Biomimetic Syntheses of Heptaketide Metabolites: Alternariol and a Derivative of Rubrofusarin

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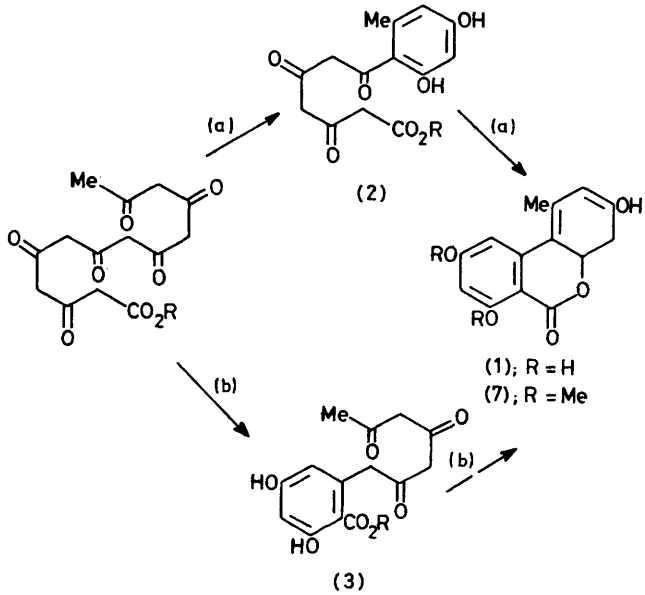
Summary Biogenetically inspired syntheses of alternariol and a methyl ether of rubrofusarin are described.

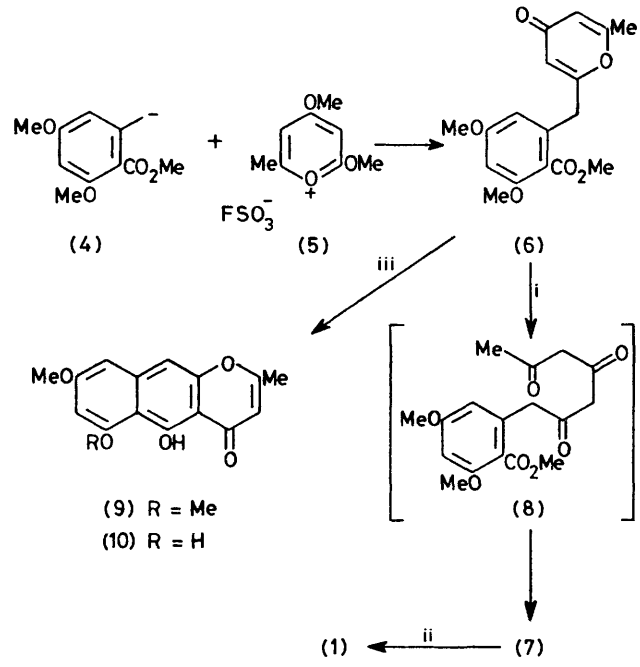
THE fungal metabolite alternariol[1] (**1**) is presumed to arise by cyclisation of a heptaketide folded as in Scheme 1. In principle the process could take place in two stages and



SCHEME 1

hence follow alternative pathways (a) or (b). A biomimetic synthesis of alternariol based on pathway (a) has been described;[2] we now describe one modelled on pathway (b). The synthesis could be varied to produce the naphthopyrone (**9**), a methyl ether of rubrofusarin (**10**).

Treatment of methyl dimethyl orsellinate with lithium di-isopropylamide in tetrahydrofuran (THF) at −78 °C generates the anion† (**4**) (Scheme 2) which reacts with the pyrylium salt (**5**)[3] to give, after aqueous work-up, the pyrone (**6**)‡§ (m.p. 125 °C; ν 1720 and 1665 cm^{-1}) in 25—35% yield, among other products. This was treated with sodium hydroxide in aqueous methanol; acidic work-up gave alternariol dimethyl ether‡ (**7**) in 83% yield with identical spectral properties to those reported,[4] m.p. 292 °C (decomp.) (lit. m.p. 292—294 °C). The product was demethylated[4] to alternariol‡ (**1**), 350 °C (decomp.) [lit.



SCHEME 2. i, OH^-; ii, conc. HI; iii, $LiNPri_2$.

m.p. 349—350 °C (decomp.)]. This synthesis can be commended not only for its relevance to a possible biosynthetic route but also for being more efficient than existing routes to alternariol.[1,2,4]

The formation of (**7**) is presumably initiated by hydrolytic cleavage of the pyrone ring of (**6**) to give a triketone (**8**). The almost complete regioselectivity in the cyclisation of this intermediate is unusual for an *in vitro* reaction. Interestingly, none of the naphthalene (**9**) could be detected by t.l.c. in the crude reaction mixture. However, this product could be formed at the expense of the biphenyl by treatment of the pyrone (**6**) with strong non-nucleophilic base (*e.g.*, lithium di-isopropylamide); a mixture of products was obtained from which the naphthalene† was isolated [17% (27% based on unrecovered starting material)] with identical spectral properties to those reported,[5] m.p. 210—214 °C (lit. m.p. 213 °C).

This work shows that pathway (b) (Scheme 1) for the biosynthesis of alternariol is no less attractive on chemical grounds than pathway (a).[6] On biosynthetic grounds, the former seems more likely since unlike the latter it conforms

† We are indebted to G. E. Evans of this laboratory for this finding.

‡ For this compound, n.m.r., i.r., u.v., and mass spectra as well as microanalysis or high resolution mass measurement were in agreement with the assigned structure.

§ This pyrone formed a hydrochloride which crystallized from ether and melted with loss of HCl at *ca.* 70 °C then resolidified and melted again at the m.p. of the pyrone.

to an almost universal feature of polyketone cyclisations *in vivo*: thus it involves an intermediate benzene derivative in which the attached residue bearing the chain starter unit is longer than that bearing the chain building unit.[7] In view of the highly regiospecific cyclisation of (**8**) *in vitro*, it is possible that *in vivo* this reaction might take place independently of an enzyme.

We thank the S.R.C. for financial support.

(*Received*, 20*th February* 1978; *Com.* 182.)

[1] H. Raistrick, C. E. Stickings, and R. Thomas; *Biochem. J.*, 1953, **55**, 421.
[2] T. M. Harris and J. V. Hay; *J. Amer. Chem. Soc.*, 1977, **99**, 1631.
[3] D. A. Griffin and J. Staunton, *J.C.S. Chem. Comm.*, 1975, 675.
[4] F. Soti, M. Incze, M. Kajtar-Peredy, E. Baitz Gacs, L. Imre, and L. Farkas; *Chem. Ber.*, 1977, **110**, 979.
[5] S. Shibata, E. Morishita, and Y. Arima; *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 1757.
[6] For discussion of chemical factors, see ref. 2.
[7] W. B. Turner, 'Fungal Metabolites,' Academic Press, London and New York, 1972, p. 198.