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KADSULIGNANS L–N, THREE DIBENZOCYCLOOCTADIENE LIGNANS FROM *KADSURA COCCINEA*

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Key Word Index—*Kadsura coccinea*; Schisandraceae; lignans; kadsulignans L–N; neokadsuranin; atropisomerization; anti-HIV.

Abstract—Three new lignans, kadsulignans L–N, were isolated from the seeds of *Kadsura coccinea*, of which kadsulignan M shows anti-HIV activity *in vitro*. Their structures, including absolute configurations, were elucidated by spectroscopic analysis and chemical conversions. In addition, their atropisomerization and CD rule for assignment of biphenyl configuration were also discussed and the biphenyl configuration of neokadsuranin was revised as *R*.

INTRODUCTION

Kadsura coccinea (Lem.) A.C. Sm. is an ethno-medicine used for treatment of gastroenteric disorders and rheumatoid arthritis in southern China. In our previous papers we reported two novel spiro-dienone lignans, kadsulignan A and B [1], and five dibenzocyclooctadiene lignans, schisantherins L–O and acetyl schisantherin L [2], isolated from the seeds of the plant.

A continuing investigation of the extract led to the isolation of three new lignans, designated as kadsulignans L (**1**), M (**2**) and N (**3**), along with the known lignan **4** [3]. In the anti-HIV screening, **2** exhibits a significant activity against HIV *in vitro* (IC_{50} 1.19×10^{-4} M, EC_{50} 6.03 $\times 10^{-6}$ M) [Anti-HIV report of NCI using CEM-IW cell line (T4 lymphocytes), personal communication from Dr John P. Bader].

The present paper describes the isolation, structural elucidation, including absolute configurations, and atropisomerization of **1**–**3**. In addition, the structure revision of neokadsuranin, a related known compound [4], and the experimental CD rule [5] for the absolute configuration assignment of biphenyl are also discussed.

RESULTS AND DISCUSSION

Kadsulignan L (**1**) exhibits spectral features resembling those of the known lignan **4** [3]. The ^{1}H NMR spectrum of **1** (Table 1) indicates that structural differences between **1** and **4** are in aromatic ring substitution: two methoxyls in **1** replace one methylenedioxy group in **4**. Furthermore, the ^{1}H NMR spectrum also reveals that **1** is reversibly atropisomerizing into **1c**, a diastereomer of **1**, and the final equilibrium ratio of atropisomers, **1** and **1c**, is close to 1:1 in a $CDCl_3$ solution standing over 72 hr at room temperature. In addition, a mutarotated specific rotation in $CHCl_3$ or methanol and a variable CD spectrum in methanol (Table 2) were observed, while the UV spectrum has no observable change in the interconversion of atropisomers. The relative stereochemistry of **1** was determined by NOE measurements (Table 3).

In order to elucidate the position of the methylenedioxy group and absolute stereochemistry, a chemical conversion was conducted. Treatment of **1** in acetonitrile with $MgBr_2$–Ac_2O at room temperature for 3 hr afforded an optically active dibenzocyclooctadiene lignan compound (**1a**) in 60% yield. The CD spectrum of **1a** showed a negative Cotton effect at 242 and 253 nm, and a positive Cotton effect at 224 nm, predicting an *S*-configuration of biphenyl according to an experimental CD rule [5]. Reduction of **1** or **1a** with $LiAlH_4$–$AlCl_3$ provided the known compound, (−)-gomisin N (**1b**) [6, 7], in 80 and 59% yield, respectively, which firmly verified the position of the methylenedioxy group at 12, 13 and the *S*-configuration of biphenyl, as well as the absolute stereochemistry shown in **1**. Therefore, the structure of kadsulignan L was unambiguously assigned to **1** with the configuration of 6*S*, 7*S*, 8*R*, 9*R* and *S*-biphenyl.

However, the CD spectrum of **1** displays a positive Cotton effect at 243 nm and a negative one at 223 nm, predicting a contrary configuration of biphenyl according to the experimental CD rule [5], in accordance with the positive Cotton effect around 240 nm with a negative Cotton effect around 220 nm which is used to predict an *R*-biphenyl configuration. Our chemical conversion result demonstrated that the 6,9-oxygen bridged dibenzocyclooctadiene lignan (e.g. in **1** and **2**) is an exception of the above experimental CD rule, which is usually employed

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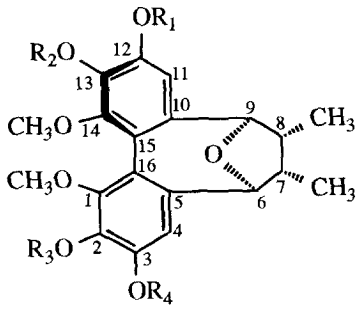


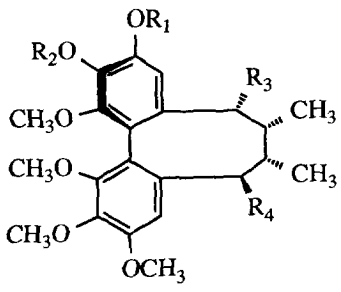
1 $R_1 + R_2 = CH_2$, $R_3 = R_4 = CH_3$

2 $R_1 + R_2 = CH_2$, $R_3 = CH_3$, $R_4 = H$

3 $R_1 = R_2 = R_3 = R_4 = CH_3$

4 $R_1 + R_2 = R_3 + R_4 = CH_2$

5 $R_1 = R_2 = CH_3$, $R_3 + R_4 = CH_2$

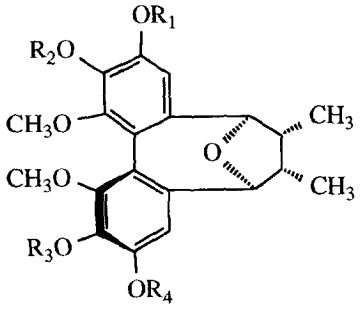


1a $R_1 + R_2 = CH_2$, $R_3 = OAc$, $R_4 = OH$

1b $R_1 + R_2 = CH_2$, $R_3 = R_4 = H$

3a $R_1 = R_2 = CH_3$, $R_3 = OAc$, $R_4 = OH$

3b $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$



1c $R_1 + R_2 = CH_2$, $R_3 = R_4 = CH_3$

2c $R_1 + R_2 = CH_2$, $R_3 = CH_3$, $R_4 = H$

6 $R_1 = R_2 = CH_3$, $R_3 + R_4 = CH_2$

to assign the biphenyl configuration of the common dibenzocyclooctadiene lignans (e.g. **1a** and **1b**). It is doubtless that there was no configuration inversion of biphenyl incurred in the course of chemical transformation from **1** via **1a** to **1b**, or from **1** direct to **1b**, since the reaction was completed within 3 hr at room temperature and provided the optical compound **1a** in 60% yield or **1b** in 80% yield. In that condition, the atropisomer of **1** may be less than 5% on the basis of indication of ^{1}H NMR spectroscopic study.

In addition, it was reported that a similar compound, neokadsuranin, with structure **5**, was isolated from the stem of the same species of plant [4]. However, the ^{1}H NMR spectroscopic data of neokadsuranin are quite similar to that of **1c** instead of **1** (Table 1), and its CD data (Table 2) shows the opposite Cotton effect with a different amplitude to those of **1**, indicating that neokadsuranin may have an *R*-configuration of biphenyl instead of an *S*-configuration as reported in [4] and the structure of neokadsuranin may be revised as **6**. The misassignment of biphenyl configuration of neokadsuranin was incurred by employing the above experimental CD rule [5].

Kadsulignan M (**2**) also shows the atropisomerization properties in a solution, e.g. a mutarotated specific rotation, a variable CD spectrum (Table 2) and two atropisomers (**2** and **2c**) ^{1}H NMR spectra (Table 1). A comparison of ^{1}H NMR and CD spectra of **2** with those of **1** revealed that **2** is a 3-demethyl kadsulignan L. The 3-hydroxyl of **2** was also indirectly proved by none of the methoxyl protons showing NOE enhancement to the aromatic proton H-4 (Table 3). Methylation of **2** provided the identical compound **1**, further verifying kadsulignan M possesses a structure **2** with the same stereochemistry as **1**.

Kadsulignan N (**3**) has no optical activity and no methylenedioxy group in the molecule. The structural difference between **3** and **1** indicated by ^{1}H NMR spectroscopy (Table 1) is only that two methoxyls in **3** replace the methylenedioxy group of **1**. Treatment of **3** with $MgBr_2$–Ac_2O provided (±)-**3a** and reduction of **3** with $LiAlH_4$–$AlCl_3$ afforded (±)-deoxyschizandrin (**3b**), leading to a conclusion that kadsulignan N is a racemate of **3**. In contrast to **1** and **2**, the atropisomers of **3** and **4** are the enantiomers instead of their diastereomers due to the

Table 1. ^{1}H NMR data* of **1**–**4** and their atropisomers (δ, ppm in $CDCl_3$, 400 MHz)

H	1	1c	2	2c	3	4†
4	6.49 *s*	6.44 *s*	6.53 *s*	6.44 *s*	6.48 *s*	6.44 *s*
11	6.30 *s*	6.35 *s*	6.31 *s*	6.42 *s*	6.33 *s*	6.31 *s*
6	4.33 *d* (6.9)	4.96 *s*	4.29 *d* (6.9)	4.95 *s*	4.35 *d* (6.9)	4.31 *d* (6.9)
7	2.66 *qdd* (6.9/6.9/6.9)	2.06 *qd* (6.9/6.9)	2.63 *qdd* (6.9/6.9/6.9)	2.04 *qd* (6.9/6.9)	2.64 *qdd* (6.9/6.9/6.9)	2.65 *qdd* (6.9/6.9/6.9)
8	2.06 *qd* (6.9/6.9)	2.66 *qdd* (6.9/6.9/6.9)	2.04 *qd* (6.9/6.9)	2.63 *qdd* (6.9/6.9/6.9)	2.07 *qd* (6.9/6.9)	2.08 *qd* (6.9/6.9)
9	4.90 *s*	4.33 *d* (6.9)	4.96 *s*	4.32 *d* (6.9)	4.96 *s*	4.90 *s*
Me-7	1.05 *d* (6.9)	1.05 *d* (6.9)	1.02 *d* (6.9)‡	1.04 *d* (6.9)‡	1.07 *d* (6.9)	1.01 *d* (6.9)
Me-8	1.05 *d* (6.9)	1.05 *d* (6.9)	1.04 *d* (6.9)‡	1.03 *d* (6.9)‡	1.07 *d* (6.9)	1.01 *d* (6.9)
OCH_2O	5.93 *s*	5.92 *s*	5.90 *s*	5.89 *s*	—	5.92 2H, *s*
	5.95 *s*	5.96 *s*	5.96 *s*	5.97 *s*	—	5.97 2H, *s*
OMe-1	3.48 *s*	3.45 *s*	3.43 *s*	3.39 *s*	3.50 *s*	3.76 *s*‡
OMe-2	3.90 *s*	3.87 *s*	3.96 *s*	3.94 *s*	3.85 *s*	—
OMe-3	3.90 *s*	3.93 *s*	—	—	3.88 *s*	—
OMe-12	—	—	—	—	3.88 *s*	—
OMe-13	—	—	—	—	3.85 *s*	—
OMe-14	3.85 *s*	3.83 *s*	3.85 *s*	3.78 *s*	3.50 *s*	3.85 *s*
OH	—	—	5.57 *br s*	5.57 *br s*	—	—

*J (Hz) in parentheses; the data of **1** and **2** were obtained within 2 hr when no atropisomer was observed while the data of **1c** and **2c** were acquired from an equilibrium mixture of atropisomers in $CDCl_3$.

†Recorded on 100 MHz instrument.

‡May be exchanged in column.

Table 2. The variable CD data* of **1** and **2** in methanol

	1		2		5†
Compound	Within 10 min	After 72 hr	Within 10 min	After 72 hr	
	−31.36 (223)	−3.58 (215)	−22.73 (225)	unobservable	
	0 (231)	0 (225)	0 (232)	0 (220)	0 (235)
Δε (nm)	+76.17 (243)	+23.30 (240)	+53.03 (242)	+10.10 (238)	−0.75 (248)
		0 (250)		0 (245)	
		−4.84 (254)		−8.84 (252)	
	0 (260)		0 (260)		0 (275)
	−19.71 (287)	−2.69 (285)	−12.63 (290)	unobservable	+0.19 (293)

*At room temperature.

†The data is quoted from ref. [4].

symmetry of substituents in the molecule. Therefore, ^{1}H NMR spectra of **3** and **4** in an atropisomerizing solution only show one compound signals, respectively (Table 1).

EXPERIMENTAL

Mps: uncorr. Silica gel: Quingdao Haiyang Chemicals. HPTLC plates: Yantai Institute of Chemical Technology.

Extraction and preliminary separation. As carried out in ref. [2] to yield 4 frs, A–D.

Kadsulignan L (**1**). Fr. A was chromatographed over silica gel eluted with petrol–Et_2O (10:1, 5:1 and 3:1) in turn. The fr. eluted by petrol–Et_2O (5:1) gave **1** (28.5 g, 0.39%), recrystallized from MeOH as needles, mp 149–150°, $[\alpha]_D$ +12.2° (initial, $CHCl_3$; *c* 3.301); UV λ_{max}^{MeOH} nm (log ε): 228 (4.91), 262 (4.11, sh), 288 (4.58); IR ν_{max}^{KBr} cm^{-1}: 2960, 1610, 1590; ^{1}H NMR: Table 1; HRMS *m/z* (rel. int.): 414.1721 ($[M]^+$, calcd for $C_{23}H_{26}O_7$, 414.1679) (100), 249.1127 $[C_{14}H_{17}O_4]^+$ (6.4), 233.0834 $[C_{13}H_{13}O_4]^+$ (9.9); CD: Table 2.

Compound **4**. The frs eluted with petrol–Et_2O (10:1) in above CC were combined and rechromatographed over silica gel using petrol–Et_2O (8:1), giving **4** (15.2 g), recrystallized from MeOH, mp 177–178°, $[\alpha]_D$ 0° (MeOH); UV λ_{max}^{MeOH} nm (log ε): 228 (4.52), 264 (3.67, sh), 290 (4.18); IR ν_{max}^{KBr} cm^{-1}: 1600, 1477; ^{1}H NMR: Table 1; HRMS *m/z* (rel. int.): 398.1351 ($[M]^+$, calcd for $C_{22}H_{22}O_7$, 398.1366) (100); CD in MeOH: no Cotton curver over 200 nm. All data are coincidental with those reported in ref. [3].

Table 3. NOE enhancements of **1** and **2** in $CDCl_3$

Compound	Irradiation	δ	Observation	δ	NOE enhancement (%)
1	OMe-3	3.90	H-4	6.49	15
	H-6	4.33	H-4	6.49	20
	H-7	2.66	H-8	2.06	13
	H-8	2.06	H-7	2.66	14
	H-9	4.90	H-11	6.30	19
	Me-7, 8	1.05	H-6	4.33	18
			H-9	4.90	18
2	OMe-1	3.43	H-4	6.53	0
	OMe-2	3.96	H-4	6.53	0
	OMe-14	3.85	H-4	6.53	0
	H-6	4.29	H-4	6.53	26
	H-7	2.63	H-8	2.04	11
	H-8	2.04	H-7	2.63	12
	H-9	4.96	H-11	6.31	21
	Me-7, 8	1.03	H-6	4.29	17
			H-9	4.96	18

Kadsulignan M (**2**). Fr. B was chromatographed over silica gel using petrol–Me_2CO (5:1). The front frs were combined and rechromatographed over silica gel eluting with petrol–Et_2O (5:1 and 3:1). The fr. eluted with petrol–Et_2O (3:1) afforded **2** (110 mg, 0.0015%), recrystallized from MeOH, mp 199–201°; $[\alpha]_D$ +17.5° (initial, MeOH; *c* 0.628); UV λ_{max}^{MeOH} nm (log ε): 220 (4.95), 268 (4.15, sh), 286 (4.28); IR ν_{max}^{KBr} cm^{-1}: 3520–3450, 1615, 1590; ^1H NMR: Table 1; ^{13}C NMR ($CDCl_3$, 25.2 MHz): δ13.4, 14.0 (*q*, Me-7, Me-8), 37.8, 52.5 (*d*, C-7, C-8), 59.8, 60.6, 60.9 (*q*, OMe × 3), 90.2, 90.4 (*d*, C-6, C-9), 100.9 (*t*, OCH_2O), 100.1, 109.9 (*d*, C-11, C-4), 117.8, 119.4 (*s*, C-16, C-15), 136.8, 138.0 (*s*, C-5, C-10), 140.1, 141.4 (*s*, C-13, C-2), 147.4, 148.2 (*s*, C-14, C-1), 152.4, 154.1 (*s*, C-12, C-3); HRMS *m/z* (rel. int.): 400.1528 ($[M]^+$, calcd for $C_{22}H_{24}O_7$, 400.1522) (100), 330.0716 $[C_{17}H_{14}O_7]^+$ (15.9), 233.0830 $[C_{13}H_{13}O_4]^+$ (14.3); CD: Table 2.

Kadsulignan N (**3**). Fr. C was chromatographed over silica gel using petrol–Et_2O (5:1, 2:1 and 1:1). The fr. eluted with petrol–Et_2O (5:1) gave **3** (25.6 g, 0.36%), recrystallized from MeOH, mp 113–115°; $[\alpha]_D$ 0° (MeOH); UV λ_{max}^{MeOH} nm (log ε): 225 (4.99), 258 (4.23, sh), 283 (4.73); IR ν_{max}^{KBr} cm^{-1}: 1600, 1570; ^1H NMR: Table 1; HRMS *m/z* (rel. int.): 430.1974 ($[M]^+$, calcd for $C_{24}H_{30}O_7$, 430.1992) (100), 399.1009 $[M-OMe]^+$ (7.5), 360.1232 $[C_{19}H_{20}O_7]^+$ (8.1), 356.1630 $[C_{21}H_{23}O_5]^+$ (8.3), 249.1133 $[C_{14}H_{17}O_4]^+$ (18.9); CD in MeOH: no Cotton curve over 200 nm.

Compound **1a**. Compound **1** (200 mg) was added to a MeCN (10 ml) soln of $MgBr_2$ (freshly prepd from Mg 24 mg and CH_2BrCH_2Br 0.1 ml [8]) under N_2, and then Ac_2O (0.2 ml) was slowly added to the soln at −5°. The mixt. was allowed to react at room temp. for 3 hr with stirring and the reaction was quenched by adding a soln of $NaHCO_3$ to hydrolyse the excess Ac_2O. Then, the mixt. was extracted with Et_2O and the extract was purified by CC over silica gel to afford **1a** (138 mg, 60%), powder; IR ν_{max}^{KBr} cm^{-1}: 3480, 1734, 1620, 1597; ^1H NMR ($CDCl_3$, 100 MHz): δ0.97 (6H, *d*, *J* = 7.0 Hz, Me-7, Me-8), 1.64 (3H, *s*, Ac), 1.92, 2.14 (1H each, *m*, H-7, H-8), 3.58 (3H, *s*, OMe), 3.89 (9H, *s*, OMe × 3), 4.48 (1H, *d*, *J* = 7.6 Hz, H-6α), 5.73 (1H, *d*, *J* = 4.3 Hz, H-9β), 5.99 (2H, *s*, OCH_2O), 6.45 (1H, *s*, H-11), 6.55 (1H, *s*, H-4); MS *m/z*: 474 $[M]^+$, 414 $[M-AcOH]^+$, 249; CD $\Delta\varepsilon$ (nm) in MeOH: +16.60 (224), 0 (235), −8.65 (242), −7.10 (253), −1.75 (288).

(−)-Gomisin N (**1b**). Compound **1** (50 mg) in dry Et_2O (10 ml) was added to an Et_2O soln of $AlCl_2H$ (1 mmol, freshly prepd from $LiAlH_4$–$AlCl_3$ [9]) and reacted at room temp. for 3 hr. The reaction was quenched by adding H_2O (10 ml) and then the mixt. was extracted with Et_2O. The extract afforded **1b** (38.8 mg, 80%), crystallized from MeOH, mp 104–105°. All spectroscopic data agreed with that previously reported [6, 7]. Treatment of **1a** as described above also provided **1b** (25 mg, 59%).

Methylation of **2**. Compound **2** (15 mg) in MeOH (2 ml) was methylated with an Et_2O soln of CH_2N_2. The reaction mixt. so resulting was purified by prep. TLC using petrol–Et_2O (3:1) to afford **1** (11 mg) identical (by IR, ^1H NMR and CD spectra) to the natural product.

(±) Compound **3a**. Compound **3** (200 mg) was treated with $MgBr_2$–Ac_2O as described in **1a**, providing **3a** (180 mg, 79%), powder, $[\alpha]_D$ 0° (MeOH); IR ν_{max}^{KBr} cm^{-1}: 3470, 1695, 1592, 1575; ^1H NMR ($CDCl_3$, 100 MHz): δ0.93, 1.00 (3H each, *d*, *J* = 7.0 Hz, Me-7, Me-8), 1.56 (3H, *s*, OAc), 1.96, 2.16 (1H each, *m*, H-7, H-8), 3.59, 3.70 (3H each, *s*, OMe × 2), 3.90 (12H, *s*, OMe × 4), 4.52 (1H, *d*, *J* = 8.0 Hz, H-6α), 5.76 (1H, *d*, *J* = 4.0 Hz, H-9β), 6.50 (2H, *s*, H-11, H-4); MS *m/z*: 490 $[M]^+$, 430 $[M-AcOH]^+$, 249; CD in MeOH: no Cotton curve over 200 nm.

(±)-Deoxyschizandrin (**3b**). Compound **3** (50 mg) in dry Et_2O (5 ml) was treated with $AlCl_2H$ as described in **1b**. The product was purified by prep. TLC, providing **3b** (40 mg, 83%), recrystallized from MeOH, mp 116–117°, $[\alpha]_D$ 0° (MeOH), identical to the authentic (+)-deoxyschizandrin by R_f and MS, ^1H NMR, and IR (coating film) spectra.

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