

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.

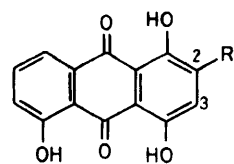
OVER the past few years there has been extensive synthetic work directed towards the synthesis of anthracyclonones and a number of elegant solutions to the regiochemical problem have been produced.¹ We chose the readily available 5-hydroxyquinizarin (**1**) as starting point, which required the development 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 established³ that nitronate carbanions add with >95% selectivity to C-2 of compound (**1**). We have now used this selectivity for the synthesis of an anthracyclonone derivative.

An appropriate nitro-compound (**9**) was synthesised from ethyl levulinate which was brominated ($\text{Br}_2\text{-CCl}_4$) and dehydrobrominated ($\text{Et}_3\text{N-CH}_2\text{Cl}_2$) to give (**5**). Reduction of (**5**) with $\text{NaBH}_4\text{-MeOH}$ gave the alcohol (**6**) (82%)

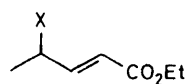
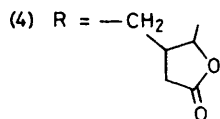
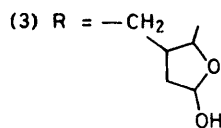
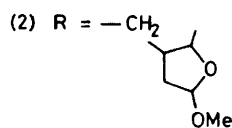
which underwent Michael addition⁴ ($\text{MeNO}_2\text{-Triton B-Bu}^t\text{OH}$) and lactonisation *in situ* to form (**7**)† (79%) [ν_{max} 1770, 1545 cm^{-1} , τ 5.4 (1H, m), 5.50 (2H, d, J 6 Hz), and 8.60 (3H, pair d, J 6 and 7 Hz)]. $\text{Bu}^t_2\text{AlH-PhMe}$ at -78°C reduced the lactones (**7**) to the lactols (**8**)† which were converted ($\text{MeOH-H}_2\text{SO}_4$) 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 ArH:OCH_3 4:3]. Hydrolysis of (**2**) (1N $\text{HCl-dimethoxyethane}$) yielded the lactols‡ (**3**)† (85%) which were reduced and the *leuco*-derivatives were cyclised ($\text{Na}_2\text{S}_2\text{O}_4\text{-1\% NaOH}$, 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 chlorochromate⁵ 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**).

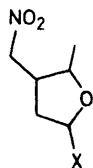


(1) R = H



(5) X = =O

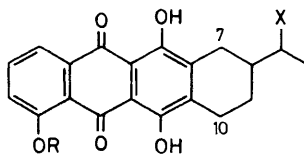
(6) X = H,OH



(7) X = =O

(8) X = H,OH

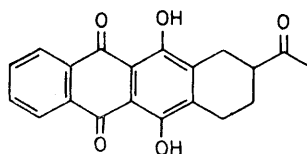
(9) X = H,OMe



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

(11) R = H, X = =O

(12) R = Me, X = =O



(13)

$\text{CH}_2\text{N}_2\text{-CH}_2\text{Cl}_2$ (32% yield on 52% conversion)[§] or by trimethylation ($\text{MeI-K}_2\text{CO}_3\text{-Me}_2\text{CO}$) followed by silver(II) oxide cleavage⁷ (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 ($\frac{3}{2}\text{H,d}$, J 7 Hz), and 8.72 ($\frac{3}{2}\text{H,d}$, 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 ($\text{Na}_2\text{S}_2\text{O}_4$) 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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