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Communication

New seco-dibenzocyclooctadiene lignans with nitric oxide production inhibitory activity from the roots of *Kadsura longipedunculata*

Xinzhu Qi, Jiabao Liu, Jiabao Chen, Qi Hou, Shuai Li*

State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

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ABSTRACT

Four new seco-dibenzocyclooctadiene lignans, kadlongilignans A–D (**1**–**4**), consisting of a rare 6,7-seco-(**1**), two 15,16-seco-(**2** and **3**) and a 9,10-seco-dibenzocyclooctadiene (**4**) lignans, were isolated from the roots of *Kadsura longipedunculata*. Their structures were elucidated by spectroscopic analysis, including extensive NMR, MS and ECD (electronic circular dichroism) spectra. Compounds **3** and **4** exhibited potent inhibitory activities against NO (nitric oxide) production of LPS (lipopolysaccharide)-induced murine macrophages with the inhibition rates of 36.3% and 26.9%, respectively.

Kadsura longipedunculata Finet et Gagnep is widely distributed in the middle and southwest region of China. Its roots and stems have been used in Chinese folk medicine, and have the effect of promoting blood circulation and dispersing swelling, dispelling wind and activating collaterals, regulating qi-flowing for relieving pain, and have been used for the treatment of rheumatoid arthritis, traumatic injury, canker, gastroenteritis, *etc*. [1]. Phytochemical studies showed that the main principal bioactive constituents of *Kadsura* were lignans and triterpenoids. Schisandraceae lignans mainly contain dibenzocyclooctadiene lignans, tetrahydrofurans, cyclolignans, and simple lignans [2]. As the characteristic component of genus *Kadsura* and *Schizandra*, dibenzocyclooctadiene lignans have the effect of anti-inflammatory [3–6], antineoplastic [7–9], and anti-HIV activities [10–13], and its anti-inflammatory activity has been a hot research field for natural product researchers during recent years [3–6]. As the study to seek components with anti-inflammatory activity from *K. longipedunculata*, four new seco-dibenzocyclooctadiene lignans, named kadlongilignans A–D (**1**–**4**) (Fig. 1), were isolated from the active fraction (Experimental section in Supporting information). Their inhibitory activity of NO (nitric oxide) production of LPS (lipopolysaccharide)-induced murine macrophages were evaluated. The isolation, structural identification, and bioactivity evaluation of these compounds were reported in the text.

Compound **1** had the molecular formula of $C_{29}H_{30}O_{10}$, as deduced by HRESIMS (Fig. S4 in Supporting information), which showed a *quasi*-molecular ion peak at *m/z* 561.1736 $[M+Na]^+$ (calcd. for $C_{29}H_{30}O_{10}Na$: 561.1731) and ^{13}C NMR data. The UV spectrum (Fig. S1 in Supporting information) with λ_{max} values at 210 and 279 nm, along with its IR spectrum (Fig. S3 in Supporting information) with absorption bands at 1613, 1582, and 1503 cm^{-1} (aromatic moiety), indicated the presence of a biphenyl moiety. The IR (ν_{max} 3419 and 1716 cm^{-1}) bands revealed hydroxyl and carbonyl groups of **1**. The ^1H NMR spectrum (Fig. S5 in Supporting information) of **1** displayed two aromatic singlets for a octa-substituted biphenyl moiety at δ_H 6.93 (H-4) and 6.70 (H-11), five aromatic proton signals for a mono-substituted benzene system at δ_H 8.04 (dd, 2H, J = 8.0, 1.5 Hz, H-3′ and H-7′), 7.57 (tt, 1H, J = 8.0, 1.5 Hz, H-5′), and 7.44 (t, 2H, J = 8.0 Hz, H-4′ and H-6′), three singlets for methoxy groups at δ_H 3.98 (3 H), 3.94 (3 H), 3.82 (3 H), a signal of methylenedioxy at δ_H 5.99 and 5.96, an oxymethine at δ_H 5.69 (d, 1H, J = 6.0 Hz, H-9), an oxymethylene at δ_H 4.24 (br d, 2H, J = 6.0 Hz, H-6), a methine at δ_H 3.15 (m, 1H, H-8), an acetyl methyl at δ_H 2.02 (s, 3H, H-17) and a methyl at δ_H 0.96 (d, 3H, J = 7.0 Hz, H-18) (Table 1). The ^{13}C NMR data of **1** indicated 29 carbon signals (Table 1), including a ketone carbonyl (δ_C 209.8), an ester carbonyl (δ_C 165.9), 18 aromatic carbons [δ_C 152.1, 149.4, 147.0, 141.6, 137.2, 136.8, 134.4, 133.5, 132.0, 129.9 (2×), 129.5, 128.6 (2×), 120.8, 112.7, 104.2, 101.0], a methylenedioxy carbon (δ_C 101.5), an oxygenated methine carbon (δ_C 75.4), an oxygenated methylene carbon (δ_C 62.4), three methoxy carbons (δ_C 61.1, 59.9, 55.7), a methine carbon (δ_C 51.1), and two methyl carbons (δ_C 30.6, 14.0). The HMBC

* Corresponding author.
E-mail address: lishuai@imm.ac.cn (S. Li).

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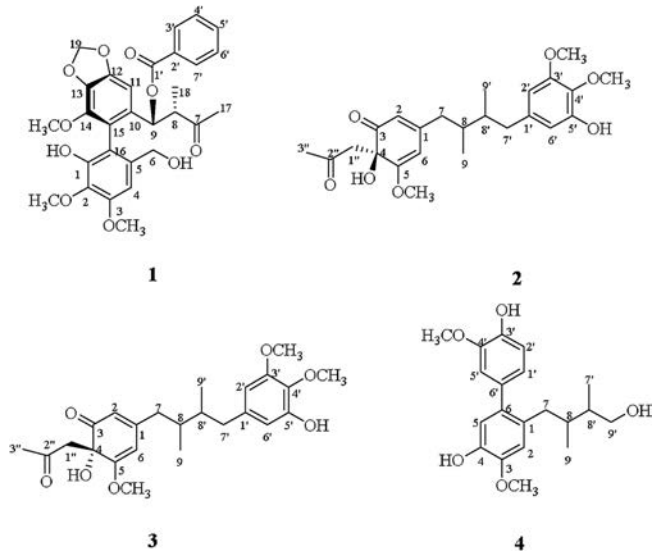

Fig. 1. Structures of compounds **1**–**4**.

Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of **1** in $CDCl_3$.

Pos.	δ_H	δ_C	Pos.	δ_H	δ_C
1		147.0	19a	5.99 (d, 1.5)	101.5
2		134.4	19b	5.96 (d, 1.5)	
3		152.1	1′		165.9
4	6.93 (s)	104.2	2′		129.5
5		137.2	3′	8.04 (dd, 8.0, 1.5)	128.6
6	4.24 (br d, 6.0)	62.4	4′	7.44 (t, 8.0)	129.9
7		209.8	5′	7.57(tt, 8.0, 1.5)	133.5
8	3.15 (m)	51.1	6′	7.44 (t, 8.0)	129.9
9	5.69 (d, 6.0)	75.4	7′	8.04 (dd, 8.0, 1.5)	128.6
10		132.0	1-OH	5.86 (s)	
11	6.70 (s)	101.0	6-OH	3.20 (t, 7.0)	
12		149.4	2-OCH_3	3.94 (s)	61.1
13		136.8	3-OCH_3	3.98 (s)	55.7
14		141.6	14-OCH_3	3.82 (s)	59.9
15		120.8			
16		112.7			
17	2.02 (s)	30.6			
18	0.96 (d, 7.0)	14.0			

correlations of the aromatic protons at δ_H 6.93 (H-4) with δ_C 134.4 (C-2), 152.1 (C-3), 137.2 (C-5), 112.7 (C-16), 147.0 (C-1), 120.8 (C-15) and δ_H 6.70 (H-11) with δ_C 149.4 (C-12), 136.8 (C-13), 120.8 (C-15), 132.0 (C-10), 141.6 (C-14), 112.7 (C-16) further proved the biphenyl moiety. The HMBC correlations of the methylenedioxyl protons at δ_H 5.99, 5.96 (H-19) with the aromatic carbons of the biphenyl moiety at δ_C 149.4 (C-12) and 136.8 (C-13) suggested the methylenedioxyl group was connected on C-12 and C-13. The HMBC correlations of 2-OCH_3 C-2, 3-OCH_3 with C-3 and 14-OCH_3 with C-14 suggested that the three methoxy groups were located at C-2, C-3 and C-14 of biphenyl moiety, respectively. The HMBC correlations of OH signal at δ_H 5.86 with δ_C 147.0 (C-1), 134.4 (C-2) and 112.7 (C-16) showed that the hydroxyl group was linked to C-1. The HMBC correlations of oxygenated methylene signal at δ_H 4.24 (H-6) with δ_C 104.2 (C-4), 137.2 (C-5), 112.7 (C-16) assigned the methylene group on C-5 of the biphenyl moiety. The HMBC correlations of the methyl at δ_H 2.02 (H-17) with the carbonyl of δ_C 209.8 (C-7) and 51.1 (C-8), and the methyl at δ_H 0.96 (H-18) with δ_C 209.8 (C-7), 51.1 (C-8) and 75.4 (C-9), and the methine at δ_H 3.15 (H-8) with δ_C 209.8 (C-7), 75.4 (C-9), 132.0 (C-10), 30.6 (C-17) and 14.0 (C-18), and δ_H 5.69 (H-9) with δ_C 209.8 (C-7), 51.1 (C-8), and 14.0 (C-18) suggested the presence of a C-7 keto-isoprene moiety.

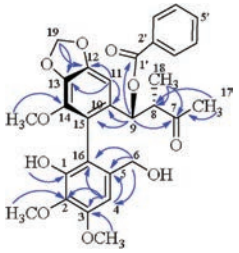

Fig. 2. Key HMBC (H→C) correlations of **1**.

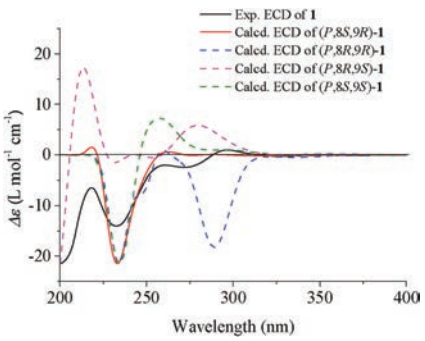

Fig. 3. Experimental and calculated ECD spectra of **1**.

Furthermore, the HMBC correlations of H-9 with C-10, C-11 (δ_C 101.0), C-15 indicated that the C-7 keto-isoprene moiety was attached on C-10 of the biphenyl moiety. The HMBC correlations of mono-substituted benzene aromatic protons of H-3′ and H-7′ (δ_H 8.04) with the ester carbonyl of C-1′ (δ_C 165.9) showed a benzoyloxy group, and the HMBC correlations of H-9 with C-1′ suggested that the benzoyloxy moiety was attached on C-9 of the C-7 keto-isoprene moiety (Fig. 2). The interpretation above indicated that **1** is a 6,7-seco-dibenzocyclooctadiene lignan.

The ECD curve of **1** exhibited a negative Cotton effect near 240 nm (Fig. S2 in Supporting information), which consequently reflected a *P*-biphenyl absolute configuration [14–16]. After defining the biphenyl axial chirality, the absolute configurations of C-8 and C-9 of **1** were determined to be 8*S* and 9*R* by comparison of the experimental and calculated ECD curves (Fig. 3). Thus, the structure of **1**, and its absolute configuration (*P*,8*S*,9*R*) were established as shown in Fig. 1, and it was named as kadlongilignan A.

Compounds **2** and **3**, belonging to a pair of isomers, were obtained by separation of chiral HPLC, and had the same molecular formula of $C_{24}H_{32}O_7$ by HRESIMS and ESIMS ion at *m*/*z* 433.2219 $[M + H]^+$ (calcd.: 433.2221) (Figs. S13 and S22 in Supporting information) and ^{13}C NMR data. The IR spectrum (Figs. S12 and S21 in Supporting information) showed the presence of hydroxyl (3399 cm^{-1}), carbonyl (1711 cm^{-1}), arylalkenyl (1661 cm^{-1}) and aromatic (1593, 1511 and 1458 cm^{-1}) groups. The ^{1}H NMR data (Table 2) showed the presence of two aromatic methine protons at δ_H 6.42 (d, 1H, *J* = 2.0 Hz) and 6.26 (d, 1H, *J* = 2.0 Hz) indicating the presence of one 1,3,4,5-tetrasubstituted benzene system, two olefinic protons at δ_H 5.78 (br s, 1 H) and 5.10 (br s, 1H), three methoxy groups at δ_H 3.87 (s, 3 H), 3.85 (s, 3 H), 3.70 (s, 3H), two methylenes at δ_H 2.06 (dd, 1H, *J* = 13.0, 10.0 Hz, H-7a) and 2.47 (dd, 1H, *J* = 13.0, 4.5 Hz, H-7b), 2.34 (dd, 1H, *J* = 14.0, 8.5 Hz, H-7′a) and 2.58 (dd, 1H, *J* = 14.0, 6.5 Hz, H-7′b), two methines at δ_H 1.81 (m, 2H, H-8 and H-8′), two methyls at δ_H 0.91 (d, 3H, *J* = 7.0 Hz, H-9) and 0.87 (d, 3H, *J* = 6.5 Hz, H-9′). The ^{13}C NMR data of **2** (Table 2) displayed signals for one ketone carbonyl carbon at δ_C 199.3, ten aromatic or olefin carbons at δ_C 166.4, 161.9, 152.3, 149.0, 137.5,

Table 2
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of **2**–**4** in $CDCl_3$.

Pos.	**2**		**3**		**4**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		161.9		161.8		130.3
2	5.78 (s)	115.2	5.78 (br s)	115.4	6.86 (s)	113.5
3		199.3		199.2		146.2
4		75.4		75.5		144.1
5		166.4		166.3	6.67 (s)	116.9
6	5.10 (s)	96.4	5.10 (br s)	96.3		135.3
7a	2.47 (dd, 13.0, 4.5)	40.7	2.47 (dd, 13.0, 4.5)	40.6	2.77 (dd, 13.5, 5.0)	35.7
7b	2.06 (dd, 13.0, 10.0)		2.05 (dd, 13.0, 10.0)		2.28 (dd, 13.5, 10.0)	
8	1.81 (m)	35.2	1.80 (m)	35.1	1.66 (m)	36.5
9	0.91 (d, 7.0)	16.8	0.89 (d, 6.0)	16.9	0.69 (d, 7.0)	16.0
1′		137.5		137.5	6.72 (dd, 8.0, 2.0)	122.1
2′	6.26 (d, 2.0)	104.7	6.27 (d, 2.0)	104.7	6.86 (d, 8.0)	114.5
3′		152.3		152.3		145.3
4′		133.6		133.7		146.9
5′		149.0		149.0	6.84 (d, 2.0)	113.1
6′	6.42 (d, 2.0)	108.5	6.43 (d, 2.0)	108.5		133.7
7′a	2.58 (dd, 14.0, 6.5)	39.8	2.58 (dd, 14.0, 6.5)	39.9	0.78 (d, 7.0)	13.2
7′b	2.34 (dd, 14.0, 8.5)		2.35 (dd, 14.0, 8.5)			
8′	1.81 (m)	39.3	1.80 (m)	39.4	1.44 (m)	40.4
9′	0.87 (d, 6.5)	15.9	0.87 (d, 6.5)	15.8	3.36 (m)	64.6
					3.19 (m)	
3-OCH_3					3.87 (s)	55.4
5-OCH_3	3.70 (s)	56.2	3.70 (s)	56.2		
3′-OCH_3	3.85 (s)	55.9	3.84 (s)	55.9		
4′-OCH_3	3.87 (s)	61.0	3.86 (s)	61.2	3.88 (s)	55.5
1″a	2.85 (s)	53.2	2.88 (d, 14.0)	53.1		
1″b			2.83 (d, 14.0)			
2″		205.8		206.0		
3″	2.22 (s)	31.7	2.23 (s)	31.8		
4-OH	3.60 (s)		3.63 (s)			
5′-OH	5.78 (s)		5.76 (s)			

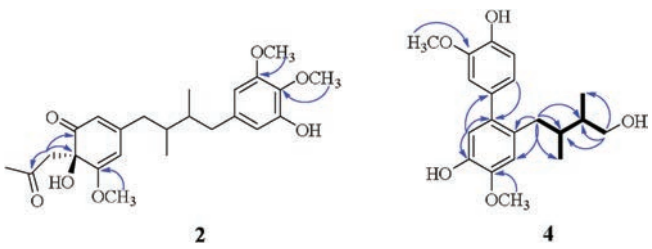

Fig. 4. Key HMBC (H→C) correlations of **2** and **4**, ^{1}H-^{1}H COSY (–) correlations of **4**.

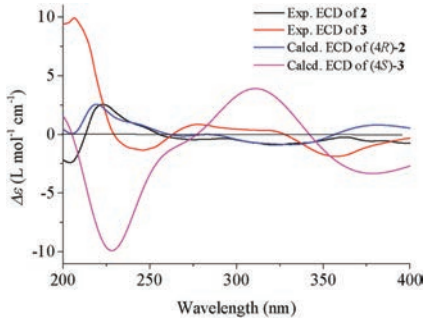

Fig. 5. Experimental and calculated ECD spectra of **2** and **3**.

133.6, 115.2, 108.5, 104.7 and 96.4, a quaternary carbon at δ_C 75.4, two methylenes at δ_C 40.7 and 39.8, two methines at δ_C 35.2 and 39.3, and two methyls at δ_C 16.8 and 15.9, which suggested that **2** was a deformed simple lignan with one cyclohexadienone ring. Additionally, a methylene at δ_H 2.85 (s, 2H), a methyl at δ_H 2.22 (s, 3H) of the ^{1}H NMR data and a ketone carbon at δ_C 205.8, a methylene at δ_C 53.2, a methyl at δ_C 31.7 of the ^{13}C NMR data indicated that an acetonyl group was in **2**. The HMBC correlations of δ_H 2.85 (H-1″) with δ_C 199.3 (C-3), 75.4 (C-4), 166.4 (C-5), 205.8 (C-2″), and 31.7 (C-3″) indicated that the acetonyl group was connected at C-4 of the lignan. The HMBC correlations of three methoxyl signals at δ_H 3.70 (5-OCH_3), 3.85 (3′-OCH_3), 3.87 (4′-OCH_3) with δ_C 166.4 (C-5), 152.3 (C-3′) and 133.6 (C-4′) showed that they were located at C-5, C-3′ and C-4′, respectively (Fig. 4). The mainly difference between compounds **2** and **3** was the absolute configuration of C-4. By comparison of the experimental and calculated ECD curves, the absolute configurations of C-4 of **2** and **3** were assigned as 4*R* and 4*S*, respectively (Fig. 5). Meanwhile, according to the octant rule of cyclohexanone [17,18], using the cotton effect at around 360 nm (n→π^*, R band), the absolute configurations of C-4 of **2** and **3** was determined to be *R* and *S*, too. Since the C—C bonds rotated freely, the configurations of C-8 and C-8′ of **2** and **3** could not be determined exactly. Thus, the structures of **2** and **3** were determined as 15,16-seco-dibenzocyclooctene lignans in Fig. 1 and named as kadlongilignan B and kadlongilignan C.

Compound **4** was given a molecular formula of $C_{20}H_{26}O_5$ based on HRESIMS ion at *m/z* 369.1673 $[M+Na]^+$ (calcd. 369.1672) (Fig. S27 in Supporting information). The UV bands (207, 289 nm) (Fig. S25 in Supporting information) and IR absorptions (Fig. S26 in Supporting information) at 1593, 1507 cm^{-1} indicated the presence of biphenyl moiety. The ^{1}H NMR data of **4** (Table 2) showed three AMX coupling aromatic protons at δ_H 6.86 (d, 1H, *J* = 8.0 Hz, H-2′), 6.84 (d, 1H, *J* = 2.0 Hz, H-5′) and 6.72 (dd, 1H, *J* = 8.0, 2.0 Hz, H-1′) indicating the presence of one 1,3,4-trisubstituted benzene system, two singlet aromatic methine protons at δ_H 6.86 (s, 1H, H-2) and 6.67 (s, 1H, H-5) indicating the presence of one 1,2,4,5-tetrasubstituted benzene system, two methoxy groups at δ_H 3.87 (s, 3H, 3-OCH_3) and 3.88 (s, 3H, 4′-OCH_3), an oxymethylene at δ_H 3.36 (m,

Table 3
Inhibition effects of compounds **1**–**4** on LPS-induced NO production.

Group	Inhibition rate of NO (%)	Inhibition rate of cell proliferation (%)
1	3.5	2.3
2	−2.2	0.1
3	36.3	−1.6
4	26.9	−8.1
DEX[a]	61.8	18.2

[a] DEX (dexamethasone): positive control substance.

1H, H-9′) and 3.19 (m, 1H, H-9′), a methylene at δ_H 2.77 (dd, 1H, *J* = 14.0, 5.0 Hz, H-7) and 2.28 (dd, 1H, *J* = 13.5, 10.0 Hz, H-7), two methyls at δ_H 0.78 (d, 3H, *J* = 7.0 Hz, H-7′) and 0.69 (d, 3H, *J* = 7.0 Hz, H-9), and two methines at δ_H 1.66 (m, 1H, H-8) and 1.44 (m, 1H, H-8′). The ^{1}H-^{1}H COSY correlations of H-7/H-8/H-8′/H-9′, H-8/H-9, and H-7′/H-8′, along with the HMBC correlations of H-7 (δ_H 2.28, 2.77) with C-8 (δ_C 36.5), C-9 (δ_C 16.0), and C-8′ (δ_C 40.4), H-9′ (δ_H 3.19, 3.36) with C-8′, C-7′ (δ_C 13.2), and C-8 suggested the structural unit of 2,3-dimethylbutan-1-ol was in **4** (Fig. 4). The structural unit was attached on C-1 of the aromatic ring by the HMBC correlations of the aromatic proton at δ_H 6.86 (H-2) with δ_C 130.3 (C-1) and 35.7 (C-7). The HMBC correlations of one aromatic proton at δ_H 6.67 (H-5) with δ_C 135.3 (C-6) and 133.7 (C-6′) and another aromatic proton at δ_H 6.72 (H-1′) with δ_C 135.3 (C-6) (Fig. 4) indicated the presence of bibenzyl by the C—C bond connection between C-6 and C-6′. Because of the free rotation of C—C bonds, the configurations of C-8 and C-8′ of **4** were not be determined. Thus, the planar structure of **4**, determining as shown in Fig. 1, was 9,10-seco-dibenzocyclooctene lignan and named as kadlongilignan D.

In summary, kadlongilignans A–D (**1**–**4**) were four new seco-dibenzocyclooctadiene lignans from the roots of *K. longipedunculata*. Notably, compound **1** was a rare 6,7-seco-dibenzocyclooctadiene lignan, and **2** and **3** possessed a novel cyclohexadienone structure. In a view of biosynthesis, the 6,7-seco-, 9,10-seco- and 15,16-seco-type structures deriving from dibenzocyclooctadiene lignans may be degradated by the oxidases in this plant [19]. The original 3,4-dihydroxy moiety of **2** and **3** was first oxidized to be *o*-quinone unit and then coupled with acetoacetyl-CoA to form acetonylcyclohexadienone structure [20]. The four compounds were tested for their capacity to inhibit the production of NO through LPS-induced murine macrophages (Table 3). Compounds **3** and **4** exhibited inhibition effect on the NO production with the inhibition rates of 36.3% and 26.9% at the concentration of 10 μmol/L, respectively (dexamethasone as positive control).

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.06.006.

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