STRUCTURES AND TOTAL SYNTHESIS OF TWO NOVEL BIS(BIBENZYLS), 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).

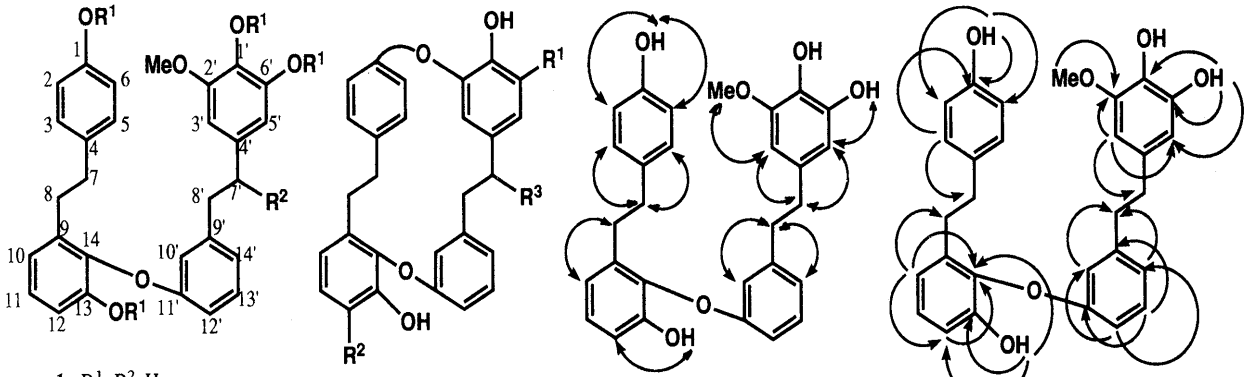

Fig. 2. NOESY and HMBC Spectra of Paleatin A (1)

1: R^1=R^2=H
2: R^1=H, R^2=OMe
8: R^1=Ac, R^2=H
18: R^1=Ac, R^2=OMe

3: R^1=OH, R^2=R^3=H
4: R^1=R^2=OH, R^3=H;
5: R^1=R^2=R^3=H
6: R^1=R^3=OH, R^2=H
7: R^1=OH, R^2=H; R^3=OMe

The IR spectrum of paleatin A (**1**) ($C_{29}H_{28}O_6$) indicated the presence of a phenolic hydroxyl groups (3300 cm^{-1}). The ^1H and ^{13}C NMR spectrra of **1** showed one methoxyl [δ_H 3.70(s) and δ_C

56.0] and four benzyl methylene signals [δ_H2.83(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 ^{1}H and ^{13}C NMR spectra of paleatin B (**2**) ($C_{30}H_{30}O_7$) 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=6.8Hz) 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 (H_2 /10%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 $[\alpha]_D \pm 0°$(c1.0, MeOH).

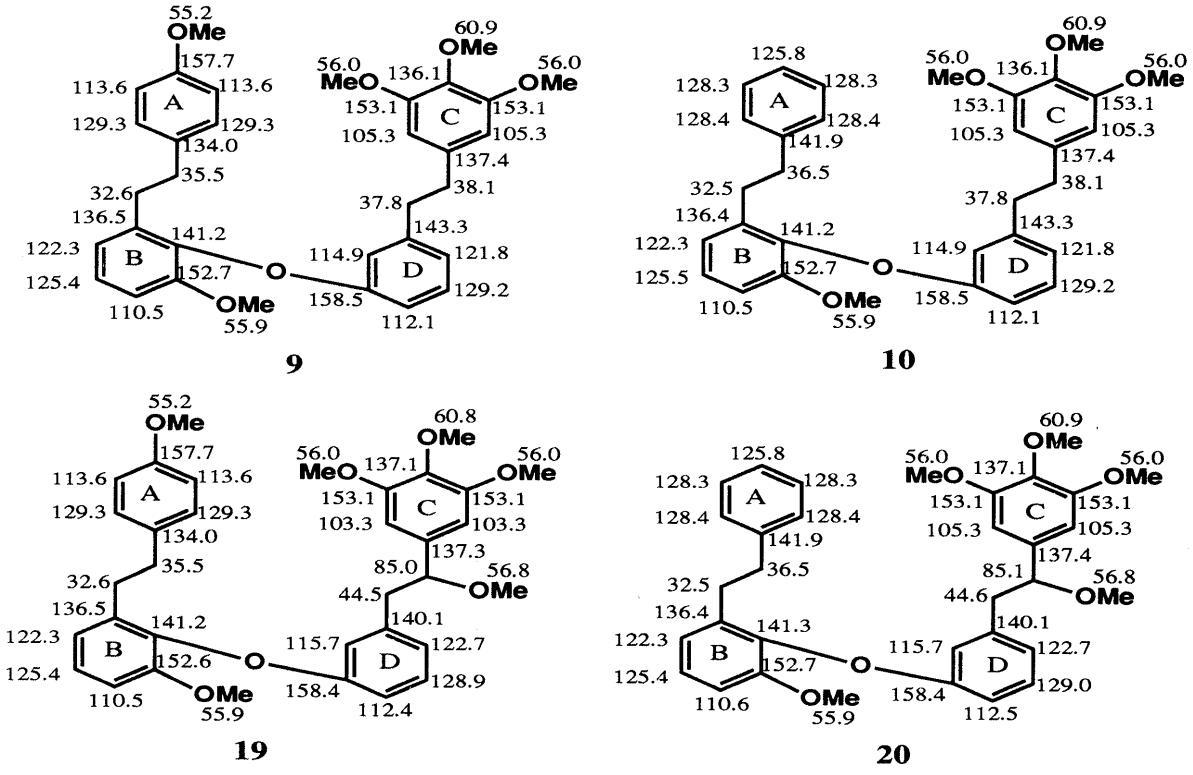

Fig. 1. ^{13}C NMR Spectra of 9, 10, 19 and 20

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 muscule 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.

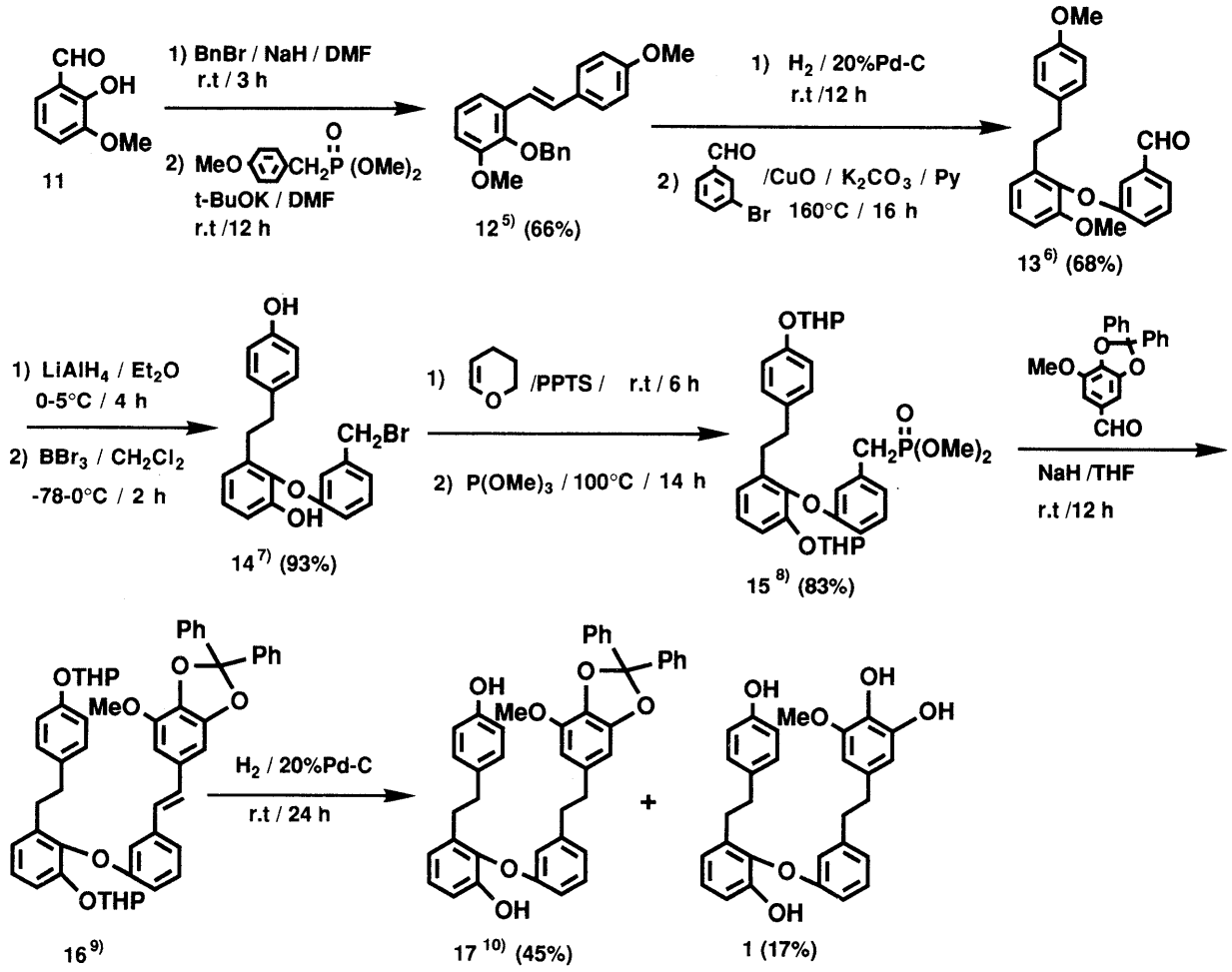

Chart 1. Synthetic Pathway of Paleatin A (1)

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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, $C_{29}H_{28}O_6$ requires 472.1986; EI-MS: m/z 472 (M^+), 349, 153 (100%) ; IR (KBr) ν cm^{-1}: 3300 (OH), 1590; UV (EtOH) λ_{max} nm (logε): 210 (4.58), 278 (365).
4) Amorphous powder; HR-MS: *m/z* 502.1985 $C_{30}H_{30}O_7$ 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 (logε): 210 (4.61), 273 (3.65).
5) EI-MS: m/z 346 (M^+), 255 (100%) ; ^{1}H NMR ($CDCl_3$): δ 3.81, 3.88 (each s, -OMe), 5.00 (s, -CH_2-Ph).
6) EI-MS: m/z 362 (M^+), 121 (100%) ; ^{1}H NMR ($CDCl_3$): δ 3.71, 3.73 (each s, -OMe), 9.90 (s, -CHO).
7) EI-MS: m/z 398 (M^+), 400 (M^++2); IR ($CHCl_3$) ν cm^{-1}: 3300 (OH) ^{1}H NMR($CDCl_3$): δ 4.39 (s, -CH_2Br).
8) EI-MS: m/z 512 (M^+-THP); ^{1}H NMR ($CDCl_3$): δ 3.11(d, J=22Hz, -CH_2P), 3.60, 3.65 (each s, -OMe).
9) EI-MS: m/z 718 (M^+-THP); ^{1}H NMR ($CDCl_3$): δ 3.95 (s, -OMe).
10) EI-MS: m/z 636 (M^+), 317 (100%); IR ($CHCl_3$) ν cm^{-1}: 3410 (OH); ^{1}H NMR($CDCl_3$): δ 3.83 (s, -OMe).
11) Z. Taira, M. Takei, K. Endo, T. Hashimoto, Y. Sakiya, Y. Asakawa, *Chem. Pharm. Bull*, **42**, 52 (1994).

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