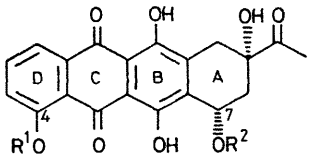
Synthetic Routes to (±)-Daunomycinone: Elaboration of the Hydroxy-ketone Group from an α-Tetralone Derivative, and Selective Methylation of the C(4)-Hydroxy Group Using Diazomethane

By ROBERT J. BLADE and PHILIP HODGE*
(*Chemistry Department, University of Lancaster, Lancaster* LA1 4YA)

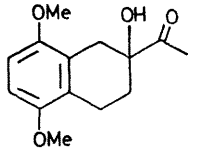
Summary A 12-step synthetic route to (±)-daunomycinone is described which uses Friedel–Crafts reactions to assemble the ring system; (−)-carminomycinone reacts with diazomethane to give (+)-daunomycinone.

THE clinically useful anti-tumour activity of daunomycin (**1**) has resulted in considerable interest in this and other anthracyclins.[1–3] The original synthesis of daunomycinone (**2**) assembled the tetracyclic ring system using Friedel–Crafts reactions and required 22 steps.[2] We report a related synthetic route which affords (±)-daunomycinone (**2**) in 12 steps, a length comparable with the shortest synthesis to date, which used quite a different synthetic route.[3] The reduction in length was achieved by procedures which may well find application in other anthracyclinone syntheses. These are: (i) improved synthetic routes to the hydroxy-ketone (**3**) including one in which the hydroxy-ketone function is elaborated from an α-tetralone, and (ii) the selective methylation of the C(4)-hydroxy group using diazomethane.

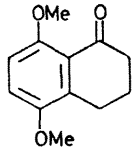
The hydroxy-ketone (**3**) was prepared by two routes, one involving the α-tetralone (**4**) (6 steps) and the other the β-tetralone (**5**) (5 steps). The α-tetralone (**4**) was obtained (45%) from 1,4-dimethoxybenzene by a Haworth-type sequence (succinic anhydride–$AlCl_3$; H_2–Pd; polyphosphoric acid).[4] Reaction of the α-tetralone (**4**) with acetic anhydride–BF_3 gave the diketone (**6**)† (90%) and this was selectively hydrogenolysed (H_2–Pd–H^+) to the ketone (**7**) (62%). Hydroxylation of the latter as previously described[5] gave the hydroxy-ketone (**3**) (86%). Elaboration of the hydroxy-ketone side chain from an α-tetralone has not previously been reported. α-Tetralone derivatives hold considerable promise as starting points for the elaboration of the various functions found in ring A of other anthracyclinones.[6]



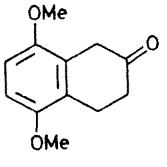
(1), R^1 = Me; R^2 = daunosamine
(2), R^1 = Me; R^2 = H
(12), R^1 = R^2 = H



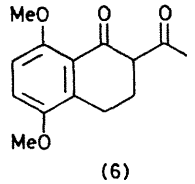
(3)



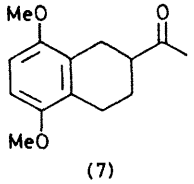
(4)



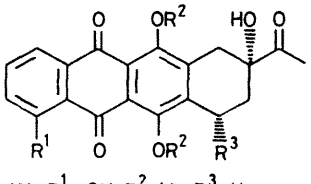
(5)



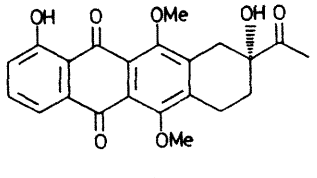
(6)



(7)



(8) R^1 = OH, R^2 = Me, R^3 = H
(10) R^1 = OH, R^2 = R^3 = H
(11) R^1 = OMe, R^2 = R^3 = H
(13) R^1 = R^2 = H, R^3 = OH
(14) R^1 = H, R^2 = Me, R^3 = H
(15) R^1 = R^2 = R^3 = H



(9)

† Satisfactory analyses and spectral data have been obtained for new compounds.

The β-tetralone (**5**) was prepared from the Diels–Alder adduct of benzoquinone and chloroprene‡ by a modification of the literature procedure (Me_2SO_4–K_2CO_3; conc. H_2SO_4).[7] Reaction of the β-tetralone (**5**) with ethynyl magnesium bromide and hydration (H_2O–H^+–Hg^{2+}) of the product† gave the hydroxy-ketone (**3**) in 35% overall yield.

Using the procedure outlined by Wong *et al.*[2] the hydroxy-ketone (**3**) was treated with 3-acetoxyphthalic acid half ester (mixture of isomers) and the product (38%) converted in two steps into a mixture of the dimethyl ethers (**8**) and (**9**) (87%). Demethylation of the mixture followed by preparative layer chromatography gave (±)-quinone (**10**) (37%), identified by comparison (i.r., u.v., and t.l.c.) with (−)-quinone (**10**) prepared[8] from daunomycin (**1**).

Selective methylation of the C(4)-hydroxy group of (±)-quinone (**10**) was achieved by treatment with an excess of diazomethane in methylene chloride at 20 °C. This gave (±)-7-deoxydaunomycinone (**11**) (60%), m.p. 228—230 °C (lit.[9] 229 °C), identified by comparison (i.r., u.v., ^1H n.m.r., and mass spectra and t.l.c.) with (−)-7-deoxydaunomycinone (**11**) obtained[10] from daunomycin (**1**). Compound (**11**) has been converted by Kende *et al.*[3] into (±)-daunomycinone (**2**) in two steps. The selective methylation appears to be a general reaction of ααʹα″-trihydroxyanthraquinones. Thus, 1,4,5-trihydroxyanthraquinone gives 5-methoxy-1,4-dihydroxyanthraquinone (60%), 1,2,5,8-tetrahydroxyanthraquinone gives 1,2-dimethoxy-5,8-dihydroxyanthraquinone (79%), and (+)-carminomycinone (**12**)[3,8] gives (+)-daunomycinone (**2**) (45%).

The shorter synthesis of the hydroxy-ketone (**3**) allows (±)-4-demethoxydaunomycinone (**13**) to be synthesised in 11 steps. Thus reaction of the hydroxy-ketone (**3**) with 2-methoxycarbonylbenzoyl chloride in the presence of $AlCl_3$, hydrolysis of the ester, and cyclisation of the acid with liquid HF gave the dimethyl ether (**14**) (40% overall yield). Demethylation ($AlCl_3$–PhH) gave the trihydroxyquinone (**15**) (60%), which has been converted into (±)-4-demethoxydaunomycinone (**13**) in two steps.[11]

We thank the S.R.C. for a grant, Dr. C. R. Harrison for experimental assistance, and Rhône-Poulenc and Farmitalia for daunomycin samples.

(*Received*, 10*th October* 1978; *Com.* 1090.)

‡ An intermediate in the commercial production of certain plastics.

[1] See L. H. Harwood, L. C. Hodgkinson, and J. K. Sutherland, *J.C.S. Chem. Comm.*, 1978, 712; A. S. Kende and Y-G. Tsay, *ibid.*, 1977, 140.
[2] C. M. Wong, R. Schwenk, D. Popien, and T-L. Ho, *Canad. J. Chem.*, 1973, **51**, 466.
[3] A. S. Kende, Y-G. Tsay, and J. E. Mills, *J. Amer. Chem. Soc.*, 1976, **98**, 1967.
[4] J. A. Moore and M. Rahm, *J. Org. Chem.*, 1961, **26**, 1109.
[5] C. M. Wong, D. Popien, R. Schwenk, and J. T. Raa, *Canad. J. Chem.*, 1971, **49**, 2712.
[6] R. H. Thomson, in 'Naturally Occurring Quinones,' Academic Press, London, 1971, Ch. 6.
[7] C. A. Grob and W. Jundt, *Helv. Chim. Acta*, 1952, **35**, 2111.
[8] M. C. Wani, H. L. Taylor, M. E. Wall, A. T. McPhail, and K. D. Onan, *J. Amer. Chem. Soc.*, 1975, **97**, 5955.
[9] R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, *Tetrahedron Letters*, 1976, 3385.
[10] T. H. Smith, A. N. Fujiwara, D. W. Henry, and W. W. Lee, *J. Amer. Chem. Soc.*, 1976, **98**, 1969.
[11] A. S. Kende, D. P. Curran, Y-G.Tsay, and J. E. Mills, *Tetrahedron Letters*, 1977, 3537.