

STRUCTURES AND TOTAL SYNTHESIS OF TWO NOVEL BIS(BIBENZYL), PALEATINS A AND B, FROM THE LIVERWORT *MARCHANTIA PALEACEA* VAR. *DIPTERA*

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Two novel bis(bibenzyls) named paleatins A (1) and B (2) have been isolated from the liverwort, *Marchantia paleacea* var. *diptera*. Their structures have been established by a combination of high-resolution NMR spectra and chemical degradation. A total synthesis of paleatin A has been accomplished in ten steps.

KEYWORDS liverwort; *Marchantia paleacea* var. *diptera*; bis(bibenzyls); paleatin A; paleatin B; total synthesis

Liverworts are rich sources of both terpenoids and aromatic compounds with biological activities. For example, marchantin A (3), a novel macrocyclic bis(bibenzyl) ether isolated from the liverwort *Marchantia* species, possesses cytotoxic, 5-lipoxygenase and calmodulin inhibitory activities, and d-tubocurarine-like muscle relaxing activity.^{1, 2)} In the course of the isolation of the biologically active substances from the liverwort *Marchantia* species, we isolated two novel bis(bibenzyls), paleatins A (1)³⁾ and B (2)⁴⁾, with five known macrocyclic bis(bibenzyl) ethers, marchantins A-E (3-7) from the MeOH extract of *Marchantia paleacea* var. *diptera* belonging to the Marchantiaceae. Here we wish to report the isolation and structure elucidation of 1 and 2.

The MeOH extract (176 g) of the fresh material (6.67 kg) of *M. paleacea* collected in Tokushima in 1991 was subjected repeatedly to column chromatography on Sephadex LH-20 (CHCl_3 : MeOH = 1 : 1) and on silica gel (*n*-hex.-AcOEt, gradient) to afford paleatins A (1)³⁾ (0.38 g) and B (2)⁴⁾ (1.09 g) as well as five known bis(bibenzyls), marchantins A (3) (79.5 g), B (4) (0.89 g), C (5) (1.12 g), D (6) (0.35 g), and E (7) (8.34 g).

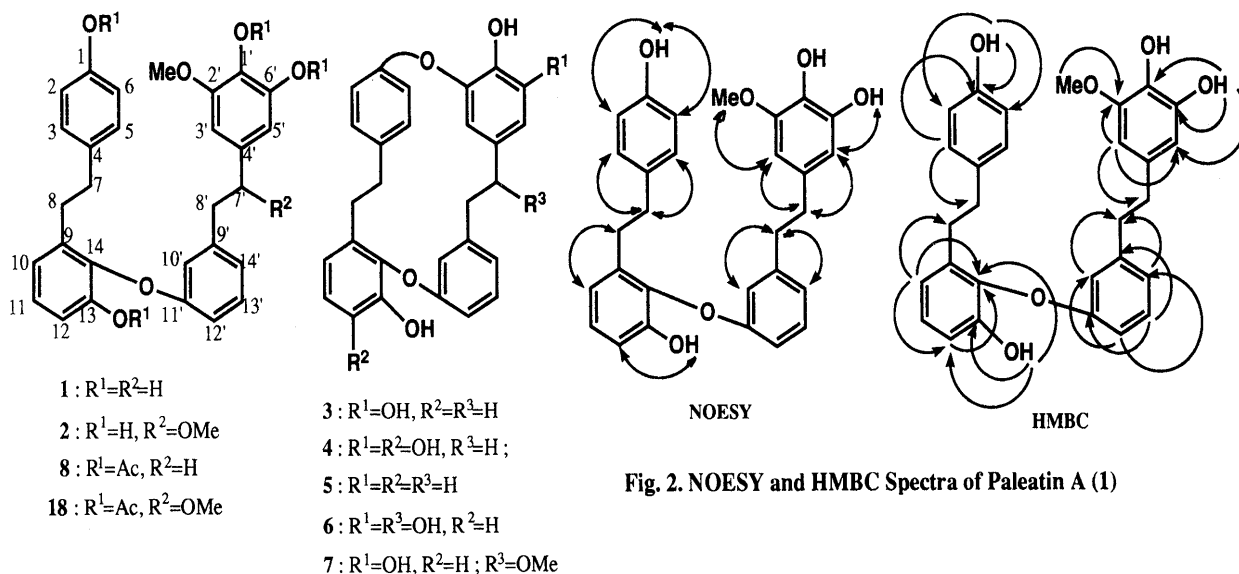


Fig. 2. NOESY and HMBC Spectra of Paleatin A (1)

The IR spectrum of paleatin A (1) ($\text{C}_{29}\text{H}_{28}\text{O}_6$) indicated the presence of a phenolic hydroxyl groups (3300 cm^{-1}). The ^1H and ^{13}C NMR spectra of 1 showed one methoxyl [δ_{H} 3.70(s) and δ_{C}

56.0] and four benzyl methylene signals [δ_{H} 2.83(m) and δ_{C} 32.5, 35.4, 37.1 and 37.5], which were similar to those of marchantin A (**3**). Acetylation of **1** afforded a tetraacetate (**8**) [δ_{H} 1.93, 2.25, 2.26 and 2.28 (s)], and the methylation gave a pentamethyl ether (**9**), indicating the presence of four phenolic hydroxyl groups. The ^{13}C NMR chemical shifts of B, C, and D rings of **9** were quite similar to those of **10** derived from marchantin A (**1**) *via* three steps (1. MeI, K_2CO_3 ; 2. H_2/PtO_2 ; 3. MeI, K_2CO_3), as shown in Fig. 1. The structure of **1** was derived from careful analysis of the 2D NMR spectra including DQF-COSY, HMQC, HMBC (Fig. 2) and NOESY (Fig. 2), and finally established by total synthesis of **1** from *o*-vanillin (**11**) *via* ten steps as shown in Chart 1.

The ^1H and ^{13}C NMR spectra of paleatin B (**2**) ($\text{C}_{30}\text{H}_{30}\text{O}_7$) were similar to those of paleatin A (**1**), except for signals of one methoxyl (δ_{H} 3.11 and δ_{C} 52.0) and methine-bearing oxygen function [δ_{H} 4.12(t, $J=6.8\text{Hz}$) and δ_{C} 85.0]. Acetylation of **3** afforded a tetraacetate (**18**), and the methylation gave a hexamethyl ether (**19**), indicating the presence of four phenolic hydroxyl groups. The ^{13}C NMR chemical shifts of B, C and D rings of **19** were quite similar to those of **20** derived from marchantin E (**7**) in a similar manner to that shown in Fig. 1. Compound **18** was refluxed with *p*-TsOH in benzene to give a 7', 8'-dehydro derivative, followed by hydrogenation ($\text{H}_2/10\%\text{Pd-C}$) to afford paleatin A tetraacetate (**8**). The structure of paleatin B was determined as C-7' methoxylated compound of **1** from the above results and careful analysis of the 2D NMR spectra as depicted in the formula 2. Paleatin B (**1**) and marchantin E (**7**) may be racemates since their optical rotations are $[\alpha]_{\text{D}} \pm 0^\circ(\text{c}1.0, \text{MeOH})$.

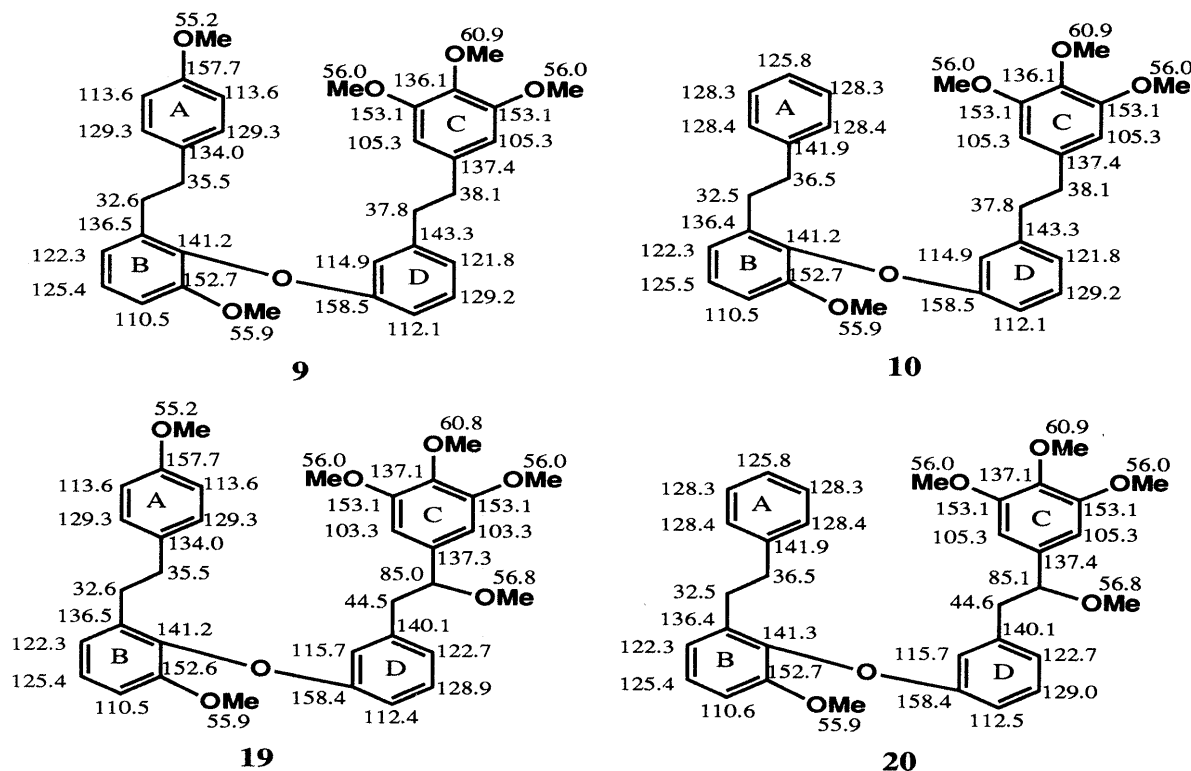


Fig. 1. ^{13}C NMR Spectra of **9**, **10**, **19** and **20**

Paleatins A (**1**) and B (**2**) are the new type of bis(bibenzyls) without an ether linkage between A and C rings of marchantins A (**3**) and E (**7**), and presumed to be biogenetic intermediates of **3** and **7** (*vice versa*). As the macrocyclic conformation of **3** was of importance for biological activity such as d-tubocurarine-like muscle relaxing activity,¹¹ paleatins A (**1**) and B (**2**) may be important compounds to understand the structure-activity relationship. The total synthesis of **2** and bioassay of the new compounds are in progress.

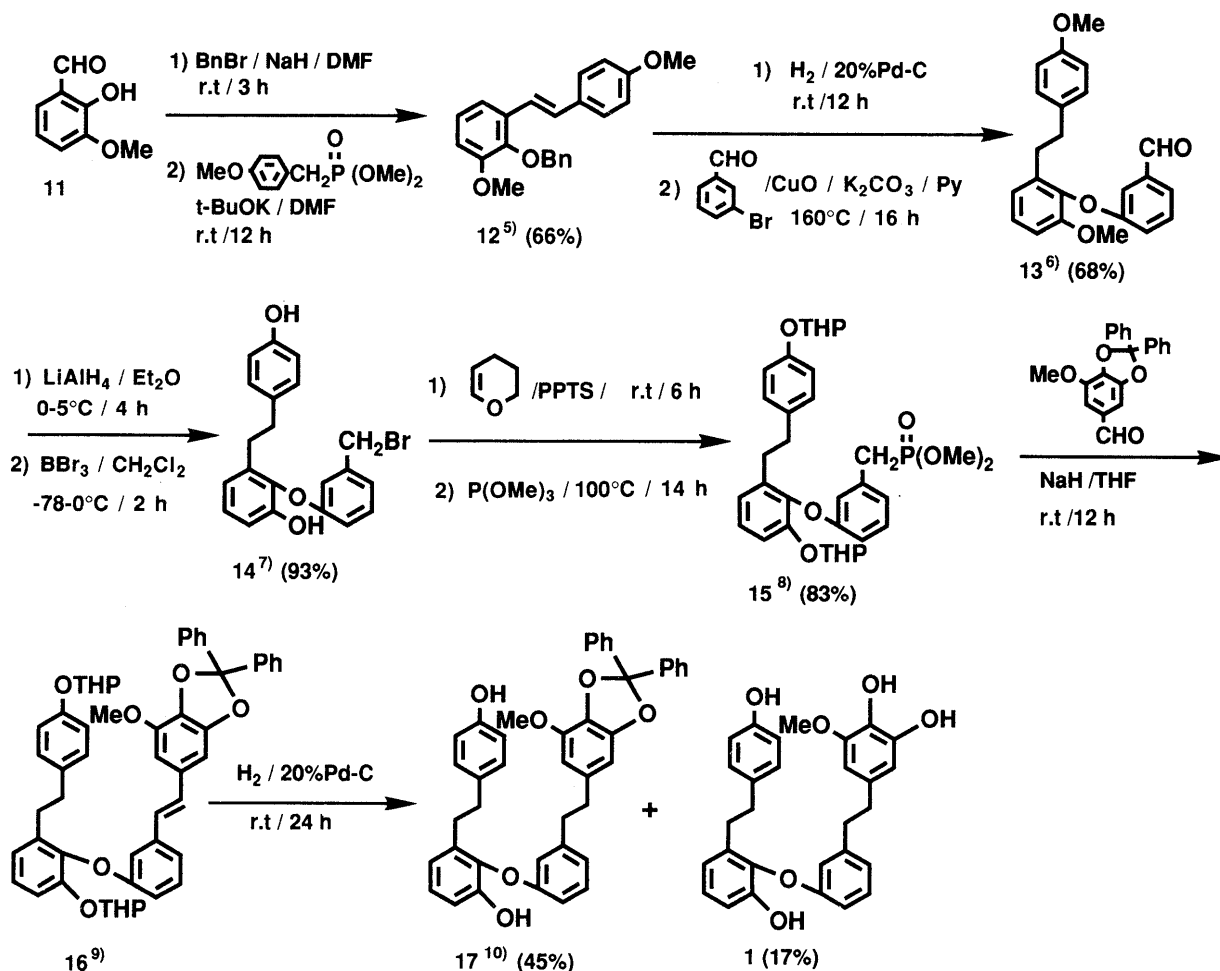


Chart 1. Synthetic Pathway of Paleatin A (1)

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REFERENCES AND NOTES

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- 2) Y. Asakawa (1993) Biologically Active Terpenoids and Aromatic Compounds from Liverworts and the Inedible Mushroom *Cryptoporus volvatus*, in "Bioactive Natural Products: Detection, Isolation, and Structural Determination" (S. M. Colegate and R. J. Molyneux eds.) P. 319, CRC Press, Florida.
- 3) Amorphous powder; HR-MS: m/z 472.1991, $\text{C}_{29}\text{H}_{28}\text{O}_6$ requires 472.1986; EI-MS: m/z 472 (M^+), 349, 153 (100%); IR (KBr) $\nu \text{ cm}^{-1}$: 3300 (OH), 1590; UV (EtOH) λ_{max} nm (log ϵ): 210 (4.58), 278 (3.65).
- 4) Amorphous powder; HR-MS: m/z 502.1985 $\text{C}_{30}\text{H}_{30}\text{O}_7$ requires 502.1992; EI-MS: m/z 502 (M^+), 470, 347, 183 (100%), IR (KBr) cm^{-1} : 3250 (OH), 1603; UV (EtOH) λ_{max} nm (log ϵ): 210 (4.61), 273 (3.65).
- 5) EI-MS: m/z 346 (M^+), 255 (100%); ^1H NMR (CDCl_3): δ 3.81, 3.88 (each s, -OMe), 5.00 (s, -CH₂-Ph).
- 6) EI-MS: m/z 362 (M^+), 121 (100%); ^1H NMR (CDCl_3): δ 3.71, 3.73 (each s, -OMe), 9.90 (s, -CHO).
- 7) EI-MS: m/z 398 (M^+), 400 ($\text{M}^+ + 2$); IR (CHCl_3) $\nu \text{ cm}^{-1}$: 3300 (OH) ^1H NMR (CDCl_3): δ 4.39 (s, -CH₂Br).
- 8) EI-MS: m/z 512 ($\text{M}^+ - \text{THP}$); ^1H NMR (CDCl_3): δ 3.11 (d, $J=22\text{Hz}$, -CH₂P), 3.60, 3.65 (each s, -OMe).
- 9) EI-MS: m/z 718 ($\text{M}^+ - \text{THP}$); ^1H NMR (CDCl_3): δ 3.95 (s, -OMe).
- 10) EI-MS: m/z 636 (M^+), 317 (100%); IR (CHCl_3) $\nu \text{ cm}^{-1}$: 3410 (OH); ^1H NMR (CDCl_3): δ 3.83 (s, -OMe).
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