Novel Bis(bibenzyl) and (Propylphenyl)bibenzyl Derivatives from *Dendrobium nobile*

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Two novel compounds possessing a bis(bibenzyl) (see **1**) and a (propylphenyl)bibenzyl skeleton (see **2**) and eight known compounds were isolated from the stems of *Dendrobium nobile* LINDL. (Orchidaceae). Their structures were identified by spectroscopic analyses.

Introduction. – The stems of *Dendrobium nobile* LINDL. (Orchidaceae) are famous in traditional Chinese medicine and used as a 'Yin' tonic, and extracts of the plant have been reported to exhibit immunomodulatory activity [1]. A number of sesquiterpenes, diterpenes, phenanthrenes, alkaloids, and bibenzyls (=1,1′-(ethane-1,2-diyl)bis[benzenes]) have been isolated from *D. nobile* [2–11]. During our ongoing chemical study on this species, two novel compounds **1** and **2** (*Fig. 1*), together with eight known compounds, were isolated from the stems of *D. nobile*. Herein, we report the isolation and structural elucidation of these compounds.

Results and Discussion. – Compound **1** was obtained as a gray powder with a molecular formula $C_{32}H_{32}O_8$ deduced by NMR analyses and HR-ESI-MS. Its IR spectrum indicated the existence of OH groups (3425 cm^{-1}) and aromatic rings (1454, 1510, and 1601 cm^{-1}). The structure of **1** was deduced from ^{1}H- and ^{13}C-NMR (*Table*), ^{1}H,^{1}H-COSY and HMBC (*Fig. 1*), and NOESY data (*Fig. 2*) as 2,2′,9,9′-tetramethoxy-13′,14′-peroxy-1,1′-bis(bibenzyl)-6,6′-diol¹). To the best of our knowledge, **1** is a new compound and was assigned the trivial name dendronophenol A.

The ^{13}C-NMR spectrum of **1** displayed 32 signals constituted by four MeO, two CH_2, and two OCH groups and 24 aromatic (or olefinic) C-atoms. Analysis of its 1D- and 2D-NMR spectra revealed the existence of two 1,3-disubstituted benzene rings and two 1,2,3,5-tetrasubstituted benzene systems, which accounted for the 16 of 17 unsaturation degrees. The remaining unsaturation degree, together with the two OCH groups (δ(C) 80.5 and 80.6) suggested the presence of a 1,2-dioxetane unit. The constitution of **1** was established on the basis of the ^{13}C,^{1}H-HMBC cross-peaks C(1)/H–C(3) and H–C(5), C(2)/Me(15), C(13)/H–C(3) and H–C(5), C(14)/H–C(8) and H–C(12), C(9)/Me(16), C(1′)/H–C(3′)/H–C(5′), C(13′)/H–C(5′), C(2′)/Me(15′), C(14′)/H–C(8′) and H–C(12′), and C(9′)/Me(16′) (*Fig. 1*). The signals of H–C(13′) and H–C(14′) in the NOESY plot were superimposed in several deuterated solvents, which made it impossible to establish the relative configuration of the four-membered 1,2-dioxetane ring in **1**.

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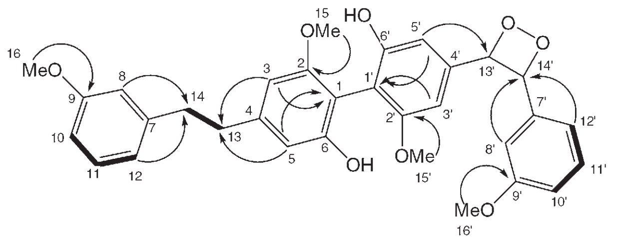
¹) Trivial atom numbering; for systematic names, see *Exper. Part.*



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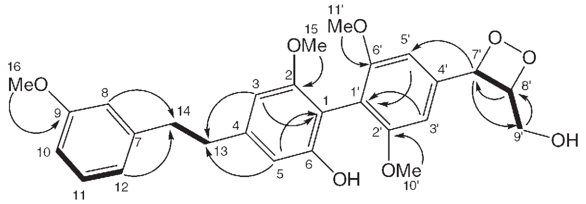

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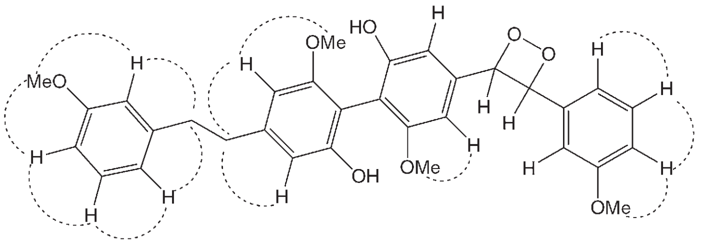
Fig. 1. *^{1}H,^{1}H COSY (—) and key ^{1}H,^{13}C long-range correlation signals* (^{1}H⌒→^{13}C) *from the HMBC plot of* **1** *and* **2**1))



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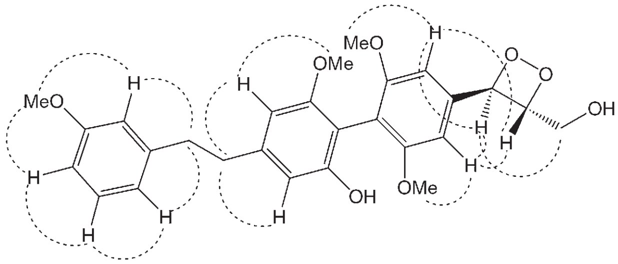

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Fig. 2. *Main NOE signals* (⌒) *observed in the NOESY plots of* **1** *and* **2**

Table. *^{1}H- and ^{13}C-NMR Data* (400 and 100 MHz, resp.; CDCl$_3$) *of* **1** *and* **2**[1]). δ in ppm, J in Hz.

	1		**2**	
	δ(C)	δ(H)	δ(C)	δ(H)
C(1)	131.7 (*s*)		131.0 (*s*)	
C(2)	148.7 (*s*)		148.4 (*s*)	
H−C(3)	105.0 (*d*)	6.38 (*d*, J = 1.8)	104.7 (*d*)	6.32 (*d*, J = 1.8)
C(4)	134.4 (*s*)		134.3 (*s*)	
H−C(5)	109.4 (*d*)	6.60 (*d*, J = 1.8)	109.5 (*d*)	6.50 (*d*, J = 1.8)
C(6)	144.1 (*s*)		144.1 (*s*)	
C(7)	143.4 (*s*)		143.2 (*s*)	
H−C(8)	114.3 (*d*)	6.79 (*dd*, J = 1.8, 1.8)	114.3 (*d*)	6.72 (*dd*, J = 1.2, 1.2)
C(9)	159.6 (*s*)		159.7 (*s*)	
H−C(10)	111.2 (*d*)	6.75 (*ddd*, J = 1.8, 1.8, 7.6)	111.1 (*d*)	6.73 (*ddd*, J = 1.0, 1.2, 6.6)
H−C(11)	129.3 (*d*)	7.23 (*t*, J = 7.6)	129.3 (*d*)	7.20 (*dt*, J = 1.2, 6.6)
H−C(12)	120.9 (*d*)	6.82 (*dd*, J = 1.8, 1.8, 7.6)	120.9 (*d*)	6.78 (*ddd*, J = 1.2, 1.2, 6.6)
CH$_2$(13)	37.6 (*t*)	2.83–2.87 (*m*)	37.5 (*t*)	2.80–2.83 (*m*)
CH$_2$(14)	38.0 (*t*)	2.89–2.93 (*m*)	37.8 (*t*)	2.86–2.89 (*m*)
Me(15)	55.3 (*q*)	3.84 (*s*)	56.0 (*q*)	3.84 (*s*)
Me(16)	55.2 (*q*)	3.81 (*s*)	55.1 (*q*)	3.79 (*s*)
C(1′)	132.5 (*s*)		135.3 (*s*)	
C(2′)	146.5 (*s*)		147.3 (*s*)	
H−C(3′)	102.8 (*d*)	6.08 (*d*, J = 1.7)	104.1 (*d*)	6.66 (*s*)
C(4′)	128.1 (*s*)		127.2 (*s*)	
H−C(5′)	108.2 (*d*)	6.43 (*d*, J = 1.7)	104.1 (*d*)	6.66 (*s*)
C(6′)	143.7 (*s*)		147.3 (*s*)	
C(7′) or H−C(7′)	137.8 (*s*)		76.4 (*d*)	4.92 (*d*, J = 8.2)
H−C(8′)	120.4 (*d*)	6.69 (*dd*, J = 1.7, 1.7)	78.3 (*d*)	3.97–4.00 (*m*)
C(9′) or CH$_2$(9)	159.4 (*s*)		61.5 (*t*)	3.54 (*dd*, J = 3.7, 12.6, H$_a$), 3.89 (*dd*, J = 5.2, 12.6, H$_b$)
H−C(10′) or Me(10′)	114.2 (*d*)	6.77 (*ddd*, J = 1.7, 1.8, 7.7)	56.4 (*q*)	3.90 (*s*)
H−C(11′) or Me(11′)	129.2 (*d*)	7.11 (*t*, J = 7.7)	56.4 (*q*)	3.90 (*s*)
H−C(12′)	113.3 (*d*)	6.68 (*ddd*, J = 1.7, 1.8, 7.7)		
H−C(13′)	80.5 (*d*)	4.78–4.80 (*m*)		
H−C(14′)	80.6 (*d*)	4.78–4.80 (*m*)		
Me(15′)	55.3 (*q*)	3.68 (*s*)		
Me(16′)	55.2 (*q*)	3.71 (*s*)		

Compound **2** was obtained as an off-red amorphous powder with a molecular formula $C_{27}H_{30}O_8$ deduced by NMR analyses and HR-ESI-MS. Its IR spectrum indicated the presence of an OH group (3485 cm^{-1}) and aromatic rings (1465, 1508, and 1593 cm^{-1}). The structure of **2** was established by the ^{1}H- and ^{13}C-NMR (*Table*), ^{1}H,^{1}H-COSY and HMBC (*Fig. 1*), and NOESY data (*Fig. 2*) as 1-(2′,6′-dimethoxy-7′,8′-peroxyphenylpropyl)-2,9-dimethoxybibenzyl-6,9′-diol[1]). To the best of our knowledge, **2** represents a novel compound and was assigned the trivial name dendronophenol B.

The ^{13}C-NMR spectrum of **2** displayed 27 signals arising from four MeO, three CH$_2$ (one OCH$_2$), and two OCH groups and 18 aromatic C-atoms. Its ^{1}H-NMR spectrum revealed the presence of one 1,3-

disubstituted benzene unit and two 1,2,3,5-tetrasubstituted benzene rings, which accounted for the 12 of 13 unsaturated degrees. Analysis of the $^1H,^1H$-COSY data resulted in the deduction of the fragments CH_2CH_2 and $CH(-O-)CH(-O-)$, and in combining the latter fragment with the remaining unsaturation degree, the presence of a 1,2-dioxetane ring was suggested. The constitution of **2** was established on the basis of HMBC cross-peaks C(1)/H–C(3) and H–C(5), C(2)/Me(15), CH_2(13)/C(3) and C(5), CH_2(14)/C(8) and C(12), Me(16)/C(9), Me(10′)/C(2′), Me(11′)/C(6′), H–C(7′)/C(5′) and C(9′), H–C(8′)/C(7′), and H–C(9′)/C(8′) (*Fig. 1*). The relative configuration of the 1,2-dioxetane ring was established on the basis of its NOESY spectrum, in which an NOE correlation was observed between H–C(7′) and CH_2(9′) (*Fig. 2*).

The biosynthetic origin of compounds **1** and **2** is hypothesized as illustrated in the *Scheme*. The 3-methoxy-5-[2-(3-methoxyphenyl)ethyl]phenol (**A**), 3-methoxy-5-[2-(3-(methoxyphenyl)ethenyl]phenol (**C**), and 3-methoxy-5-(3-hydroxyprop-1-en-1-yl)-phenol (**E**) are oxidized with NADPH/O_2 to afford the radicals **B**, **D**, and **F**, respectively [12]. Radical coupling reaction between **B** and **D** yields the precursor of **1**, which is then peroxydated with O_2 to afford **1** [13]. Radical coupling between **B** and **F** gives the precursor of **2**, which is then methylated and peroxydated with O_2 to afford **2** [14]. To the best of our knowledge, the two new compounds with a C–C linkage between two bibenzyls or between a propylphenyl and a bibenzyl are rare among natural products.

The eight known compounds were identified as gigantol [15][16], dendrobin A [10], moscatilin [15][17], batatasin III [18][19], trisitin [15], 9,10-dihydro-3,7-dimethoxyphenanthrene-4,5-diol [20], (+)-syringaresinol [21], and (+)-syringaresinol 4-*O*-*β*-glucopyranoside [22] by comparison of their NMR and MS data with those reported in the literature.

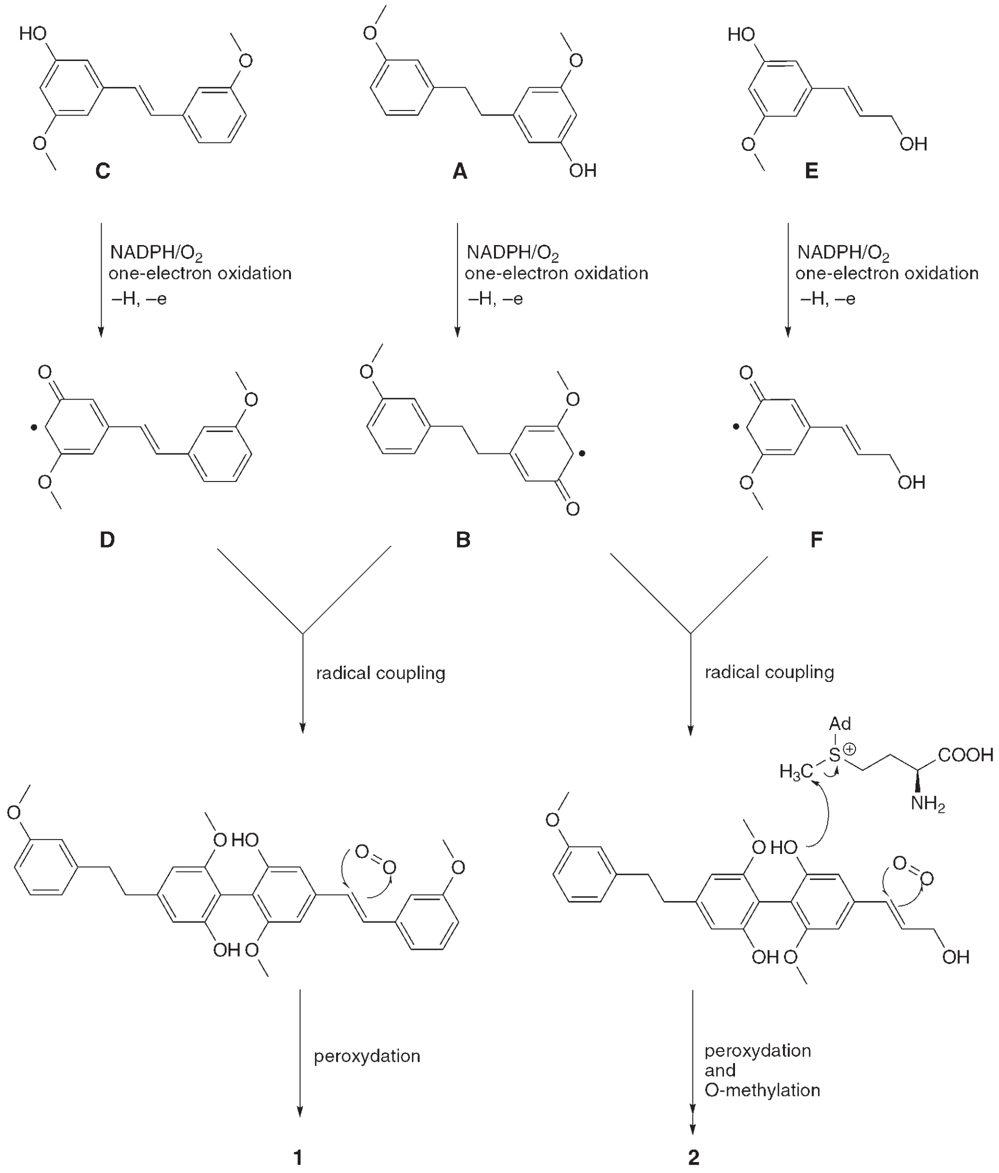
Experimental Part

General. Column chromatography (CC): silica gel *H60* (*Qingdao Haiyang Chemical Group Corporation*, Qingdao, People's Republic of China), *Sephadex LH-20* (*Pharmacia Biotech AB*, Uppsala, Sweden), and *RP-18* (100–200 mesh; *Tianjin No. 2 Chemical Reagent Factory*, Tianjin, People's Republic of China) as packing materials; *LiChroprep RP-18-Lobar* column (40–63 μm; *Merck*). TLC: HSG_{254} silica gel plates (*Yantai Chemical Industrial Institute*, Yantai, People's Republic of China). M.p.: *Fisher-Johns* melting-point apparatus. Optical rotations: *Perkin-Elmer 341MC* polarimeter. UV Spectra: λ_{max} (log ε) in nm. IR Spectra: *Perkin-Elmer 577* spectrometer; in cm^{-1}. NMR Spectra: *Bruker AM-400* spectrometer; δ in ppm rel to $SiMe_4$ as internal standard, J in Hz. HR-MS: *MAT-212* instrument for ESI and *Ktatos-1 H* spectrometer for EI; in *m/z*.

Extraction and Isolation. Powdered and air-dried stems of *D. nobile* (3 kg) were refluxed with 95% aq. EtOH thrice (3 × 15 l). After evaporation of the EtOH, the aq. residue (1 l) was extracted with petroleum ether, $CHCl_3$, AcOEt, and BuOH (3 × 1 l), successively, to give a $CHCl_3$ extract (30.0 g), an AcOEt extract (15.0 g), and a BuOH extract (281.0 g). The $CHCl_3$ fraction was separated by CC (silica gel, $CHCl_3$/acetone 30:1 → 0:1): *Fractions 1–5. Fr. 1* (5.0 g) was subjected to CC (silica gel, CH_2Cl_2/acetone 10:1 → 0:1): **1** (18 mg), **2** (13 mg), gigantol (20 mg), batatasin III (21 mg), and 9,10-dihydro-3,7-dimethoxyphenanthrane-4,5-diol (16 mg). *Fr. 2* (1.2 g) was subjected to CC (silica gel, $CHCl_3$/acetone 40:1, 35:1, and 30:1): dendrobin A (17 mg), moscatilin (25 mg), and (+)-syringaresinol (25 mg). *Fr. 3* (3.0 g) was filtered through a *Sephadex-LH-20* column (EtOH), and then subjected to CC (silica gel, $CHCl_3$/AcOEt/MeOH 15:1:2): trisitin (8 mg) and (+)-syringaresinol 4-*O*-*β*-glucopyranoside (15 mg).

Dendronophenol A (*=6,6′-Dimethoxy-4-[4-(3-methoxyphenyl)-1,2-dioxetan-3-yl]-4′-[2-(3-methoxyphenyl)ethyl][1,1′-biphenyl]-2,2′-diol*; **1**): Gray powder. M.p. 173–174°. $[\alpha]_D^{22} = -2.0$ ($c = 0.25$, $CHCl_3$).

Scheme. *Suggested Biosynthetic Process for* **1** *and* **2**



UV (MeOH): 201 (3.12), 273.5 (2.06). IR (KBr): 3425, 1601, 1510, 1454, 1267, 1219, 1151, 1047, 831, 785, 698. HR-ESI-MS: 567.1989 ([*M* + Na]$^+$, $C_{32}H_{32}NaO_8^+$, 567.1968).

Dendronophenol B (=*4-{2′-Hydroxy-2,6,6′-trimethoxy-4′-[2-(3-methoxyphenyl)ethyl][1,1′-biphenyl]-4-yl}-1,2-dioxetane-3-methanol*; **2**): Off-red amorphous powder. M.p.: 154–155°. $[\alpha]_D^{22} = -4.0$ ($c = 0.18$, $CHCl_3$). UV (MeOH): 208.5 (3.13), 272 (1.98). IR (KBr): 3485, 1593, 1508, 1465, 1340, 1220, 1112, 1047, 835, 694. HR-ESI-MS: 521.1572 ([*M* + K]$^+$, $C_{27}H_{30}KO_8^+$; calc. 521.1555).

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