

DIBENZOCYCLOOCTADIENE LIGNANS FROM *KADSURA*  
*ANGUSTIFOLIA*YE-GAO CHEN, PING WANG, ZHONG-WEN LIN,<sup>†</sup> HAN-DONG SUN,<sup>†</sup> GUO-WEI QIN\* and YU-YUAN XIE

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

<sup>†</sup> 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.  
© 1998 Elsevier Science Ltd. All rights reserved

## 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

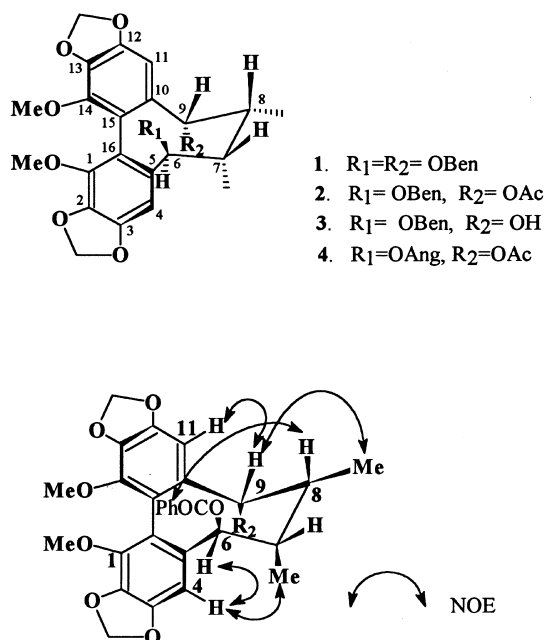
The ethanol extract of the stems of *K. angustifolia* was fractionated into petrol-, EtOAc- and *n*-BuOH-soluble fractions. Repeated CC of the petrol fraction followed by preparative TLC led to the isolation of three new dibenzocyclooctadiene lignans, angustifolin A, B and C (1–3).

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  $\lambda_{max}$  228.5 (log  $\epsilon$  4.59), 256 (log  $\epsilon$ , 4.12, sh) and 284 (log  $\epsilon$ , 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 ( $\delta$  6.72, 6.60, each 1H, *s*), two methylenedioxy moieties ( $\delta$  5.84, 5.81, each 1H, *d*,  $J = 1.2$  Hz;  $\delta$  5.81, 5.75, each 1H, *d*,  $J = 1.4$  Hz) and two methoxy groups ( $\delta$  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  $\delta$  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  $\delta$  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 ( $\delta$  1.11, 1.20, each 3H, *d*,  $J = 7.2$  Hz and  $\delta$  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  $\alpha$ -oriented. The signals at  $\delta$  5.98 (1H, *d*,  $J = 7.1$  Hz) and 5.94 (1H, *d*,  $J = 2.9$  Hz), which correlated with the multiplet signals at  $\delta$  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 acetylshisantherin 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.



enhancements between H-4 and H-6, and H-11 and H-9, indicating that two benzoyl groups were located at the 6 $\beta$  and 9 $\alpha$  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*,*S*-biar)-6,9-dibenzoyloxy-6,7,8,9-tetrahydro-1,14-di-methoxy-2,3,12,13-dimethylenedioxy-7,8-dimethyl-dibenzo[a,c]cyclooctene. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data were assigned by <sup>1</sup>H-<sup>1</sup>H COSY and comparison with literature

Table 2. <sup>13</sup>C 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 <sub>2</sub> 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. <sup>1</sup>H 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 <sub>2</sub> 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 <sub>6</sub> H <sub>5</sub> 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 <sub>3</sub> CO-		1.65 <i>s</i>	

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

Table 3. NOE enhancement of compounds **1**–**3**

Compound	Irradiation	Observation	NOE enhancement (%)
<b>1</b>	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
<b>2</b>	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
	Me-7	H-4	2.3
		H-6	2.2
<b>3</b>	H-6	H-4	22.4
	Me-7	H-4	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 $\beta$  and H-9 $\beta$  and the NOEs between H-4 and Me-7, H-4 and H-6 $\alpha$ , 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 C<sub>31</sub>H<sub>30</sub>O<sub>10</sub> and C<sub>29</sub>H<sub>28</sub>O<sub>9</sub>, 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 $\alpha$ . The <sup>1</sup>H NMR (Table 1), <sup>13</sup>C NMR (Table 2) and EIMS data a 9 $\alpha$ -acetyl group ( $\delta$  1.62, 3H, *s*,  $\delta$  169.9, 20.4) in **2** and a 9 $\alpha$ -hydroxy group in **3**, instead of the benzoyl group in **1**. The NOEs between H-4 and H-6 $\alpha$ , H-4 and Me-7, H-9 $\beta$  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-acetyloxy-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, CDCl<sub>3</sub> 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. H<sub>2</sub>O (2500 ml) was added to the residue, and the resulting soln was extracted with petrol, EtOAc and *n*-BuOH successively. The petrol extract was concd to give a brown mass (130 g) which was applied to a silica gel column, eluting with petrol containing increasing amounts of Me<sub>2</sub>CO. The fractions obtained from petrol–Me<sub>2</sub>CO. The fractions obtained from petrol–Me<sub>2</sub>CO (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  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 1716 (ester C=O), 1622, 1580, 1500, 1479, 713; UV  $\lambda_{\max}^{\text{MeOH}}$  nm (log  $\epsilon$ ): 228.5 (4.59), 256 sh (4.12), 284 sh (3.79); EIMS *m/z* (rel. int.): 624 [M]<sup>+</sup> (3), 502 [M–C<sub>6</sub>H<sub>5</sub>COOH]<sup>+</sup> (7), 380 [M–C<sub>6</sub>H<sub>5</sub>COOH × 2]<sup>+</sup> (18), 340 (20), 149 (13), 122 [C<sub>6</sub>H<sub>5</sub>COOH]<sup>+</sup> (78), 105 [C<sub>6</sub>H<sub>5</sub>CO]<sup>+</sup> (100), 77 [C<sub>6</sub>H<sub>5</sub>]<sup>+</sup> (37); HRMS *m/z* 624.1965 (calc. for C<sub>36</sub>H<sub>32</sub>O<sub>10</sub>: 624.1995); CD (MeOH; *c* 0.0125)  $\Delta\epsilon_{202} -38.41$ ,  $\Delta\epsilon_{230} +7.87$ ,  $\Delta\epsilon_{244} +8.17$ ,  $\Delta\epsilon_{282} -2.72$ ; <sup>1</sup>H NMR: Table 1; <sup>13</sup>C NMR: Table 2.

**Angustifolin B (2).** Colourless gum,  $[\alpha]_D^{25} -3.03^\circ$  (MeOH; *c* 0.363). IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 1739, 1716 (C=O), 1621, 1580, 1500, 1479, 715; UV  $\lambda_{\max}^{\text{MeOH}}$  nm (log  $\epsilon$ ): 224.5 (4.76), 257 sh (4.08), 282 sh (3.73); EIMS *m/z* (rel. int.): 562 [M]<sup>+</sup> (100), 502 [M–CH<sub>3</sub>COOH]<sup>+</sup> (2), 440 [M–C<sub>6</sub>H<sub>5</sub>COOH]<sup>+</sup> (5), 380 [M–C<sub>6</sub>H<sub>5</sub>COOH–CH<sub>3</sub>COOH]<sup>+</sup> (12), 341 (15), 313 (17), 122 (46), 105

(100), 77 (72); HRMS *m/z* 562.1831 (calc. for C<sub>31</sub>H<sub>30</sub>O<sub>10</sub>: 562.1838); CD (MeOH; *c* 0.0115)  $\Delta\epsilon_{204} -31.10$ ,  $\Delta\epsilon_{232} +13.03$ ,  $\Delta\epsilon_{248} -7.40$ ,  $\Delta\epsilon_{285} -1.18$ ; <sup>1</sup>H NMR: Table 1; <sup>13</sup>C NMR: Table 2.

**Angustifolin C (3).** Colourless gum,  $[\alpha]_D^{25} -14.46^\circ$  (MeOH; *c* 0.277). IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 3436 (OH), 1714 (C=O), 1619, 1500, 1477, 715; UV  $\lambda_{\max}^{\text{MeOH}}$  nm (log  $\epsilon$ ): 223 (4.78), 256 sh (4.01), 283 sh (3.75); EIMS *m/z* (rel. int.): 520 [M]<sup>+</sup> (86), 502 [M–H<sub>2</sub>O]<sup>+</sup> (6), 398 [M–C<sub>6</sub>H<sub>5</sub>COOH]<sup>+</sup> (100), 380 [M–C<sub>6</sub>H<sub>5</sub>COOH–H<sub>2</sub>O]<sup>+</sup> (18), 340 (55), 328 (62), 313 (65), 299 (42), 233 (60), 122 (40), 105 (98), 77 (88); HRMS *m/z* 520.1732 (calc. for C<sub>29</sub>H<sub>28</sub>O<sub>9</sub>: 520.1733); CD (MeOH; *c* 0.0105)  $\Delta\epsilon_{204} -24.90$ ,  $\Delta\epsilon_{228} +10.50$ ,  $\Delta\epsilon_{250} -9.00$ ,  $\Delta\epsilon_{285} -1.50$ ; <sup>1</sup>H NMR: Table 1; <sup>13</sup>C NMR: Table 2.

### REFERENCES

1. Yunnan Provincial Crude Drugs Company, *Name Lists of Chinese Herbal Medicine Resources in Yunnan*, Science Press, Beijing, 1993, p. 151.
2. Ikeya, Y., Taguchi, H., Yoshioka, I. and Kobayashi, H., *Chemical and Pharmaceutical Bulletin*, 1979, **27**, 1383.
3. Ikeya, Y., Taguchi, H., Nakajima, K. and Yoshioka, I., *Chemical and Pharmaceutical Bulletin*, 1980, **28**, 2414.
4. Ikeya, Y., Taguchi, H. and Yoshioka, I., *Chemical and Pharmaceutical Bulletin*, 1982, **30**, 3207.
5. Chen, Y.-Y., Shu, Z.-B. and Li, L.-N., *Scientia Sinica*, 1976, **19**, 276.
6. Liu, J.-S. and Li, L., *Phytochemistry*, 1993, **32**, 1293.