Tetrahedron Letters,Vol.28,No.25,pp 2899-2900,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE CONSTITUTION OF RICCARDIN B

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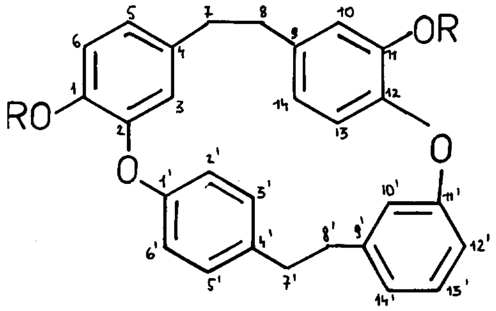
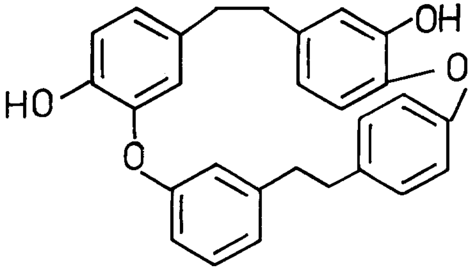
SUMMARY: - The constitution of riccardin B, a macrocyclic bis(bibenzyl) isolated from Riccardia multifida was established by the unambigous synthesis of its di-O-methyl ether.

The cytotoxic macrocyclic bis(bibenzyl) riccardin B was isolated from the liverwort Riccardia multifida (L.) S. Gray by Asakawa et al. in 1983.[1] Available evidence (^{1}H NMR, MS) did not permit decision between the isomeric constitutions 1a and 2. The unambigous synthesis of the dimethylether 1b, to be presented in this paper, proves that constitution 1a can be assigned to riccardin B.



1a R = H
1b R = Me



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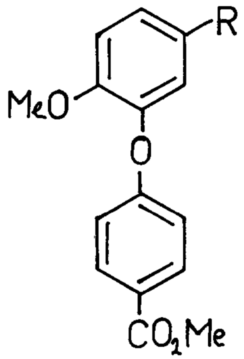
A logical scheme for the synthesis of 1b offered itself by dissecting the molecule accross bonds C(7)-C(8) and C(7')-C(8') followed by that accross the ether bonds. The diphenyl ether intermediates had to be provided with different functionalities at both ends of the molecule as to permit a stepwise linking of rings A and B followed by that of C and D, or vice versa. This scheme was realized as follows:

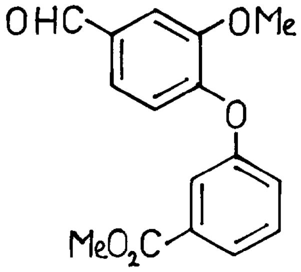
Ullmann coupling of methyl 4-bromobenzoate and isovanilline dimethyl acetal in pyridine in the presence of CuO gave, after hydrolysis and chromatography, the diphenyl ether 3a (32%, m.p. 117-119 °C from MeOH), while that of methyl 3-bromobenzoate and vanilline dimethyl acetal provided 4 (10%, m.p. 60-62 °C from hexane).

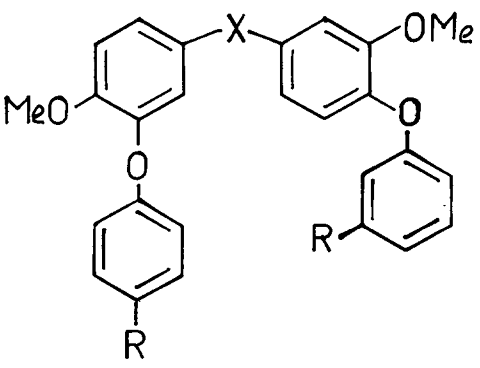
Reduction of the aldehyde 3a with $NaBH_4$ gave the alcohol 3b (78%, m.p. 77-79 °C from ether), treatment of a benzene solution of 3b with 48% aq. HBr afforded the benzyl bromide 3c (85%, m.p. 80-82 °C from acetone). Brief boiling of **3c** with Ph_3P in MeCN yielded the phosphonium bromide **3d** (95%, m.p. 218-219 °C (dec.) from benzene).

Wittig reaction of the key intermediates **3d** and **4** was carried out in methanol with NaOMe as base and led, after separation from Ph_3PO and by-products by chromatography, to an 85:15 mixture of *E* and *Z* stilbenes (**5a**) (65%, oil, (*E*)-CH=CH: δ = 6.26 ppm). The stilbenes were hydrogenated without separation over Pd/C in MeOH-EtOAc to give the bibenzyl **5b** (100%, oil, CH_2CH_2: δ = 2.88 ppm). **5b** was reduced with $LiAlH_4$ in THF to the diol **5c** (87%, oil, CH_2OH: δ = 4.62 ppm (4H)) and then treated with PBr_3 in benzene at 80 °C to give the dibromide **5d** (95%, oil, CH_2Br: δ = 4.42 and 4.48 ppm).

Intramolecular Wurtz reaction of **5d** at high dilution in THF, using sodium and tetraphenylethene[2] gave a product in 28% yield which had the same m.p. (151-152 °C) and ^1H NMR spectrum (at 400 MHz) as riccardin B di-*O*-methyl ether.[1] Therefore constitution **1a** has to be assigned to riccardin B.







3a R = CHO
3b R = CH_2OH
3c R = CH_2Br
3d R = $CH_2P^+Ph_3\ Br^-$

4

5a X = CH=CH, R = CO_2Me
5b X = CH_2CH_2, R = CO_2Me
5c X = CH_2CH_2, R = CH_2OH
5d X = CH_2CH_2, R = CH_2Br

^1H-NMR spectra of the new compounds described in this paper were in accordance with their assigned structures.

REFERENCES

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2) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, J. Am. Chem. Soc. 1961, 83, 943.

(Received in UK 14 April 1987)