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SYNTHESIS AND STRUCTURE CONFIRMATION OF RICCARDIN B, A MACROCYCLIC BIS(BIBENZYL) FROM THE LIVERWORT, RICCARDIA MULTIFIDA

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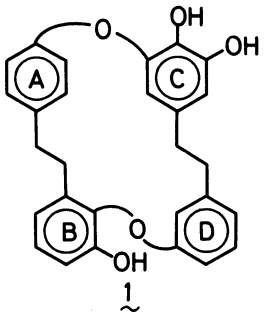
Riccardin B, a cytotoxic bis(bibenzyl) obtained from a liverwort was synthesized *via* an intramolecular Wittig-type reaction and the structure was established unequivocally.

In a previous paper[1] we reported the synthesis of marchantin A (1), a cytotoxic bis(bibenzyl) present in some liverworts. In the course of the synthesis of 1 we found that the Wadsworth-Emmons reaction is highly effective for the construction of the macrocycle of this type. In order to explore the usefulness of this well known reaction for the synthesis of macrocyclic natural products, we examined the synthesis of riccardin B, a macrocyclic bis(bibenzyl) isolated from a liverwort, Riccardia multifida, and reported to have cytotoxic activity against KB cells.[2] While the structure of riccardin B has been proposed as the formula 2 by Asakawa *et al.* on the basis of the spectral analysis and biogenetic considerations, alternative structure 3 could not be excluded.

We now wish to report the total synthesis of riccardin B. The present synthesis unequivocally established the structure of this novel natural product as 2.



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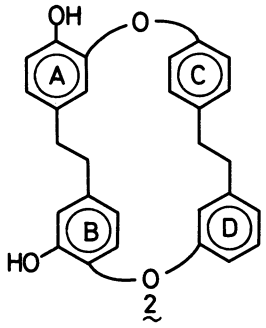

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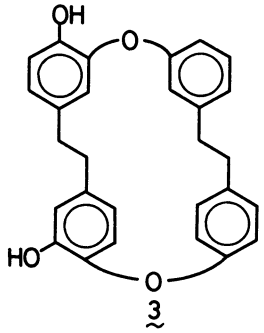

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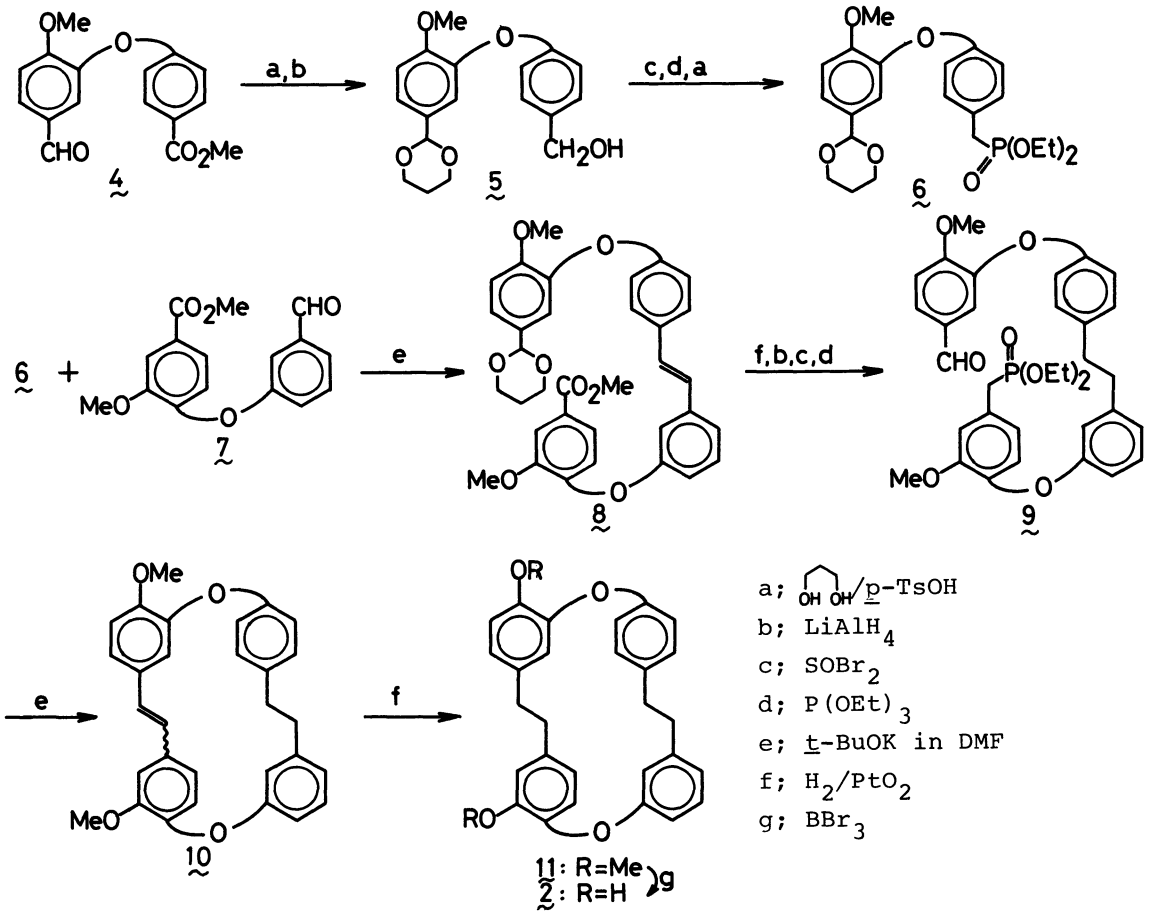
In the synthesis of 1, the B and D rings were added to the A-C ring segment in a stepwise manner. In the present synthesis, the unsymmetrically substituted biphenyl ethers 6 and 7 were combined by employing two Wadsworth-Emmons reactions. The A-C ring segment 6 was synthesized as follows. Isovanillin was allowed to react with methyl p-bromobenzoate (K_2CO_3-CuO in refluxing pyridine) to give the biphenyl ether 4, mp 87-89 °C, in 79% yield. After protection of the aldehyde group the ester group was reduced to the alcohol 5, which was converted to the diethyl phosphonate 6 *via* the corresponding bromide (60% yield from 4). The B-D ring part 7, mp 96-98 °C, was accessible by simple coupling of methyl 4-hydroxy-3-methoxybenzoate and m-bromobenzaldehyde (K_2CO_3-CuO in pyridine-quinoline at 170 °C, 49%).

Condensation of 6 and 7 was effected with t-BuOK in dry DMF. The stilbene-



type product 8 obtained in 84% yield was then converted to the diethyl phosphonate 9 by the similar sequence of reactions used for the preparation of 6 in 62% overall yield. The key step, the intramolecular Wadsworth-Emmons olefination, was carried out by treating 9 with t-BuOK in dry DMF under high dilution conditions and the desired product 10 was obtained in 89% yield. The ^{1}H NMR spectrum of 10 showed the presence of methoxy signals as two sets of two singlets in the ratios of 1:3 respectively, indicating 10 to be a mixture of cis and trans isomers. In addition, two aromatic proton signals appeared at abnormally high field (5.28 and 5.59 ppm), which revealed that the cyclization took place as expected. Hydrogenation of 10 afforded riccardin B dimethyl ether 11, mp 151-152 °C. The methoxy groups in 11 were finally cleaved with boron tribromide to give riccardin B (2) in quantitative yield. The IR and ^{1}H NMR spectra of the synthetic material were identical with those of the natural riccardin B. Thus, the structure of riccardin B was established.

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References

1) M. Kodama, Y. Shiobara, K. Matsumura, and H. Sumitomo, Tetrahedron Lett., 26, 877 (1985).
2) Y. Asakawa, M. Toyota, Z. Taira, T. Takemoto, and M. Kido, J. Org. Chem., 48, 2164 (1983).

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