerial parts of *K. philippinensis* by column chromatography using normal and reversed phase HPLC. Their structures were determined by analysis of spectroscopic data including 2D NMR (HMQC, COSY, HMBC and NOESY), CD spectra, as well as by X-ray analysis.

Compound **1** possessed a molecular formula $C_{25}H_{32}O_9$, as deduced from its HRESIMS (m/z 499.1942 $[M + Na]^+$). The UV absorption (λ_{max} 222, 254 and 287 nm), and IR bands (3503, 1734, 1598 cm^{-1}) suggested that **1** was a C_{18}-dibenzocyclooctadiene lignan with both hydroxyl group(s) and ester substitution (Liu and Li, 1993; Ookawa et al., 1995). The ^1H NMR spectrum of **1** (Table 1) showed two aromatic singlets of a biphenyl moiety at δ_H 6.57 and 6.43 (H-4 and H-11), as well as five singlets of methoxyl groups at δ_H 3.92, 3.90, 3.89 (6H) and δ_H 3.75. The cyclooctadiene ring was evident from two secondary methyl doublets at δ_H 1.09 and 0.92 (H-18 and H-17), two methines at δ_H 2.09 and 2.05 (H-8 and H-7), and two benzylic oxymethines at δ_H 5.71 and 4.71 (H-6 and H-9), implying acylation at the former oxymethine. An

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Table 1
^{1}H NMR spectroscopic data ($CDCl_3$, 300 MHz) of **1**–**5**.[a]

Position	1	2	3	4	5
4	6.57 s	6.65 s	6.68 s	6.94 s	6.48 s
6	5.71 d (7.7)	5.73 s	5.91 s	5.68 s	5.67 s
7	2.05 m				
8	2.09 m	2.18 q (7.2)	2.18 q (7.6)	2.24 q (7.2)	2.10q (7.2)
9	4.71 d (5.1)	5.70 s	4.95 s	5.91 s	5.79 s
11	6.43 s	6.54 s	6.42 s	6.49 s	6.37 s
17	0.92 d (6.9)	1.33 s	1.35 s	1.36 s	1.24 s
18	1.09 d (7.2)	1.30 d (7.2)	1.43 d (7.6)	1.29 d (7.2)	1.29 d (7.2)
19			5.80 d (1.0)	6.03 d (1.0)	5.96 d (0.9)
			5.64 d (1.0)	6.00 d (1.0)	5.91 d (0.9)
20					4.73 d (9.0)
					4.09 d (9.0)
1-OCH_3				3.47 s	
2-OCH_3	3.89 s	3.92 s	3.92 s	3.70 s	3.76 s
3-OCH_3	3.92 s	3.93 s	3.95 s	3.99 s	4.06 s
12-OCH_3	3.89 s	3.86 s			
13-OCH_3	3.90 s	3.81 s			
14-OCH_3	3.75 s	3.53 s	3.37 s		
2′				5.71 d (15.7)	
3′		5.93 q (6.6)	7.52 d (8.0)	7.08 d (15.7)	6.10 q (6.9)
4′		1.81 d (6.6)	7.31 t (8.0)		1.89 dd (6.9, 1.2)
5′		1.29 s	7.45 t (8.0)	7.37 br s	1.28 s
6′			7.31 t (8.0)	7.37 br s	
7′			7.52 d (8.0)	7.37 br s	
8′,9′				7.37 br s	
6-OAc	1.76 s			1.63 s	
9-OAc		1.54 s			1.85 s

[a] J values (Hz) in parentheses.

acetate methyl was observed at δ_H 1.76 and this was supported by both C-13 signals (δ_C 21.0, 170.1) and an EIMS fragment ion (m/z 416 $[M\text{-}AcOH]^+$). The ^{13}C NMR spectrum (Table 2) indicated presence of 10 quaternary aromatic signals, as well as two aromatic upfield methines (δ_C 108.0 and 106.8) adjacent to two oxygenated carbons with hydroxyl groups and five methoxyl groups (δ_C 61.1–56.0). The positions of the methoxyl, hydroxyl, and acetate groups were determined by comparison of ^{1}H and ^{13}C NMR spectroscopic data with those of closely related compounds (Yang et al., 1992; Chen et al., 1998, 2002) as well as a meticulous inspection of the HMBC (Fig. 1), ^{13}C NMR, and NOESY (Fig. 2) spectra. The aromatic proton at δ_H 6.57 (H-4) showed long-range correlations to C-3, C-2, C-16, C-1 and C-6, whereas the aromatic proton at δ_H 6.43 (H-11) correlated to C-12, C-13, C-15, C-14 and C-9. The five methoxyls were located at C-2, C-3, C-12, C-13 and C-14 as a result of the HMBC correlation of the previous carbons and the attached methoxyl singlets. The correlations of the oxymethine at δ_H 5.71 (H-6) to C-4, C-16 and C-8, as well as the acetate carbonyl at δ_C 170.1, located the acetyloxy group at C-6. An hydroxyl proton observed at δ_H 1.26 had a COSY correlation to δ_H 4.71 (H-9), while the latter proton showed HMBC correlations to the aromatic carbon signals at δ_C 106.8 (C-11) and 119.5 (C-15), and the signal at 16.9 (C-18). The structure of the cyclooctadiene ring was also established by COSY connectivities between H-6/H-7/H-8/H-9; H-7/H-17; and H-8/H-18. It was concluded that **1** was a dibenzocyclooctadiene lignan with hydroxyl and acetoxyl substitutions at C-1 and C-9, respectively, and methoxyl substitutions at C-2, C-3, C-12, C-13 and C-14. The CD curve of **1** showed a negative cotton effect around 249 nm and a positive one around 224 nm favoring the *S*-biphenyl configuration (Liu and Li, 1993; Ookawa et al., 1995). The relative stereochemistry of **1** was determined through inspection of a molecular model, as well as the NOESY spectrum (Fig. 2) that demonstrated correlations between H-4/H-6, H-17; H-6/H-17 indicating the α-configuration of H_{eq}-6 and H_{ax}-17. An NOE interaction between H_{eq}-9/H-11 and H_{ax}-8 indicated a β-orientation of H-8 and H-9 (Chen et al., 2001). Based on these findings, structure **1** was identified as kadsuphilol I.

Table 2
^{13}C NMR spectroscopic data ($CDCl_3$, 75 MHz) of **1**–**5**.[a]

Position	1	2	3	4	5
1	147.7 s	147.0 s	146.5 s	149.8 s	196.2 s
2	135.6 s	135.2 s	134.7 s	142.0 s	131.9 s
3	151.4 s	150.6 s	150.5 s	152.2 s	155.7 s
4	108.0 d	107.5 d	107.8 d	112.4 d	123.0 d
5	131.5 s	130.1 s	132.8 s	131.7 s	142.0 s
6	81.3 d	84.8 d	85.7 d	84.6 d	82.3 d
7	38.4 d	74.1 s	74.1 s	73.5 s	75.1 s
8	41.0 d	42.8 d	43.4 d	43.0 d	44.0 d
9	80.8 d	83.8 d	84.0 d	83.2 d	81.5 d
10	138.4 s	134.7 s	136.3 s	133.6 s	129.2 s
11	106.8 d	107.1 d	101.9 d	101.7 d	101.2 d
12	153.2 s	153.3 s	148.8 s	148.1 s	150.2 s
13	141.0 s	141.2 s	135.7 s	134.7 s	130.1 s
14	152.2 s	151.0 s	140.0 s	136.9 s	143.5 s
15	119.5 s	119.8 s	119.1 s	117.8 s	119.8 s
16	115.3 s	116.1 s	115.0 s	120.0 s	63.3 s
17	13.4 q	28.9 q	29.6 q	28.5 q	28.5 q
18	16.9 q	17.2 q	17.8 q	16.7 q	17.8 q
19			100.9 t	101.8 t	101.9 t
20					78.7 t
1-OCH_3				61.2 q	
2-OCH_3	61.1 q	60.8 q	60.9 q	60.8 q	58.8 q
3-OCH_3	56.1 q	55.9 q	55.7 q	56.3 q	58.9 q
12-OCH_3	56.0 q	56.1 q			
13-OCH_3	60.9 q	60.5 q			
14-OCH_3	60.9 q	60.8 q	59.1 q		
1′		165.8 s	164.8 s	164.8 s	166.3 s
2′		126.6 s	130.0 s	116.6 d	126.0 s
3′		141.3 d	129.4 d	145.7 d	142.0 d
4′		15.6 q	127.8 d	131.7 s	15.7 q
5′		19.8 q	132.8 d	129.0 d	19.2 q
6′			127.8 d	128.2 d	
7′			129.4 d	133.6 d	
8′				128.2 d	
9′				129.0 d	
OAc-6	170.1 s			169.5 s	
	21.0 q			20.1 q	
OAc-9		168.9 s			168.6 s
		20.1 q			20.3 q

[a] Assignments were aided by HMQC and HMBC experiments.