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THE SYNTHESIS OF RICCARDIN C

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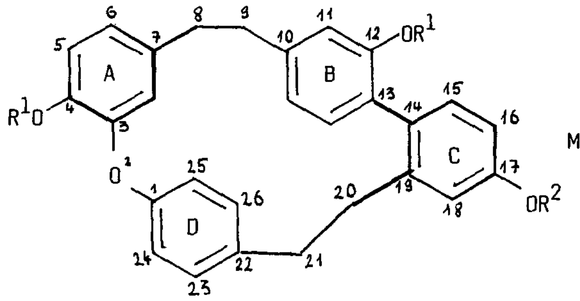
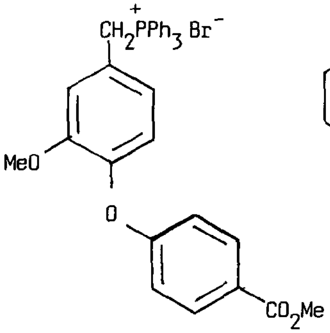
SUMMARY - The macrocyclic bis(bibenzyl) riccardin C, isolated from Riccardia multifida was synthesized in an unambiguous way by Ni(0) assisted intramolecular aryl-aryl bond formation from a diiodobenzoate as the key step.

Cytotoxic macrocyclic bis(bibenzyls) called riccardins were isolated from liverwort species; riccardin A (1) and B from Riccardia multifida in 1983[1] and riccardin C (2) from Reboulia hemispherica in 1982[2] by Asakawa et al. Riccardin B was synthesized recently both by Kodama et al.[3] and us[4]. Now we report the synthesis of riccardin C via riccardin A di-O-methylether (3).

Since it was anticipated that the weakest point of the synthesis was the elaboration of the asymmetric biphenyl moiety (linking rings C and D) and also because a convenient A-D-ring intermediate (4) was available[4], bond formation in the order C(13)-C(14)→C(8)-C(9)→ C(20)-C(21) seemed to be expedient.



1 R^1=H, R^2=Me
2 R^1=R^2=H
3 R^1=R^2=Me



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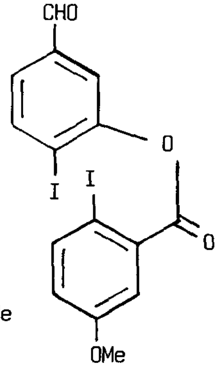

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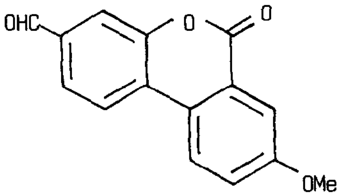
After having repeatedly failed to prepare an asymmetric biphenyl by intermolecular Ullmann reaction, we resorted to intramolecular tactics. Thus from 2-iodo-3-methoxybenzoyl chloride[5] and 4-iodo-3-methoxybenzaldehyde[7] the ester 5 was prepared which was subjected to Ni(0)(Ph$_3$P)$_4$ assisted coupling[9] to give the lactone 6 17-20% yield. Wittig reaction of 4 and 6 afforded the styrene 7, which was hydrogenated to the bibenzyl 8. Reduction with LiAlH$_4$/THF followed by methylation with diazomethane gave a diol (9) which was then converted with PBr$_3$/C$_6$H$_6$ to the dibromide 10). Finally tetraphenylethene catalyzed Wurtz reaction (Na/THF) gave riccardin A dimethylether (3) which was demethylated with BBr$_3$ to riccardin C (2).

400 MHz ^{1}H-NMR and mass spectral data of synthetic 3 were identical with those reported for riccardin A dimethylether[1].



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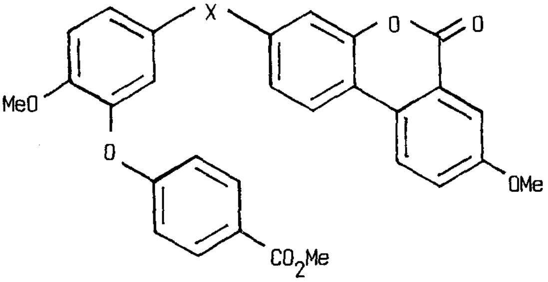
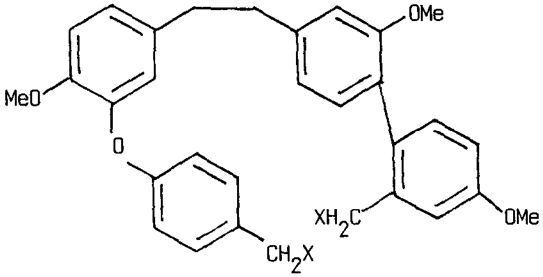


7 X = -CH=CH

8 X = -CH$_2$CH$_2$



9 X = OH

10 X = Br

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3) M. Kodama, Y. Shiobara, H. Sumitomo, K. Matsumura, M. Tsukamoto, and C. Harada, J. Org. Chem. 1988, 53, 72.

4) M. Nógrádi, B. Vermes, and M. Kajtár-Peredy, Tetrahedron Lett. 1987, 28, 2899 (as the dimethylether; demethylation to riccardin B by BBr$_3$ to be published).

5) Prepared from the acid[6] by boiling with thionyl chloride.

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7) Prepared by reduction and subsequent Sandmeyer reaction from 3-hydroxy-4-nitrobenzaldehyde[8].

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