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Synthesis of marchantin C, a novel microtubule inhibitor from liverworts

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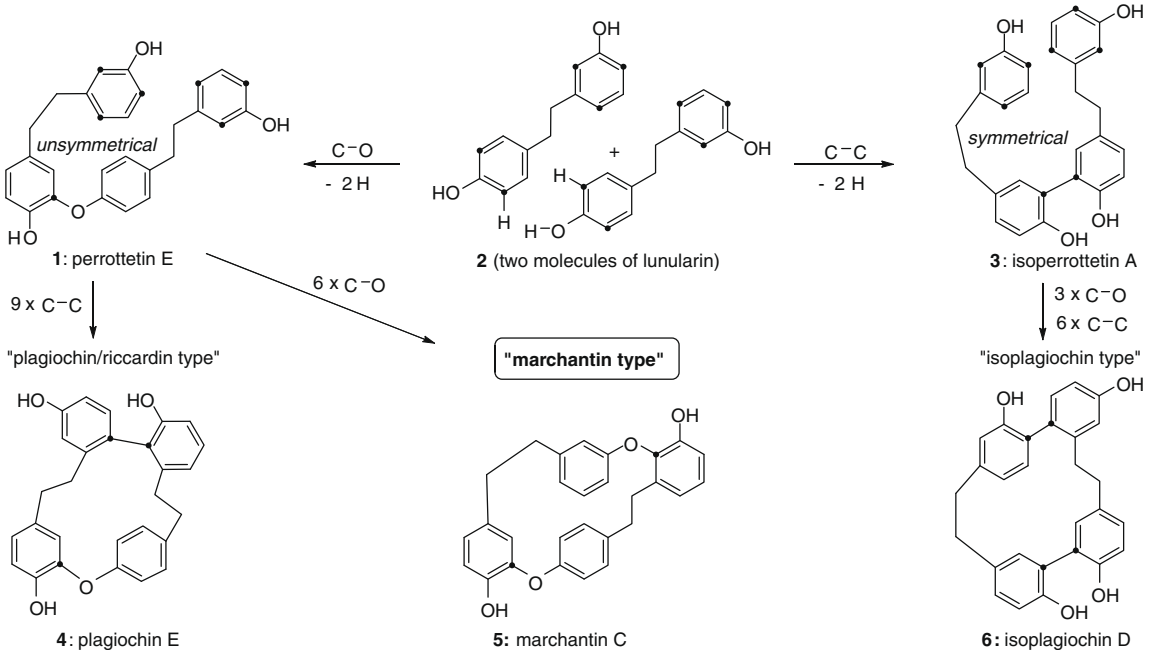
ABSTRACT

Recently, remarkable microtubule inhibitor and anti-tumor activities of the bisbibenzyl marchantin C—isolated from liverworts like *Marchantia polymorpha* since 1983—were found. In this Letter we describe the first and efficient total synthesis of this subtype of bisbibenzylic compounds with two biarylether connections. The structure was confirmed by the spectroscopic data which were analyzed carefully to exclude any errors in arene connection and substitution pattern.

Bisbibenzyls are acyclic or cyclic phenolic natural products that are found exclusively in bryophytes.[1] Biosynthetically, they originate from two units of the bibenzyl lunularin (**2**), which can be combined by several modes of O–C and/or C–C attachment on the basis of phenol oxidation coupling to different subtypes (Scheme 1).[2,3]



Scheme 1. Different subtypes of acyclic or cyclic bisbibenzyls.

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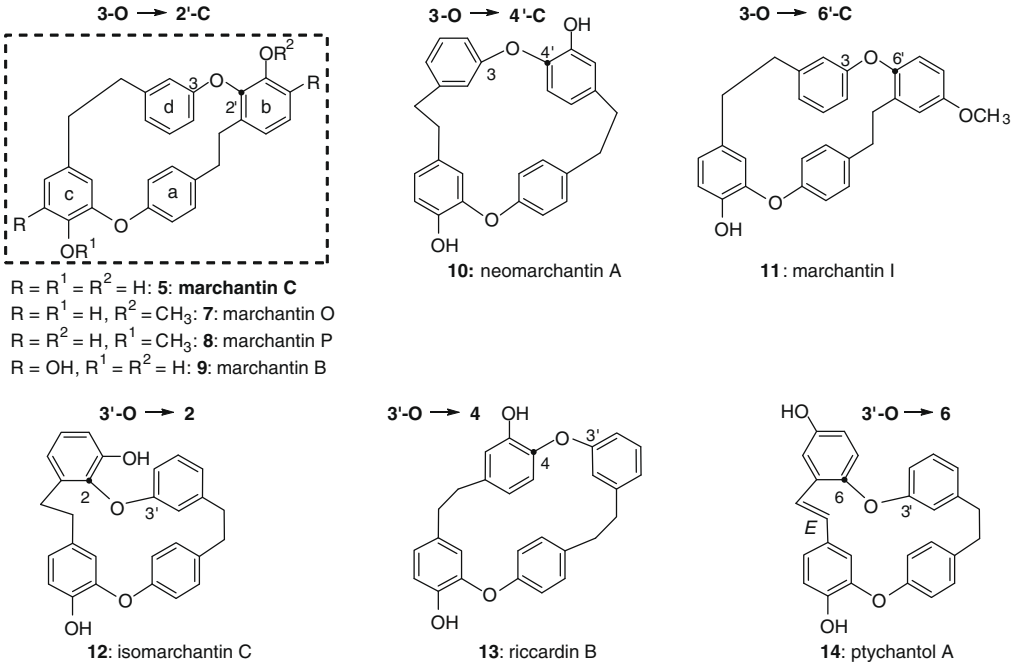


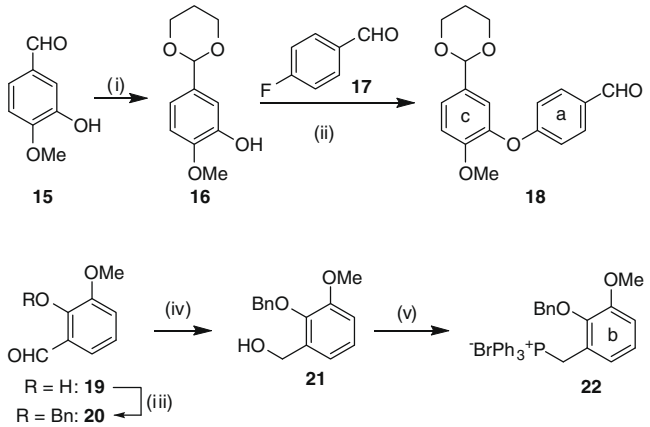
Figure 1. Different subtypes in the marchantin series.

From the acyclic precursors perrottetin E (**1**) with O–C connection and isoperrottetin A (**3**) with C–C connection, respectively, are derived cyclic bisbibenzyls of the plagiochin/riccardin type like plagiochin E (**4**), the marchantin type like marchantin C (**5**), or the isoplagiochin type like isoplagiochin D (**6**) by a second O–C or C–C connection. Not all possible subtypes were isolated yet from bryophytes, for an overview see Ref. 4.

In the marchantin series, six subtypes are possible by the second O–C connection (Fig. 1). Unfortunately, the nomenclature for these compounds is not standardized (plant source, historical aspects). Furthermore, derivatives containing additional hydroxyl or methyl ether functionalities were also isolated or the parent compound itself was not yet found.[4] Marchantin C (**5**) represents the 3-O→2′-C cyclization type of **1** with no further modification and was first isolated from *Marchantia polymorpha, Marchantia paleacea* var. *diterpa* and *Marchantia tosana*[5] and then from additional six different liverwort species.[6–8] Its monomethylethers were isolated as marchantin O (**7**)[9,10] and P (**8**),[11] the dimethylether, however was not yet found. It should further be mentioned, that originally the dihydroxylated compound **9** was also named marchantin C but later on was renamed marchantin B.[5]

The following moderate biological activities were previously reported for marchantin C (**5**): cytotoxic activity against KB cell lines, anti-HIV-1 activity and DNA polymerase β inhibition,[4,12] cytotoxicity in the P388 assay and some antimicrobial activity against the Gram-positive bacterium *Bacillus subtilis* and against *Trichophyton mentagrophyte*,[13] inhibition of lipopolysaccharide-induced nitric oxide synthase (NOS) in RAW 264.7 macrophages,[14] and α-glucosidase inhibitory activity.[8]

But more recently, macrocyclic bisbibenzyls especially of the plagiochin/riccardin type and of the marchantin type are attracting an enhanced attention due to new significant biological activities.[15–17] Marchantin C (**5**) induces apoptosis of human glioma A 172 cells.[18] Furthermore, it is a novel microtubule inhibitor with anti-tumor activity both in vivo and in vitro.[19] Surprisingly, **5** or one of its methylether derivatives was never synthesized and only small amounts from natural sources were used for testing.

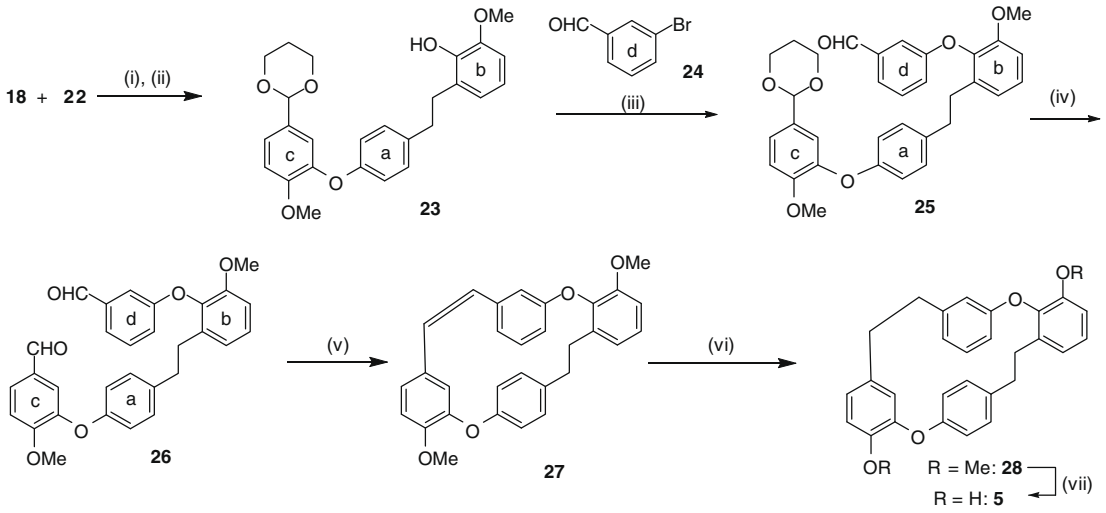


Scheme 2. Reaction conditions: (i) $CH(OEt)_3$, tetrabutylammonium tribromide, 1,3-propanediol, 50 °C, 2 h (91%); (ii) **16**, K_2CO_3, DMF, 165 °C, 12 h (97%); (iii) BnBr, K_2CO_3, THF, reflux, 12 h (95%); (iv) $NaBH_4$, EtOH, 0 ° to rt, 12 h (92%); (v) PPh_3·HBr, MeCN, 95 °C, 12 h (85%).

Continuing our efforts on total syntheses of biological active liverwort constituents especially of the bisbibenzyl type,[20] we can now report on a short and efficient total synthesis of marchantin C (**5**) with subsequent construction of the a–b–c–d arene skeleton.

The c–a fragment **18**[21,22] is now obtained by a more straightforward sequence[20] starting from isovanilline (**15**) and S_NAr with 4-fluorobenzaldehyde (**17**). The 1,2,3-trisubstituted segment b is prepared as phosphonium salt **22** starting from *o*-vanilline **19** with O-benzylation and reduction (Scheme 2).

Wittig reaction of **18** and **22** followed by hydrogenation gives bibenzyl **23** with a free o,o′-disubstituted phenolic OH group. The segment d is introduced by an Ullmann reaction of the phenol **23** with 3-bromo-benzaldehyde (**24**) yielding the acyclic precursor **25**. After deprotection of the second aldehyde functionality (to **26**), the dialdehyde is ring closed under McMurry conditions to give the stilbene **27**. Finally, the bisbibenzylic macrocycle is



Scheme 3. Synthesis of marchantin C (**5**). Reagents and conditions: (i) K_2CO_3, 18-crown-6, CH_2Cl_2, reflux, 12 h (62%); (ii) H_2, Pd/C, 3 bar, 24 h (98%); (iii) CuO, K_2CO_3, pyridine, 160 °C, 12 h (97%); (iv) 2 M HCl/THF, rt, 12 h (97%); (v) Zn, $TiCl_4$, THF, −10 °C to reflux, 12 h (47%); (vi) H_2, Pd/C, 3 bar, 24 h (96%); (vii) BBr_3, CH_2Cl_2, −78 °C to rt, 12 h (85%).

Table 1
^{1}H NMR data of synthetic compounds **5** (see Fig. 2) and the published data for marchantin C (400 MHz, $CDCl_3$, δ in ppm)

	Synthetic **5**	Natural product **5**[23]
H-2	6.62 (dd, *J* = 2.3, 1.5 Hz)	6.62 (dd, *J* = 2.5, 1.5 Hz)
H-4	6.54 (ddd, *J* = 8.0, 2.5, 0.8 Hz)	6.54 (ddd, *J* = 7.8, 2.5, 0.7 Hz)
H-5	6.98 (t, *J* = 8.0 Hz)	6.98 (t, *J* = 7.8 Hz)
H-6	6.37 (t, not resolved, *J* = 8.0 Hz)	6.38 (ddd, *J* = 7.8, 1.5, 0.7 Hz)
H_2-7	2.75–2.78 (m)	2.75–2.86 (m)
H_2-8	2.83–2.86 (m)	
H-10	5.53 (d, *J* = 2.0 Hz)	5.52 (d, *J* = 2.0 Hz)
H-13	6.88 (d, *J* = 8.0 Hz)	6.88 (d, *J* = 8.1 Hz)
H-14	6.73 (dd, *J* = 8.3, 2.0 Hz)	6.74 (dd, *J* = 8.1, 2.0 Hz)
H-4′	7.02 (dd, *J* = 7.8, 1.5 Hz)	7.02 (dd, *J* = 7.8, 1.6 Hz)
H-5′	7.15 (t, *J* = 7.8 Hz)	7.15 (t, *J* = 7.8 Hz)
H-6′	6.87 (dd, *J* = 8.0, 1.5 Hz)	6.87 (dd, *J* = 7.8, 1.6 Hz)
H_2-7′	2.97–3.04 (m)	2.97–3.03 (m)
H_2-8′		
H-10′	6.94 (d, *J* = 8.5 Hz)	6.94 (d, *J* = 8.5 Hz)
H-11′	6.59 (d, *J* = 8.3 Hz)	6.60 (d, *J* = 8.5 Hz)

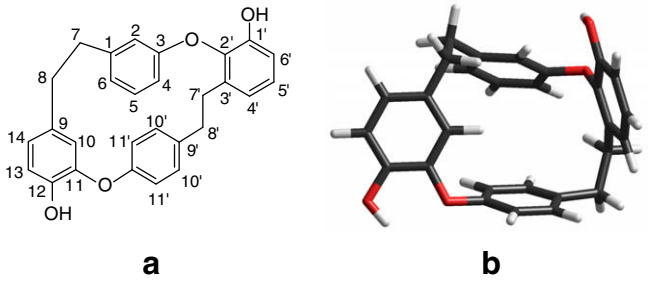


Figure 2. (a) Molecule numbering for NMR correlation; (b) AM1 structure of **5**.[24]

obtained by hydrogenation (to **28**) and deprotection of the phenolic OH groups yields compound **5** in 22% overall yield (six steps from **18** and **22**, Scheme 3).

The molecular formula $C_{28}H_{24}O_4$ is confirmed by HR-EI-MS; M^+ peak at *m/z* = 424.1690 (calcd 424.1675). The spectroscopic data (see Tables 1 and 2) match with those reported in the literature[23] for the isolated marchantin C (**5**). To exclude any errors in arene connection and substitution pattern[20], the structure of **4** is strongly verified by further NMR experiments (H,H COSY, C,H COSY, HMBC).

Table 2
^{13}C NMR data of synthetic compounds **5** and the published data for marchantin C (100 MHz, $CDCl_3$, δ in ppm)

	Synthetic **5**	Natural product **5**[23]
C-1	143.0	142.6
C-2	115.6	115.4
C-3	156.8	156.8
C-4	112.0	111.9
C-5	128.9	128.6
C-6	123.3	122.9
C-7	35.83	35.5
C-8	34.00	33.7
C-9	132.7	132.5
C-10	115.5	115.5
C-11	146.1	146.0
C-12	143.5	143.1
C-13	115.0	115.1
C-14	122.4	122.2
C-1′	148.7	148.6
C-2′	139.7	139.6
C-3′	136.2	136.0
C-4′	122.0	121.7
C-5′	126.0	125.8
C-6′	114.4	114.4
C-7′	30.34	30.1
C-8′	35.34	35.1
C-9′	139.1	138.8
C-10′	129.6	129.4
C-11′	121.3	121.1
C-12′	152.9	152.7

Acknowledgment

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