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THE SYNTHESIS OF DI-O-METHYLSTREPSILIN[1]

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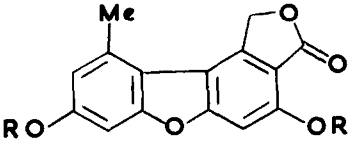
Genuine dibenzofurans constitute a rare group of natural products isolated almost exclusively from lichens[2]. One such compound is strepsilin (I), isolated from the lichen *Cladonia strepsilis* (Ach.) Wain[3,4]. The structure of I was elucidated by Shibata[5] from a combination of chemical, degradative and spectroscopic evidence.



I, R = H

II, R = Me

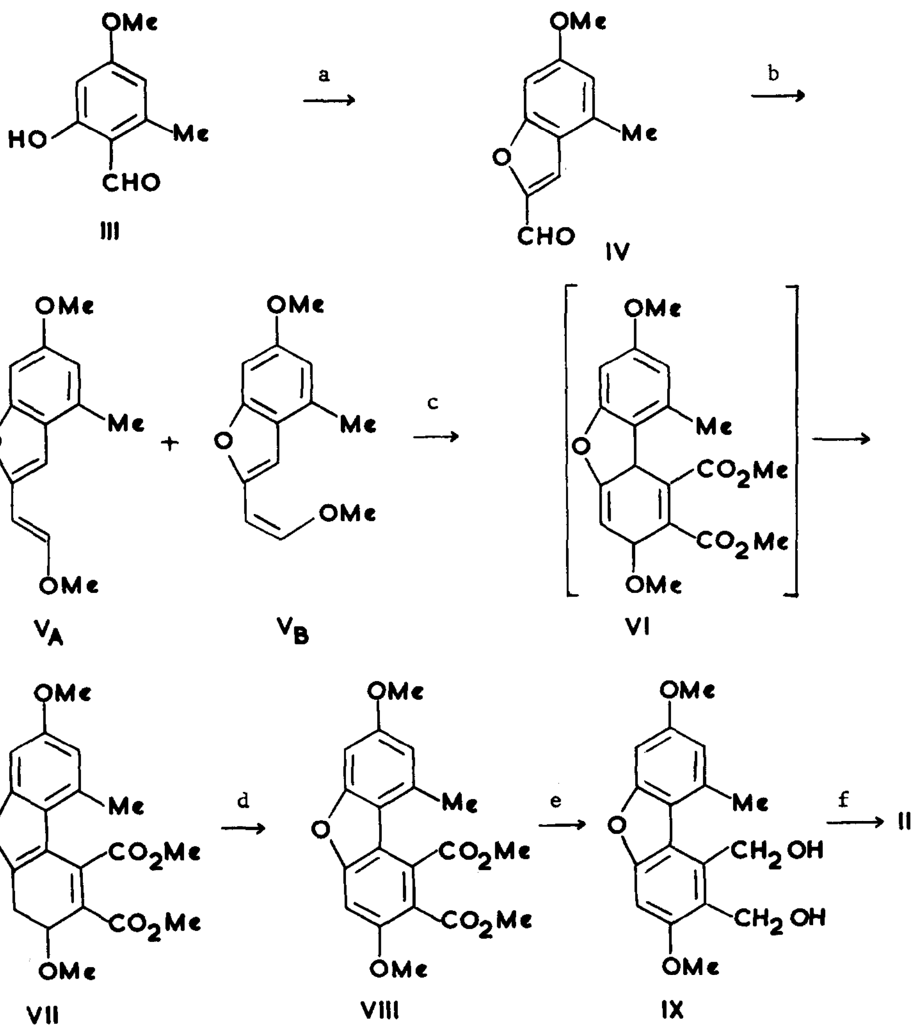
We now report the synthesis of di-O-methylstrepsilin (II) and thereby confirmation of the structure I for strepsilin.

The cycloaddition of dimethyl acetylenedicarboxylate to the appropriate 2-(β-methoxyvinyl) benzofuran provided the key step in this synthetic approach[6] (see Scheme I).

The alkylation of evernininaldehyde (III)[7] with bromoacetaldehyde in the presence of potassium carbonate was accompanied by ring closure and dehydration to give 6-methoxy-4-methylbenzofuran-2-aldehyde (IV)[8] [53% yield; sublimed at 80°/0.5 mm to form pale yellow needles, m.p. 129-130°; τ(CCl_4) 0.26 (1H,s), 2.61 (1H,s), 3.21 (1H,d, J 2Hz), 3.34 (1H,d, J 2Hz), 6.17 (3H,s) and 7.61 (3H,s)].

The treatment of IV with methoxymethylenetriphenylphosphorane gave a 2:1 mixture of *trans* and *cis* 6-methoxy-4-methyl-2-(β-methoxyvinyl) benzofuran (V_A, V_B respectively; overall yield 70%). Although the enol ethers (V_A, V_B) could

SCHEME I



(a) $BrCH_2CHO, K_2CO_3$, D.M.F.

(b) $Ph_3P = CHOMe$

(c) $MeCO_2C \equiv CCO_2Me$

(d) N.B.S., $(PhCO)_2O_2$

(e) $LiAlH_4$

(f) Na_2Cr_2O7

readily be separated chromatographically, the mixture was utilised directly in the Diels-Alder reaction.

The predominant product (12%) from the reaction of dimethyl acetylenedicarboxylate with the mixture of V_A, V_B in boiling toluene was the rearranged adduct, dimethyl 3,4-dihydro-3,7-dimethoxy-9-methyldibenzofuran-1,2-dicarboxylate (VIII) [yellow oil, νmax(film) 1730, 1630 cm^{-1}, λmax (EtOH) 246 nm (ε22000), 256 (22600), 288 (8200), 295 sh (8200) and 353 (4800); τ(CCl_4) 3.25 (1H,d, J 2Hz), 3.42 (1H,d, J 2Hz), 5.40-5.55 (1H,m, proton 3), 6.13 (3H,s), 6.19 (6H,s), 6.66 (3H,s), 6.84 (2H,m) and 7.62 (3H,s)]. Apparently the initially formed adduct (VI) is unstable under the reaction conditions, the driving force for rearrangement being the aromatisation of the benzofuran ring. The required diester (VII) was actually isolated from a complex mixture of products by preparative layer chromatography.

The oxidation of VII was achieved by treatment with *N*-bromosuccinimide and dibenzoyl peroxide and gave dimethyl 3,7-dimethoxy-9-methyldibenzofuran-1,2-dicarboxylate (VIII)]47% yield; sublimed at 140°/0.2 mm to give pale yellow crystals, m.p. 121-123°; λmax (EtOH) 229 nm (ε21500), 255 (16800), 298 sh (7100), 305 (9000) and 324 (8000); τ(CCl_4) 2.96 (1H,s), 3.24 (1H,d, J 2Hz), 3.42 (1H,d, J 2Hz), 6.11 (3H,s), 6.16 (3H,s) 6.20 (6H,s) and 7.58 (3H,s)].

Lithium aluminium hydride reduction of VIII proceeded readily to give the diol IX which was oxidised directly with sodium dichromate in dilute sulphuric acid. Preferential oxidation of the less hindered hydroxymethyl group occurred and di-*O*-methylstrepsilin (II) (20%) was isolated after chromatography of the crude [illegible] tion mixture. Compound (II) formed colourless needles from benzene, m.p. 249-251° (lit.[5] 251-252°) undepressed on admixture with authentic material prepared by methylation of strepsilin; the infrared, ultraviolet, p.m.r. and mass spectra of the two samples were identical.

ACKNOWLEDGMENT

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