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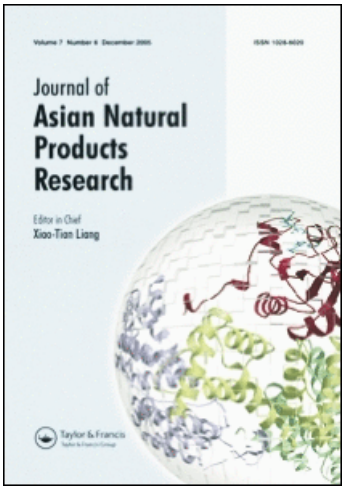

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Heteroclitin H, a new lignan from *Kadsura heteroclita*

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Heteroclitin H, a new lignan from *Kadsura heteroclita*

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A new dibenzocyclooctadiene lignan, heteroclitin H (**1**), was isolated together with seven known compounds, heteroclitin D (**2**), interiorin B (**3**), interiorin (**4**), neokasuranin (**5**), interiotherin C (**6**), gomisin J (**7**) and (+)-anwulignan (**8**), from the stems of *Kadsura heteroclita*. Their structures were elucidated by spectroscopic methods. This is the first report of the isolation of compounds **3**, **5**, **6**, **7** and **8** from *K. heteroclita*.

Keywords: Dibenzocyclooctadiene lignan; *Kadsura heteroclita*; Schisandraceae; *Kadsura*; Heteroclitin H

1. Introduction

The stems of *Kadsura heteroclita* are commonly used as a herbal Chinese medicine to promote vital energy and blood circulation, to expel wind-evil and to remove wetness-evil [1]. The drug is also used for the treatment of rheumatic arthritis, traumatic injury, gastric and duodenal ulcer, acute and chronic gastroenteritis, dysmenorrhea, postpartum abdominal pain, and related diseases in Chinese folk medicine [2]. In our previous studies, dibenzocyclooctadiene lignans were isolated from *Kadsura heteroclita* [1,3], and their various bioactivities, such as calcium antagonist, and anti-lipid peroxidation, were investigated [4–6]. Our continuing efforts to search for bioactive natural products from *Kadsura heteroclita* indigenous to southern China led to the isolation and identification of a new dibenzocyclooctadiene lignan, heteroclitin H (**1**), together with seven known compounds, heteroclitin D (**2**) [1], interiorin B (**3**) [7], interiorin (**4**) [7], neokasuranin (**5**) [8], interiotherin C (**6**) [9], gomisin J (**7**) [10] and (+)-anwulignan (**8**) [11]. Compounds **3**, **5**, **6**, **7** and **8** were isolated from *K. heteroclita* for the first time. This paper deals with the isolation and characterization of these lignans.

2. Results and discussion

Repeated column chromatography of the Et_2O extract of the stems of *Kadsura heteroclita* yielded one new dibenzocyclooctadiene lignan, heteroclitin H (**1**) (figure 1), and seven

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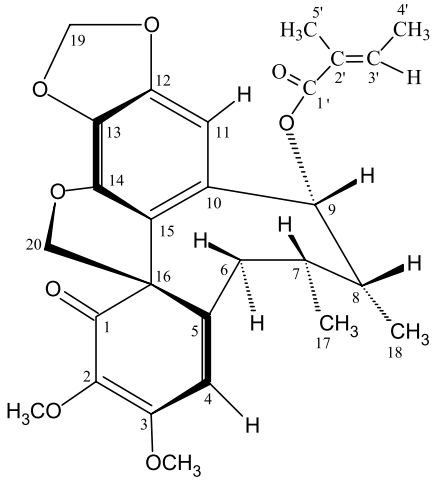

Figure 1. Structure of compound **1**.

known lignans. Their structures and stereochemistries were elucidated by spectroscopic methods.

Compound **1** was assigned the molecular formula $C_{27}H_{30}O_8$ by HR-EI-MS (*m/z* 482.1935). The ^{1}H-NMR and ^{13}C-NMR data indicated that **1** is a dibenzocyclooctadiene lignan. The UV spectrum of **1**, with absorption maxima at 217 (log ε 4.83) and 335 (log ε 3.73) nm, the characteristic proton signals at δ 4.45 and 4.24 (2H, ABq, $J = 8.7$ Hz) and the quaternary carbon signal at δ 65.0 (s) indicated that **1** possessed a spiroenone ring [12].

The ^{1}H-NMR spectrum of **1** (table 1) showed two methyl doublets at δ 0.89 (3H, d, $J = 6.8$ Hz) and 1.02 (3H, d, $J = 7.4$ Hz), indicating the presence of two secondary methyl groups on the cyclooctadiene ring, which could be assigned to CH_3-17 and CH_3-18, respectively [9].

The ^{1}H-NMR spectrum showed the presence of two aromatic H-atoms at δ 6.08 (1H, d, $J = 2.2$ Hz) and 6.39 (1H, s), two methoxy groups (δ 4.01, 3.65, each 3H, s), one methylenedioxy group (δ 5.95, 6.01, each 1H, ABq, $J = 1.5$ Hz), two methylene protons at δ

Table 1. ^{1}H-NMR and ^{13}C-NMR spectral data (δ, ppm) for compound **1** (*J* in Hz).

No.	*Proton* (δ_H)	*Carbon* (δ_C)	*No.*	*Proton* (δ_H)	*Carbon* (δ_C)
1		195.2 (s)	15		121.6 (s)
2		156.4 (s)	16		65.0 (s)
3		132.5 (s)	17	0.89 (3H, d, 6.8)	9.9 (q)
4	6.08 (1H, d, 2.2)	120.7 (d)	18	1.02 (3H, d, 7.4)	21.5 (q)
5		146.8 (s)	19	5.95, 6.01 (2H, ABq, 1.5)	102.0 (t)
6	2.26 (1H, dd, 15.7/12.0)	40.2 (t)	20	4.45, 4.24 (2H, ABq, 8.7)	78.3 (t)
	2.58 (1H, ddd, 15.7/5.7/2.4)				
7	1.85 (1H, m)	31.7 (d)	CH_3O-2	3.65 (3H, s)	58.6 (q)
8	1.99 (1H, dq, 7.0/2.8)	42.7 (d)	CH_3O-3	4.01 (3H, s)	59.2 (q)
9	5.58 (1H, d, 7.0)	78.7 (d)	1′		168.2 (s)
10		129.6 (s)	2′		128.8 (s)
11	6.39 (1H, s)	101.4 (d)	3′	6.44 (1H, dq, 7.0/1.3)	136.1 (d)
12		130.1 (s)	4′	1.72 (3H, d, 7.4)	12.2 (q)
13		150.3 (s)	5′	1.69 (3H, m)	14.2 (q)
14		144.2 (s)			

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2.26 (1H, dd, $J = 15.7$, 12.0 Hz) and 2.58 (1H, ddd, $J = 15.7$, 5.7, 2.4 Hz), and two methine protons at δ 1.85 (1H, m) and 1.99 (1H, dq, $J = 7.0$, 2.8 Hz).

The cross peaks of δ_H 1.85 with δ_C 9.9 (CH_3-17), and δ_H 1.99 with δ_C 21.5 (CH_3-18) in HMBC suggested that these two protons were H-7 and H-8, respectively. Their corresponding carbon signals were assigned as δ 31.7 (C-7) and 42.7 (C-8) by HMQC, respectively. The correlations of δ_H 5.58 with δ_C 31.7 (C-7) and 121.6 (C-15), and of δ_H 2.58 with δ_C 42.7 (C-8) and δ_H 2.26 with δ_C 65.0 (C-16) in HMBC indicated that these three protons were H-9 and H_2-6, respectively. The HMBC correlations of δ_H 6.39 (1H, s) with C-9 (δ_C 78.7) and δ_H 6.08 with C-6 (δ_C 40.2) confirmed that these two aromatic protons were H-11 and H-4, respectively (figure 2).

The correlation of H-9 at δ 5.58 (1H, d, $J = 7.0$ Hz) with C-1′ (δ 168.2), C-7 (δ 31.7) and C-8 (δ 42.7) in HMBC could be assigned to a benzylic oxymethine, indicating an ester group substituted at C-9, similar to the known heterioclitin D [1], which was confirmed by the absorption band at 1705 cm^{-1} in the IR spectrum.

The correlations of H-4 with δ_C 132.5 and 156.4, H-11 with δ_C 130.1 and 150.3 in HMBC suggested that these four carbons were located at C-3, C-2, C-12 and C-13, respectively. The protons in the spiroenone ring at δ 4.45 correlated with the carbonyl carbon at δ_C 195.2 (C=O) and 144.2 (C-14), and the correlation of δ 4.24 with δ_C 146.8 (C-5) suggested that **1** contained an α,β,γ,δ-dienone structure [7]. The correlations of methylenedioxy protons δ 5.95, 6.01 (2H, ABq, $J = 1.5$ Hz) with δ_C 130.1 (C-12) and 150.3 (C-13) in HMBC indicated that the methylenedioxy group was connected to C-12 and C-13. The cross peaks of the methoxy group δ_H 4.01 (3H, s) with carbon at δ_C 132.5, and δ_H 3.65 (3H, s) with δ_C 156.4 in HMBC revealed that these two methoxy groups were located at C-3 and C-2, respectively.

The ion peaks at *m/z* 382 $[M - C_4H_7COOH]^+$ and 83 $[C_4H_7CO]^+$ observed in the EI-MS spectrum suggested the presence of a tigloxyl or an angeloxyl group. The proton signals at δ 6.44 (1H, dq, $J = 7.0/1.3$ Hz), 1.72 (3H, d, $J = 7.4$ Hz) and 1.69 (3H, m) in the ^{1}H-NMR spectrum and the carbon signals at δ 168.2, 128.8, 136.1, 12.2 and 14.2 in the ^{13}C-NMR spectrum confirmed that the substitution is a tigloxyl group [1].

The CD spectrum of **1** with negative *Cotton* at 227 nm and a positive *Cotton* at 209 nm indicated that **1** was in the *S*-biphenyl configuration [13]. The correlations CH_3-18 (δ 1.02)/

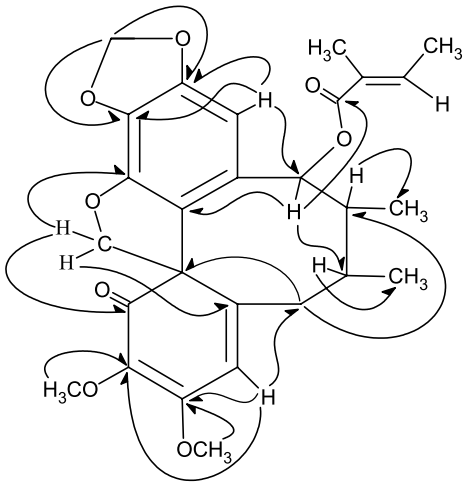

Figure 2. Key HMBC correlations of **1**.

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H-4 (δ 6.08), H-4/Ha-6 (δ 2.26), CH_3-17 (δ 0.89)/H_a-6, H_b-6 (δ 2.58)/H-7 (δ 1.85), H-7/H-8 (δ 1.99), H-8/H-9 (δ 5.58) and H-9/H-11 (δ 6.39) in the NOESY spectrum indicated that Ha-6, CH_3-17 and CH_3-18 were in the α-orientation, and that H_b-6, H-7, H-8 and H-9 were in the β-orientation (see figure 3). NOESY correlations CH_3-18/H-4, H-4/Ha-6, CH_3-17/Ha-6 and H-9/H-11 indicated a twist-boat (TB) conformation for the cyclooctadiene ring [14]. Other NOESY correlations CH_3O-2/CH_3O-3, CH_3O-3/H-4, CH_3-17/CH_3-18 and CH_3-18/H-Tig (δ 6.44, H-3′) supported the substituent positions and the stereochemical assignments. Thus **1** was elucidated as shown in figure 1. It is a new compound, heteroclitin H.

Compounds **2**–**8** were identified as heteroclitin D (**2**), interiorin B (**3**), interiorin (**4**), neokasuranin (**5**), interiotherin C (**6**), gomisin J (**7**) and (+)-anwulignan (**8**) by comparison of their UV, IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR data with those reported in the literature [1,8,11–14], and TLC comparison with the authentic compounds for **5** and **7**. Compounds **3**, **5**, **6**, **7** and **8** were isolated from *K. heteroclita* for the first time. These known lignans were found to exhibit various biological activities, such as anti-HIV activity [15], a calcium antagonist effect [4], anti-lipid peroxidation [3], an antitumor-promoting effect [8,9] and an anti-HbsAg effect [8].

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3. Experimental

3.1 General experimental procedures

Melting points were determined on a XT-4 micromelting point apparatus (Tai-Ke Instrument Company, Beijng, China) and are uncorrected. The IR spectra were recorded as KBr pellets on an Avatar 360E.S.P spectrophotometer (Themo Nicolet Co.). The UV spectra were measured on a Shimadzu UV-260 spectrophotometer in absolute MeOH. Optical rotations were measured with a JASCO P-1020 spectropolarimeter. The CD spectra were measured with a JASCO J-715 spectropolarimeter. Mass spectra were determined on a HP5989A mass spectrometer for EI-MS and a Kratos Concept 1H series mass spectrometer for HR-EI-MS. ^{1}H-NMR and ^{13}C-NMR spectra were measured on Bruker AV500 or DRX400 spectrometer with TMS as internal standard and $CDCl_3$ as solvent. Analytical TLC was performed using

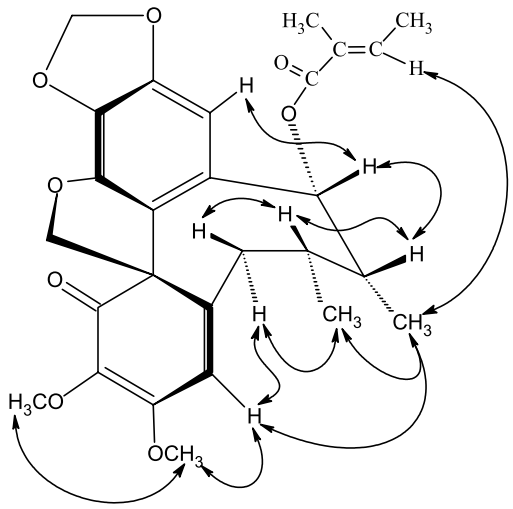

Figure 3. Key NOESY correlations of **1**.

silica gel plates (Yan-tai Institute of Chemical Technology) with petroleum ether–EtOAc (3:1). Silica gel (100–200, 200–300 and 300–400 mesh, Qingdao Marine Chemical Factory) was used for column chromatography. Spots on the plates were observed under UV light and visualized by spraying with 10% H_2SO_4 followed by heating.

3.2 Plant material

The stems of *Kadsura heteroclita* were collected from Fengqing County, Yunnan Province, China, in July 1997. A voucher specimen (DFC-JXT9707) has been deposited at the Herbarium of Materia Medica, Department of Pharmacognosy, School of Pharmacy, Fudan University, Shanghai, China.

3.3 Extraction and isolation

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The stems (9 kg) of *Kadsura heteroclita* were air-dried, ground and extracted exhaustively with 95% ethanol at room temperature. The alcoholic extract was evaporated *in vacuo* to yield a semisolid (1200 g). The semisolid was suspended in water (2000 ml) and extracted seven times with diethyl ether. This ether solution was concentrated to yield 75 g of residue. The residue was chromatographed on silica gel (1500 g), employing petroleum ether (60–90%) containing increasing amounts of ethyl acetate as eluent. Fraction 6 eluted by petroleum ether–EtOAc (7:3) gave 800 mg of **2** after recrystallization from PE–EtOAc (6:4). Repeated column chromatography of fraction 6–2 with petroleum ether–ethyl acetate (6:1–4:1) gave **1** (37 mg), **3** (25 mg) and **4** (44 mg). Further purification of fraction 6–5 eluted with petroleum ether–ethyl acetate (4:1) by preparative TLC with benzene–EtOAc (3:1) yielded **7** (2 mg). Fraction 4 eluted with petroleum ether–EtOAc (9:1) was subjected to repeated column chromatography with petroleum ether–EtOAc (10:1) to yield **5** (205 mg) and **8** (30 mg). Fraction 5 eluted with petroleum ether–EtOAc (8:2) was rechromatographed using the petroleum ether–EtOAc system (5:1) to give **6** (15 mg).

Heteroclitin H (**1**) was obtained as colorless needles from PE–EtOAc; 37 mg; mp 171–173°C; $C_{27}H_{30}O_8$; $[\alpha]_D^{22}$ − 30 (*c* 0.06, MeOH); UV (MeOH) λ_{max} (nm) (log ε): 335 (3.73), 217 (4.83); CD (*c* 0.06, MeOH) $\Delta\varepsilon_{251} = -5.12$, $\Delta\varepsilon_{227} = -24.16$, $\Delta\varepsilon_{209} = +2.11$, $\Delta\varepsilon_{195} = +1.18$; IR (KBr) υ_{max} (cm^{-1}): 1705, 1651, 1586, 1500; ^{1}H-NMR and ^{13}C-NMR see table 1; EI-MS *m/z* 482 $[M]^+$(25), 382 (47), 367 (28), 340 (10), 326 (13), 311 (15), 283 (10), 241 (7), 83 (100), 55 (68); HR-EI-MS: 482.1935 $[M]^+$ (calcd for $C_{27}H_{30}O_8$, 482.1941).

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