A Biomimetic Synthesis of (±)-Scytalone (3,6,8-Trihydroxytetralone)

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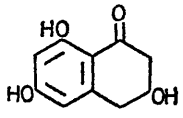
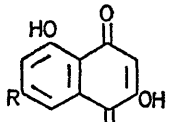
Summary A biomimetic synthesis of the tetralone scytalone from methyl curvulinate is described; some biosynthetic implications such as aromatic dehydroxylation are discussed.

THE tetralone scytalone (**1**) has been isolated from a *Scytalidium* strain[1] and more recently from *Phialophora lagerbergii*[2] along with the naphthaquinone flaviolin (**2**; R = OH). The oxygenation pattern of both (**1**) and (**2**; R = OH) corresponds to that anticipated for the cyclisation of a simple pentaketide system with the introduction of an additional oxygen in the case of flaviolin.†

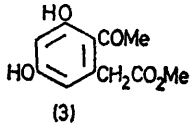
As part of an earlier biomimetic synthesis of flaviolin from methyl curvulinate (**3**),[3] we demonstrated the intermediacy of the unstable tetrahydroxynaphthalene (**4**; R = H) which was characterised as the tetramethoxy-derivative (**4**; R = Me). The easy aerial oxidation of (**4**; R = H) to flaviolin under basic conditions (NaOMe,MeOH–DMSO), together with the well established fact that β-naphthol derivatives readily undergo reactions through the keto tautomer led us to consider a direct synthesis of scytalone from (**4**; R = H).



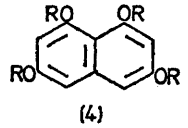
(1)



(2)



(3)



(4)

† Flaviolin is significant in the history of the polyketide theory (A. J. Birch and F. W. Donovan, *Austral. J. Chem.*, 1955, **8**, 529) and it was surprising that its biosynthesis has not been established. The acetate origin of scytalone has been determined.[2]

Excess of sodium borohydride[4] was added to a basic methanolic solution of (**4**; R = H) prepared *in situ* from (**3**). Careful neutralisation with sodium potassium tartrate and dilute hydrochloric acid gave after chromatography (±)-scytalone in *ca.* 40% yield.

The ^1H and ^{13}C n.m.r. (CD_3COCD_3) spectra, as well as the mass spectrum of the synthetic product were identical with those of the natural material, but noticable differences were apparent in the i.r. spectra (KBr) and the m.p.s. The discrepancies were consistent with the differences between a racemate and one of its enantiomers.‡ This was confirmed by converting both natural and synthetic scytalone into 1,3,8-trihydroxynaphthalene under either acidic or basic conditions.

Aerial oxidation of this naphthalene under the same conditions as for flaviolin afforded the naphthaquinone (**2**; R = H).[5] Neither this particular quinone nor the naphthalene have been observed in nature but the synthetic sequence provides an easy means of aromatic dehydroxylation.

It is generally assumed[6] and there is indirect evidence to support[7] the concept that keto functions are reduced at the polyketide level in the biosynthesis of simple acetate-derived monocyclic aromatic compounds. However, there is growing circumstantial evidence that for certain groups of polycyclic compounds *e.g.* anthraquinones reduction may occur on an intermediate which has reached an aromatic level.[8] The above synthesis demonstrates the chemical feasibility of the reduction of acetate-derived phenolic derivatives to the corresponding alcohols and their dehydration to the dehydroxylated aromatics.

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‡ Natural scytalone has $[\alpha]_D = 0$. As a result of this investigation a re-examination revealed that the metabolite possesses a weak negative Cotton effect at 220 nm. Hence the natural material is (−)-scytalone.

[1] J. A. Findlay and D. Kwan, *Canad. J. Chem.*, 1973, **51**, 1617.
[2] D. C. Aldridge, A. B. Davies, M. R. Jackson, and W. B. Turner, in the press; W. B. Turner personal communication.
[3] P. M. Baker and B. W. Bycroft, *Chem. Comm.*, 1968, 71.
[4] See G. I. Fray, *Tetrahedron*, 1958, **3**, 316.
[5] R. H. Thomson, *J. Org. Chem.*, 1948, **13**, 870.
[6] See J. D. Bu'lock, 'The Biosynthesis of Natural Products,' McGraw-Hill, London, 1965, ch. 2.
[7] P. Dimroth, M. Walter, and F. Lynen, *European J. Biochem.*, 1970, **13**, 98.
[8] See, for example, J. D. Bu'lock and J. R. Smith, *J. Chem. Soc.* (*C*), 1968, 1941; N. Takeda, S. Seo, Y. Ogihara, U. Sankawa, I. Iitaka, I. Kitagawa, and S. Shibata, *Tetrahedron*, 1973, **29**, 3703; S. Seo, U. Sankawa, Y. Ogihara, Y. Iitaka, and S. Shibata, *ibid.*, 1973, **29**, 3721; U. Sankawa, Y. Ebizaka, and S. Shibata, *Tetrahedron Letters*, 1973, 2125.