Synthetic Anthracyclines: Regiospecific Total Synthesis of a *D*-Ring Pyridine Analogue of 11-Deoxydaunomycin

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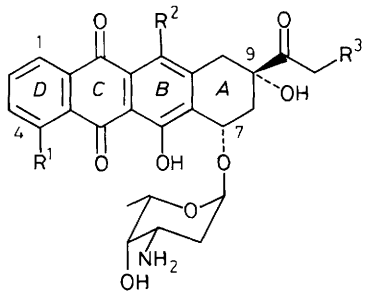
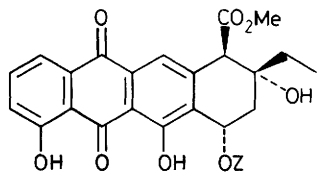
The strong base-induced cycloaddition of 6-ethynyl-6-hydroxy-5,6,7,8-tetrahydrohomophthalic anhydride (**10**) to 5,8-dihydro-5,8-dioxoquinoline (**11**) constitutes a regiospecific and efficient route to the *D*-ring pyridine analogue (**5**) of 11-deoxydaunomycin (**2a**).

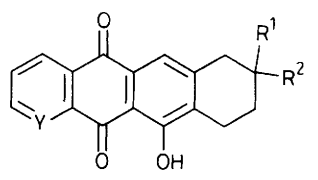
The anthracycline antibiotics such as daunomycin (**1a**) and adriamycin (**1b**) have a wide spectrum of antitumour activity but are cardiotoxic and cause bone marrow depression.[1] It is suggested that the antitumour activity and cardiotoxicity are caused by reactive oxygen species such as $O_2^{\cdot -}$, H_2O_2, and $OH^{\cdot}$, which are formed by a cyclic redox reaction of anthracyclines.[2] The *C*-ring quinone moiety of anthracyclines plays an important role in the redox reaction and modification of the chromophore is expected to affect the *C*-ring quinone moiety. As part of our continuing studies on synthetic



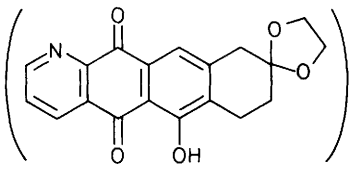
(1)a; R^1 = OMe, R^2 = OH, R^3 = H
b; R^1 = OMe, R^2 = R^3 = OH
(2)a; R^1 = OMe, R^2 = R^3 = H
b; R^1 = R^2 = R^3 = H



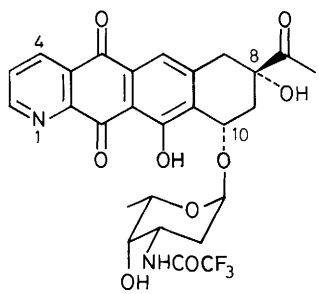
(2c), (2d); z = sugars



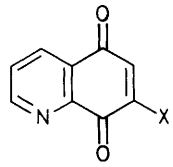
(3); R^1, R^2 = $O(CH_2)_2O$, Y = N
(4); R^1 = C≡CH, R^2 = OH, Y = N
(6); R^1, R^2 = $O(CH_2)_2O$, Y = CH
(7); R^1 = C≡CH, R^2 = OH, Y = CH



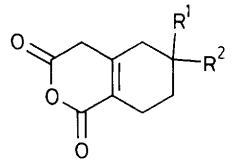
(3′)



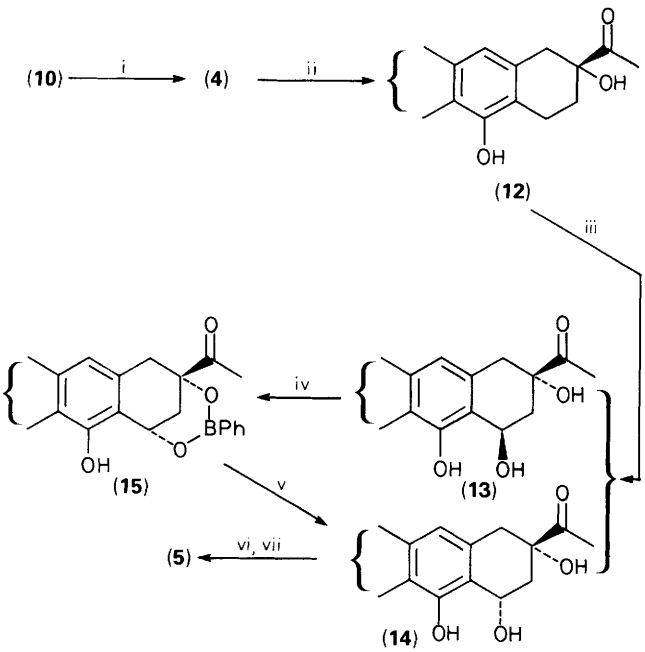
(5)



(8)a; X = Cl
b; X = Br
(11); X = H



(9); R^1, R^2 = $O(CH_2)_2O$
(10); R^1 = C≡CH, R^2 = OH



Scheme 1. *Reagents and conditions:* i, NaH (1.0 equiv.), (**11**), tetrahydrofuran (THF), room temp., 4 h; ii, HgO–dil.H_2SO_4, THF, 70 °C, 1.5 h; iii, Br_2–AIBN, H_2O–CCl_4–$CHCl_3$, room temp., 4 h; iv, PhB $(OH)_2$ (3.0 equiv.), CF_3CO_2H, toluene, room temp., 5 days; v, 2-methylpentane-2,4-diol, AcOH, CH_2Cl_2–acetone, room temp., 12 h; vi, 2,3,6-trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-lyxopyranose (**16**) (1.3 equiv.), $CF_3SO_3SiMe_3$, molecular sieves 4 Å, CH_2Cl_2–Et_2O, −15 °C, 4 h; vii, 0.1 M NaOH–MeOH, 0 °C, 30 min.

anthracyclines,[3] we have recently reported a total synthesis of the *D*-ring indole[4] and thiophene analogues[5] of (**1a**), which showed inhibition activity against L-1210 cell growth (*in vitro*) comparable to that of (**1a**). Furthermore, recently developed 11-deoxyanthracyclines such as 11-deoxydaunomycin (**2a**), 4-demethoxy-11-deoxydaunomycin (**2b**), aclacinomycin A (**2c**), and aklavin (**2d**) show stronger antineoplastic activity and/or less cardiotoxicity than the older established agents,[6,7] so that our attention has been focused on synthesis of *D*-ring hetero analogues of 11-deoxydaunomycin (**2a**). The present paper describes the first regiospecific total synthesis of a *D*-ring pyridine analogue of (**2a**).

We first investigated an effective synthesis of the pivotal intermediates (**3**) and (**4**) for the *D*-ring pyridine analogue (**5**), since 11-deoxydaunomycin (**2a**) could be synthesised from the similar key intermediates (**6**) and (**7**).[7] Initial attempts to obtain the key intermediates (**3**) and (**4**) by a similar method to that for (**6**) and (**7**) failed, probably owing to the instability of the 7-halogeno-5,8-dihydro-5,8-dioxoquinolines (**8a,b**) under the strongly basic conditions. Thus, treatment of the sodium salt generated from suitably functionalised tetrahydrohomophthalic anhydrides (**9**) and (**10**) with the halogenoquinones (**8a,b**) gave complex mixtures instantly. However, the use of the unsubstituted quinone (**11**) instead of (**8**) caused cycloaddition to the anhydride (**9**) to give a single cycloadduct (**3**) or (**3′**) (62% yield, m.p. 223—225 °C), regioselectively. It was difficult to determine that the structure of the adduct is (**3**) [not the regioisomer (**3′**)] from the normal spectral data. The problem could be resolved by the help of ^{13}C–^1H long-range selective proton decoupling (LSPD method) and also by *X*-ray analysis.† Similarly, reaction of the sodium salt generated from compound (**10**) with (**11**) regiospecifically gave the cycloadduct (**4**) (60% yield), which was identical with the compound obtained from (**3**) by hydrolysis with trifluoroacetic acid followed by ethynylation using trimethylsilylethynylcerium(III) chloride.[7,8]

The synthesis of (**5**) from (**10**) is outlined in Scheme 1. Treatment of (**4**) with HgO–dil.H_2SO_4 gave the α-hydroxyketone (**12**) (98% yield, m.p. 177—180 °C). Hydroxylation of

† The detailed discussion of the LSPD method and *X*-ray analysis will be described in a forthcoming full paper.

(**12**) with Br_2 in the presence of 2,2'-azoisobutyronitrile (AIBN) at the benzylic position gave a mixture of the *trans*-diol (**13**) and the *cis*-diol (**14**) (*trans* : *cis* 4 : 1, 79% yield). The *trans*-diol (**13**) was epimerised to (**14**) [86% yield, m.p. 218 °C (decomp.)]‡ *via* the *cis*-boronate intermediate (**15**).[9] Condensation of (**14**) with the appropriately protected daunosamine (**16**), under the conditions developed by Terashima *et al.*,[10] followed by base hydrolysis gave the desired α-glycoside (**5**) as an inseparable mixture of two diastereoisomers [52% yield based on (**14**)]. The preparation of other *D*-ring hetero-11-deoxyanthracyclines by the use of this synthetic method and biological testing are in progress.

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‡ *Spectroscopic data* for (**14**): IR ($CHCl_3$) 1720 and 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (1H, dd, *J* 15, 5 Hz, H-9), 2.39 (1H, dt, *J* 15, 5 Hz, H-9), 2.43 (3H, s, COMe), 3.05 (1H, dd, *J* 17.5, 2 Hz, H-7), 3.31 (1H, d, *J* 17.5 Hz, H-7), 5.40 (1H, m, $\nu_{1/2}$ 11 Hz, H-10), 7.69 (1H, s, H-6), 7.77 (1H, dd, *J* 8, 5 Hz, H-3), 8.63 (1H, dd, *J* 8, 1.5 Hz, H-4), 9.14 (1H, dd, *J* 5, 1.5 Hz, H-2), and 13.21 (1H, s, 11-OH). High resolution MS: found M^+, *m/z* 353.0898; $C_{19}H_{15}NO_6$ requires 353.0898.