Total Synthesis of (±)-Flavipucine

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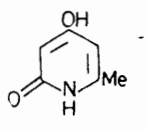
Summary The total synthesis of (±)-flavipucine and its diastereoisomer (±)-isoflavipucine is reported.

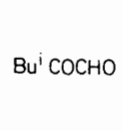
THE novel antibiotic flavipucine was isolated from a strain of *Aspergillus flavipes* by Casinovi *et al.*[1] and found to be active against both gram-positive and gram-negative organisms. These authors proposed a structure for this substance which was subsequently revised by Findlay and Radics[2] to the spirobicyclic epoxide (**5**). We now report the total synthesis of this antibiotic.

Condensation of the pyridone (**1**)[3] with the keto-aldehyde (**2**)[4] in methanol containing 1 equiv. of sodium methoxide at 25 °C yielded quantitatively the sodium salt (**3a**),[5] i.r. (Nujol) 5·84 and 6·08—6·29 μm; n.m.r. (D_2O) δ 5·82 (broad s, 5-H), 5·35 (s, 1′-H), 2·15 (s, 6-Me), and 0·85 and 0·82 (each d, *J* 6 Hz, $CHMe_2$). Acetylation of (**3a**) in acetic anhydride at 25 °C provided the diacetate (**3b**) likewise in excellent yield,†‡ m.p. 129—130 °C; M^+ 323; i.r. ($CHCl_3$) 5·63, 5·73, 5·79, and 6·08 μm; λ_{max} (MeOH) 309 (ε, 8800) and 230 nm (5500); n.m.r. ($CDCl_3$) δ 6·43 (s, 1′-H), 6·05 (broad s, 5-H), 2·37 (s, 6-Me), 2·28 and 2·12 (each s, 2OAc), and 0·93 and 0·90 (each d, *J* 6 Hz, $CHMe_2$).

Saponification of the diacetate (**3b**) in methanolic sodium hydroxide at ambient temperatures proceeded rapidly with incorporation of a methoxy-function to produce (**3c**) in high yield as a crystalline solid of indefinite m.p.;† M^+ 253;



(1)



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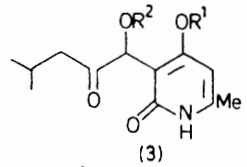
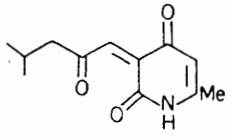
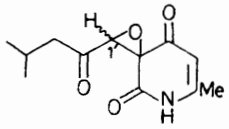


(3)

a; R^1 = Na, R^2 = H
b; R^1 = R^2 = Ac
c; R^1 = H, R^2 = Me



(4)



(5)

† Satisfactory analytical data were obtained.

‡ A minor amount of lactim triacetate is also formed depending on the duration of acetylation. The latter in turn can be selectively converted into the diacetate (**3b**) by methanolysis.

i.r. ($CHCl_3$) 5·83, 6·09, and 6·18 μm; λ_{max} (MeOH) 289 nm (ϵ, 6900): n.m.r. ($CDCl_3$) δ 3·45 (s, OMe). This replacement reaction indicated the occurrence of an hydrolysis–elimination sequence; the intermediate formation of the enedione (**4**) is most likely, although this reactive species has not yet been isolated.§ The diacetate (**3b**) was accordingly treated with alkaline H_2O_2 in Bu^tOH or preferably with $KOBu^t$–Bu^tOH in t-butyl hydroperoxide as solvent at 0—25 °C, whereby incorporation of the epoxide function indeed occurred to yield (±)-flavipucine (**5**) together with its diastereoisomer in 55% yield.

The two isomers were separated by fractional crystallization from benzene. The isomer which crystallized initially as plates, m.p. 154—155 °C,† was identical (t.l.c., and u.v., i.r., n.m.r., and mass spectra) with natural (−)-flavipucine.[1] The stereoisomer, (±)-isoflavipucine, was isolated as thin rectangular prisms, m.p. 136—138 °C; M^+ 237; i.r. ($CHCl_3$) 2·92, 3·06, 3·14, 5·82, 6·00, and 6·12 μm; λ_{max} (MeOH) 326 nm (ϵ, 6400); n.m.r. ($CDCl_3$) δ 5·65 (broad s, 5-H), 3·92 (s, 1′-H), 2·20 (s, 6-Me), and 0·98 (d, J 6·5 Hz $CHMe_2$).

The authors are indebted to Dr. Casinovi for a sample of natural (−)-flavipucine for comparison purposes.

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§ These attempts invariably resulted in the incorporation of groups from solvents or reagent to give side-chain-substituted species. These and other findings will be reported elsewhere.

[1] C. G. Casinovi, G. Grandolini, R. Mercantini, N. Oddo, R. Olivieri, and A. Tonolo, *Tetrahedron Letters*, 1968, 3175.
[2] J. A. Findlay and L. Radics, *J.C.S. Perkin I*, 1972, 2071.
[3] Prepared in excellent yield by the method of S. Seto, H. Sasaki, and K. Ogura, *Bull. Chem. Soc. Japan*, 1966, **39**, 281.
[4] H. D. Dakin and H. W. Dudley, *J. Biol. Chem.*, 1914, **18**, 29. This aldehyde was presently prepared by condensation of ethyl isovalerate with dimsyl sodium (method of E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1345) to give $MeSOCH_2C(:O)Bu^t$; the latter was converted by the procedure of H.-D. Becker, G. J. Mikal, and G. A. Russell, (*J. Amer. Chem. Soc.*, 1963, **85**, 3410; *Org Synth.*, Coll. vol. V, 937) into the keto-aldehyde (**2**) in 70—75% overall yield.
[5] J. A. Findlay and F. Y. Shum (*Synth. Comm.*, 1973, 355) reported the uncatalysed condensation of the pyridone (**1**) with α-keto aldehydes. No particulars were mentioned regarding the pertinent compound (**3a**; R^1 = H).