

## Novel Bibenzyl Derivatives from the Tubers of *Bletilla striata*

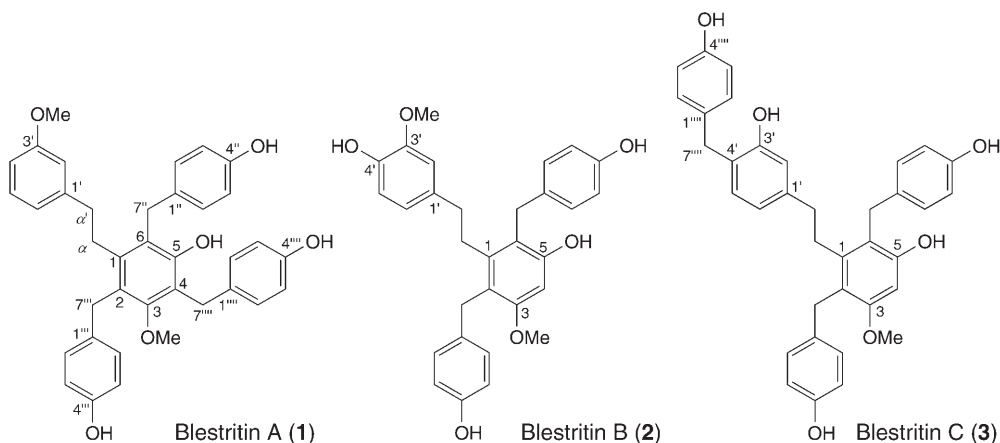
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Three novel bibenzyl derivatives, blestritins A–C (**1–3**), along with 18 known constituents, were isolated from the tubers of *Bletilla striata* (Orchidaceae), a traditional Chinese medicine used for the treatment of tuberculosis and haemorrhage of the stomach and lungs. Their structures were identified on the basis of spectroscopic analyses.

**Introduction.** – *Bletilla striata* (THUNB.) REICHB. F. (Orchidaceae) is mainly distributed in East Asia, and its tubers are used as a Chinese traditional medicine for the treatment of tuberculosis and haemorrhage of the stomach or lung [1]. Previous phytochemical studies on *Bletilla* species have led to the isolation of phenanthrene derivatives [2–11], bibenzyls [2][4], flavonoids and phenolic compounds [5], and cyanidin glycosides [12]. As part of our ongoing chemical study on *Bletilla striata*, three novel bibenzyl derivatives, blestritins A–C (**1–3**), were isolated from the tubers of *B. striata*, together with 18 known constituents. We report herein the isolation and structural elucidation of these compounds.



**Results and Discussion.** – Compound **1** was obtained as a white amorphous powder. Its molecular formula was established as  $C_{37}H_{36}O_6$  by HR-ESI-MS, giving a quasimolecular ion ( $m/z$  599.2408 ( $[M+Na]^+$ )), and by NMR analysis. The IR spectrum showed absorptions at 3405 (OH), 2937 ( $CH_2$ ), and 1596 and 1511 (aromatic)

$\text{cm}^{-1}$ . The UV spectrum with a maximum at 281 nm was in agreement with a bibenzyl (=1,1'-(ethane-1,2-diyl)bis[benzene]) derivative [2]. The structure of **1** was deduced from the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR (Table),  $^1\text{H}$ , $^1\text{H}$ -COSY and HMBC (Figure), and ROESY data as 2,4,6-tris(4-hydroxybenzyl)-3,3'-dimethoxybibenzyl-5-ol<sup>1)</sup>; **1** is a new compound and was assigned the trivial name blestritin A.

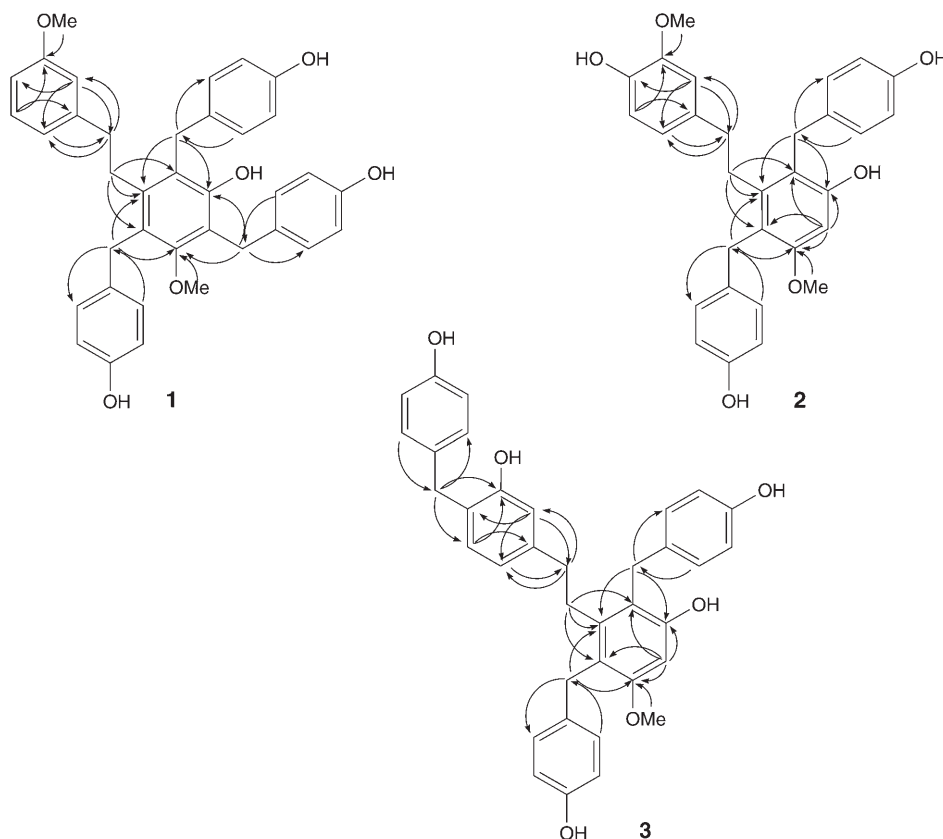


Figure. Key  $^1\text{H}$ , $^{13}\text{C}$  long-range correlation signals ( $^1\text{H} \rightarrow ^{13}\text{C}$ ) in the HMBC spectra of **1–3**

The  $^1\text{H}$ -NMR displayed six *d* or *m* at  $\delta(\text{H})$  6.89 (*d*,  $J = 8.6$  Hz, 2 H), 6.60–6.64 (*m*, 2 H), 6.83 (*d*,  $J = 8.4$  Hz, 2 H), 6.59–6.63 (*m*, 2 H), 7.02 (*d*,  $J = 8.5$  Hz, 2 H), and 6.63–6.66 (*m*, 2 H) due to three *AABB* systems characteristic of 4-substituted benzyl groups, and three *s* at  $\delta(\text{H})$  4.02 (2 H), 3.93 (2 H), and 4.04 (2 H) due to three benzyl  $\text{CH}_2$  groups. Four aliphatic protons due to bibenzyl  $\text{CH}_2$  groups appeared as a pair of *m* at  $\delta(\text{H})$  2.30–2.40 (2 H) and 2.61–2.71 (2 H), and two MeO at  $\delta(\text{H})$  3.45 (*s*) and 3.67 (*s*) and four aromatic protons at  $\delta(\text{H})$  6.40 (*br. s*, 1 H), 6.63–6.67 (*m*, 1 H), 7.08 (*t*,  $J = 7.6$  Hz, 1 H), and 6.57 (*d*,  $J = 7.6$  Hz, 1 H), assigned to H–C(2'), H–C(4'), H–C(5'), and H–C(6') by the  $^1\text{H}$ , $^1\text{H}$ -COSY cross-peaks and coupling patterns, were also observed in the  $^1\text{H}$ -NMR spectrum. The  $^{13}\text{C}$ -NMR spectrum showed 37 C-signals assigned by DEPT experiments to two Me, five  $\text{CH}_2$ , and sixteen CH groups, and

<sup>1)</sup> Trivial atom numbering; for systematic names, see *Exper. Part*.

Table.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Data (400 and 100 MHz, resp.,  $\text{CD}_3\text{OD}$ ) of **1–3**).  $\delta$  in ppm,  $J$  in Hz.

	<b>1</b>		<b>2</b>		<b>3</b>	
	$\delta(\text{H})$	$\delta(\text{C})$	$\delta(\text{H})$	$\delta(\text{C})$	$\delta(\text{H})$	$\delta(\text{C})$
C(1)		141.2 (s)		143.2 (s)		143.2 (s)
C(2)		126.2 (s)		121.8 (s)		120.7 (s)
C(3)		158.3 (s)		158.7 (s)		158.8 (s)
C(4) or H–C(4)		121.7 (s)	6.48 (s)	98.4 (d)	6.47 (s)	98.4 (d)
C(5)		154.6 (s)		156.2 (s)		156.4 (s)
C(6)		125.5 (s)		120.7 (s)		120.0 (s)
$\text{CH}_2(\alpha)$	2.61–2.71 (m)	33.9 (t)	2.60–2.70 (m)	34.0 (t)	2.62–2.71 (m)	33.8 (t)
C(1')		145.5 (s)		135.6 (s)		143.2 (s)
H–C(2')	6.40 (br. s)	115.0 (d)	6.38 (d, $J=1.8$ )	113.3 (d)	6.52 (d, $J=1.6$ )	116.1 (d)
C(3')		161.5 (s)		149.0 (s)		156.4 (s)
H–C(4') or C(4')	6.63–6.67 (m)	113.2 (d)		145.8 (s)		127.6 (s)
H–C(5')	7.08 (t, $J=7.6$ )	130.7 (d)	6.60–6.65 (m)	116.3 (d)	6.79 (d, $J=7.6$ )	131.7 (d)
H–C(6')	6.57 (d, $J=7.6$ )	122.1 (d)	6.44 (dd, $J=8.0, 1.8$ )	121.8 (d)	6.38 (dd, $J=7.6, 1.6$ )	120.9 (d)
$\text{CH}_2(\alpha')$	2.30–2.40 (m)	38.2 (t)	2.16–2.26 (m)	37.5 (t)	2.16–2.26 (m)	37.9 (t)
C(1'')		133.9 (s)		134.7 (s)		134.9 (s)
H–C(2'',6'')	6.89 (d, $J=8.6$ )	130.5 (d)	6.94 (d, $J=8.4$ )	130.4 (d)	6.92 (d, $J=8.6$ )	130.6 (d)
H–(3'',5'')	6.60–6.64 (m)	116.5 (d)	6.60–6.64 (m)	116.2 (d)	6.59–6.63 (m)	116.4 (d)
C(4'')		156.8 (s)		156.3 (s)		156.4 (s)
$\text{CH}_2(7'')$	4.02 (s)	32.5 (t)	3.91 (s)	31.5 (t)	3.90 (s)	31.7 (t)
C(1''')		134.7 (s)		134.8 (s)		134.9 (s)
H–(2''',6''')	6.83 (d, $J=8.4$ )	130.4 (d)	6.85 (d, $J=8.8$ )	130.2 (d)	6.84 (d, $J=8.7$ )	130.4 (d)
H–(3''',5''')	6.59–6.63 (m)	116.5 (d)	6.58–6.62 (m)	116.2 (d)	6.56–6.59 (m)	116.4 (d)
C(4''')		156.8 (s)		156.3 (s)		156.4 (s)
$\text{CH}_2(7''')$	3.93 (s)	32.4 (t)	3.89 (s)	31.4 (t)	3.89 (s)	31.5 (t)
C(1''''')		133.9 (s)				134.2 (s)
H–C(2''',6''''')	7.02 (d, $J=8.5$ )	130.7 (d)			6.97 (d, $J=8.3$ )	131.3 (d)
H–C(3''',5''''')	6.63–6.66 (m)	116.5 (d)			6.63–6.66 (m)	116.4 (d)
C(4''''')		156.8 (s)				156.7 (s)
$\text{CH}_2(7''''')$	4.04 (s)	30.6 (t)			3.79 (s)	35.9 (t)
MeO–C(3)	3.45 (s)	62.7 (q)	3.76 (s)	56.3 (q)	3.78 (s)	56.4 (q)
MeO–C(3')	3.67 (s)	56.1 (q)	3.78 (s)	56.7 (q)		

fourteen quaternary C-atoms. According to the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data and the molecular formula, the basic structure of **1** was characterized as a bibenzyl derivative with three 4-substituted benzyl, one OH and two MeO groups. In the ROESY plot, the NOE correlations H–C( $\alpha$ )/H–C(7'') and H–C(7'''), MeO ( $\delta(\text{H})$  3.67)/H–C(2') and H–C(4'), and MeO ( $\delta(\text{H})$  3.45)/H–C(7''') and H–C(7''''') were observed, indicating the location of three 4-substituted benzyl groups at C(2), C(4), and C(6), and of the MeO groups at C(3') and C(3), which were further supported by  $^{13}\text{C}$ , $^1\text{H}$  long-range correlation signals in its HMBC plot (Figure).

Compound **2** was isolated as a white, amorphous powder with the molecular formula  $\text{C}_{30}\text{H}_{30}\text{O}_6$  as established by HR-ESI-MS. The IR and UV spectra of **2** were similar to those of **1**. The structure of **2** was deduced as 2,6-bis(4-hydroxybenzyl)-3,3'-

dimethoxybibenzyl-4',5-diol<sup>1</sup>), called blestritin B, from <sup>1</sup>H- and <sup>13</sup>C-NMR (Table), <sup>1</sup>H,<sup>1</sup>H-COSY and HMBC (Figure), and ROESY data.

The <sup>1</sup>H-NMR of **2** exhibited the resonances of two pairs of 4-substituted benzyl groups at  $\delta$ (H) 6.94 (*d*, *J* = 8.4 Hz, 2 H), 6.60–6.64 (*m*, 2 H), 6.85 (*d*, *J* = 8.8 Hz, 2 H), and 6.58–6.62 (*m*, 2 H), two benzyl CH<sub>2</sub> groups at  $\delta$ (H) 3.91 (*s*, 2 H) and 3.89 (*s*, 2 H), four aliphatic protons due to bibenzyl CH<sub>2</sub> groups at  $\delta$ (H) 2.16–2.26 (*m*, 2 H) and 2.60–2.70 (*m*, 2 H), two MeO groups at  $\delta$ (H) 3.76 (*s*) and 3.78 (*s*), an *ABX* system at  $\delta$ (H) 6.38 (*d*, *J* = 1.8 Hz, 1 H), 6.44 (*dd*, *J* = 8.0, 1.8 Hz, 1 H), 6.60–6.65 (*m*, 1 H), and one *s* at 6.48 (*s*, 1 H). In the <sup>13</sup>C-NMR and DEPT spectra, 30 C-signals belonging to two Me, four CH<sub>2</sub>, and twelve CH groups, and twelve C-atoms were observed. These data revealed a bibenzyl skeleton with two 4-substituted benzyl, two OH, and two MeO groups. The aromatic protons appearing as an *ABX* system at  $\delta$ (H) 6.38, 6.60–6.65, and 6.44 were assigned to H–C(2'), H–C(5'), and H–C(6'), and the *s* at  $\delta$ (H) 6.48 to H–C(4), respectively, according to the <sup>13</sup>C,<sup>1</sup>H long-range correlation signals observed for H–C( $\alpha'$ )/C(1'), C(2'), and C(6'), H–C(2'')/C(4') and C(6'), H–C(5'')/C(1') and C(3'), and H–C(4'')/C(2), C(3), C(5), and C(6) in the HMBC plot (Fig.). In the ROESY plot of **2**, NOE correlations MeO ( $\delta$ (H) 3.76)/H–C(4) and H–C(7''') and MeO ( $\delta$ (H) 3.78)/H–C(2') were found, indicating the location of two MeO groups at C(3) and C(3').

To compound **3**, obtained as a white amorphous powder, the elemental formula C<sub>36</sub>H<sub>34</sub>O<sub>6</sub> was assigned as deduced from HR-ESI-MS and NMR data. The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra and molecular formula suggested that the structure of **3** was very similar to that of **2**, except for the appearance of another 4-substituted benzyl group and the absence of a MeO group in **3**. The additional benzyl group was located at C(4') according to the <sup>13</sup>C,<sup>1</sup>H long-range correlation signals at H–C(7''''')/C(3'), C(4'), and C(5') (Fig.), and also the NOE correlation H–C(7''''')/H–C(5'). The NOE correlations MeO/H–C(4) and H–C(7''''') suggested the location of the MeO group at C(3). Thus, compound **3** was determined as 2,4',6-tris(4-hydroxybenzyl)-3-methoxybibenzyl-3',5-diol<sup>1</sup>), which has been given the trivial name blestritin C.

In addition to the three new compounds, 18 known ones were also isolated and characterized as 3'-*O*-methylbatatasin III (= 5-methoxy-3-[2-(3-methoxyphenyl)ethyl]phenol) [13], batatasin III (= 3-[2-(3-hydroxyphenyl)ethyl]-5-methoxyphenol) [13], 5,4'-dimethoxybibenzyl-3,3'-diol [14], bulbocol (= 4-[(4-hydroxyphenyl)methyl]-3-methoxy-5-[2-(3-methoxyphenyl)ethyl]phenol) [15], gymconopin D (= 2-[(4-hydroxyphenyl)methyl]-5-methoxy-3-[2-(3-methoxyphenyl)ethyl]phenol) [16], 2-(4-hydroxybenzyl)-3-methoxybibenzyl-3',5-diol [4], 2-(4-hydroxybenzyl)-5-methoxybibenzyl-3,3'-diol [4], bulbocodin (= 3-[2-{2-hydroxy-5-[4-hydroxyphenyl)methyl]phenyl}ethyl]-2,4-bis[(4-hydroxyphenyl)methyl]-5-methoxyphenol) [15], bulbocodin D (= 3-[2-(3-hydroxyphenyl)ethyl]-2,6-bis[(4-hydroxyphenyl)methyl]-5-methoxyphenol) [17], 2,6-bis(4-hydroxybenzyl)-5,3'-dimethoxybibenzyl-3-ol [2], 2',6'-bis(4-hydroxybenzyl)-5-methoxybibenzyl-3,3'-diol [2], 4-methoxyphenanthrene-2,7-diol [18], 3,4-dimethoxyphenanthrene-2,7-diol [18], 2,4-dimethoxyphenanthrene-3,7-diol [18], dactylorhin A (= [(2*R*)-2-( $\beta$ -D-glucopyranosyloxy)-2-(2-methylpropyl)-1,4-dioxobutane-1,4-diyl]) bis-(oxymethylene-4,1-phenylene) bis[ $\beta$ -D-glucopyranoside] [19], dactylorhin E (= 4-[[[(2*R*)-2-(carboxymethyl)-2-( $\beta$ -D-glucopyranosyloxy)-4-methyl-1-oxopentyl]oxy]methyl]phenyl  $\beta$ -D-glucopyranoside] [19], gymnoside I (= 4-[[[(2*R*)-2-(carboxymethyl)-2-hydroxy-4-methyl-1-oxopentyl]oxy]methyl]phenyl  $\beta$ -D-glucopyranoside) [20], and gymnoside II (= 4-[[[(3*R*)-3-carboxy-3-hydroxy-5-methyl-1-oxohexyl]oxy]methyl]phenyl  $\beta$ -D-glucopyranoside) [20]. Among them, 3'-*O*-methylbatatasin III, batatasin

III, 5,4'-dimethoxybibenzyl-3,3'-diol, gymconopin D, bulbocodin, bulbocodin D, 4-methoxyphenanthrene-2,7-diol, 3,4-dimethoxyphenanthrene-2,7-diol, 2,4-dimethoxyphenanthrene-3,7-diol, dactylorhin A, dactylorhin E, gymnoside I, and gymnoside II were found for the first time in this plant.

### Experimental Part

*General.* Column chromatography (CC): silica gel H60 (Qingdao Haiyang Chemical Group Corporation, Qingdao, P. R. China), Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden). Prep. HPLC: Varian SD-1 instrument equipped with a RP-C<sub>18</sub> column (Merck NW25, 20 mm × 250 mm; 10 ml/min) and ProStar 320-UV-Vis detector (254 nm). TLC: HSG<sub>254</sub> silica gel plates (Yantai Chemical Industrial Institute, Yantai, P. R. China). UV Spectra: Beckman DU-7 spectrometer; λ (log ε) in nm. IR Spectra: Perkin-Elmer 577 spectrometer;  $\tilde{\nu}$  in cm<sup>-1</sup>. NMR Spectra: Bruker AM-400 spectrometer; δ in ppm rel. to SiMe<sub>4</sub> as internal standard, J in Hz. HR-ESI-MS: Mariner spectrometer; in m/z.

*Plant Material.* The tubers of *Bletilla striata* were purchased from the Shanghai Yanghetang Herb Medicine Company in September, 2006, and identified by Prof. Jin-Gui Shen of the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. A voucher specimen was deposited in the Herbarium of the Shanghai Institute of Materia Medica (No. 20070330).

*Extraction and Isolation.* Powdered air-dried tubers of *B. striata* (3.0 kg) were percolated with 95% EtOH (20.0 l) at r.t. The extract was concentrated, the residue suspended in H<sub>2</sub>O (2.0 l) and then extracted successively with CHCl<sub>3</sub> (3 × 2.0 l), and BuOH (3 × 2.0 l), yielding a CHCl<sub>3</sub> extract (60.0 g) and a BuOH extract (25.3 g). The CHCl<sub>3</sub> extract (60.0 g) was subjected to CC (SiO<sub>2</sub>, petroleum ether/acetone 10:1 → 1:1): Fractions 1–7. Fr. 2 (820 mg) was resubjected to CC (Sephadex LH-20, EtOH): 3'-O-methylbatatasin III (129 mg). Fr. 4 (4.0 g) was separated by CC (Sephadex LH-20, EtOH): Fr. 4.1 (1.5 g), Fr. 4.2 (2.0 g), and Fr. 4.3 (581 mg). Fr. 4.2 (2.0 g) was separated by prep. HPLC (RP-18, MeOH/H<sub>2</sub>O 4:6 → 10:0): batatasin III (592 mg), 4,5-dimethoxybibenzyl-3,3'-diol (9 mg), bulbocol (125 mg), gymconopin D (122 mg), and 2-(4-hydroxybenzyl)-3-methoxybibenzyl-3',5'-diol (10 mg). Fr. 4.3 (581 mg) was subjected to prep. HPLC (RP-18, MeOH/H<sub>2</sub>O 4:6 → 10:0): 4-methoxyphenanthrene-2,7-diol (12 mg), 3,4-dimethoxyphenanthrene-2,7-diol (14 mg), and 2,4-dimethoxyphenanthrene-3,7-diol (8 mg). Fr. 6 (4.1 g) was separated by prep. HPLC (RP-18, MeOH/H<sub>2</sub>O 4:6 → 10:0): **1** (9 mg), **2** (7 mg), 2-(4-hydroxybenzyl)-5-methoxybibenzyl-3',3'-diol (60 mg), bulbocodin D (61 mg), 2,6-bis(4-hydroxybenzyl)-3',5'-dimethoxybibenzyl-3-ol (63 mg), and 2',6'-bis(4-hydroxybenzyl)-5-methoxybibenzyl-3,3'-diol (152 mg). Fr. 7 (6.1 g) was subjected to prep. HPLC (RP-18, MeOH/H<sub>2</sub>O 4:6 → 10:0): **3** (5 mg) and bulbocodin (41 mg). The BuOH extract (25.3 g) was subjected to CC (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O 3:1:0.1 → 7:3:0.5): gymnoside I (420 mg), gymnoside II (165 mg), dactylorhin E (85 mg), and dactylorhin A (50 mg).

*Blestitin A* (= 2,4,6-Tris(4-hydroxybenzyl)-3,3'-dimethoxybibenzyl-5-ol = 2,4,6-Tris[4-(4-hydroxyphenyl)methyl]-3-methoxy-5-[2-(3-methoxyphenyl)ethyl]phenol; **1**): White amorphous powder. UV (MeOH): 281 (2.14). IR (KBr): 3405, 2937, 1612, 1596, 1511, 1438, 1384, 1236, 1170, 1085, 819. <sup>1</sup>H- and <sup>13</sup>C-NMR: Table. HR-ESI-MS: 599.2408 ([M + Na]<sup>+</sup>, C<sub>37</sub>H<sub>36</sub>NaO<sub>6</sub><sup>+</sup>; calc. 599.2410).

*Blestitin B* (= 2,6-Bis(4-hydroxybenzyl)-3,3'-dimethoxybibenzyl-4',5'-diol = 3-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2,4-bis[4-(4-hydroxyphenyl)methyl]-5-methoxyphenol; **2**): White amorphous powder. UV (MeOH): 281 (2.17). IR (KBr): 3413, 2919, 1614, 1511, 1459, 1384, 1236, 1105, 819. <sup>1</sup>H- and <sup>13</sup>C-NMR: Table. HR-ESI-MS: 509.1924 ([M + Na]<sup>+</sup>, C<sub>30</sub>H<sub>30</sub>NaO<sub>6</sub><sup>+</sup>; calc. 509.1940).

*Blestitin C* (= 2,4',6'-Tris(4-hydroxybenzyl)-3-methoxybibenzyl-3',5'-diol = 3-[2-{3-hydroxy-4-[(4-hydroxyphenyl)methyl]phenyl}ethyl]-2,4-bis[4-(4-hydroxyphenyl)methyl]-5-methoxyphenol; **3**): White amorphous powder. UV (MeOH): 281 (2.27). IR (KBr): 3403, 2917, 1594, 1511, 1444, 1382, 1232, 1170, 1107, 815. <sup>1</sup>H- and <sup>13</sup>C-NMR: Table. HR-ESI-MS: 585.2230 ([M + Na]<sup>+</sup>, C<sub>36</sub>H<sub>34</sub>NaO<sub>6</sub><sup>+</sup>; calc. 585.2253).

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