

## Total Synthesis and Stereostructure of Methyl (*E*)-*O*-Methylmulticolanate, a 4-Ylidenetetronic Acid from *Penicillium multicolor*

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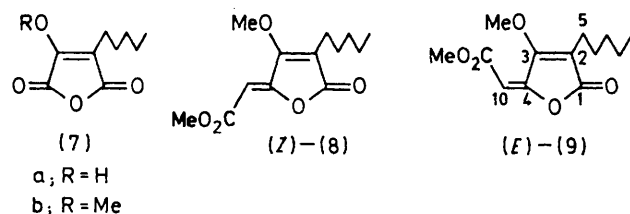
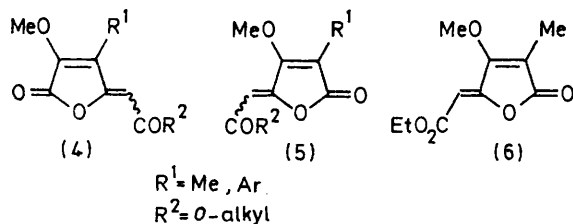
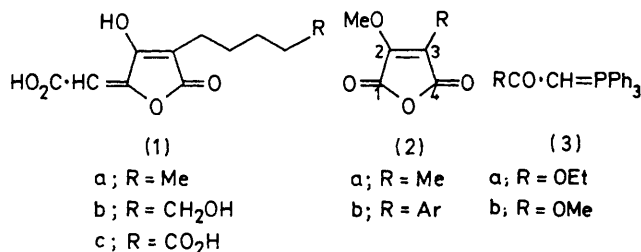
**Summary** A total synthesis of methyl (*E*)-*O*-methylmulticolanate (**9**), and its geometrical isomer (**8**), is described; the stereostructure of (**9**) was established by comparative spectral studies and *X*-ray analysis of the synthetic analogue (**6**).

MULTICOLANIC ACID (**1a**), and the related metabolites (**1b**) and (**1c**) comprise a novel group of 4-ylidenetetronic acids

isolated recently from cultures of *Penicillium multicolor*.<sup>1†</sup> The detailed structure of multicolic acid (**1b**) was uniquely worked out largely from an examination of the <sup>13</sup>C-couplings observed in the n.m.r. spectrum of the dimethyl derivative enriched with doubly labelled <sup>13</sup>C acetate; the stereochemistry about the 4-ylidene bond was not determined. Here we report a total synthesis of the geometrical isomers of methyl *O*-methylmulticolanate (**9**), which confirms the

† Multicolanic acid (**1a**) has only recently been isolated from *P. multicolor*; personal communication from Dr. J. S. E. Holker.

overall structures assigned to the three natural metabolites (**1a—c**), and furthermore establishes their (*E*)-stereochemistry at the same time.



Earlier studies have shown that condensation reactions between 2-methoxy-substituted maleic anhydrides (**2**) and stabilised phosphoranes of type (**3**) provide flexible routes to (*Z*)-(E) mixtures of the corresponding ylidenebutenolide derivatives [(**4**) or (**5**)] resulting from regioselective addition, at either C-1 or C-4, in the anhydrides.<sup>2</sup> Although <sup>1</sup>H n.m.r. shift data and isomerisation studies permitted the assignment of (*Z*)- and (*E*)-geometry to the ylidene derivatives, they did not by themselves distinguish unambiguously the

site of attack (C-1 *vs.* C-4) in the anhydrides. In our earlier work we assigned orientation (**4**) to these derivatives. Circumstances necessitated a re-examination of this proposal, and *X*-ray measurements on the (*Z*)-isomer, m.p. 66–67 °C, produced from the phosphorane (**3a**) and the anhydride (**2a**) now show that this molecule has the alternative orientation (**6**);<sup>†</sup> this observation suggested a simple route to the carbon skeleton in multicolanin acid (**1a**).

Condensation between ethyl heptanoate and diethyl oxalate, followed by treatment of the resulting oxalacetic ester<sup>3</sup> with sulphuric acid led to the 2-hydroxymaleic anhydride (**7a**),<sup>4</sup> m.p. 92–94 °C,  $\nu_{\max}$  1845, 1768, and 1698 cm<sup>-1</sup>, which on methylation with diazomethane gave the 2-methoxy-derivative (**7b**). Reaction between the anhydride (**7b**) and the phosphorane (**3b**) then led to a 3:1 mixture of (*Z*)- and (*E*)-isomers (**8**) and (**9**), respectively, of methyl *O*-methylmulticolanate which was separated by chromatography. The structures and geometries of (**8**) and (**9**) followed from comparison between their spectral data and those of the 2-methyl analogue (**6**). The crystalline (*Z*)-isomer (**8**), m.p. 72–73 °C, is easily distinguished from the oily (*E*)-isomer by <sup>1</sup>H n.m.r. studies, since the olefinic hydrogen in (**9**) is considerably deshielded ( $\tau$  4.17 *vs.* 4.37) by virtue of its *cis*-relationship to the butenolide oxygen. The corresponding olefinic hydrogen absorptions in the dimethyl derivatives of the naturally derived 4-ylidene-tetronic acids (**1a—c**) appear at  $\tau$  ca. 4.17, which suggests that they all have the same (*E*)-stereochemistry. Confirmation of this assignment came from comparison of the <sup>13</sup>C shift data of (**9**) [ $\delta$  161.1 (C-1), 110.6 (C-2), 168.7 (C-3), 150.9 (C-4), 22.3 (C-5), 297 (C-6), 23.5 (C-7), 31.6 (C-8), 13.9 (C-9), 101.1 (C-10), 164.4 (C-11), 59.7 (OMe), and 52.1 p.p.m. (OMe)] and of (**8**) [ $\delta$  160.6, 109.7, 168.3, 150.2, 23.4, 29.7, 25.5, 32.2, 62.2, 100.9, 163.8, 59.5, and 52.0 p.p.m.], with those determined for naturally derived methyl *O*-methylmulticolanate.

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<sup>†</sup> Details of the *X*-ray measurements will be published separately.

<sup>1</sup> J. A. Gudgeon, J. S. E. Holker, and T. J. Simpson, *J.C.S. Chem. Comm.*, 1974, 636.

<sup>2</sup> M. J. Begley, D. W. Knight, and G. Pattenden, *Tetrahedron Letters*, 1975, 4279; D. W. Knight, Ph.D. Thesis, University of Nottingham, 1975.

<sup>3</sup> F. Adickes and G. Andesen, *Annalen*, 1943, 555, 41.

<sup>4</sup> Cf. H. Schinz and M. Hinder, *Helv. Chim. Acta.*, 1947, 30, 1349.