Three New Bibenzyl Derivatives from the Chinese Liverwort *Marchantia polymorpha* L.

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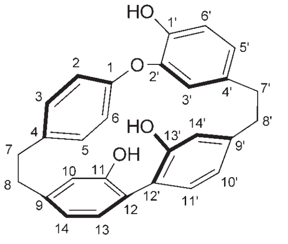
From the Et_2O extract of the Chinese liverwort *Marchantia polymorpha* L., three new bibenzyl (=1,1′-(ethane-1,2-diyl)bisbenzene) derivatives, compounds **1**–**3**, were obtained, together with the two known compounds marchantin J and perrottetin E. Their structures were established by NMR and HR-EI-MS analyses. Polymorphatin A (**1**) represents a new type of bis[bibenzyl] skeleton, and compound **3** is the first example of a bibenzyl oxidatively coupled to a phenylmethanol.

Introduction. – Liverworts are rich sources of bis[bibenzyl] (bibenzyl = 1,1′-(ethane-1,2-diyl)bisbenzene compounds [1][2]. *Marchantia polymorpha* L. is one of the large thalloid liverworts, and widely distributed in the world. Since marchantin A was first isolated from *M. polymorpha* L. [3], a variety of bis[bibenzyl] compounds have been discovered in this species [4][5]. In our previous study, seven such constituents with antifungal and antimicrobial activities were isolated from Chinese *M. polymorpha* L. [5]. During our search for minor bioactive substances from this species, we now isolated three new bis[bibenzyl] derivatives, compounds **1**–**3**, together with two known compounds, marchantin J and perrottetin E. Herein, we report the isolation and structure elucidation of the new compounds.



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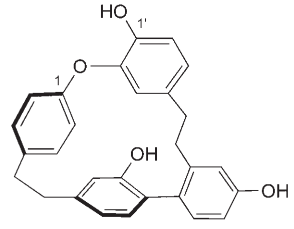

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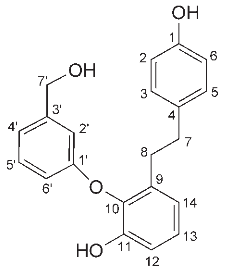

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Results and Discussion. – The Et_2O extract of *M. polymorpha* L. was purified by repeated column chromatography on silica gel and *Sephadex LH-20* gel, followed by semi-preparative HPLC, to afford five compounds.

Compound **1**, obtained as a colorless powder, had the molecular formula $C_{28}H_{24}O_4$, as deduced by HR-EI-MS (*m*/*z* 424.1678 (M^+; calc. 424.1675)). The ^1H- and ^{13}C-NMR spectra of **1** (*Table*)1) displayed four benzyl CH$_2$ groups [δ(H) 3.04–3.08 (*m*, 2 H), 3.06–3.10 (*m*, 2 H), 2.68–2.74 (*m*, 2 H), 2.25–2.32 (*m*, 2 H); δ(C) 36.2 (C(7)), 37.3 (C(8)), 38.7 (C(7′)), 38.1 (C(8′))] and 24 benzene-ring C-atoms bearing 13 aromatic H-atoms, which indicated that **1** was a bis[bibenzyl] derivate [6]. In the ^{1}H-NMR spectrum, a 1,4-disubstituted aromatic ring (ring *A*) [δ(H) 6.89 (*dd*, $J = 8.2$, 2.2 Hz, 1 H), 7.17 (*dd*, $J = 8.2$, 2.1, 1 H), 7.00 (*dd*, $J = 8.3$, 2.1, 1 H), 6.77 (*dd*, $J = 8.3$, 2.2 Hz, 1 H)] and three 1,2,4-trisubstituted aromatic rings (rings *B* – *D*) [δ(H) 6.44 (*d*, $J = 1.4$ Hz, 1 H), 6.77 (*d*, $J = 7.6$ Hz, 1 H), 6.55 (*dd*, $J = 7.6$, 1.4 Hz, 1 H); 5.88 (*d*, $J = 1.9$ Hz, 1 H), 6.66 (*dd*, $J = 8.1$, 1.9 Hz, 1 H), 6.72 (*d*, $J = 8.1$ Hz, 1 H); 6.62 (*dd*, $J = 8.2$, 2.6 Hz, 1 H), 6.88 (*d*, $J = 8.2$ Hz, 1 H), 6.76 (*d*, $J = 2.6$ Hz, 1 H)] were

Table. *^{1}H- and ^{13}C- NMR Data for Compounds* **1–3**. At 600/150 MHz, resp., in (D$_6$)acetone; δ in ppm, J in Hz. Arbitrary atom numbering.

Position	**1**		**2**		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1		155.6		153.8		156.4
2	6.89 (*dd*, $J = 8.2$, 2.2)	122.1	6.84 (*dd*, $J = 8.2$, 2.5)	120.7	6.68 (*d*, $J = 8.5$)	115.9
3	7.17 (*dd*, $J = 8.2$, 2.1)	131.6	7.17 (*dd*, $J = 8.2$, 2.1)	130.3	6.89 (*d*, $J = 8.5$)	130.1
4		135.4		136.8		133.5
5	7.00 (*dd*, $J = 8.3$, 2.1)	131.7	7.06 (*dd*, $J = 8.2$, 2.1)	130.3	6.89 (*d*, $J = 8.5$)	130.1
6	6.77 (*dd*, $J = 8.3$, 2.2)	122.3	6.77 (*dd*, $J = 8.2$, 2.5)	120.6	6.69 (*d*, $J = 8.5$)	115.9
7	3.04–3.08 (*m*)	36.2	3.01–3.14 (*m*)	34.5	2.64–2.70 (*m*)	36.4
8	3.06–3.10 (*m*)	37.3	2.89–2.94 (*m*)	35.6	2.64–2.70 (*m*)	33.8
9		141.9		140.3		137.1
10	6.44 (*d*, $J = 1.4$)	117.4	6.54 (*d*, $J = 1.8$)	119.9		140.9
11		155.1		153.7		151.3
12		127.1		125.3	6.88 (*dd*, $J = 7.8$, 1.5)	115.7
13	6.77 (*d*, $J = 7.6$)	131.8	6.80 (*d*, $J = 8.0$)	130.1	7.06 (*t*, $J = 7.8$)	126.6
14	6.55 (*dd*, $J = 7.6$, 1.4)	121.2	6.54 (*dd*, $J = 8.0$, 1.8)	115.5	6.81 (*dd*, $J = 7.8$, 1.5)	122.0
1′		145.6		144.4		159.5
2′		149.7		147.9	6.90 (*d*, $J = 2.2$)	113.8
3′	5.88 (*d*, $J = 1.9$)	117.0	5.86 (*d*, $J = 2.0$)	115.3		145.3
4′		135.4		144.4	6.95–6. 98 (*m*)	120.4
5′	6.66 (*dd*, $J = 8.1$, 1.9)	122.6	6.71 (*dd*, $J = 8.0$, 2.0)	121.3	7.23 (*t*, $J = 7.8$)	130.0
6′	6.72 (*d*, $J = 8.1$)	116.6	6.76 (*d*, $J = 8.0$)	115.0	6.67–6.72 (*m*)	114.0
7′	2.68–2.74 (*m*)	38.7	2.37–2.44 (*m*)	37.0	4.59 (*d*, $J = 5.8$)	64.4
8′	2.25–2.32 (*m*)	38.1	2.26–2.34 (*m*)	36.5		
9′		143.3		141.9		
10′	6.62 (*dd*, $J = 8.2$, 2.6)	116.3		128.6		
11′	6.88 (*d*, $J = 8.2$)	135.4	6.90 (*d*, $J = 8.2$)	131.2		
12′		131.0	6.67 (*dd*, $J = 8.2$, 2.6)	112.5		
13′		157.6		156.4		
14′	6.76 (*d*, $J = 2.6$)	116.5	6.83 (*d*, $J = 2.6$)	115.2		
1-OH					8.29 (*s*)	
11-OH	7.65 (*s*)		7.40 (*s*)		8.12 (*s*)	
1′-OH	7.82 (*s*)		7.78 (*s*)			
13′-OH	8.01 (*s*)		8.15 (*s*)			

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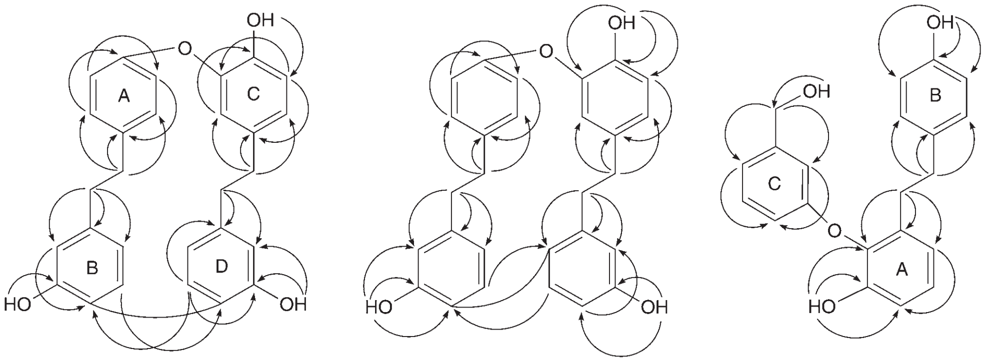
1) Arbitrary atom numbering.

distinguished, which was further supported by HMQC and HMBC experiments (*Fig.*). Furthermore, the linkage between rings *A* and *B via* $CH_2(7)-CH_2(8)$ was supported by the HMBC correlations between H−C(7) (δ(H) 3.04–3.08) and both C(3) and C(5) (δ(C) 131.6, 131.7, resp.), and between H−C(8) (δ(H) 3.06–3.10) and both C(10) and C(14) (δ(C) 117.4, 121.2, resp.). Also, rings *C* and *D* were linked *via* $CH_2(7')-CH_2(8')$, as inferred from HMBC correlations between H−C(7′) (δ(H) 2.68–2.74) and both C(3′) and C(5′) (δ(C) 117.0, 122.6, resp.), as well as between H−C(8′) (δ(H) 2.25–2.32) and both C(10′) and C(14′) (δ(C) 116.3, 116.5, resp.). The high-field-shifted characteristic resonance for H−C(3′) at δ(H) 5.88 suggested an ether linkage between C(1) and C(2′) [7]. The biphenyl linkage between C(12) and C(12′) was derived from HMBC correlations between H−C(13) (δ(H) 6.77) and C(12′) (δ(C) 131.0), and between H−C(11′) (δ(H) 6.88) and C(12) (δ(C) 127.1). In addition, the HMBC correlations from 13′-OH (δ(H) 8.01) to C(12′), C(13′), and C(14′) (δ(C) 131.0, 157.6, 116.5, resp.), those from 1′-OH (δ(H) 7.82) to C(1′), C(2′), and C(6′) (δ(C) 145.6, 149.7, 115.0), as well as those from 11-OH (δ(H) 7.65) to C(10), C(11), and C(12) (δ(C) 117.4, 155.1, 127.1, resp.) implied that these three OH groups were connected to C(13′), C(1′), and C(11), respectively. From these data, the structure of compound **1** was established as 12-oxapentacyclo[18.2.2.$2^{2,5}$.$2^{8,11}$.$1^{13,17}$]nonacosa-1(22),2,4,8,10,13(25),14,16,20,23,26,28-dodecaene-3,14,22-triol, and named *polymorphatin A*, which represents a new type of bis[bibenzyl] skeleton [6].

Compound **2**, obtained as a colorless powder, had the same molecular formula ($C_{28}H_{24}O_4$) as **1**, as revealed by HR-EI-MS (*m*/*z* 424.1674 (M^+; calc. 424.1675)). Compound **2** was determined to be an isorricardin bis[bibenzyl] derivative [8], based on its characteristic NMR spectra (*Table*). The ^{1}H-NMR spectra of **2** showed signals of four benzyl CH_2 [δ(H) 3.01–3.14 (*m*, 2 H), 2.89–2.94 (*m*, 2 H), 2.37–2.44 (*m*, 2 H), 2.26–2.34 (*m*, 2 H)], a 1,4-dissubstituted aromatic ring (ring *A*) [δ(H) 6.84 (*dd*, *J* = 8.2, 2.5 Hz, 1 H), 7.17 (*dd*, *J* = 8.2, 2.1 Hz, 1 H), 7.06 (*dd*, *J* = 8.2, 2.1 Hz, 1 H), and 6.77 (*dd*, *J* = 8.2, 2.5 Hz, 1 H)], as well as three 1,2,4-trisubstitued aromatic rings (rings *B* – *D*) [δ(H) 6.54 (*d*, *J* = 1.8 Hz, 1 H), 6.80 (*d*, *J* = 8.0 Hz, 1 H), 6.54 (*dd*, *J* = 8.0, 1.8 Hz, 1 H); 5.86 (*d*, *J* = 2.0 Hz, 1 H), 6.71 (*dd*, *J* = 8.0, 2.0 Hz, 1 H), 6.76 (*d*, *J* = 8.0 Hz, 1 H); 6.90 (*d*, *J* = 8.2 Hz, 1 H), 6.67 (*dd*, *J* = 8.2, 2.6 Hz, 1 H), 6.83 (*d*, *J* = 2.6 Hz, 1 H)]. In the HMBC spectrum, long range correlations were observed between H−C(7) (δ(H) 3.01–3.14) and both C(3) and C(5) (δ(C) 130.3, 130.3), resp., between H−C(8) (δ(H) 2.89–2.94) and both C(10) and C(14) (δ(C) 119.9, 115.5, resp.). This indicated that rings *A* and *B* were linked *via* $CH_2(7)-CH_2(8)$. Analogously, rings *C* and *D* were linked *via* $CH_2(7')-CH_2(8')$, based on HMBC correlations between H−C(7′) (δ(H) 2.37–2.44) and both C(3′) and C(5′) (δ(C) 115.3, 121.3, resp.), and between H−C(8′) (δ(H) 2.26–2.34) and both C(10′) and C(14′) (δ(C) 128.6, 115.2, resp.). The characteristic resonance for H−C(3′) at δ(H) 5.86 indicated an ether linkage between C(1) and C(2′) [7]. The presence of a biphenyl linkage between C(12) and C(10′) was inferred from the HMBC cross-peaks between H−C(13) (δ(H) 6.80) and C(10′) (δ(C) 128.6), and between H−C(11′) (δ(H) 6.90) and C(12) (δ(C) 125.3). In addition, three OH groups (δ(H) 8.15, 7.78, 7.40) were positioned at C(13′), C(1′), and C(11), respectively, as confirmed by HMBC correlations between 13′-OH and C(12′), C(13′), and C(14′), between 1′-OH and C(1′), C(2′), and C(6′), and between 11-OH and C(10), C(11), and C(12), respectively.

From the above data, the structure of compound **2** was established as 11,1′,13′-trihydroxyisorricardin, which corresponds to 15-oxapentacyclo[$20.2.2.2^{16,19}.1^{10,14}.0^{2,7}$]-nonacosa-1(24),2,4,6,10(29),11,13,16,18,22,25,27-dodecaene-5,13,24-triol, and was named *isorricardin D*.

As a matter of fact, the conformational strains of, at that time, 'hypothetical' **1** and **2** were computed some time ago on the DTMM and MM2 levels [9]. However, these two compounds have not been isolated before from a natural source, nor have they been synthesized. Both compounds (as well as **3**) possibly result from intra- or intermolecular oxidative-coupling processes.



1 **2** **3**

Figure. *Key HMBC correlations for compounds* **1**–**3**

Compound **3**, obtained as a colorless oil, had the molecular formula $C_{21}H_{20}O_4$, as determined by HR-EI-MS (*m*/*z* 336.1359 (M^+; calc. 336.1362)). The ^{1}H-NMR spectra (*Table*) of **3** revealed the presence of three benzyl CH_2 [δ(H) 2.64–2.70 (*m*, 2 H), 2.64–2.70 (*m*, 2 H), 4.59 (*d*, 2 H)], a 1,4-disubstituted aromatic ring (ring *B*) [δ(H) 6.68 (*d*, *J* = 8.5, 1 H), 6.89 (*d*, *J* = 8.5 Hz, 1 H), 6.88 (*d*, *J* = 8.5 Hz, 1 H), 6.69 (*d*, *J* = 8.5 Hz, 1 H)], a 1,2,3-trisubstituted aromatic ring (ring *A*) [δ(H) 6.88 (*dd*, *J* = 7.8, 1.5 Hz, 1 H), 7.06 (*t*, *J* = 7.8 Hz, 1 H), 6.81 (*dd*, *J* = 7.8, 1.5 Hz, 1 H)], and a 1,3-disubstituted aromatic ring (ring *C*) [δ(H) 6.90 (*d*, *J* = 2.2 Hz, 1 H), 6.95–6.98 (*m*, 1 H), 7.23 (*t*, 7.8 Hz, 1 H), 6.67–6.72 (*m*, 1 H)). Rings *A* and *B* were connected *via* the fragment $CH_2(7)-CH_2(8)$, based on the HBMC correlations (*Figure*) between H–C(7) (δ(H) 2.64–2.70) and both C(3) and C(5) (δ(C) 130.1, 130.1, resp.), as well as between H–C(8) (δ(H) 2.64–2.70) and both C(10) and C(14) (δ(C) 140.9, 122.0, resp.). The linkage between rings *A* and *C* was suggested to be C(10)–O–C(1′), as inferred from the ^{13}C-NMR chemical shifts of C(10) (δ(C) 140.9) and C(1′) (159.5). The two OH groups at δ(H) 8.29 and 8.12 were positioned at C(1) (δ(C) 156.4) and C(11) (151.3), respectively, supported by the HBMC cross-peaks shown in the *Figure*. From the above data, the structure of **3** was determined as 2-[3-(hydroxymethyl)phenoxy]-3-[2-(4-hydroxyphenyl)ethyl]phenol.

The two known compounds, marchantin J [4] and perrottetin E [10], were identified by comparison of their NMR and MS data with those reported previously.

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Experimental Part

General. Column chromatography (CC): silica gel (200–300 mesh; *Qingdao Marine Chemical Factory*, China) and *Sephadex LH-20* (*Amersham Biosciences*). Melting points (m.p.) were determined on an *X*-6 micro-melting-point apparatus (*Beijing Tech Co.*). Semi-prep. HPLC was performed on a liquid-chromatography system consisting of a *Waters W600E* multi-solvent delivery system, a *Waters-600* controller, a *Waters-delta-600* controller, and a *Waters-996* photodiode-array detector. The anal. HPLC system included a *ZORBAX Eclipse XDB-C18* column (4.6 × 150 mm, eluting with H_2O/MeOH; detection wavelength 280 nm. ^{1}H- and ^{13}C- NMR Spectra: *Bruker Avance-DRX-600* spectrometer, at 600 (^{1}H) and 150 MHz (^{13}C); δ in ppm rel. to Me_4Si, J in Hz. ESI-MS: *API 4000* (*Applied Biosystems*) mass spectrometer. EI- and HR-EI-MS: *Finnigan MAT-95* mass spectrometer with a *Waters GCT* system; in *m/z*.

Plant Material. The Chinese liverwort was collected in October 2002 from Leshan Mountain, Sichuan Province, P. R. China, and was identified by Prof. *Qian Gao*, Shenyang Institute of Applied Ecology, Chinese Academy of Sciences. A voucher specimen (No. 20021002) was deposited at the Department of Natural Products Chemistry, School of Pharmaceutical Sciences, Shandong University, P. R. China.

Extraction and Isolation. The Et_2O extract (198 g) of *M. polymorpha* L., obtained as reported before [5], was subjected to CC (SiO_2; petroleum ether (PE)/acetone gradient) to provide nine fractions (*Fr. A–I*). *Fr. C* was subjected to CC (SiO_2; PE/acetone 8:1 → 6:1) to yield marchantin J (60 mg) [4]. *Fr. D* was subjected to CC (*Sephadex LH-20*; MeOH/$CHCl_3$ 1:1) to afford five subfractions (*Fr.* D_1–D_5). *Fr.* D_2 was submitted to repeated CC (SiO_2; PE/acetone 7:1) to afford perrottetin E (4 mg) [10]. *Fr. E* was subjected to repeated CC (SiO_2; PE/acetone 5:1), followed by semi-prep. HPLC (H_2O/MeOH 30:70), to yield **1** (0.8 mg; t_R 28 min) and **2** (0.9 mg; t_R 29 min). *Fr. F* was purified by repeated CC (SiO_2; PE/acetone 11:3) and semi-prep. HPLC (H_2O/MeOH 35:65; t_R 24 min) to afford **3**.

Polymorphatin A (=*12-Oxapentacyclo[18.2.2.2*^{2,5}*.2*^{8,11}*.1*^{13,17}*]nonacosa-1(22),2,4,8,10,13(25),14,16,20,23,26,28-dodecaene-3,14,22-triol*; **1**). Colorless powder. M.p. 234–235° (MeOH). ^{1}H- and ^{13}C-NMR: see the *Table*. EI-MS: 424 (100, M^+), 376 (10), 244 (15), 165 (5), 113 (5), 89 (10). HR-EI-MS: 424.1678 (M^+, $C_{28}H_{24}O_4^+$; calc. 424.1675).

Isorricardin D (=*15-Oxapentacyclo[20.2.2.2*^{16,19}*.1*^{10,14}*.0*^{2,7}*]nonacosa-1(24),2,4,6,10(29),11,13,16,18,22,25,27-dodecaene-5,13,24-triol*; **2**). Colorless powder. M.p. 251–252° (MeOH). ^{1}H- and ^{13}C-NMR: see the *Table*. EI-MS: 424 (100, M^+), 381 (10), 344 (10), 324 (5), 302 (10), 294 (5), 250 (8), 233 (10). HR-EI-MS: 424.1674 (M^+, $C_{28}H_{24}O_4^+$; calc. 424.1675).

2-[3-(Hydroxymethyl)phenoxy]-3-[2-(4-hydroxyphenyl)ethyl]phenol (**3**). Colorless oil. ^{1}H- and ^{13}C-NMR: see the *Table*. EI-MS: 336 (100, M^+), 220 (15), 113 (10), 108 (25), 91 (5), 62 (10). HR-EI-MS: 336.1359 (M^+, $C_{21}H_{20}O_4^+$; calc. 336.1362).

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