Regioselective Synthesis of 4,10-Dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one, the Basic Skeleton in Fulvic Acid

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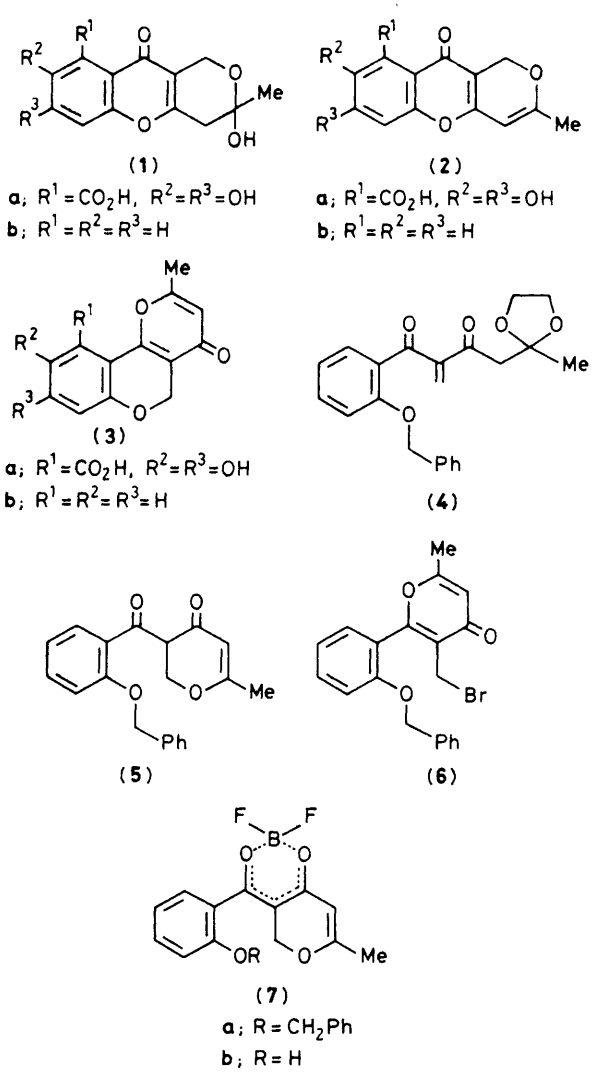
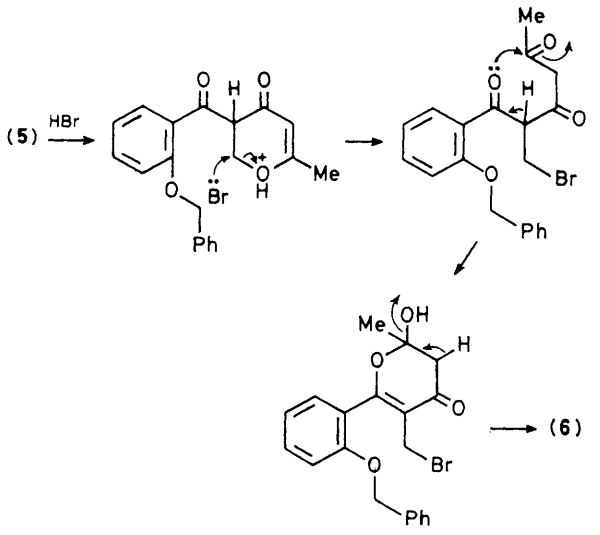
The first synthesis of 4,10-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one, the basic skeleton in fulvic acid, was achieved by sequential cyclization, which involved hydrogenation of the boron complex of the dione (**5**) obtained by regioselective cyclization of the acetal (**4**) with HCl in tetrahydrofuran.

Fulvic acid (**1a**),[1] the metabolite produced by several fungi including *Penicillium*, *Carpenteles*, and *Cereospora* species, has the pyrano[4,3-*b*][1]benzopyran ring. Despite several attempts[2] the synthesis of this ring system has not been





Scheme 1

successful. We reported the synthesis of 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one (**3b**),[3] the basic skeleton in citromycetin (**3a**) and a structural isomer of unsubstituted dehydrofulvic acid (**2b**). We report herein the first synthesis of 4,10-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]-benzopyran-10-one (**1b**), the basic skeleton in fulvic acid (**1a**).

Treatment of the acetal (**4**)[3] with 5% HCl–tetrahydrofuran (1 : 2) at ambient temperature gave the pyrone (**5**), (positive $FeCl_3$ test), as a single cyclization product in 97% yield. Hydrogenolysis of (**5**) with palladium–carbon resulted in the cleavage of not only the benzyl group but also the pyrone ring to afford complex products. Debenzylation of (**5**) with dry hydrogen bromide in acetic acid gave the pyrone (**6**) for which the synthesis and conversion into (**3b**) has been reported.[3] The rearrangement of (**5**) into (**6**) can be explained by the reaction mechanism shown in Scheme 1. Treatment of (**5**) with $BF_3{\cdot}OEt_2$–Me_2S–CH_2Cl_2 (Fujita's method)[4] gave the debenzylated boron complex (**7b**) in *ca.* 15% yield. These facts suggest that prior formation of the boron complex (**7a**) would improve the yield of the debenzylation product (**7b**). In fact the pyrone (**5**) afforded the boron complex (**7a**) in 70% yield on treatment with boron trifluoride–diethyl ether in dichloromethane.

Although catalytic hydrogenation of (**7a**) gave complex products, application of Fujita's method to (**7a**) gave (**7b**) in 88% yield. Acid catalysed cyclization of (**7b**) with conc. HCl–acetic acid (1 : 10) gave the pyranobenzopyran (**2b**) in 79% yield. The ^1H and ^{13}C n.m.r. spectra of (**2b**) had similarities to those[5] of dehydrofulvic acid (**2a**). Treatment of (**2b**) with 5% HCl–acetone (1 : 1) at ambient temperature for 4 days afforded 4,10-dihydro-3-hydroxy-3-methyl-1*H*,3*H*-pyrano[4,3-*b*][1]benzopyran-10-one (**1b**) (m.p. 182–183.5 °C) in 78% yield. The spectral data of (**1b**) [ν_{max} 3300, 1645, 1595 cm^{-1}; λ_{max} (log ϵ) (EtOH) 226 (4.44), 265 (3.89), 297 nm (3.93); ^1H n.m.r. δ 1.57 (3H, s, CH_3), 2.79 (2H, q, *J* 17.6 Hz, 4-H), 4.65 (2H, s, 1-H), 7.32—7.81 (3H, m, 6-, 7-, 8-H), 8.11 (1H, dd, *J* 8.3, 1.5 Hz, 9-H): ^{13}C n.m.r. 28.6 (CH_3), 38.0 (C-4), 56.9 (C-1), 115.8 (C-10a), 160.3 (C-4a), 175.6 p.p.m. (C-10)] showed a great resemblance to the data[6] reported for fulvic acid (**1a**).

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References

1 (a) For the first isolation see A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, 1935, **29**, 1102; (b) for structure determination see F. M. Dean, R. A. Eade, R. A. Moubasher, and A. Robertson, *Nature*, 1957, **179**, 366; (c) *J. Chem. Soc.*, 1957, 3497.

2 (a) F. M. Dean and D. R. Randell, *J. Chem. Soc.*, 1961, 798; (b) F. M. Dean, S. Murray, and D. A. Smith, *J. Chem. Res.* 1977, (*S*), 230; (*M*), 2656.

3 T. Watamabe, S. Katayama, Y. Nakashita, and M. Yamauchi, *J. Chem. Soc., Chem. Commun.*, 1981, 761.

4 K. Fuji, T. Kawabata, and E. Fujuta, *Chem. Pharm. Bull.*, 1980, **28**, 3662.

5 (a) For ^1H n.m.r. spectrum of (**2a**) see ref. 2(a); (b) for ^{13}C n.m.r. spectrum of (**2a**) see I. Kurobane, C. R. Hutchinson, and L. C. Vining, *Tetrahedron Lett.*, 1981, **22**, 493.

6 For i.r. and u.v. spectra of (**1a**) see ref. 1(c); for ^{13}C n.m.r. spectrum of (**1a**) see ref. 5(b); for ^1H n.m.r. spectrum of (**1a**) see T. Sakai, A. Ichihara, and S. Sakamura, *Agric. Biol. Chem.*, 1981, **45**, 1275.