Two New Compounds from *Dendrobium candidum*

Yan Li, Chun-Lan Wang, Shun-Xing Guo,* Jun-Shan Yang, and Pei-Gen Xiao

Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College; No. 151, Malianwa North Road, Haidian District, Beijing 100193, P. R. China.

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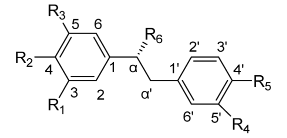
Two new compounds were isolated from the stems of *Dendrobium candidum*: (*R*)-3,4-dihydroxy-5,4′,*α*-trimethoxybibenzyl (1), named dendrocandin A; and 4-[2-[(2*S*,3*S*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-hydroxymethyl-8-methoxy-2,3-dihydrobenzo[1,4]dioxin-6-yl]ethyl]-1-methoxyl benzene (2), dendrocandin B. Five previously known bibenzyls were also identified: 4,4′-dihydroxy-3,5-dimethoxybibenzyl (3), 3,4-dihydroxy-5,4′-dimethoxybibenzyl (4), 3-*O*-methylgigantol (5), dendrophenol (6), and gigantol (7).

Key words *Dendrobium candidum*; dendrocandin A; dendrocandin B

The traditional Chinese medicine "Shi Hu", prepared from the dried or fresh stems of several *Dendrobium* species (Orchidaceae), is widely used as both traditional Chinese and folk remedies for antipyretic, eyes-benefiting, and tonic purposes.[1] *Dendrobium candidum* Wall. ex Lindl. is one of the most popular and valuable *Dendrobium* species and has been recorded in the Chinese Pharmacopoeia (2005 Edition) as one of the original materials of "Shi Hu". However, no phytochemical study of *D. candidum* has been reported to date. So, a phytochemical investigation on *D. candidum* has been undertaken by our group. As a result, two new compounds (**1**, **2**) were isolated, along with five known compounds (**3**—**7**).[2—5] The known compounds were identified by comparisons with previously reported physical and spectral data. The structures of new compounds were determined as follows:

Dendrocandin A (1) Dendrocandin A (**1**) was obtained as an amorphous solid, $[\alpha]_D^{20}$ $-4.3°$ ($c=0.19$, $CHCl_3$). The HR-EI-MS (m/z 304.1308, $[M]^+$) and NMR analysis revealed the molecular formula $C_{17}H_{20}O_5$. The structure of **1** was deduced from its 1D- and 2D-NMR data and comparison with those of 3,4-dihydroxy-5,4′-dimethoxybibenzyl (**4**).[3] The absolute configuration of **1** was established as (*R*) on the basis of the negative Cotton effect at 230 nm ($\Delta\varepsilon$ -1.29) in its circular dichroism (CD) spectrum, which was opposite to those of analogs (notice that the stereodescriptor is (*S*) in those cases).[6]



1 R$_1$=R$_2$=OH, R$_3$=R$_5$=R$_6$=OCH$_3$, R$_4$=H

3 R$_2$=R$_5$=OH, R$_1$=R$_3$=OCH$_3$, R$_4$=R$_6$=H

4 R$_1$=R$_2$ =OH, R$_3$=R$_5$=OCH$_3$, R$_4$=R$_6$=H

5 R$_1$=OH, R$_3$=R$_4$=R$_5$ = OCH$_3$, R$_2$=R$_6$=H

6 R$_2$= R$_4$=R$_5$=OH, R$_1$=R$_3$=OCH$_3$, R$_6$=H

7 R$_1$=R$_5$=OH, R$_3$=R$_4$=OCH$_3$, R$_2$=R$_6$=H

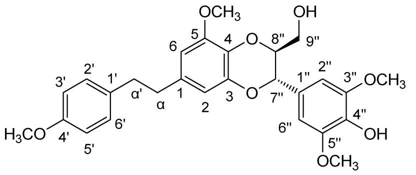


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Fig. 1. Structures of Compounds **1**—**7**

The ^{1}H- and ^{13}C-NMR data of **1** indicated the presence of three MeO groups [δ_H 3.19 (3H, s), 3.78 (3H, s) and 3.83 (3H, s); δ_C 55.2, 56.2 and 56.6], one CH_2 group [δ_H 2.81 (1H, dd, $J=14.0$, 6.0 Hz) and 3.02 (1H, dd, $J=14.0$, 7.5 Hz); δ_C 43.8], and one oxygenated CH group [δ_H 4.15 (1H, t, $J=7.5$, 6.0 Hz); δ_C 85.2]. In addition, the signals of six aromatic protons were observed and distributed to two aromatic rings on the basis of the coupling constants in the ^{1}H-NMR spectrum, where two groups of *o*-coupled signals of one aromatic ring appeared at δ_H 6.78 (2H, d, $J=8.5$ Hz) and 7.02 (2H, d, $J=8.0$ Hz), indicating the presence of a 1,4-substituted aromatic ring; and two protons of the other aromatic ring appeared at δ_H 6.34 (1H, br s) and 6.49 (1H, br s), indicating the presence of a tetrasubstituted aromatic ring. According to the ^{1}H- and ^{13}C-NMR data, a bibenzyl skeleton with two hydroxyl and three methoxyl groups were deduced to the structure of **1**. But the significant difference between **1** and the 3,4-dihydroxy-5,4′-dimethoxybibenzyl (**4**) reported[3] was observed at benzylic protons. The four equivalent benzylic proton signals in upfield region of the known bibenzyl were replaced by the signals for one oxygenated methine and two methylene protons in **1**. In combination with the ^{13}C–^1H long-range correlation between δ_H 3.19 (α-OMe–H_3) and δ_C 85.2 (C-α) in the HMBC spectrum, the fragment of one benzylic proton substituted by a methoxyl group was determined. Other key HMBC correlations are shown in Fig. 2. Thus, the structure of **1** was established as (*R*)-3,4-dihydroxy-5,4′,α-trimethoxybibenzyl.

Dendrocandin B (2) Dendrocandin B (**2**) was obtained as a white powder, $[\alpha]_D^{20}$ $-4.6°$ ($c=0.11$, $CHCl_3$). The HR-EI-MS (m/z 482.1951, $[M]^+$) and NMR analysis revealed the molecular formula $C_{27}H_{30}O_8$. The structure of **2** was deduced from its 1D- and 2D-NMR data and comparison with those of bilagrewin and 7*S*,8*S*-nitidanin.[7,8)]

The ^{1}H- and ^{13}C-NMR data of **2** indicated the presence of four MeO groups [δ_H 3.79 (3H, s), 3.85 (3H, s) and 3.92 (6H, s); δ_C 55.3, 56.0 and 56.4], three CH_2 groups (one oxy-

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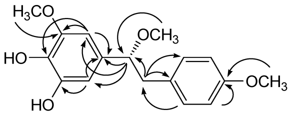
* To whom correspondence should be addressed. e-mail: sxguo2006@yahoo.com.cn



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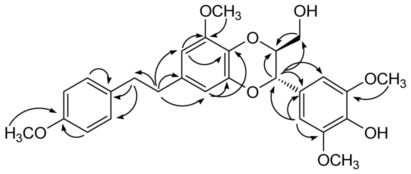

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Fig. 2. Key HBMC Correlations of Compounds **1** and **2**

genated) [δ_H 2.82 (4H, m), 3.55 (1H, dd, J=12.0, 3.0 Hz) and 3.90 (1H, overlapped with the signals of MeO); δ_C 37.0, 38.0 and 61.5], and two oxygenated CH groups [δ_H 3.98 (1H, m, J=8.0, 3.0, 3.0 Hz) and 4.96 (1H, d, J=8.5 Hz); δ_C 76.4 and 78.2]. In addition, the signals of eight aromatic protons were observed and distributed to three aromatic rings on the basis of the coupling constants in the ^{1}H-NMR spectrum, where two groups of *o*-coupled signals of one aromatic ring appeared at δ_H 6.83 (2H, d, J=8.0 Hz) and 7.10 (2H, d, J=8.0 Hz), indicating the presence of a 1,4-disubstituted aromatic ring; two *m*-coupled signals appeared at δ_H 6.32 (1H, d, J=1.5 Hz) and 6.52 (1H, d, J=1.0 Hz), indicating the presence of a 1,3,4,5-tetrasubstituted aromatic ring; and a two-proton singlet appeared at δ_H 6.68 (2H, s), indicative of a symmetrically tetrasubstituted aromatic ring.

In the HMBC plot, the ^{13}C–^{1}H long-range correlation peaks between α-H$_2$/C-1, C-2, C-6, C-α', between 2-H/C-3, C-4, C-6, C-α, between 6-H/C-1, C-2, C-4, C-5, C-α, between α'-H$_2$/C-1′, C-2′, C-6′, C-α, between 2′-H/C-3′, C-4′, C-6′, C-α', and between 3′-H/C-1′, C-4′, C-5′ were observed, which deduced the presence of a bibenzyl unit. The HMBC correlation peaks between 2″-H/C-1″, C-3″, C-4″, C-7″, and between 7″-H/C-1″, C-2″, C-6″, C-8″, C-9″ deduced the presence of a phenylpropane unit. The deshielded doublet at δ_H 4.96 (1H, d, J=8.5 Hz), typical of a benzylic methine substituted by an oxygen, and the multiplet at δ_H 3.98 (1H, m, J=8.0, 3.0, 3.0 Hz), which were coupled to each other, implied the presence of a 1,4-dioxane ring between a bibenzyl moiety and a phenyl ring.[7,8] The NOE correlation between H-8″ and H-5-OMe indicated the positions of 7″ and 8″ in the dioxane ring. The coupling constant ($J_{7'',8''}$=8.5 Hz) between H-7″ and H-8″, and the NOE correlations between H-7″/H-9″ and H-8″/H-2″, H-6″ clearly indicated a *threo* configuration of the chiral centers of the dioxane ring.[7—9] The absolute configurations at C-7″ and C-8″ were determined based on the rotation direction comparison with synthetic analogs, (−)-aiphanol and (+)-aiphanol.[8] The (−) rotation direction of **2** allowed the assignment of (*S*)-configuration of the chiral centers. Therefore, compound **2** was elucidated as 4-[2-[(2*S*,3*S*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-hydroxymethyl-8-methoxy-2,3-dihydrobenzo[1,4]dioxin-6-yl]ethyl]-1-methoxyl benzene.

Table 1. ^{1}H- and ^{13}C-NMR Data of Compounds **1** and **2** (CDCl$_3$)

No.	1		2	
	δ_H	δ_C	δ_H	δ_C
1		131.6		134.5
2	6.49 (1H, br s)	107.4	6.52 (1H, d, 1.0)	109.5
3		143.6		144.1
4		133.7		131.0
5		146.8		148.4
6	6.34 (1H, br s)	101.4	6.32 (1H, d, 1.5)	104.8
1′		130.6		133.7
2′	7.02 (1H, d, 8.0)	130.4	7.10 (1H, d, 8.0)	129.4
3′	6.78 (1H, d, 8.5)	113.5	6.83 (1H, d, 8.0)	113.7
4′		158.0		160.1
5′	6.78 (1H, d, 8.5)	113.5	6.83 (1H, d, 8.0)	113.7
6′	7.02 (1H, d, 8.0)	130.4	7.10 (1H, d, 8.0)	129.4
α	4.15 (1H, t, 7.5, 6.0)	85.2	2.82 (2H, m)	38.0
α'	2.81 (1H, dd, 14.0, 6.0), 3.02 (1H, dd, 14.0, 7.5)	43.8	2.82 (2H, m)	37.0
MeO-5	3.83 (3H, s)	56.2	3.85 (3H, s)	56.0
MeO-4′	3.78 (3H, s)	55.2	3.79 (3H, s)	55.3
MeO-α	3.19 (3H, s)	56.6		
1″				127.3
2″			6.68 (1H, s)	104.0
3″				147.2
4″				135.2
5″				147.2
6″			6.68 (1H, s)	104.0
7″			4.96 (1H, d, 8.5)	76.4
8″			3.98 (1H, m, 8.0, 3.0, 3.0)	78.2
9″			3.55 (1H, dd, 12.0, 3.0), 3.90 (1H, m)	61.5
MeO-3″			3.92 (3H, s)	56.4
MeO-5″			3.92 (3H, s)	56.4

Experimental

General ^{1}H-, ^{13}C- and 2D-NMR spectra were measured on an INOVA-501 spectrometer (^{1}H at 500 MHz and ^{13}C at 125 MHz). Chemical shifts are given in δ values (ppm) relative to tetramethylsilane (TMS) as an internal standard. EI- and HR-EI-MS spectra were measured with an AUTOSPEC ULTIMA-TOF spectrometer. Optical rotations were measured using a PERKIN-ELMER 341 digital polarimeter. CD spectra were recorded on a Jasco J-815, λ ($\Delta\varepsilon$) in nm. UV spectra were measured with a Shimadzu UV-2550 UV–VIS recording spectrometer. IR spectra were measured with a Shimadzu FTIR-8400S infrared spectrometer. Silica gel (300—400 mesh, Qingdao Marine Chemical Factory) and Sephadex LH-20 (Pharmazia) was used for column chromatography, and silica gel GF$_{254}$ plates (Yantai Marine Chemical Co., Ltd.) were used for thin-layer chromatography. Preparative HPLC was carried out on a Waters HPLC system (pump: DSC; detector: DUAL λ ABSORBANCE detector).

Plant Materials The stems of *D. candidum* were collected in Zhejiang province in 2006 and identified by Prof. Shun-Xing Guo of the Institute of Medicinal Plant Development, Peking Union Medical College. A voucher specimen (TPSH-2006) was deposited in the herbarium of the Institute of Medicinal Plant Development.

Extraction and Isolation The powdered air-dried stems of *D. candidum* (2.6 kg) were refluxed with AcOEt three times to get the AcOEt extract (57 g). The AcOEt extract was first subjected to column chromatography on silica gel (1000 g, petroleum–AcOEt). The fractions obtained were further purified by repeated column chromatography and Sephadex LH-20, followed by prep HPLC on Waters-Symmetry Prep C$_{18}$ column, to give compounds **1** (52 mg), **2** (3 mg), **3** (80 mg), **4** (100 mg), **5** (5 mg), **6** (19 mg), and **7** (24 mg).

Dendrocandin A (**1**): Amorphous solid, $[\alpha]_D^{20}$ −4.3° (c=0.19, CHCl$_3$), CD (MeOH): nm ($\Delta\varepsilon$): 230 (−1.29), IR (KBr) cm^{-1}: 3510, 3139, 2941, 2925, 2867, 2829, 1614, 1514, 1467, 1373, 1305, 1244, 1193, 1174, 1081, 1029, 970, 939, UV λ_{max} (MeOH): nm (log ε): 215 (4.4), 275 (3.3), ^{1}H-NMR (CDCl$_3$, 500 MHz) and ^{13}C-NMR (CDCl$_3$, 125 MHz), see Table 1, EI-MS *m/z*: 304 (M$^+$), 273, 272, 183, 168, 167, 121, HR-EI-MS *m/z*: 304.1308 [M]$^+$ (Calcd for $C_{17}H_{20}O_5$: 304.1311).

Dendrocandin B (**2**): White powder, $[\alpha]_D^{20}$ −4.6° (c=0.11, CHCl$_3$), CD

($CHCl_3$: MeOH, 1 : 1): nm ($\Delta\varepsilon$): 219.5 (-2.70), 230.5 ($+2.75$), and 237.5 (-1.49), IR (KBr) cm^{-1}: 3487, 3271, 3002, 2947, 2918, 2848, 1618, 1591, 1510, 1469, 1377, 1338, 1222, 1112, 1037, 827, UV λ_{max} ($CHCl_3$): nm ($\log \varepsilon$): 238 (4.3), 273 (3.8), ^1H-NMR ($CDCl_3$, 500 MHz) and ^{13}C-NMR ($CDCl_3$, 125 MHz), see Table 1, EI-MS *m*/*z*: 482 (M^+), 361, 210, 167, 153, 121, HR-EI-MS *m*/*z*: 482.1951 $[M]^+$ (Calcd for $C_{27}H_{30}O_8$: 482.1941).

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