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TOTAL SYNTHESIS OF MARCHANTIN A, A CYTOTOXIC BIS(BIBENZYL) ISOLATED FROM LIVERWORTS

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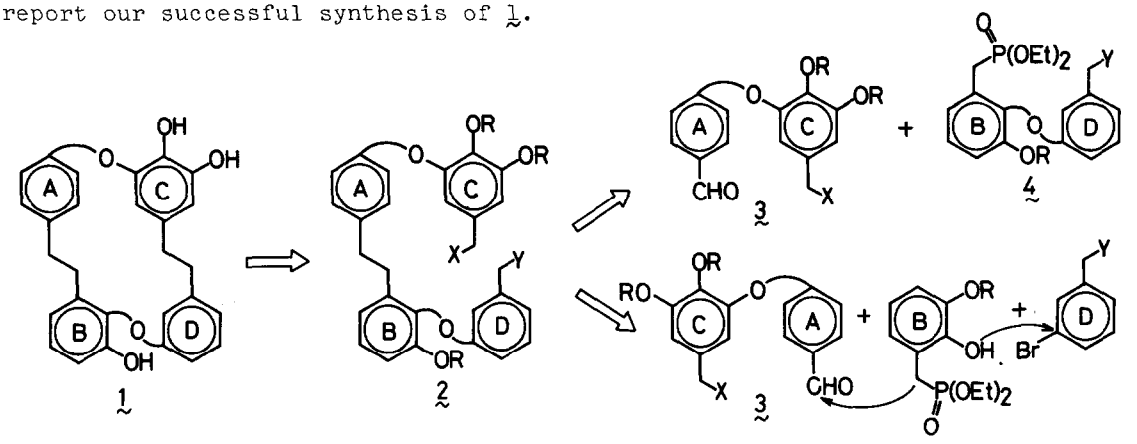
Abstract: Total synthesis of marchantin A, a novel cytotoxic bis(bibenzyl) isolated from some liverworts, has been accomplished in 12 steps.

Some liverworts have been shown to contain novel cyclic bis(bibenzyls).[1] A representative compound of this new class of natural products is marchantin A (1), isolated as the major component of Marchantia polymorpha and related liverworts.

In this molecule two unsymmetrically substituted bibenzyls are joined by two ether linkages forming a macrocyclic ionophore-like structure. The novel structure 1 has been deduced on the basis of spectral analysis and chemical degradations and confirmed by X-ray crystallographic analysis of its trimethyl ether.[1] Marchantin A, as well as other congeners, has been shown to exhibit cytotoxic activity against KB cell and P388 lymphocytic leukemia.[1]

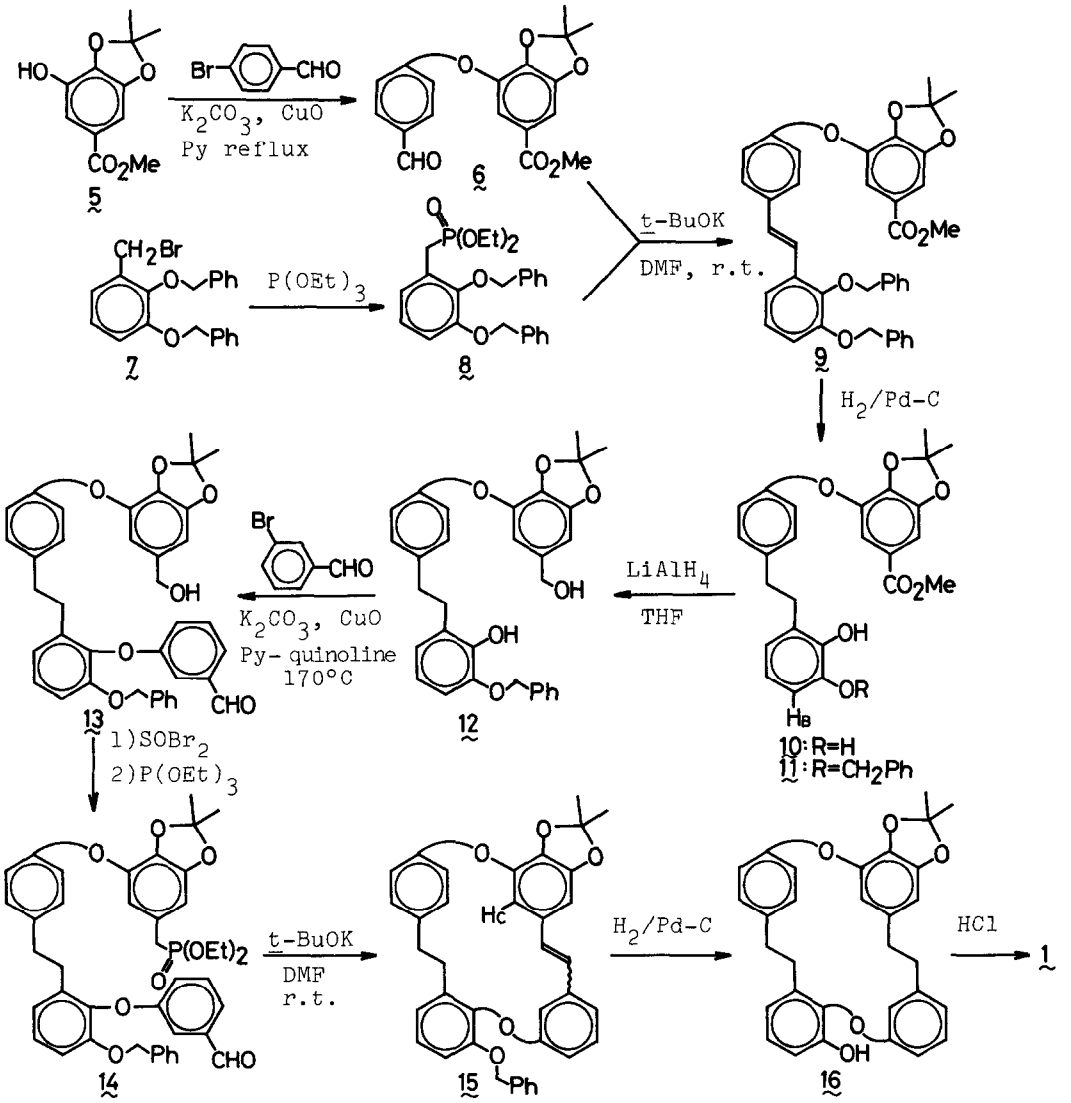
The reported biological activity and hitherto unknown structural type stimulated our interests in the total synthesis. In this communication we wish to report our successful synthesis of 1.



For the synthesis of C,D-seco compound 2, a promising intermediate toward 1, we first examined the route connecting two biphenyl ethers corresponding to the A-C segment (e.g. 3) and the B-D segment (e.g. 4) by for instance a Wittig type reaction. The A-C fragment 3 was accessible readily by simple coupling of benzene derivatives. However, after many efforts, we found that the phosphonate 4 is not

practical since efficient synthesis of 4 or equivalent compounds was rather difficult. Therefore, we changed the synthetic route to stepwise connection of B and D rings to the A-C segment.

Coupling of the acetonide of methyl gallate 5 and p-bromobenzaldehyde in the presence of anhydrous K_2CO_3 and CuO in dry pyridine afforded the ether 6, m.p. 93-94°C, in 68% yield. The phosphonate 8 was prepared by the reaction of (2,3-bisbenzyloxy)benzylbromide 7[2] and triethyl phosphite in 74% yield. The B ring fragment thus obtained was combined with the A-C ring fragment 6 by treating with t-BuOK in dry DMF. The product 9[3] formed in 71% yield was subjected to catalytic hydrogenation to give the catechol derivative 10, m.p. 142-144°C, in high yield. One of the phenolic hydroxyl groups was protected as the benzyl ether[4] and the ester group of 11[3] was reduced to the benzyl alcohol 12. Reaction of 12 with



m-bromobenzaldehyde at 170°C afforded the product 13[3] in which C-A-B-D rings are connected linearly in 42% yield. Bromination of 13 followed by reaction with triethyl phosphite yielded the phosphonate 14 in 60% yield.

Intramolecular Wadsworth-Emmons olefination took place smoothly when 14 was treated with t-BuOK under high dilution conditions.[5] Although the product 15 obtained in 60% yield was an inseparable mixture of two compounds, its PMR spectrum showed two signals at higher field (5.54 and 5.79 ppm), assignable to H_C of each product, suggesting both to be the cyclized products.[6] Actually, when the mixture was catalytically hydrogenated, a single product 16,[3] the acetonide of marchantin A, m.p. 201-202°C, was obtained in 87% yield. Thus, the above product 15 was confirmed to be a cis, trans-mixture of double bonds and the ratio was determined from the PMR as 3 : 2. Simple acid treatment of 16 afforded marchantin A (1). The identity was confirmed by comparison of TLC, IR and PMR spectra with those of authentic specimen.

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References and Notes

1) Y. Asakawa, M. Toyota, R. Matsuda, K. Takikawa and T. Takemoto, Phytochemistry, 22, 1413 (1983); Y. Asakawa, M. Toyota, Z. Taira, T. Takemoto and M. Kido, J. Org. Chem., 48, 2164 (1983); Y. Asakawa, Rev. Latinoamer. Quim., 14-3, 109 (1984).

2) B. Marchand and C. Benezra, J. Med. Chem., 25, 650 (1982).

3) Spectral properties of key intermediates: 9; m/z 614(M^+), 91(b.p.), υ(liq. film) 1718, 1632, 1601, 1576 cm^{-1}, δ ($CDCl_3$) 1.72(6H, s), 3.84(3H, s), 5.04(2H, s), 5.15(2H,s), 6.90-7.02(4H, m), 7.04(1H, d, J=16.6), 7.23-7.48(16H, m). 11; m/z 526(M^+), 91(b.p.), υ (liq. film) 3540, 1719, 1633, 1610 cm^{-1}, δ ($CDCl_3$) 1.72(6H, s), 2.92(4H, m), 3.81(3H, s), 5.09(2H, s), 6.71(1H, dd, J=7.3, 2.0), 6.74(1H, t, J=7.3), 6.81(1H, dd, J=7.3, 2.0), 6.92(2H, d, J=8.8), 7.15(2H, d, J=8.8), 7.21(1H, d, J=1.5), 7.26(1H, d, J=1.5), 7.37-7.46(5H, m). 13; m/z 602(M^+), 91(b.p.), υ (liq. film) 3430, 1698, 1632, 1606 cm^{-1}, δ ($CDCl_3$) 1.67 (6H, s), 2.84(4H, m), 4.98(2H, s), 6.44(1H, br.s), 6.59(1H, br.s), 6.85-6.92 (2H, m), 6.87(2H, d, J=8.7), 7.01(2H, d, J=8.7), 7.00-7.05(1H), 7.10(1H, t, J= 7.8), 7.16-7.23(5H, m), 7.28(1H, br.s), 7.43(1H, t, J=7.8), 7.51(1H, d, J=7.8), 9.90(1H, s). 16; m/z 480(M^+, b.p.), υ (Nujol) 3520, 1632, 1612, 1590 cm^{-1}, δ ($CDCl_3$) 1.72(6H, s), 2.76(2H, t-like), 2.83(2H, t-like), 3.00(4H, br.s), 5.14(1H, d, J=1.5), 6.31(1H, d, J=1.5), 6.43(1H, br.d, J=7.8), 6.57(1H, br.d, J=7.8), 6.58(1H, br.s), 6.63(2H, d, J=8.8), 6.86(1H, dd, J=7.8, 1.5), 6.91(2H, d, J=8.8),7.01(1H, t, J=7.8), 7.01(1H, dd, J=7.8, 1.5), 7.15(1H, t, J=7.8).

4) The position of benzyl ether was confirmed by the observation of an NOE between H_B (6.81 ppm) and $OC\underline{H}_2Ph$ (5.09 ppm) in the difference spectrum.
5) The intramolecular olefination was carried out at a concentration of 1.4 mM. When the concentration was raised to 2.8 mM, substantial amounts of the cyclic dimer was formed. The hydrogenation product of the dimer showed the following spectral data: m/z 960(M^+, b.p.), δ 1.68(12H, s), 2.66(8H, m), 2.73(8H, m), 6.17(2H, d, J=1.5), 6.38(2H, d, J=1.5), 6.67(2H, br.d, J=7.8), 6.74(2H, br.s), 6.78-6.83(4H, m), 6.80(4H, d, J=8.8), 6.89(4H, d, J=8.8), 6.92(2H, dd, J=7.8, 1.5), 7.07(2H, t, J=7.8), 7.16(2H, t, J=7.8).
6) In the PMR spectrum of 1, one of the aromatic protons on C-ring is known to appear at abnormally higher field (5.13 ppm) due to the anisotropic effect of the other benzene rings (See Y. Asakawa, M. Toyota, Z. Taira and T. Takemoto, Abstracts of 25th Symposium on the Chemistry of Natural Products, Tokyo, 1982, p 337).

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