A Regioselective Synthesis of 8,10-Dideoxycarminomycinone

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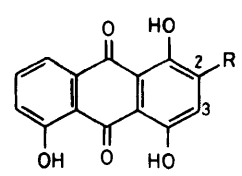
Summary A carminomycinone derivative has been synthesised from 5-hydroxyquinizarin and 2-methoxy-5-methyl-4-nitromethyltetrahydrofuran.

OVER the past few years there has been extensive synthetic work directed towards the synthesis of anthracyclinones and a number of elegant solutions to the regiochemical problem have been produced.[1] We chose the readily available 5-hydroxyquinizarin (**1**) as starting point, which required the development of methods for selective substitution at C-2 or C-3. We have shown that Marshalk (aldol) condensation of *leuco*-5-hydroxyquinizarin can be made selective for alkylation at C-2 or C-3 under differing conditions.[2] More recently we have established[3] that nitronate carbanions add with >95% selectivity to C-2 of compound (**1**). We have now used this selectivity for the synthesis of an anthracyclinone derivative.

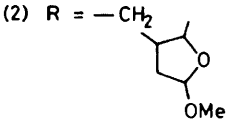
An appropriate nitro-compound (**9**) was synthesised from ethyl levulinate which was brominated (Br_2–CCl_4) and dehydrobrominated (Et_3N–CH_2Cl_2) to give (**5**). Reduction of (**5**) with $NaBH_4$–MeOH gave the alcohol (**6**) (82%) which underwent Michael addition[4] ($MeNO_2$–Triton B–Bu^tOH) and lactonisation *in situ* to form (**7**)† (79%) [ν_{max} 1770, 1545 cm^{-1}, τ 5·4 (1H, m), 5·50 (2H, d, J 6 Hz), and 8·60 (3H, pair d, J 6 and 7 Hz)]. Bu^i_2AlH–PhMe at −78 °C reduced the lactones (**7**) to the lactols (**8**)† which were converted (MeOH–H_2SO_4) into the ethers (**9**)† (55% overall) [ν_{max} 1550 cm^{-1}, τ 5·02 (1H, m), 5·3—5·8 (2H, m), 6·72 (3H, br.s), and 8·6—8·9 (3H, m)]. Refluxing a mixture of the quinone (**1**), ethers (**9**), and NaOMe (1 : 3 : 1·4) in MeOH gave the substitution products (**2**)† (65%) [τ 6·62(s), 6·64(s), 6·66(s), and 6·69(s) (1 : 3 : 2·5 : 3); ratio Ar*H* : OC*H*$_3$ 4 : 3]. Hydrolysis of (**2**) (1N HCl–dimethoxyethane) yielded the lactols‡ (**3**)† (85%) which were reduced and the *leuco*-derivatives were cyclised ($Na_2S_2O_4$–1% NaOH, 90 °C) to the alcohols (**10**)† (65%) [τ 2·12 (1H, dd, J 7 and 2 Hz), 2·35 (1H, t, J 7 Hz), 2·75 (1H, dd, J 7 and 2 Hz), and 8·67 (3H, d, J 6 Hz)]. Pyridinium chlorochromate[5] oxidized (**10**) to the ketone[1c] (**11**) (67%) [ν_{max} 1705 cm^{-1}; τ 2·12 (1H, dd, J 7 and 2 Hz), 2·35 (1H, t, J 7 Hz), 2·70 (1H,dd, J 7 and 2 Hz), and 7·70 (3H,s)]. The structure of (**11**) was shown to be 8,10-dideoxycarminomycinone by conversion into the daunomycinone derivative (**12**) with

† Mixture of diastereoisomers.

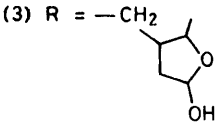
‡ This compound was characterised by oxidation to the γ-lactones (**4**).



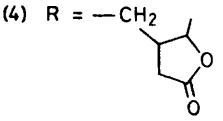
(1) R = H



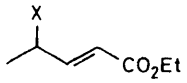
(2) R = —CH$_2$



(3) R = —CH$_2$

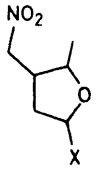


(4) R = —CH$_2$



(5) X = =O

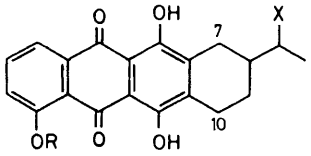
(6) X = H,OH



(7) X = =O

(8) X = H,OH

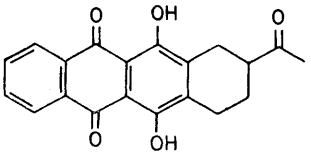
(9) X = H,OMe



(10) R = H, X = H,OH

(11) R = H, X = =O

(12) R = Me, X = =O



(13)

CH_2N_2–CH_2Cl_2[6] (32% yield on 52% conversion)§ or by trimethylation (MeI–K_2CO_3–Me_2CO) followed by silver(II) oxide cleavage[7] (24% overall). The ether (**12**) was shown to be identical to an authentic sample[1b,c] by usual criteria; in particular we were unable to detect any of the regioisomer which has an n.m.r. spectrum distinctive from that of (**12**).

When the same sequence of reactions is carried out using quinizarin as starting material the deoxy-compound (**13**) can be prepared efficiently (27% overall yield).

Reaction of the nitrolactones (**7**) with (**1**) and NaOMe–MeOH gave the lactones (**4**)† (8%) [ν_{max} 1770 cm^{-1}; τ 2·17 (1H,dd, J 7 and 2 Hz), 2·29 (1H,t, J 7 Hz), 2·65 (1H,dd, J 7 and 2 Hz), 2·85 (1H,s), 5·35 (1H,m), 8·60 ($\frac{3}{2}$H,d, J 7 Hz), and 8·72 ($\frac{3}{2}$H,d, J 7 Hz)]; a control experiment established that the low yield was due to destruction of (**7**) under the reaction conditions. In principle the nitrolactols (**8**) could react with (**1**) by the sequence Michael addition, aldol cyclisation of the *leuco*-adduct, and elimination of nitrite to give the 7-hydroxy-derivatives of (**10**). In practice reaction of (**1**) and (**8**) in NaOMe–MeOH gave the lactols (**3**) (7%), the ethers (**2**) (2%), and an ether (2%) which on reduction ($Na_2S_2O_4$) yields the alcohol (**10**).¶ From this it would appear that, under our conditions, elimination of nitrite is faster than aldol condensation. Compounds (**3**) and (**8**) gave satisfactory accurate mass measurements. All other new compounds gave satisfactory combustion analyses.

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§ Another monomethyl ether (16%) was isolated. Since it shows only hydrogen-bonded quinone carbonyl absorption in the i.r. it is assumed to be the 6-methoxy-compound.

¶ This result suggests that the other ether terminus is at C-7 or C-10.

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