



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

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(Received in revised form 25 May 1994)

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} 6.03×10^{-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

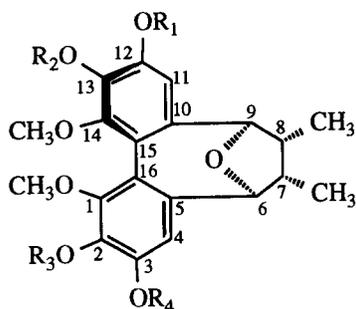
Kadsulignan L (1) exhibits spectral features resembling those of the known lignan 4 [3]. The 1H NMR spectrum of 1 (Table 1) indicates that structural differences between 1 and 4 are in aromatic ring substitution: two methoxyls in 1 replace one methylenedioxy group in 4. Furthermore, the 1H NMR spectrum 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).

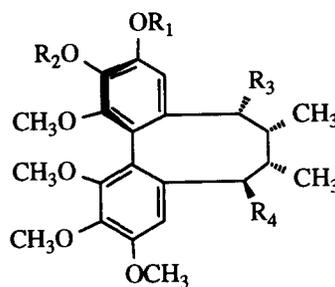
In order to elucidate the position of the methylenedioxy group and absolute stereochemistry, a chemical conversion was conducted. Treatment of 1 in acetonitrile with $MgBr_2 \cdot Ac_2O$ at room temperature for 3 hr afforded an optically active dibenzocyclooctadiene lignan compound (1a) in 60% yield. 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 6S, 7S, 8R, 9R 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

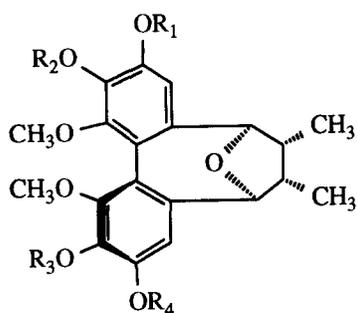
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- 1 $R_1 + R_2 = \text{CH}_2$, $R_3 = R_4 = \text{CH}_3$
 2 $R_1 + R_2 = \text{CH}_2$, $R_3 = \text{CH}_3$, $R_4 = \text{H}$
 3 $R_1 = R_2 = R_3 = R_4 = \text{CH}_3$
 4 $R_1 + R_2 = R_3 + R_4 = \text{CH}_2$
 5 $R_1 = R_2 = \text{CH}_3$, $R_3 + R_4 = \text{CH}_2$



- 1a $R_1 + R_2 = \text{CH}_2$, $R_3 = \text{OAc}$, $R_4 = \text{OH}$
 1b $R_1 + R_2 = \text{CH}_2$, $R_3 = R_4 = \text{H}$
 3a $R_1 = R_2 = \text{CH}_3$, $R_3 = \text{OAc}$, $R_4 = \text{OH}$
 3b $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$



- 1c $R_1 + R_2 = \text{CH}_2$, $R_3 = R_4 = \text{CH}_3$
 2c $R_1 + R_2 = \text{CH}_2$, $R_3 = \text{CH}_3$, $R_4 = \text{H}$
 6 $R_1 = R_2 = \text{CH}_3$, $R_3 + R_4 = \text{CH}_2$

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 $^1\text{H NMR}$ 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 $^1\text{H NMR}$ 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**) $^1\text{H NMR}$ spectra (Table 1). A comparison of $^1\text{H NMR}$ 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 $^1\text{H NMR}$ spectroscopy (Table 1) is only that two methoxyls in **3** replace the methylenedioxy group of **1**. Treatment of **3** with $\text{MgBr}_2 \cdot \text{Ac}_2\text{O}$ provided (\pm)-**3a** and reduction of **3** with $\text{LiAlH}_4 - \text{AlCl}_3$ afforded (\pm)-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. ^1H 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 ₂ O	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

Compound	1		2		5†
	Within 10 min	After 72 hr	Within 10 min	After 72 hr	
$\Delta\epsilon$ (nm)	–31.36 (223)	–3.58 (215)	–22.73 (225)	unobservable	0 (235)
	0 (231)	0 (225)	0 (232)	0 (220)	
	+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, ^1H 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–Et₂O (10:1, 5:1 and 3:1) in turn. The fr. eluted by petrol–Et₂O (5:1) gave 1 (28.5 g, 0.39%), recrystallized from MeOH as needles, mp

149–150°, $[\alpha]_D + 12.2^\circ$ (initial, CHCl_3 ; c 3.301); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 228 (4.91), 262 (4.11, sh), 288 (4.58); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2960, 1610, 1590; ^1H NMR: Table 1; HRMS m/z (rel. int.): 414.1721 ($[\text{M}]^+$, calcd for $\text{C}_{23}\text{H}_{26}\text{O}_7$, 414.1679) (100), 249.1127 [$\text{C}_{14}\text{H}_{17}\text{O}_4$]⁺ (6.4), 233.0834 [$\text{C}_{13}\text{H}_{13}\text{O}_4$]⁺ (9.9); CD: Table 2.

Compound 4. The frs eluted with petrol–Et₂O (10:1) in above CC were combined and rechromatographed over silica gel using petrol–Et₂O (8:1), giving 4 (15.2 g), recrystallized from MeOH, mp 177–178°, $[\alpha]_D 0^\circ$ (MeOH); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 228 (4.52), 264 (3.67, sh), 290 (4.18); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1600, 1477; ^1H NMR: Table 1; HRMS m/z (rel. int.): 398.1351 ($[\text{M}]^+$, calcd for $\text{C}_{22}\text{H}_{22}\text{O}_7$, 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 CDCl₃

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–Me₂CO (5:1). The front frs were combined and rechromatographed over silica gel eluting with petrol–Et₂O (5:1 and 3:1). The fr. eluted with petrol–Et₂O (3:1) afforded **2** (110 mg, 0.0015%), recrystallized from MeOH, mp 199–201°; $[\alpha]_D^{25} +17.5^\circ$ (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; ¹³C NMR (CDCl₃, 25.2 MHz): δ 13.4, 14.0 (q , Me-7, Me-8), 37.8, 52.5 (d , C-7, C-8), 59.8, 60.6, 60.9 (q , OMe \times 3), 90.2, 90.4 (d , C-6, C-9), 100.9 (t , OCH₂O), 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 C₂₂H₂₄O₇, 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–Et₂O (5:1, 2:1 and 1:1). The fr. eluted with petrol–Et₂O (5:1) gave **3** (25.6 g, 0.36%), recrystallized from MeOH, mp 113–115°; $[\alpha]_D^{25} 0^\circ$ (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 C₂₄H₃₀O₇, 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 MgBr₂ (freshly prepd from Mg 24 mg and CH₂BrCH₂Br 0.1 ml [8]) under N₂, and then Ac₂O (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 NaHCO₃ to hydrolyse the excess Ac₂O. Then, the mixt. was extracted with Et₂O 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

(CDCl₃, 100 MHz): δ 0.97 (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 \times 3), 4.48 (1H, d , $J = 7.6$ Hz, H-6 α), 5.73 (1H, d , $J = 4.3$ Hz, H-9 β), 5.99 (2H, s , OCH₂O), 6.45 (1H, s , H-11), 6.55 (1H, s , H-4); MS m/z : 474 $[M]^+$, 414 $[M-AcOH]^+$, 249; CD $\Delta\epsilon$ (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 Et₂O (10 ml) was added to an Et₂O soln of AlCl₃H (1 mmol, freshly prepd from LiAlH₄-AlCl₃ [9]) and reacted at room temp. for 3 hr. The reaction was quenched by adding H₂O (10 ml) and then the mixt. was extracted with Et₂O. 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 Et₂O soln of CH₃N₂. The reaction mixt. so resulting was purified by prep. TLC using petrol–Et₂O (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 MgBr₂-Ac₂O as described in **1a**, providing **3a** (180 mg, 79%), powder, $[\alpha]_D^{25} 0^\circ$ (MeOH); IR ν_{max}^{KBr} cm⁻¹: 3470, 1695, 1592, 1575; ¹H NMR (CDCl₃, 100 MHz): δ 0.93, 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 \times 2), 3.90 (12H, s , OMe \times 4), 4.52 (1H, d , $J = 8.0$ Hz, H-6 α), 5.76 (1H, d , $J = 4.0$ Hz, H-9 β), 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.

(±) *-Deoxyscizandrin (3b)*. Compound **3** (50 mg) in dry Et₂O (5 ml) was treated with AlCl₃H as described in **1b**. The product was purified by prep. TLC, providing **3b** (40 mg, 83%), recrystallized from MeOH, mp 116–117°, $[\alpha]_D^{25} 0^\circ$ (MeOH), identical to the authentic (+)-deoxyscizandrin by R_f and MS, ¹H NMR, and IR (coating film) spectra.

Acknowledgements—Financial support was provided by the National Natural Science Foundation of China. The authors are grateful to Prof. Yu-Hu Liu (Huanan Institute of Botany, Academia Sinica, China) for the botanical identification of materials investigated, and to the Department of Analytical Chemistry, Shanghai Institute of Materia Medica, Academia Sinica, China, for UV, IR, NMR, MS and CD measurements.

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