Biogenetic-type Total Synthesis of Citromycetin

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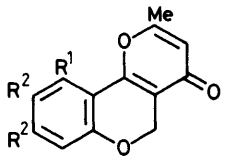
Biogenetic-type total synthesis of citromycetin (**1a**) was achieved by a route involving oxidation of a propenyl group and demethylation of a methoxy group in the pyranobenzopyranone (**1c**), synthesized by a regioselective cyclization of the enedione (**2c**).

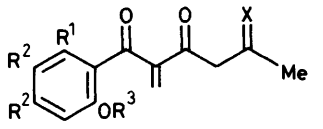
Although citromycetin (**1a**),[1] an antibiotic active on gram-positive bacteria,[2] was first isolated from *Penicillium frequentans* in 1931,[1a] its total synthesis has not been accomplished.[3] Hutchinson *et al.*[4] have proposed that citromycetin (**1a**) is biosynthesized *via* enetrione (**2a**). In our preliminary study[5] we have synthesized 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]-benzopyran-4-one (**1b**), the basic skeleton in citromycetin, *via* regioselective condensation of the enedione (**2b**) to form the methoxymethylpyrone (**3a**) as a key step. We decided to use propenyl and methoxy groups as substituents which are convertible into carboxy and hydroxy groups respectively at the last stage of the total synthesis of citromycetin (**1a**), and therefore chose enedione (**2c**)[6] as a starting material.

The enedione (**2c**), regarded as an equivalent of (**2a**) was treated with conc. HCl–MeOH (1 : 30)[5] to give the expected methoxymethylpyrone (**3b**) regioselectively in 85% yield. When (**2c**) was left standing in conc. HCl–AcOH (1 : 10) the chloromethylpyrone (**3c**) (73%) and the double-cyclization product (**4**) (22%) were obtained. Under these conditions demethylation of the methoxy group competed with chloride attack on the methylene group, and the hydroxy group in the resulting phenol condensed with the methylene group through the propenyl group to give (**4**). This led to the conclusion that demethylation might take place under the same conditions (HBr–AcOH)[5] as conversion of the methoxy group in (**3a**) into bromine. Thus the pyrone (**3c**) was used in the next stage. Application of Fujita's debenzylation method[7] to (**3c**) gave the phenol (**3d**) in 89% yield. Cyclization of the phenol (**3d**) with $NaHCO_3$–MeOH–water afforded the pyrano[3,2-*c*][1]-benzopyranone (**1c**) in 69% yield. Selective ozonolysis of (**1c**) in the presence of a dye (Oil Violet)[8] followed by oxidation of the resulting aldehyde (**1d**) with sodium chlorite and sul-



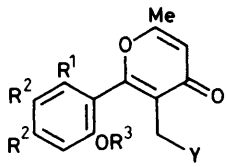
(1)

a; $R^1 = CO_2H, R^2 = OH$
b; $R^1 = R^2 = H$
c; $R^1 = CH{=}CHMe, R^2 = OMe$
d; $R^1 = CHO, R^2 = OMe$
e; $R^1 = CO_2H, R^2 = OMe$
f; $R^1 = CO_2Me, R^2 = OMe$



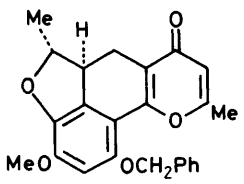
(2)

a; $R^1 = CO_2H$, $R^2 = OH, R^3 = H, X = O$
b; $R^1 = R^2 = H$, $R^3 = CH_2Ph$, $X = OCH_2CH_2O$
c; $R^1 = CH{=}CHMe, R^2 = OMe$, $R^3 = CH_2Ph, X = OCH_2CH_2O$



(3)

a; $R^1 = R^2 = H, R^3 = CH_2Ph, Y = OMe$
b; $R^1 = CH{=}CHMe, R^2 = OMe$, $R^3 = CH_2Ph, Y = OMe$
c; $R^1 = CH{=}CHMe, R^2 = OMe$, $R^3 = CH_2Ph, Y = Cl$
d; $R^1 = CH{=}CHMe, R^2 = OMe$, $R^3 = H, Y = Cl$



(4)

phamic acid[9] gave the carboxylic acid (**1e**) in 42% overall yield. Treatment of (**1e**) with diazomethane gave the trimethyl derivative (**1f**), whose u.v. and ^{1}H n.m.r. spectra were identical with those[10] reported for methyl *O,O*-dimethylcitromycetin. Finally demethylation of the acid (**1e**) with $AlCl_3$ and dimethyl sulphide in CH_2Cl_2[11] afforded citromycetin (**1a**) in 69% yield. The physical and spectral data for (**1a**) [m.p. 271—273 °C; $\nu_{max.}$ 3650—2400, 1703, and 1660 cm^{-1}; $\lambda_{max.}$ (log ε) (EtOH) 257 (3.97), 304 (3.83), and 379 nm (4.03); ^{1}H n.m.r. (CD_3OD) δ 2.33 (s, Me), 5.00 (s, 5-H), 6.20 (s, 3-H), and 6.51 (s, 7-H); ^{13}C n.m.r. (CD_3OD) δ 19.2 (Me), 63.3 (C-5), 105.3 (C-10a), 105.7 (C-7), 112.5 (C-14a), 114.2 (C-3), 118.1 (C-10), 141.7 (C-9), 153.0 (C-8), 153.7 (C-6a), 158.4 (C-10b), 167.4 (C-2), 171.2 (CO_2H), and 178.4 (C-4)] were identical with that of natural citromycetin.

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