

UNCONVENTIONAL CONSTRUCTION OF A  
SUBSTITUTED BENZENE RING\*

Keith James and Ralph A. Raphael  
University Chemistry Laboratory, Lensfield Road,  
Cambridge CB2 1EW, England

A substituted biphenyl suitable for elaboration to the anti-biotic resistomycin (1) has been synthesised by a novel double Michael process involving dimethyl  $\beta$ -oxoglutarate and the diacetylenic diester (4).

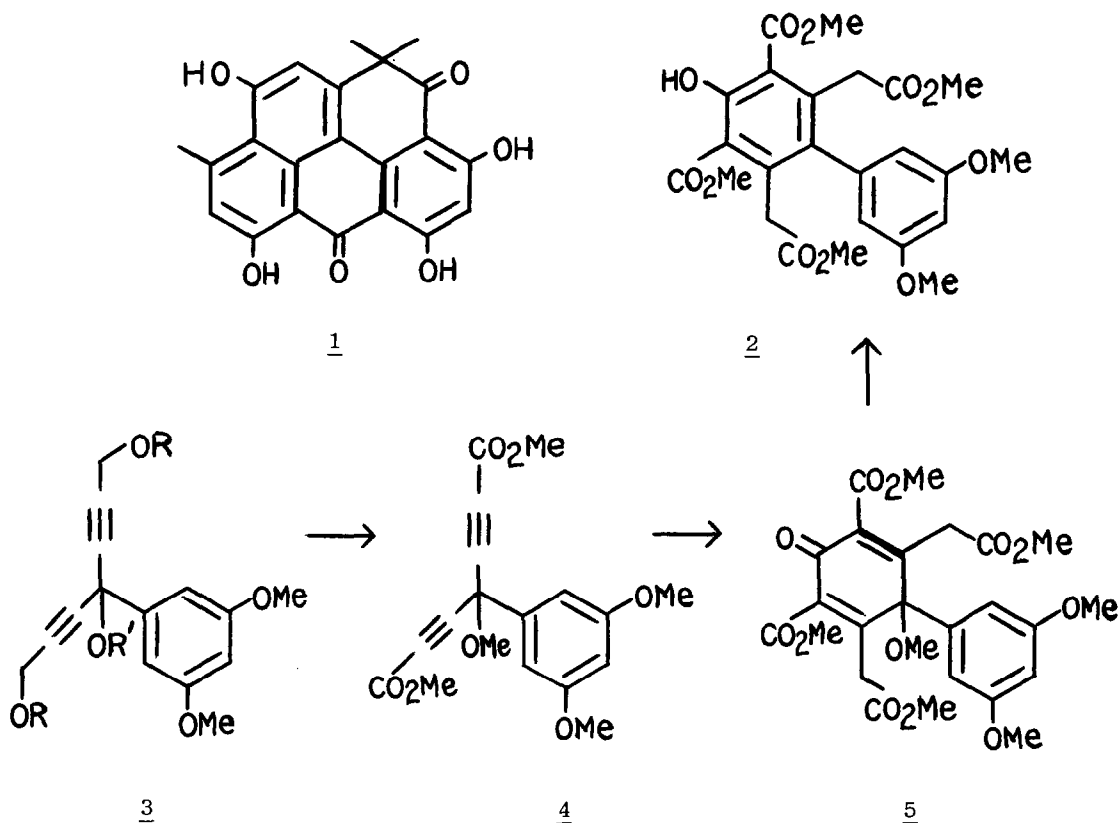
As an intermediate in the synthesis of the antibiotic resistomycin<sup>1</sup> (1) a highly substituted symmetrical biphenyl of type (2) was required. As an Ullmann coupling approach would obviously entail difficulties the following unusual approach was adopted leading to a highly effective production of (2).

Treatment of methyl 3,5-dimethoxybenzoate with excess of the lithio-derivative of tetrahydropyranyloxypropyne gave the diacetylenic alcohol<sup>2</sup> (3; R = THP, R' = H; 90%) which was converted to the more acid-stable methyl ether<sup>2</sup> (3; R = THP, R' = Me; 91%) by reaction with sodium hydride/methyl iodide. Removal of the THP groups with Dow Bio-Rad AG 50W-X2 resin in methyl alcohol gave the diacetylenic diol<sup>2</sup>, m.p. 89-90° (3; R = OH, R' = Me; 80%) which was then oxidised with Jones' reagent and subsequently esterified (BF<sub>3</sub>/MeOH) to give the diacetylenic diester<sup>2</sup> (4; 60%). When a solution of (4) was added to dimethyl  $\beta$ -oxoglutarate (2 equ.) and lithium diisopropylamide (2.2 equ.) in dimethoxyethane a smooth double Michael addition to the two electron-depleted triple bonds ensued to give the methoxydione<sup>2</sup> m.p. 114-114.5° (5; 55%). Use

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\* Dedicated to Professor André Dreiding on the occasion of his 60th birthday.

of other bases produced a complex tautomeric mixture of double bond isomers which could be isomerised to (5) with lithium diisopropylamide. Reduction of (5) by zinc/acetic acid then yielded the required biphenyl<sup>2</sup> m.p. 124.5-125° (2; 89%). Further elaboration towards resistomycin is now in train.



#### References and notes

- 1) H. Brockmann, E. Meyer, K. Schrempp, F. Reiners and T. Reschke, Chem. Ber., 1969, 102, 1224; N. A. Bailey, C. P. Falshaw, W. D. Ollis, M. Watanabe, M. M. Dhar, A. W. Khan and V. C. Vohra, J.C.S. Chem. Comm., 1968, 374; cf. L. Kingston and G. Weiler, Can. J. Chem., 1977, 55, 785.
- 2) Structure was fully confirmed by analytical and spectroscopic data.
- 3) Support from the Science Research Council and Roche Products Limited is gratefully acknowledged.

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