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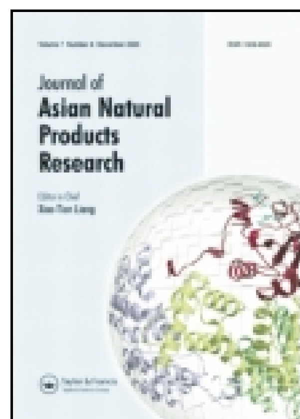

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Lignans from *Kadsura angustifolia* and *Kadsura coccinea*

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Further phytochemical investigation of *Kadsura angustifolia* and *Kadsura coccinea* led to the isolation of six lignans and one flavonoid, including two new lignans named kadangustin L (**1**) and kadcoccilignan (**2**). The structures and stereochemistry of **1** and **2** were elucidated by analysis of spectroscopic data.

Keywords: *Kadsura angustifolia*; *Kadsura coccinea*; lignan; Schisandraceae

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1. Introduction

Phytochemical studies showed that the principal bioactive constituents of the genus *Kadsura* (Schisandraceae) were lignans and triterpenoids, some of which exhibited considerable bioactivities such as cytotoxic [1–5], anti-HIV [6,7], anti-human immunodeficiency virus-1 activity [8], and antiproliferative [9] effects.

Kadsura coccinea (Lem.) A.C. Smith is an evergreen climbing shrub growing in southwest China. Its stems are used to treat fractures and rheumatoid arthritis in traditional Chinese medicine [10]. *Kadsura angustifolia* (Lem.) A.C. Smith is an evergreen liana, growing in the forests at elevations of 1280–2250 m in Yunnan Province, China [11]. Its stems are used as a folk medicine to promote blood circulation and treat fractures and menstrual irregularities. Previously, we reported 18 new compounds named kadcoccilactones A–R isolated from the stems of *K. coccinea* [4,5], and 11 new compounds named kadangustins A–K isolated from the stems of *K. angustifolia* [6]. In our continuous investigation of new biologically potent active compounds from this genus, one new lignan named Kadangustin L (**1**) was isolated from *K. angustifolia*, and six lignans and one flavonoid were isolated from *K. coccinea*, including one new lignan named kadcoccilignan (**2**). The structures of the new compounds **1** and **2** were established by means of MS and extensive NMR spectra, and the absolute configurations of **1** were determined by CD and ROESY experiments.

2. Results and discussion

A 70% aqueous acetone extract prepared from the stems of *K. angustifolia* and *K. coccinea* was partitioned between EtOAc and H_2O. The EtOAc layer was subjected repeatedly to column chromatography on silica gel, Sephadex LH-20, RP-18, and HPLC to afford compounds **1**–**7**, including two new lignans named kadangustin L (**1**) and kadcoccilignan (**2**), together with four known lignans, kadsuralignan A (**3**) [12], *ent*-isolariciresinol (**4**) [13], dehydrodiconiferyl alcohol (**5**) [14], vladirol F

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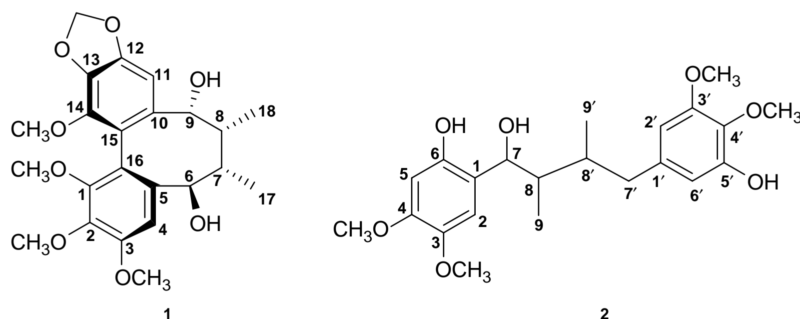

Figure 1. The structures of compounds **1** and **2**.

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(**6**) [8], and the known flavonoid ascovertin (**7**) [15] (Figure 1). The NMR spectroscopic data of the new lignans **1** and **2** are listed in Tables 1 and 2.

Kadangustin L (**1**), obtained as a pale yellow, amorphous powder, was assigned the molecular formula $C_{23}H_{28}O_8$ by HR-ESI-MS at *m/z* 455.1691 $[M + Na]^+$, with 10 degrees of unsaturation. The ^1H and ^{13}C NMR spectra of **1** indicated the presence of 12 aromatic carbons, 2 aromatic protons, and 4 methoxy groups, suggesting the presence of a biphenyl moiety [16]. HMBC correlations of H-11 with C-9,

Table 1. ^1H and ^{13}C NMR spectral data of **1** in $CDCl_3$.

No.	**1**[a] δ_H	δ_C
1		151.2 s
2		141.1 s
3		153.1 s
4	7.04 (s)	106.5 d
5		135.4 s
6	4.59 (d, 10.6)	83.9 d
7	2.04–2.08 (m)	43.7 d
8	2.14–2.19 (m)	41.7 d
9	5.97 (d, 4.9)	72.6 d
10		138.7 s
11	6.32 (s)	102.2 d
12		149.1 s
13		135.4 s
14		138.7 s
15		117.6 s
16		119.9 s
17	0.92 (d, 7.4)	9.8 q
18	1.20 (d, 7.2)	20.3 q
1-OMe	3.67 (s)	60.6 q
2-OMe	3.91 (s)	61.0 q
3-OMe	3.92 (s)	56.0 q
14-OMe	3.87 (s)	59.7 q
12,13-OCH_2O	5.97 (s)	101.2 t

[a] Data were recorded with a Bruker DRX-500 or 125 MHz spectrometer, chemical shifts (δ) are in ppm, *J* in Hz.

Table 2. ^1H and ^{13}C NMR spectral data of compound **2** in C_5D_5N.

No.	**2** δ_H	δ_C
1		135.9 s
2	7.23 (s)	109.4 d
3		143.0 s
4		151.9 s
5	6.81 (s)	102.9 d
6		154.0 s
7	4.83 (d, 8.9)	77.0 d
8	1.82–1.86 (m)	45.8 d
9	0.86 (d, 6.9)	12.0 q
1′		139.3 s
2′	6.70 (s)	105.2 d
3′		153.9 s
4′		136.6 s
5′		151.8 s
6′	7.06 (s)	111.4 d
7′a	3.31 (br d, 10.4)	38.1 t
7′b	2.28–2.32 (m)	
8′	2.90–2.93 (m)	35.6 d
9′	0.88 (d, 6.9)	18.3 q
3-OMe	3.78 (s)	55.9 q
4-OMe	3.90 (s)	60.5 q
3′-OMe	3.79 (s)	55.9 q
4′-OMe	3.90 (s)	60.5 q

Data were recorded with a Bruker DRX-500 or 125 MHz spectrometer, chemical shifts (δ) are in ppm, *J* in Hz.

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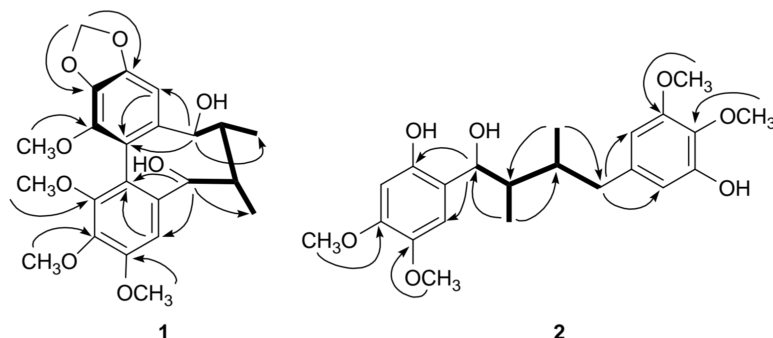

Figure 2. Selected HMBC (→) and $^{1}H-^{1}H$ COSY (—) correlations of **1** and **2**.

C-10, and C-15, and of H-4 with C-5, C-6, and C-16, together with $^{1}H-^{1}H$ COSY correlations of H-6/H-7/H-8/H-9 (Figure 2) and UV absorption bands at 360, 309, 284, and 210 nm, implied that **1** could be a dibenzocyclooctadiene lignan [16]. Further analysis of the HMBC spectrum showed that four methoxy groups were located at C-1, C-2, C-3, and C-14, respectively (Figure 1). In the cyclooctadiene ring, two secondary methyl groups (δ_H 0.92, d, $J = 7.4$ Hz; δ_H 1.20, d, $J = 7.2$ Hz) can be assigned to CH_3-17 and CH_3-18, respectively. The signals of two benzylic oxymethines were assigned to C-6 and C-9. According to the molecular formula, the benzylic oxymethines at C-6 and C-9 should both be substituted by a hydroxy group.

Since the CD spectra of dibenzocyclooctadiene lignans are dominated by the axial chirality of the biphenyl chromophore, the absolute configuration of the biphenyl axis of compound **1** could be determined by CD. The CD curve showed a negative Cotton effect around 250 nm and a positive one around 220 nm, suggesting that **1** possessed an *S*-biphenyl configuration [16]. With the axial chirality defined, a ROESY experiment was used to establish the relative configuration of the remaining stereocenters. The observed ROESY correlations of H-11 with H-8 and H-9; H-4 with H-6 and H_3-17; and H_3-18 with H-9 and H_3-17 were consistent with a cyclooctadiene lignan with a twisted boat/chair conformation and the relative configurations of C-6 (*R*), C-7 (*S*), C-8 (*R*), and C-9 (*R*) (Figure 3) [17]. Furthermore, the proton–proton coupling constants of H-6 with H-7 (d, $J = 10.6$ Hz) and of H-9 with H-8 (d, $J = 4.9$ Hz) were in accordance with the outlined relative configuration. As a result, the structure of kadangustin L (**1**) was determined as shown in Figure 1.

Kadcoccilignan (**2**) was obtained as a pale yellow, amorphous solid. Its molecular formula was determined as $C_{22}H_{30}O_7$ by the HR-ESI-MS at *m/z* 429.1895 $[M + Na]^+$ (calcd 429.1889), suggesting eight degrees of unsaturation. The functional groups appearing in the ^{1}H and ^{13}C NMR spectra included two aromatic rings, four methoxy groups, two methyl groups, one methylene group, and seven methine groups. The strong IR absorption bands indicated the presence of hydroxy groups (3436 cm^{-1}) and aromatic rings (1601, 1512, and 1463 cm^{-1}). In the HMBC spectrum, correlations were found from H-2 to C-7 and from H-2′ and H-6′ to C-7′, which implied that the two substituted aromatic moieties were not linked directly (Figure 1). Moreover, the HMBC correlations of H-9 with C-7, C-8, and C-8′; of H-9′ with C-7′, C-8′, and C-8; of H-8 with C-1, C-7, and C-7′; and of H-8′ with C-1′, C-7, and C-7′, together with the spin system of H-7/H-8/H-8′/H-7′, H-8/H-9,

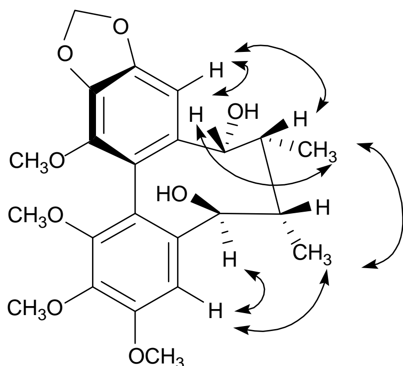

Figure 3. Key ROESY correlations of compound **1**.

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and H-8′/H-9′ in the $^1H-^1H$ COSY spectrum, suggested that the skeleton of **2** was a substituted 1,4-bisphenyl-2,3-dimethylbutane-type lignan (Figure 2) [6]. The chemical shift of C-7 (δ_C 77.0, d; Table 1) and the molecular formula suggested a hydroxy group at C-7. The correlations from the protons of four methoxy groups to C-3′, C-4′, C-3, and C-4 located these groups at C-3′, C-4′, C-3, and C-4, respectively. Considering the presence of two quaternary carbons (C-6 and C-5′) in **2** and its molecular formula, two hydroxy groups should be attached to C-6 and C-5′. On the basis of the above analysis, the structure of kadcoccilignan (**2**) was determined as shown in Figure 1.

Since the C—C bonds can rotate randomly, the relative configuration of **2** could not be determined on the basis of ROESY spectra.

3. Experimental

3.1 *General experimental procedures*

Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A Tenor 27 spectrophotometer was used for scanning IR spectroscopy with KBr pellets. CD spectra were measured on a JASCO J-810 spectropolarimeter. 1D and 2D NMR spectra were recorded on Bruker AM-400 and Bruker DRX-500 spectrometers with TMS as an internal standard. Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to the solvent signals. HR-ESI-MS and FAB-MS were obtained on an API QSTAR time-of-flight spectrometer and a VG Autospec-3000 spectrometer, respectively. Semipreparative HPLC was carried out on an Agilent 1100 liquid chromatograph with a Zorbax SB-C_{18} (9.4 mm × 25 cm) column. Preparative HPLC was carried out on a Shimadzu LC-8A preparative liquid chromatograph with a Shimadzu PRC-ODS (K) column (34 mm × 15 cm). Column chromatography was performed with silica gel (200–300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China), Lichroprep RP-18 gel (40–63 μm, Merck, Darmstadt, Germany), and MCI-gel CHP 20P (75–150 μm, Mitsubishi Chemical Corporation, Tokyo, Japan). Fractions were monitored by TLC and spots were visualized by heating silica gel plates sprayed with 5% H_2SO_4 in EtOH.

3.2 *Plant material*

The stems of *K. angustifolia* and *K. coccinea* were collected in Honghe Prefecture of Yunnan Province, China, in October 2005. The identity of the plant material was verified by Prof. Xi-Wen Li. A voucher specimen (KIB 05-10-10) has been deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, China.

3.3 *Extraction and isolation*

The air-dried and powdered stems of *K. angustifolia* (12 kg) and *K. coccinea* (13 kg) were extracted four times with 70% aqueous Me_2CO (4 × 50 liters) at room temperature and filtered to yield a filtrate, which was successively evaporated under

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reduced pressure and partitioned with EtOAc (3 × 4 liters), separately.

The EtOAc partition (636 g) of *K. angustifolia* was applied to silica gel (200–300 mesh) column chromatography eluting with a $CHCl_3$–MeOH gradient system (20:1, 9:1, 8:2, 7:3, 6:4, 5:5) to give five fractions, A–E. The separation of fraction A by silica gel column chromatography eluted with petroleum ether–acetone (20:1–6:4) yielded mixtures A1–A7. Fraction A4 (60 g) was subjected to silica gel column chromatography using petroleum ether–acetone (20:1–6:4) for elution followed by a reversed-phase column (RP-18) eluting with MeOH–H_2O (30–90%) and then by Sephadex LH-20 using MeOH as eluant. Further purifications were carried out by preparative HPLC separation (60% MeOH–H_2O, flow rate 3 ml/min, 25 ml/min) to give compound **1** (3 mg), RT 23 min.

The EtOAc-soluble portion (413 g) of *K. coccinea* was chromatographed on a silica gel column eluting with $CHCl_3$–Me_2CO (1:0, 40:1, 9:1, 8:2, 7:3, 1:1, and 0:1) to afford five fractions, I–V. Fraction III (15 g) was then chromatographed on silica gel (petroleum ether–Me_2CO, 20:1–2:1) to give 18 fractions. Fraction III-1 (950 mg) was subjected to Sephadex LH-20 using MeOH as eluant to give 40 fractions. Fraction III-4-35 (60 mg) was subjected to preparative HPLC (MeOH–H_2O, 35:65) to yield compound **4** (4 mg), RT 24 min. Fraction III-3 (325 mg) was separated over Sephadex LH-20 eluting with MeOH and then subjected to preparative HPLC (MeOH–H_2O, 60:40) to yield compounds **5** and **6** (5 mg), RT 36 min. Fraction II was chromatographed on silica gel (petroleum ether–Me_2CO, 20:1–2:1) to yield 14 fractions. Fractions II-1, II-5, and II-6 were chromatographed on reversed-phase column (RP-18) eluting with MeOH–H_2O (30–90%) and then by Sephadex LH-20 using MeOH as eluant. Subfractions II-1-6-6 was purified by preparative HPLC (MeOH–H_2O, 55:45) to afford compound **3** (3 mg), RT 40 min. Fraction II-5-18 was purified by preparative HPLC (MeOH–H_2O, 55:45) to afford compound **2** (3 mg), RT 74 min. Fraction II-6-11 was purified by preparative HPLC (MeOH–H_2O, 40:60) to afford compound **7** (3 mg), RT 20 min.

*3.3.1 Compound **1***

A pale yellow, amorphous powder. $[\alpha]_D^{17.4}$ −15.6 (*c* 0.550, MeOH). CD (MeOH) $\Delta\varepsilon_{250\,nm}$ −55.86, $\Delta\varepsilon_{221\,nm}$ +2.13. UV (MeOH): λ_{max} (log ε) 217 (4.32) nm. IR (KBr): ν_{max} 3441, 2939, 2879, 1621, 1599, 1494, 1477, 1464, 1424, 1404, 1366, 1325, 1269, 1253, 1230, 1197, 1147, 1106, 1028 cm^{-1}. ^1H and ^{13}C NMR spectral data ($CDCl_3$) see Table 1. Positive FAB-MS: *m/z* 432 (100) $[M]^+$, 415 (71), 111 (40); positive HR-ESI-MS: *m/z* 455.1691 $[M + Na]^+$ (calcd for $C_{23}H_{28}O_8Na$, 455.1681).

*3.3.2 Compound **2***

A pale yellow, amorphous powder. $[\alpha]_D^{17.4}$ −4.2 (*c* 0.076, MeOH). UV (MeOH): λ_{max} (log ε) 277 (3.64), 206 (5.10) nm. IR (KBr): ν_{max} 3436, 2960, 2934, 2875, 2834, 1709, 1601, 1512, 1463, 1432, 1418, 1380, 1349, 1268, 1237, 1165, 1130, 1039, 1001 cm^{-1}. ^1H and ^{13}C NMR spectral data (C_5D_5N) see Table 2. Positive FAB-MS: *m/z* 406 (20) $[M]^+$, 389 (100), 359 (18), 235 (40), 221 (18), 194 (18), 69 (9); positive HR-ESI-MS: *m/z* 429.1895 $[M + Na]^+$ (calcd for $C_{22}H_{30}O_7Na$, 429.1889).

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