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TOTAL SYNTHESIS OF (±)-DIHYDRO-O-METHYLSTERIGMATOCYSTIN

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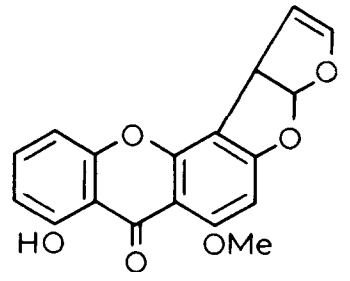
The structure of sterigmatocystin (I), a carcinogenic metabolite of Aspergillus versicolor (Vuill.) Tiraboschi, was established,[1] by spectroscopic and degradative methods, in 1962. It proved to be the first known natural product to contain the dihydrofurobenzofuran ring system. Other carcinogenic mould metabolites containing this system (notably the aflatoxins[2]) have since been isolated and have been intensively investigated. Although total syntheses of aflatoxin-B1 and -B2 have been accomplished,[3] no synthesis of sterigmatocystin or any of its congeners has yet been reported. We now describe a total synthesis of (±)-dihydro-O-methylsterigmatocystin (II).

Two different methods for the synthesis were explored. In the first, an attempt was made to build the tetrahydrofuranofuran system onto an appropriately substituted xanthone, but this attempt proved abortive. In the second method, success was attained by building the xanthone system onto a previously synthesised tetrahydrofurobenzofuran (III). The main difficulty envisaged in this method was the formation of the diphenyl ether linkage (see IV) under conditions which did not degrade the sensitive bicyclic side-chain. However, we found that the desired Ullmann-type synthesis could be achieved under sufficiently mild conditions by the method of Williams et al.[4]

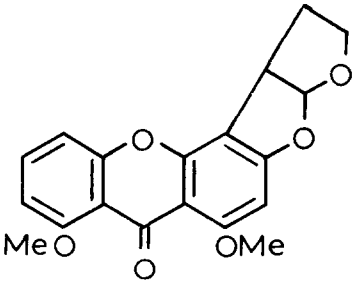
Condensation of methyl 2-bromo-6-methoxybenzoate (V)* (in refluxing pyridine and in presence of cuprous chloride) with the tetrahydrofurobenzofuran (III)[5] gave, after hydrolysis, the carboxylic acid (IV) [25% after allowing for recovered (III)][7]. The latter, when treated with an excess of oxalyl chloride in dry methylene dichloride, underwent ring-closure yielding a substance which crystallised from methanol to give the desired compound (II) (63%) as colourless prisms, m.p. 265 - 267°. This product

* Satisfactory analytical results were obtained for all new compounds.

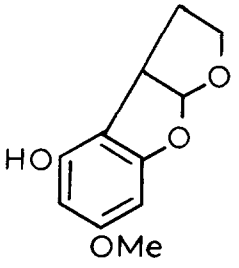
was identical in its spectroscopic (UV, IR, PMR) and chromatographic (TLC on silica) properties with a sample of (-)-dihydro-O-methylsterigmatocystin, m.p. 282 - 283°, which had been prepared from the metabolite by hydrogenation followed by methylation.



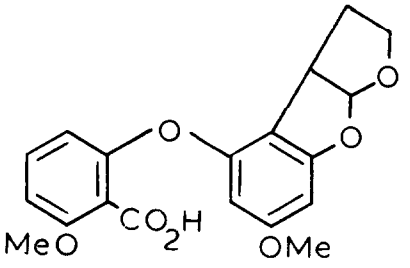
(I)



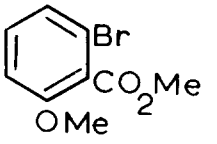
(II)



(III)



(IV)



(V)

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