



DIBENZOCYCLOOCTADIENE LIGNANS FROM *KADSURA* *ANGUSTIFOLIA*

YE-GAO CHEN, PING WANG, ZHONG-WEN LIN,† HAN-DONG SUN,† GUO-WEI QIN* and YU-YUAN XIE

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China;

† Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China

(Received 23 September 1997)

Key Word Index—*Kadsura angustifolia*; Schisandraceae; dibenzocyclooctadiene lignan; angustifolin A, B and C.

Abstract—Three new dibenzocyclooctadiene lignans, named angustifolin A, B and C, were isolated from the stems of *Kadsura angustifolia*. Their structures and stereochemistries were elucidated by spectral studies.
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INTRODUCTION

Kadsura angustifolia A.C. Smith is an evergreen liana, indigenous to Yunnan Province, China. Its stems have been used in local folk medicine to promote blood circulation and to treat fractures and irregular menstruation [1]. A literature survey showed that this plant has not been studied chemically; although many studies have been done on other *Kadsura* species. In the course of our search for bioactive natural products, we investigated this plant and isolated three new dibenzocyclooctadiene lignans, named angustifolin A, B and C (1–3), from the plant stems. This paper deals with the isolation and structure elucidation of these new lignans.

RESULTS AND DISCUSSION

The ethanol extract of the stems of *K. angustifolia* was fractionated into petrol-, EtOAc- and *n*-BuOH-soluble fractions. Repeated CC of the petrol fraction followed by preparative TLC led to the isolation of three new dibenzocyclooctadiene lignans, angustifolin A, B and C (1–3).

Compound **1** was obtained as a gum. Its HR mass spectrum contained a $[M]^+$ peak (m/z 624.1965) corresponding to the molecular formula $C_{36}H_{32}O_{10}$ (calc. 624.1995). The UV spectrum of **1** showed λ_{max} 228.5 (log ϵ 4.59), 256 (log ϵ , 4.12, sh) and 284 (log ϵ , 3.79, sh) nm, indicating that **1** was a dibenzocyclooctadiene lignan. The CD curve of **1** showed a negative Cotton effect around 244 nm and a positive one around 234

nm, suggesting that **1** possessed an *S*-biphenyl configuration [2]. The 1H NMR spectrum of **1** showed signals due to two aromatic protons (δ 6.72, 6.60, each 1H, *s*), two methylenedioxy moieties (δ 5.84, 5.81, each 1H, *d*, $J = 1.2$ Hz; δ 5.81, 5.75, each 1H, *d*, $J = 1.4$ Hz) and two methoxy groups (δ 3.29, 3.49, each 3H, *s*) on two aromatic rings. In the ^{13}C NMR spectrum, the presence of the two downfield methoxy signals at δ 58.7 and 59.0 suggested that the two methoxyls were probably located at C-1 and C-14, and that the two methylenedioxy moieties were at C-2, C-3 and C-12, C-13. Two aromatic CH signals at δ 105.4 and 102.2 were assigned to C-4 and C-11, respectively [3, 4], which was further confirmed by NOE experiments (Fig. 1 and Table 3) i.e. no observable NOE enhancement of H-4 and H-11 on irradiation of each methoxy proton.

In the cyclooctadiene ring, two secondary methyl groups (δ 1.11, 1.20, each 3H, *d*, $J = 7.2$ Hz and δ 15.5 *q*, 30.9 *q*) were assigned to CH_3 -7 and CH_3 -8, respectively. This suggested no substituent at C-7 and C-8, and that the two methyl groups were in *cis*-orientation [5]. The NOE results showed an appreciable enhancement between Me-7 and H-4 and between Me-8 and H-9, indicating that both Me-7 and Me-8 were α -oriented. The signals at δ 5.98 (1H, *d*, $J = 7.1$ Hz) and 5.94 (1H, *d*, $J = 2.9$ Hz), which correlated with the multiplet signals at δ 2.33 and 2.52 in the 1H - 1H COSY, respectively, were assigned to two oxygen-bearing benzylic methines, indicating two ester groups substituted at C-6 and C-9 respectively, similar to the known acetylschisantherin L (**4**) [6]. The presence of two benzoyl groups was deduced from the 1H NMR (Table 1), ^{13}C NMR (Table 2) and EIMS (m/z 502 $[M - C_6H_5COOH]^+$, 308 $[M - C_6H_5COOH \times 2]^+$ and 105 $[C_6H_5CO]^+$) data. The NOE experiments showed

* Author to whom correspondence should be addressed.

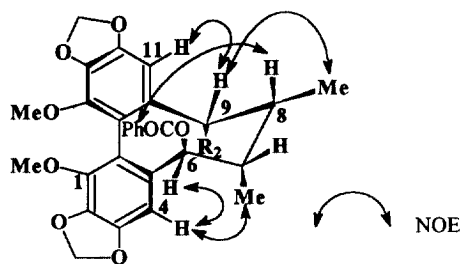
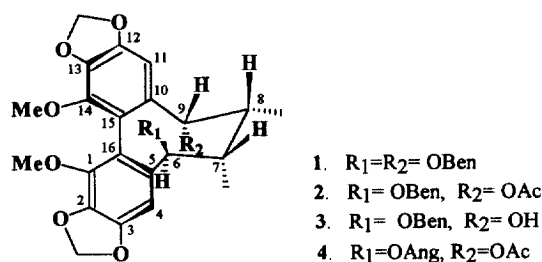


Fig. 1. NOE interactions of compounds 1–3.

enhancements between H-4 and H-6, and H-11 and H-9, indicating that two benzoyl groups were located at the 6 β and 9 α positions. On the basis of the results mentioned above, the absolute structure of **1** was thus determined as (6*R*,7*S*,8*R*,9*R*,5*S*-biar)-6,9-dibenzoyl-oxy-6,7,8,9-tetrahydro-1,14-dimethoxy-2,3,12,13-dimethylenedioxy-7,8-dimethyl-dibenzo[a,c]cyclooctene. The ¹H and ¹³C NMR spectral data were assigned by ¹H-¹H COSY and comparison with literature

Table 2. ¹³C NMR spectral data of compounds 1–3

C	1	2	3
1	141.3 <i>s</i>	141.3 <i>s</i>	141.3 <i>s</i>
2	135.7 <i>s</i>	135.5 <i>s</i>	135.1 <i>s</i>
3	147.7 <i>s</i>	147.5 <i>s</i>	148.6 <i>s</i>
4	105.4 <i>d</i>	105.7 <i>d</i>	106.1 <i>d</i>
5	130.1 <i>s</i>	130.0 <i>s</i>	130.0 <i>s</i>
6	81.3 <i>d</i>	81.3 <i>d</i>	81.3 <i>d</i>
7	38.6 <i>d</i>	38.1 <i>d</i>	39.4 <i>d</i>
8	39.1 <i>d</i>	39.3 <i>d</i>	39.5 <i>d</i>
9	82.0 <i>d</i>	81.3 <i>d</i>	82.3 <i>d</i>
10	133.7 <i>s</i>	133.8 <i>s</i>	137.2 <i>s</i>
11	102.2 <i>d</i>	101.9 <i>d</i>	101.9 <i>d</i>
12	148.7 <i>s</i>	148.6 <i>s</i>	148.7 <i>s</i>
13	136.0 <i>s</i>	135.9 <i>s</i>	136.7 <i>s</i>
14	141.4 <i>s</i>	141.3 <i>s</i>	141.7 <i>s</i>
15	120.5 <i>s</i>	120.4 <i>s</i>	119.3 <i>s</i>
16	122.0 <i>s</i>	121.9 <i>s</i>	120.8 <i>s</i>
7-Me	15.5 <i>q</i>	14.8 <i>q</i>	15.5 <i>q</i>
8-Me	30.9 <i>q</i>	30.6 <i>q</i>	31.0 <i>q</i>
OMe	58.7 <i>q</i>	58.9 <i>q</i>	59.0 <i>q</i>
	59.0 <i>q</i>	59.3 <i>q</i>	59.6 <i>q</i>
OCH ₂ O	100.8 <i>t</i>	100.9 <i>t</i>	100.8 <i>t</i>
	100.9 <i>t</i>	101.0 <i>t</i>	101.4 <i>t</i>
O-Ben C=O	165.8 <i>s</i>	165.1 <i>s</i>	165.2 <i>s</i>
1'	129.7 <i>s</i>	129.8 <i>s</i>	130.0 <i>s</i>
2',6'	129.5 <i>d</i>	130.0 <i>d</i>	129.5 <i>d</i>
3',5'	127.8 <i>d</i>	127.8 <i>d</i>	127.8 <i>d</i>
4'	132.6 <i>d</i>	132.6 <i>d</i>	132.6 <i>d</i>
C=O	165.2 <i>s</i>		
1''	129.7 <i>s</i>		
2'',6''	129.5 <i>d</i>		
3'',5''	127.8 <i>d</i>		
4''	132.6 <i>d</i>		
OAc		169.9 <i>s</i>	
		20.4 <i>q</i>	

Table 1. ¹H NMR spectral data of compounds 1–3*

H	1	2	3
4	6.72 <i>s</i>	6.65 <i>s</i>	6.67 <i>s</i>
6	5.98 <i>d</i> (7.1)	5.86 <i>d</i> (7.0)	5.87 <i>d</i> (7.0)
7	2.33 <i>m</i>	2.25 <i>m</i>	2.25 <i>m</i>
8	2.52 <i>m</i>	2.38 <i>m</i>	2.25 <i>m</i>
9	5.94 <i>d</i> (2.9)	5.64 <i>d</i> (2.0)	4.71 <i>d</i> (2.7)
11	6.60 <i>s</i>	6.49 <i>s</i>	6.36 <i>s</i>
Me-7	1.11 <i>d</i> (7.3)	0.96 <i>d</i> (7.2)	0.98 <i>d</i> (7.1)
Me-8	1.20 <i>d</i> (7.2)	1.10 <i>d</i> (7.2)	1.18 <i>d</i> (7.1)
OCH ₂ O × 2	5.84 <i>d</i> (1.2), 5.81 <i>d</i> (1.2)	5.96 <i>s</i> , 5.92 <i>s</i>	6.00 <i>d</i> (1.3), 5.92 <i>d</i> (1.3)
	5.81 <i>d</i> (1.4), 5.75 <i>d</i> (1.4)	5.83 <i>s</i> , 5.77 <i>s</i>	5.84 <i>d</i> (1.3), 5.75 <i>d</i> (1.3)
OMe × 2	3.49 <i>s</i>	3.79 <i>s</i>	3.82 <i>s</i>
	3.29 <i>s</i>	3.48 <i>s</i>	3.51 <i>s</i>
C ₆ H ₅ CO-			
4'	7.58 <i>m</i> (2H)	7.47 <i>m</i>	7.47 <i>m</i>
2',6'	7.45 <i>m</i> (4H)	7.55 <i>m</i>	7.56 <i>m</i>
3',5'	7.31 <i>m</i> (4H)	7.30 <i>m</i>	7.30 <i>m</i>
CH ₃ CO-		1.65 <i>s</i>	

* *J* (Hz) in parentheses; assignments are based on ¹H-¹H COSY and NOE experiments.

Table 3. NOE enhancement of compounds 1–3

Compound	Irradiation	Observation	NOE enhancement (%)
1	H-6	H-4	19.7
	H-9	H-11	23.0
	H-4	H-6	16.0
	H-11	H-9	14.1
	Me-8	H-9	3.3
	Me-7	H-6	2.5
		H-2',6' (6-O-Ben)	4.9
2	H-6	H-4	20.2
		H-7	7.8
		Me-7	4.1
	H-9	H-11	23.3
		H-8	8.2
		Me-8	4.3
	H-4	H-6	15.7
		Me-7	2.6
	H-11	H-9	14.2
	H-8	H-9	7.5
	H-7	H-2',6'	4.3
		H-6	9.2
	Me-8	H-9	3.6
3	H-6	H-4	22.4
		Me-7	2.0
	H-9	H-11	20.9
	H-4	H-6	14.6
	H-11	H-9	12.7
	Me-8	H-9	3.4

values [3, 6]. In addition, the *J* value (2.9 Hz) between H-8 β and H-9 β and the NOEs between H-4 and Me-7, H-4 and H-6 α , Me-8 and H-9, and H-9 and H-11 indicated a twist-boat-chair confirmation of the cyclooctadiene ring.

Compounds **2** and **3** both were obtained as colourless gums. Their molecular formulae were determined by HRMS as C₃₁H₃₀O₁₀ and C₂₉H₂₈O₉, respectively. Their IR, UV, CD and NMR data were very similar to those of **1**. The only structural difference among **2**, **3** and **1** was in the substitution at C-9 α . The ¹H NMR (Table 1), ¹³C NMR (Table 2) and EIMS data a 9 α -acetyl group (δ 1.62, 3H, *s*, δ 169.9, 20.4) in **2** and a 9 α -hydroxy group in **3**, instead of the benzoyl group in **1**. The NOEs between H-4 and H-6 α , H-4 and Me-7, H-9 β and H-11, and H-9 and Me-8 further confirmed the stereochemistry and the twist-boat-chair conformation of the cyclooctadiene ring. The *S*-biphenyl configuration of **2** and **3** was deduced from the characteristic CD spectrum, which was similar to that of **1**. Thus the structures of **2** and **3** were elucidated as (6*R*,7*S*,8*R*,9*R*,*S*-biar)-6-benzoyloxy-9-acetoxy-6,7,8,9-tetrahydro-1,14-dimethoxy-2,3,12-13-dimethylenedioxy-7,8-dimethyl dibenzo[*a,c*]cyclooctene and (6*R*,7*S*,8*R*,9*R*,*S*-biar)-6-benzoyloxy-9-hydroxy-6,7,8,9-tetrahydro-1,14-dimethoxy-2,3,12-13-dimethylenedioxy-7,8-dimethyl dibenzo[*a,c*]cyclooctene, respectively.

tene and (6*R*,7*S*,8*R*,9*R*,*S*-biar)-6-benzoyloxy-9-hydroxy-6,7,8,9-tetrahydro-1,14-dimethoxy-2,3,12,13-dimethylenedioxy-7,8-dimethyl dibenzo[*a,c*]cyclooctene, respectively.

EXPERIMENTAL

General

MS: 70 eV, Finnigan-450, Varian Mat-711; NMR: Bruker AM-400 with TMS as int. std, CDCl₃ as solvent; Optical rotation: Jasco Dip-181; CD: Jasco J-500A.

Plant material

The stems of *K. angustifolia* A.C. Smith were collected in April, 1993, in Xichou county of Yunnan Province, China and identified by Prof. Quan-an Wu, Kunming Institute of Botany, Chinese Academy of Sciences. The voucher specimen (No. 9304016) is deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and isolation

The stems of *K. angustifolia* (5.2 kg) were air-dried, ground, and extracted with 95% EtOH at room temp. The EtOH extract was evaporated *in vacuo* to yield a dark brown residue. H₂O (2500 ml) was added to the residue, and the resulting soln was extracted with petrol, EtOAc and *n*-BuOH successively. The petrol extract was coned to give a brown mass (130 g) which was applied to a silica gel column, eluting with petrol containing increasing amounts of Me₂CO. The fractions obtained from petrol–Me₂CO. The fractions obtained from petrol–Me₂CO (10:1) elution were combined and subjected to repeated CC and prep. TLC to yield **1** (40 mg), **2** (35 mg) and **3** (24 mg), respectively.

Angustifolin A (1). Colourless gum, $[\alpha]_D^{25} -43.91^\circ$ (MeOH; *c* 0.367). IR $\nu_{\max}^{\text{KBr}} \text{ cm}^{-1}$: 1716 (ester C=O), 1622, 1580, 1500, 1479, 713; UV $\lambda_{\max}^{\text{MeOH}} \text{ nm (log } \epsilon)$: 228.5 (4.59), 256 sh (4.12), 284 sh (3.79); EIMS *m/z* (rel. int.): 624 [M]⁺ (3), 502 [M–C₆H₅COOH]⁺ (7), 380 [M–C₆H₅COOH × 2]⁺ (18), 340 (20), 149 (13), 122 [C₆H₅COOH]⁺ (78), 105 [C₆H₅CO]⁺ (100), 77 [C₆H₅]⁺ (37); HRMS *m/z* 624.1965 (calc. for C₃₆H₃₂O₁₀: 624.1995); CD (MeOH; *c* 0.0125) $\Delta\epsilon_{202} -38.41$, $\Delta\epsilon_{230} +7.87$, $\Delta\epsilon_{244} +8.17$, $\Delta\epsilon_{282} -2.72$; ¹H NMR: Table 1; ¹³C NMR: Table 2.

Angustifolin B (2). Colourless gum, $[\alpha]_D^{25} -3.03^\circ$ (MeOH; *c* 0.363). IR $\nu_{\max}^{\text{KBr}} \text{ cm}^{-1}$: 1739, 1716 (C=O), 1621, 1580, 1500, 1479, 715; UV $\lambda_{\max}^{\text{MeOH}} \text{ nm (log } \epsilon)$: 224.5 (4.76), 257 sh (4.08), 282 sh (3.73); EIMS *m/z* (rel. int.): 562 [M]⁺ (100), 502 [M–CH₃COOH]⁺ (2), 440 [M–C₆H₅COOH]⁺ (5), 380 [M–C₆H₅COOH–CH₃COOH]⁺ (12), 341 (15), 313 (17), 122 (46), 105

(100), 77 (72); HRMS *m/z* 562.1831 (calc. for C₃₁H₃₀O₁₀: 562.1838); CD (MeOH; *c* 0.0115) $\Delta\epsilon_{202} -31.10$, $\Delta\epsilon_{232} +13.03$, $\Delta\epsilon_{248} -7.40$, $\Delta\epsilon_{285} -1.18$; ¹H NMR: Table 1; ¹³C NMR: Table 2.

Angustifolin C (3). Colourless gum, $[\alpha]_D^{25} -14.46^\circ$ (MeOH; *c* 0.277). IR $\nu_{\max}^{\text{KBr}} \text{ cm}^{-1}$: 3436 (OH), 1714 (C=O), 1619, 1500, 1477, 715; UV $\lambda_{\max}^{\text{MeOH}} \text{ nm (log } \epsilon)$: 223 (4.78), 256 sh (4.01), 283 sh (3.75); EIMS *m/z* (rel. int.): 520 [M]⁺ (86), 502 [M–H₂O]⁺ (6), 398 [M–C₆H₅COOH]⁺ (100), 380 [M–C₆H₅COOH–H₂O]⁺ (18), 340 (55), 328 (62), 313 (65), 299 (42), 233 (60), 122 (40), 105 (98), 77 (88); HRMS *m/z* 520.1732 (calc. for C₂₉H₂₈O₉: 520.1733); CD (MeOH; *c* 0.0105) $\Delta\epsilon_{204} -24.90$, $\Delta\epsilon_{228} +10.50$, $\Delta\epsilon_{250} -9.00$, $\Delta\epsilon_{285} -1.50$; ¹H NMR: Table 1; ¹³C NMR: Table 2.

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