Synthesis of (±)-Atrovenetin

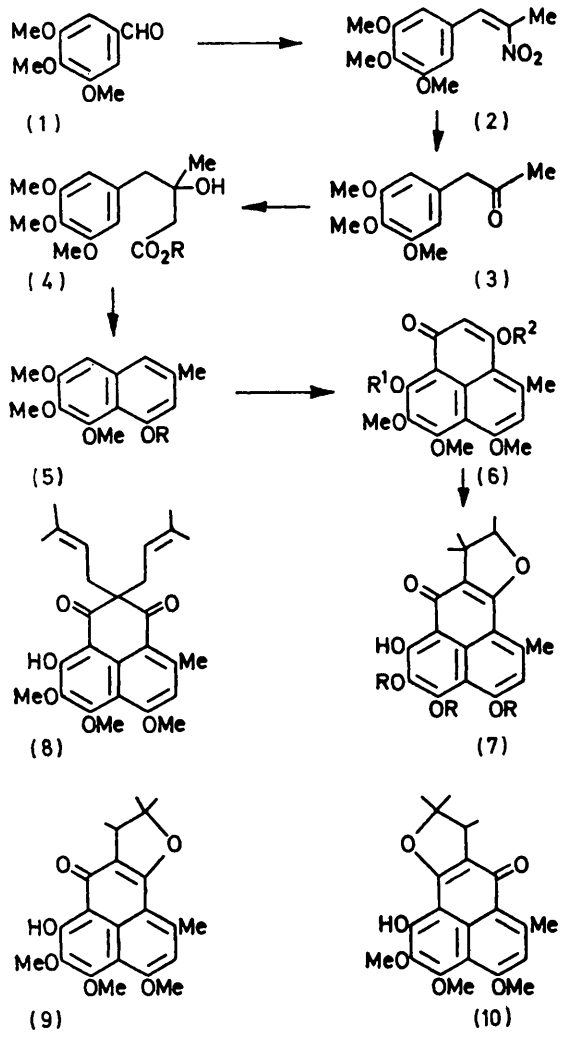
By D. A. FROST and G. A. MORRISON*

(*Department of Organic Chemistry, The University, Leeds* LS2 9JT)

Summary A synthesis of (±)-atrovenetin (7; R = H), in ten steps from 3,4,5-trimethoxybenzaldehyde (1), is described.

ATROVENETIN (7; R = H)[1] is a metabolite of *P. Atrovenetum*, and its isolation from the mycelium of *P. Herquei* has also been reported.[2] It has recently been the subject

of structural,[3] stereochemical,[4] and biosynthetic[5] investigations and some preliminary work directed towards its synthesis has been described.[6] We now report a synthesis of (±)-atrovenetin.



The substituted naphthalene (5; R = Me), required as an intermediate, has previously been obtained in an overall yield of 1% in a nine-stage synthesis starting from 3,4,5-trimethoxybenzoic acid;[7] we have now obtained it by a simpler route from 3,4,5-trimethoxybenzaldehyde (1) in an overall yield of 37%. The aldehyde (1) was converted, *via* the nitro-olefin (2), into methyl 3,4,5-trimethoxybenzyl ketone (3)[8] and thence, by means of a Reformatsky reaction with ethyl bromoacetate, into the β-hydroxy-ester (4; R = Et). The acid (4; R = H), obtained by hydrolysis, was cyclised with polyphosphoric acid to afford the phenol (5; R = H), which was methylated with methyl sulphate and sodium hydroxide to give the required tetramethyl ether (5; R = Me).

Polyphosphoric acid-catalysed reaction between the naphthalene (5; R = Me) and malonic acid gave the phenalenone (6; R^1 = Me, R^2 = H) (73%), from which the dihydric phenol (6; R^1 = R^2 = H) was obtained in a yield of 95% by brief treatment with 6N-hydrochloric acid at 100°. Alkylation with 3,3-dimethylallyl bromide and potassium carbonate in acetone gave the dimethylallyl ether (6; R^1 = H, R^2 = $CH_2CH:CMe_2$) (42%) and the dialkylated compound (8) (51%). When a solution of the allyl ether (6; R^1 = H, R^2 = $CH_2CH:CMe_2$) in dimethylformamide was heated at 100° for 16 h, the only discernible product, isolated in a yield of 70% was (±)-atrovenetin yellow trimethyl ether (7; R = Me). When the rearrangement was carried out at 155° for 3 h the yield fell to 60% and the isomeric compounds (9) and (10), arising through the abnormal Claisen rearrangement, were also obtained in yields of 22% and 6%, respectively; at 190° for 2½ h, the yields of compounds (7; R = Me), (9), and (10) were 28%, 44%, and 20% respectively. Demethylation of the trimethyl ether (7; R = Me) with pyridine hydrochloride gave (±)-atrovenetin (7; R = H) (82%), which was further characterised by preparation of its tri- and tetra-acetates.[3b]

Satisfactory analyses and spectra were obtained for all the new compounds described.

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