Regiospecific (Biogenetic-type) Synthesis of 2-Methyl-5*H*-pyrano-[3,2-*c*][1]benzopyran-4-one, the Basic Skeleton in Citromycetin

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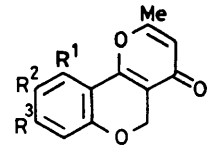
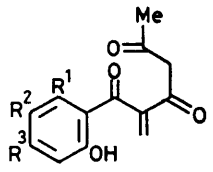
Summary Regiospecific cyclization of the acetal (**4g**), derived in 5 steps from 2′-benzyloxyacetophenone (**3a**), gave the pyrone (**6a**) which was easily converted into 2-methyl-5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (**1b**), the basic skeleton in citromycetin (**1a**).

CITROMYCETIN (**1a**),[1] the metabolite from *Penicillium frequentans*, has a characteristic pyranopyrone ring system and its biosynthesis from the enetrione (**2a**) has been proposed.[2] Only one method for the synthesis of this ring system from a chromanone has been reported.[3] We report herein that the acid-catalysed regiospecific cyclization of the acetal (**4g**) [*via* the biogenetic-type intermediate (**2b**)] gave the pyrone (**6a**), which was easily converted into 2-methyl-5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (**1b**), the basic skeleton in citromycetin (**1a**).



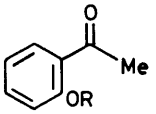
(1)



(2)

a; R^1 = CO_2H, R^2 = OH, R^3 = OH

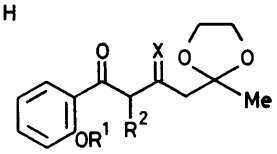
b; R^1 = R^2 = R^3 = H



(3)

a; R = CH_2Ph

b; R = CH_2OMe



(4)

a; R^1 = CH_2Ph, R^2 = H_2, X = H, OH

b; R^1 = CH_2OMe, R^2 = H_2, X = H, OH

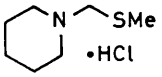
c; R^1 = CH_2Ph, R^2 = H_2, X = O

d; R^1 = CH_2OMe, R^2 = H_2, X = O

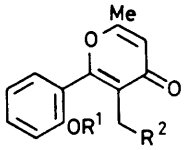
e; R^1 = CH_2Ph, R^2 = H, CH_2SMe, X = O

f; R^1 = CH_2Ph, R^2 = H, $CH_2S(O)Me$, X = O

g; R^1 = CH_2Ph, R^2 = CH_2=, X = O



(5)

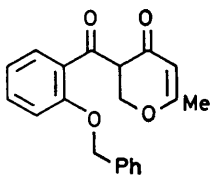


(6)

a; R^1 = CH_2Ph, R^2 = OMe

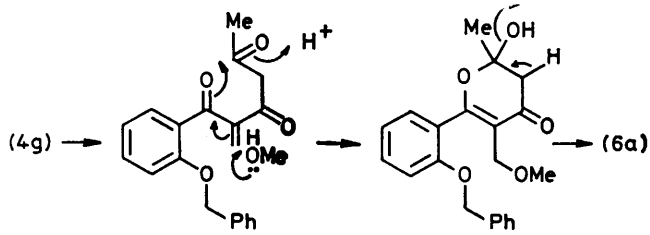
b; R^1 = H, R^2 = OMe

c; R^1 = H, R^2 = Br



(7)

Thus aldol condensation of 2′-benzyloxyacetophenone (**3a**)[4] with (2-methyl-1,3-dioxolan-2-yl)acetaldehyde[5] (lithium di-isopropylamide–$MgBr_2$–tetrahydrofuran,[6] −70 °C) followed by oxidation of the alcohol (**4a**) (CrO_3–H_2SO_4–dimethylformamide[7]) gave the diketone (**4c**) in 50% overall yield. Thiomethylation of the diketone (**4c**) with methylthiomethylpiperidine hydrochloride (**5**)† in dioxan at 80 °C for 23 h gave the monoalkylated product (**4e**) in 90% yield. Elimination of the methylthio-group from (**4e**) [i, $NaIO_4$–methanol, room temperature, 24 h; ii, $CaCO_3$–toluene, reflux, 4 d] gave the enedione (**4g**) [ν_{max} 1658 and 1590 cm^{-1}; δ 1·23 (s, Me), 2·73 (s, $COCH_2$), 3·67 (br, s, OCH_2CH_2O), 4·90 (s, OCH_2Ph), 5·70 and 6·10 (=CH_2), and 6·60—7·53 (ArH)] in 93% overall yield from compound (**4e**).



Regiospecific (biogenetic-type) cyclization was achieved by treatment of (**4g**) with concentrated hydrochloric acid in methanol to give the pyrone (**6a**) [another possible cyclization product (**7**) was not detected under these conditions]. The structure (**6a**) was confirmed by the ^1H n.m.r. spectrum [δ 3·21 (OMe) and 6·07 (dienone olefinic proton)[8]] and this result may be explained by the reaction mechanism shown in Scheme 2. This suggests that spontaneous cyclization to (**1b**) would take place using the more labile phenol-protecting group. However thiomethylation of (**4d**), prepared from (**3b**) as for (**4c**) was unsuccessful. Hydrogenolysis of compound (**6a**) with palladium–carbon in ethanol, followed by demethylation of the resultant phenol (**6b**) with dry hydrogen bromide in acetic acid gave the bromo-compound (**6c**) in 50% overall yield from compound (**4g**). Treatment of (**6c**) with aqueous sodium hydrogencarbonate in methanol resulted in the quantitative formation of 2-methyl-5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (**1b**) [m.p. 155—156 °C, ν_{max} 1655, 1620, and 1600 cm^{-1}; δ 2·38 (s, Me), 5·23 (s, OCH_2), 6·20 (s, =CH), and 6·82—7·72 (ArH)].

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† Compound (**5**) was prepared by the addition of methylthiomethylpiperidine, obtained by the modified method of Grillot *et al.* (G. F. Grillot, H. R. Felton, B. R. Garrett, H. Greenberg, R. Green, R. Clementi, and M. Moskowitz, *J. Am. Chem. Soc.*, 1954, **76**, 3969), to an HCl-saturated ether solution in an ice bath. For an alternative preparation of methylthiomethylpiperidine see H. Böhme and H.-H. Otto, *Arch. Pharm.*, 1967, **300**, 647.

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[4] U. K. Pandit and T. C. Bruice, *J. Am. Chem. Soc.*, 1960, **82**, 3386.
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