# Two New Dibenzocyclooctene Lignans from the Water Extract of *Kadsura* spp.

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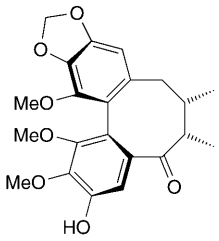
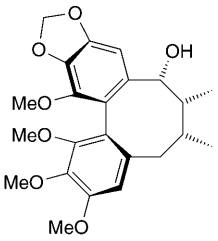
Yunnankadsurins A and B (**1** and **2**, resp.), two new dibenzocyclooctene-type lignans, were isolated from the aqueous extract of *Kadsura* spp. Their structures and configurations were elucidated by spectroscopic methods including 2D-NMR techniques.

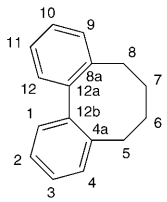
**Introduction.** – *Dian-Jixueteng-Gao*, a water extract of the stems of *Kadsura interior* and *K. heteroclita* (Schisandraceae) [1], two species mainly distributed in the Yunnan Province of China, is mainly used to produce a compound preparation *Fufang Jixueteng Gao* for the treatment of blood deficiency, numb hands and feet, painful aching of the joints, and irregular menstruation [2]. Some lignans and triterpenes have been isolated from the stems of *K. interior* [3][4] and *K. heteroclita* [5]. Dibenzocyclooctene-type lignans from these two plants show various biological activities, such as antitumor-promoting effects, calcium antagonism, antilipid peroxidation, and anti-HIV effects [6–10]. No chemical study of *Dian-Jixueteng-Gao* has been reported yet. Our investigation on the chemical constituents of *Dian-Jixueteng-Gao* led to the isolation and identification of two new dibenzocyclooctene-type lignans, named yunnankadsurins A and B (**1** and **2**, resp.). This paper deals with the isolation and characterization of the new compounds.




**1**




**2**




**A** (numbering for spectra)[1])

**Results and Discussion.** – Repeated column chromatography of the $Et_2O$ extract of *Dian-Jixueteng-Gao* yielded yunnankadsurins A and B (**1** and **2**, resp.).

[1]) The numbering of structure **A** was used for the description of spectral data; systematic numbering is used in names.

Yunnankadsurin A (**1**), obtained as yellow powder, has the molecular formula $C_{22}H_{24}O_7$, as determined by HR-ESI-MS (*m/z* 423.1426 ($[M + Na]^+$)). The UV spectrum with a maximum absorption at 208 nm and two shoulders at 250 and 278 nm, along with the corresponding $^1$H- and $^{13}$C-NMR spectra (*Tables 1* and *2*) indicated that **1** was a dibenzocyclooctene-type lignan [11]. Base on further spectral data – and after simulating the structure of **1** by means of computer modeling (*Fig. 1*), giving rise to a conformation that was in accord with the observed CD and ROESY data – the structure of yunnankadsurin A (**1**) was determined as (a*S*,6*S*,7*S*)-7,8-dihydro-3-hydroxy-1,2,13-trimethoxy-6,7-dimethylbenzo[3,4]cycloocta[1,2-*f*][1,3]benzodioxol-5(6*H*)-one[1]).

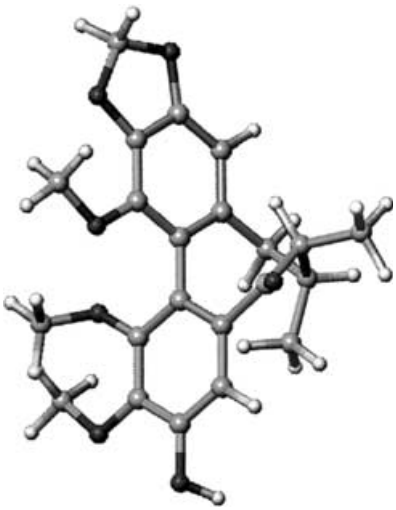


Fig. 1. *3D Structure of compound* **1** *generated by computer modeling* (see *Exper. Part*)

Table 1. *$^1$H-NMR Data* (400 MHz) *of* **1** *and* **2**[1]). In $CDCl_3$ at 27°; $\delta$ in ppm, *J* in Hz.

| | **1** | **2** |
|---|---|---|
| H–C(4) | 7.58 (*s*) | 6.47 (*s*) |
| $H_\alpha$–C(5) | – | 2.36 (*dd*, *J* = 11.6, 15.8) |
| $H_\beta$–C(5) | – | 2.71 (*dd*, *J* = 5.0, 16.0) |
| H–C(6) | 2.61 (*m*) | 1.61 (*m*) |
| H–C(7) | 1.78 (*m*) | 1.52 (*m*) |
| $H_\alpha$–C(8) | 2.18 (*t*, *J* = 12.3) | – |
| $H_\beta$–C(8) | 2.61 (*m*) | 4.23 (*d*, *J* = 8.4) |
| H–C(9) | 6.48 (*s*) | 6.79 (*s*) |
| Me–C(6) | 1.00 (*d*, *J* = 6.7) | 0.81 (*d*, *J* = 6.9) |
| Me–C(7) | 0.79 (*d*, *J* = 6.7) | 1.00 (*d*, *J* = 6.7) |
| MeO–C(1) | 3.42 (*s*) | 3.59 (*s*) |
| MeO–C(2) | 4.01 (*s*) | 3.87 (*s*) |
| MeO–C(3) | – | 3.87 (*s*) |
| MeO–C(12) | 3.85 (*s*) | 3.89 (*s*) |
| $OCH_2O$ | 6.01 (*s*, 2 H) | 5.99, 6.00 (*AB*-'*q*', *J* = 1.4) |

Table 2. *$^{13}$C-NMR Data* (100 MHz) *of* **1** *and* **2**[1]). In $CDCl_3$ at 27°; $\delta$ in ppm.

| | **1** | **2** | | **1** | **2** |
|---|---|---|---|---|---|
| C(1) | 150.2 (*s*) | 151.2 (*s*) | C(11) | 135.3 (*s*) | 135.1 (*s*) |
| C(2) | 143.5 (*s*) | 140.1 (*s*) | C(12) | 141.7 (*s*) | 141.0 (*s*) |
| C(3) | 148.3 (*s*) | 152.2 (*s*) | C(12a) | 121.1 (*s*) | 119.7 (*s*) |
| C(4) | 111.3 (*d*) | 109.5 (*d*) | C(12b) | 124.3 (*s*) | 121.7 (*s*) |
| C(4a) | 135.3 (*s*) | 136.3 (*s*) | *Me*–C(6) | 15.1 (*q*) | 20.3 (*q*) |
| C(5) | 200.9 (*s*) | 40.4 (*t*) | *Me*–C(7) | 15.2 (*q*) | 11.8 (*q*) |
| C(6) | 44.8 (*d*) | 33.2 (*d*) | *Me*O–C(1) | 60.0 (*q*) | 60.5 (*q*) |
| C(7) | 40.9 (*d*) | 47.4 (*d*) | *Me*O–C(2) | 60.9 (*q*) | 60.9 (*q*) |
| C(8) | 40.0 (*t*) | 75.0 (*d*) | *Me*O–C(3) | – | 55.8 (*q*) |
| C(8a) | 134.3 (*s*) | 138.2 (*s*) | *Me*O–C(12) | 59.7 (*q*) | 59.7 (*q*) |
| C(9) | 102.1 (*d*) | 98.2 (*d*) | $OCH_2O$ | 101.0 (*t*) | 100.9 (*t*) |
| C(10) | 149.4 (*s*) | 149.2 (*s*) | | | |

An additional absorption at 320 nm (log $\varepsilon$ 3.19) in the UV spectrum of **1**, along with IR absorption at 1652 $cm^{-1}$ and a signal at $\delta$(C) 200.9 in the $^{13}$C-NMR spectrum, revealed the presence of an $\alpha,\beta$-unsaturated-ketone moiety [12]. The $^1$H-NMR spectrum showed an aromatic proton at $\delta$(H) 7.58 (*s*, 1 H), downfield-shifted by *ca.* 1 ppm as compared with the common aromatic protons, which indicated that the aromatic ring was conjugated with the ketone group, and the aromatic proton was affected by the deshielding effect, similarly to that of schisanlignones from *Kadsura* sp. [13] and *Schisandra viridis* [14][15]. The $^1$H-NMR spectrum also showed signals for a $OCH_2O$ moiety at $\delta$(H) 6.01 (*s*, 2 H) and 3 MeO groups at $\delta$(H) 3.42, 3.85, and 4.01 (*s*) at two aromatic rings. The peak at *m*/*z* 383 ($[M - OH]^+$) in the EI-MS and the IR absorption at 3382 $cm^{-1}$ suggested the presence of 1 OH group. In the HMBC spectrum of **1** (*Fig. 2*), the correlations of $OCH_2O$ at $\delta$(H) 6.01 with $\delta$(C) 149.4 (C(10)) and 135.3 (C(11)) revealed that the $OCH_2O$ moiety was located at C(10) and C(11), and the cross-peaks of the 3 MeO groups ($\delta$(H) 3.42, 3.85, and 4.01) with $\delta$(C) 150.2 (C(1)), 141.7 (C(12)), and 143.5 (C(2)) established their connectivities[1]). The OH group was positioned at C(3) ($\delta$(C) 148.3). Furthermore, $\delta$(H) 7.58 (*s*, 1 H) correlated with $\delta$(C) 200.9 (C(5)), 143.5 (C(2)), and 148.3 (C(3)), and $\delta$(H) 6.48 (*s*, 1 H) correlated with $\delta$(C) 40.0 (C(8)), 149.4 (C(10)), and 135.3 (C(11)), indicating that the carbonyl group was located at C(5). The resonances at $\delta$(H) 2.18 and 2.61 were assigned to two H-atoms at C(8) by a HMQC experiment, and the 2 *d* at $\delta$(H) 0.79 (*d*, $J$ = 6.7 Hz, 3 H) and 1.00 (*d*, $J$ = 6.7 Hz, 3 H) were assigned to the *cis*-oriented Me–C(7) and Me–C(6) [16] respectively.

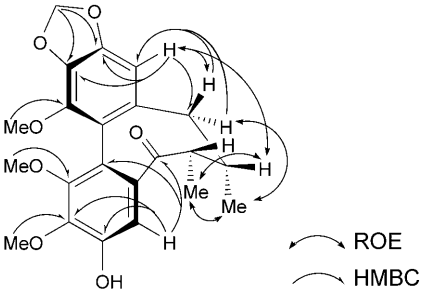



Fig. 2. *Key HMBC and ROESY correlations in* **1**

The circular dichroism (CD) spectrum showed negative and positive *Cotton* effects at 234 and 212 nm, respectively, indicating that **1** contains an axially chiral (a*S*)-1,1′-biphenyl unit ((*P*)-helicity). Since the aromatic ring was conjugated with the ketone group (C(5)), a twist-boat (TB) conformation is the only possible conformation for the dibenzocyclooctene ring system [17]. The result was strengthened by the ROESY experiments, exhibiting the correlations (*Fig. 2*) H–C(9)/$H_\beta$–C(8), H–C(9)/H–C(7), H–C(7)/Me–C(6), Me–C(6)/Me–C(7), and $H_\alpha$–C(8)/Me–C(7).

Yunnankadsurin B (**2**) was obtained as yellow powder. Its molecular formula was determined as $C_{23}H_{28}O_7$ by HR-ESI-MS (*m/z* 439.1731 ($[M + Na]^+$). The UV and NMR spectra revealed that **2** was a dibenzocyclooctene-type lignan. Further spectral data (*Tables 1* and *2*), including HMBC, ROESY, and CD data revealed that **2** has the same two-dimensional structure as deacetylkadsurin [18] and isogomisin O [19], while the optical rotations and the $^1$H-NMR signals of the cyclooctane-ring protons of these two compounds were obviously different from those of **2**, which suggested that they have different configurations. Finally, the structure of **2** was identified as (a*S*,6*R*,7*R*,8*R*)-5,6,7,8-tetrahydro-1,2,3,13-tetramethoxy-6,7-dimethylbenzo[3,4]cyclooctа[1,2-*f*][1,3] benzodioxol-8-ol[1]).

The $^1$H-NMR spectrum of **2** showed the signals of 2 secondary Me groups at $\delta$(H) 0.81 (*d*, *J* = 6.9 Hz) and 1.00 (*d*, *J* = 6.7 Hz), assignable to the *cis*-oriented Me–C(6) and Me–C(7) [16], respectively, a $OCH_2O$ moiety at $\delta$(H) 5.99 and 6.00 (*AB*-'*q*', *J* = 1.4 Hz), 2 aromatic protons at $\delta$(H) 6.47 (*s*, 1 H) and 6.79 (*s*, 1 H), and 4 MeO groups at $\delta$(H) 3.59, 3.87, 3.87, and 3.89 (*s*, each 3 H) at two aromatic rings. The *m* at $\delta$(H) 1.61 (*m*, 1 H) and 1.52 (*m*, 1 H), which exhibited $^1$H,$^1$H correlations with the 2 secondary Me groups at $\delta$(H) 0.81 and 1.00, respectively, were assigned to H–C(6) and H–C(7). The IR absorption at 3474 cm$^{-1}$ suggested the presence of an OH group. In the HMBC spectrum (*Fig. 3*), $\delta$(H) 6.79 (*s*, 1 H) correlated with $\delta$(C) 149.2 (C(10)) and 135.1 (C(11)), and the correlations of $OCH_2O$ at $\delta$(H) 5.99 and 6.00 with $\delta$(C) 149.2 (C(10)) and 135.1 (C(11)) indicated that the $OCH_2O$ moiety was located at C(10) and C(11). The HMBC correlations of the 4 MeO groups at $\delta$(H) 3.59, 3.87, 3.87, and 3.89 with $\delta$(C) 151.2 (C(1)), 140.1 (C(2)), 152.2 (C(3)), and 141.0(C(12)), respectively, revealed that these 4 MeO groups were connected to the aromatic rings. The *d* at $\delta$(H) 4.23 (*d*, *J* = 8.4 Hz, 1 H) correlated with $\delta$(C) 47.4 (C(7)), 11.8 (*Me*–C(7)), and 98.2 (C(9)) in the HMBC spectrum, and also correlated with the aromatic proton at $\delta$(H) 6.79 (H–C(9)) in the ROESY plot, indicating that this proton ($\delta$(H) 4.23) was at C(8) and $\beta$-oriented. The HMBC correlations of $\delta$(H) 2.36 (*dd*, *J* = 11.6, 15.8, 1 H) with $\delta$(C) 33.2 (C(6)), 20.3 (*Me*–C(6)), and 109.5 (C(4)), and of $\delta$(H) 2.71(*dd*, *J* = 5.0, 16.0, 1 H) with $\delta$(C) 33.2 (C(6)), 47.4 (C(7)), and 109.5 (C(4)), revealed that these two H-atoms were at C(5). Thus, the OH group should be located at C(8), and be $\alpha$-oriented.

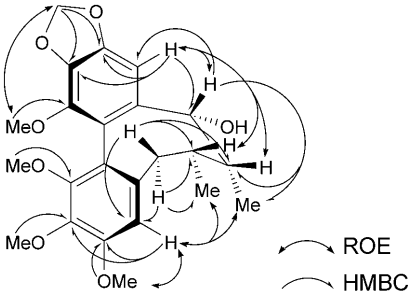



Fig. 3. *Key HMBC and ROESY correlationsin* **2**

The CD spectrum of **2** indicated an axially chiral (a*S*)-1,1′-biphenyl unit (negative and positive *Cotton* effects at 241 and 216 nm, resp.). The conformation was deduced from ROESY data (*Fig. 3*). The correlations H–C(4)/Me–C(6), H–C(4)/Me–C(7), H–C(9)/H–C(6), and H–C(9)/H–C(7) indicated a TB conformation of the fused cyclooctane ring.

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## Experimental Part

*General*. Anal. TLC: silica-gel plates (*Yan-tai Institute of Chemical Technology*), petroleum ether/acetone 3:1 as eluent; visualization under UV light and by spraying with 10% aq. $H_2SO_4$ soln., followed by heating. Column chromatographay (CC): silica gel (200–300, or 300–400 mesh; *Qingdao Marine Chemical Factory*). M.p.: *XT-4* micromelting-point apparatus (*Tai-Ke Instrument Co.,* Beijing, China), uncorrected. Optical rotations (ORD): *Jasco P-1020* spectropolarimeter. UV Spectra: *Shimadzu UV-260* spectrophotometer; in anh. MeOH; $\lambda_{max}$ in nm (log $\varepsilon$). CD Spectra: *Jasco J-715* spectropolarimeter; in $\lambda$ ($\Delta\varepsilon$). IR Spectra: *Avatar 360-E.S.P.* spectrophotometer (*Thermo Nicolet*); KBr pellets; in $cm^{-1}$. $^1$H- and $^{13}$C-NMR Spectra: *Bruker AV-500* or *DRX-400* spectrometers; in $CDCl_3$; $\delta$ in ppm rel. to $SiMe_4$ (= 0 ppm), *J* in Hz. EI-MS: *HP 5989A* mass spectrophotometers; in *m*/*z*. HR-ESI-MS: *Q-T* of *Micro*, England.

*Computer Modeling* (see *Fig. 1*). The modeling was performed with the SYBYL (v. 6.9) software on a *Silicon-Graphics* workstation. The structure was simulated by annealing and optimized subsequently with the *Tripos* force-field energy-minimizing program.

*Plant Material.* The water extract of *Kadsura* spp. (*Dian-Jixueteng-Gao*) was prepared by in the Chinese Pharmacopoeia method by the *Lingchang Pharmaceutical Factory*, Yunnan Province, P. R. China, in 1996.

*Extraction and Isolation.* The water extract of *Kadsura* spp. (1 kg) was suspended in $H_2O$ (1000 ml) and then extracted with $Et_2O$ (7 × 350 ml). The resulting $Et_2O$ soln. was evaporated and the residue (15 g) purified by CC ($SiO_2$ 400 g, petroleum ether/acetone of increasing polarity): several fractions *Fr. 3* (petroleum ether/acetone 5:1) was subjected to repeated CC ($SiO_2$, petroleum ether/AcOEt 7:3): **1** (1.4 mg) and **2** (2.0 mg).

*(a*S,*6*S,*7*S*)-7,8-Dihydro-3-hydroxy-1,2,13-trimethoxy-6,7-dimethylbenzo[3,4]cycloocta[1,2-f][1,3]benzodioxol-(6*H*)-one*[1]) (= *Yunnankadsurin A*; **1**). Yellow powder. $[\alpha]_D^{28} = -25.0$ ($c = 0.01$, MeOH). UV (MeOH): 208 (4.25), 250 (sh, 3.88), 278 (sh, 3.61), 320 (3.19). CD ($c = 0.02$, MeOH): 212 (+ 34), 234 (− 24). IR (KBr): 3382, 2963, 1652, 1478, 1261, 1097, 801. $^1$H- and $^{13}$C-NMR: *Tables 1* and *2*. EI-MS: 400 (47, $M^+$), 383 (5), 370 (22), 309 (29), 265 (69), 191 (21), 171 (100), 153 (22), 70 (47). HR-ESI-MS: 423.1426 ($[M + Na]^+$, $C_{22}H_{24}NaO_7^+$; calc. 423.1420).

*(a*S,*6*R,*7*R,*8*R*)-5,6,7,8-Tetrahydro-1,2,3,13-tetramethoxy-6,7-dimethylbenzo[3,4]cyclooctа [1,2-f][1,3]benzodioxol-8-ol* (= *Yunnankadsurin B*; **2**). Yellow powder. $[\alpha]_D^{28} = -41.8$ ($c = 0.02$, MeOH). UV (MeOH): 215 (4.20), 250 (sh, 3.75), 280 (sh, 3.30). CD ($c = 0.05$, MeOH): 216 (+ 36), 241 (− 38). IR (KBr): 3474, 2962, 1727, 1621, 1463, 1261, 1096, 801. $^1$H- and $^{13}$C-NMR: *Tables 1* and *2*. EI-MS: 416 (10, $M^+$), 356 (11), 309 (25), 289 (30), 263 (19), 245 (53), 239 (78), 219 (12), 213 (19), 195 (41), 91 (54), 77(72), 69 (81), 51 (100). HR-ESI-MS: 439.1731 ($[M + Na]^+$, $C_{23}H_{28}NaO_7^+$; calc. 439.1733).

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