Total Synthesis of a D-Ring Indole Analogue of Daunomycin

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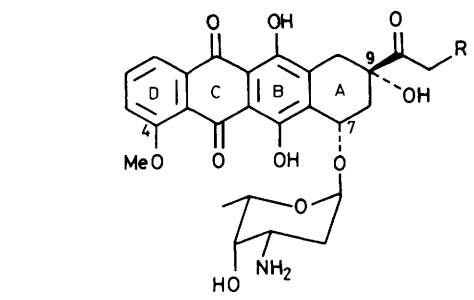
The strong base-induced cycloaddition of 4-methoxy-5-methylpyrano[4,3-*b*]indole-1,3(4*H*,5*H*)-dione (**3a**) to 2-chloro-6-oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone ethylene acetal (**4**) constitutes a regiospecific and convenient route to the D-ring indole analogue (**2**) of daunomycin.

The anthracycline antibiotics such as daunomycin (**1a**) or adriamycin (**1b**) have a wide spectrum of antitumour activity but are cardiotoxic and cause bone marrow depression.[1] There is therefore interest in the synthesis of compounds related to (**1a,b**) but possessing reduced side effects. Some progress has been made by a structural modification of the chromophore in a series of daunomycin derivatives.† Since removal of the C-4 methoxy moiety of anthracyclines is associated with enhanced potency[1,2] and heterocyclic rings can often provide useful isosteric replacement of the benzene ring in some drugs,[3] it is interesting to synthesize anthracycline analogues of (**1a,b**) in which the D-ring is heterocyclic.[4]

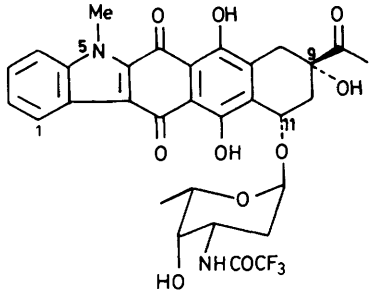
† Some 4-demethoxy- or/and 11-deoxydaunomycines are found to be much more potent than the ordinary anthracyclines.[1]

We now report the first total synthesis of the D-ring indole analogue (**2**) of (**1a**) *via* a strong base-induced cycloaddition of hetero-fused pyran-diones recently developed by our group.[5] Key features of the sequence include good control of regiochemistry and ready availability of the *para*-oxidised pentacyclic intermediate (**5a**; R = OMe) by the cycloaddition of (**3a**; R = OMe) to the chloroquinone acetal (**4**).

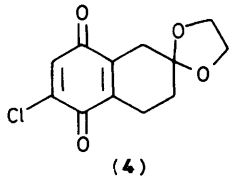
Initial attempts to obtain the key intermediate (**5b**; R = OAc) failed, probably owing to the instability of the indole nucleus. Thus, *para*-oxidation of the known tetracyclic compound (**6**)[6] with lead tetra-acetate (LTA) did not give (**5b**) and an attempt to prepare (**3b**; R = OAc) by LTA-oxidation of the ketene silyl acetal intermediate generated from (**7**) followed by dehydration also failed,[7] After many unsuccessful attempts, the useful anhydride (**3a**) was obtained by hypervalent iodine oxidation of (**8**).



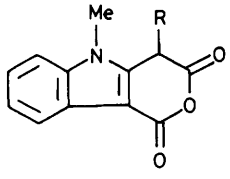
(1) a; R = H
b; R = OH



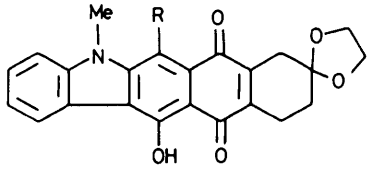
(2)



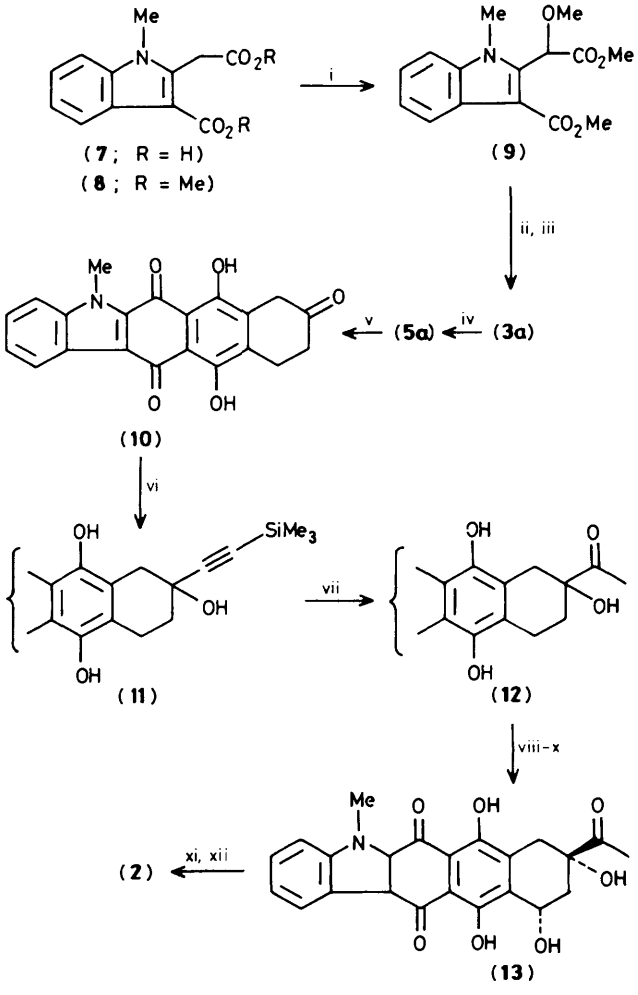
(4)



(3) a; R = OMe
b; R = OAc
c; R = H



(5) a; R = OMe
b; R = OAc
(6) R = H



Scheme 1. *Reagents:* i, $PhI(OAc)_2$ (1.3 equiv.), KOH–MeOH, room temp., 3 days; ii, KOH, aq. EtOH, reflux, 2 h; iii, (trimethylsilyl)-ethoxyacetylene (2 equiv.), $ClCH_2CH_2Cl$, room temp., 2 days; iv, NaH (1.1 equiv.), (4), tetrahydrofuran (THF), room temp., 5 h; v, CF_3CO_2H–H_2O, 50 °C, 1.5 h; vi, trimethylsilylethynylcerium(III) chloride (20 equiv.), THF, −78 °C, 2 h; vii, HgO–d.H_2SO_4, THF, 70 °C, 1.5 h: viii, ethylene glycol–*p*-$MeC_6H_4SO_3H$, C_6H_6, reflux, 3 h; ix, Br_2–AIBN (AIBN = azobisisobutyronitrile), H_2O–CCl_4–$CHCl_3$, reflux, 5 h; x, CF_3CO_2H–H_2O, 0 °C, 1 h; xi, 2,3,6-trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-L-lyxopyranose (1.3 equiv.), $CF_3SO_3SiMe_3$, molecular sieves 4A, CH_2Cl_2–Et_2O, −15 °C, 6.5 h; xii, 0.1 M NaOH–MeOH, 0 °C, 30 min.

The sequence for synthesising (2) from (8) is outlined in Scheme 1. Treatment of (8) with the hypervalent reagent, diacetoxyiodobenzene [$PhI(OAc)_2$][8] gave the 2-methoxy ester (9) (37% yield). Saponification of (9) followed by dehydration with (trimethylsilyl)ethoxyacetylene[9] gave the anhydride (3a) (86% yield). Reaction of the sodium salt generated from (3a) and the chloroquinone acetal (4) regiospecifically gave the cycloadduct (5a) (57% yield).‡ Acid hydrolysis of both methoxy and acetal groups of (5a) with aqueous trifluoroacetic acid gave the triketone (10) (81% yield). Side chain elaboration of the enolizable 9-keto group of (10) was accomplished by the use of trimethylsilylethynylcerium(III) chloride[10] giving the alcohol (11) (67% yield), which was directly converted into the α-hydroxyketone (12) (89% yield). Acetalisation of (12), followed by hydroxylation at the benzylic position by the standard procedure,[11] gave the desired aglycone (13) (22% yield, m.p. 110—116 °C). Condensation of (13) with the appropriately protected daunosamine (14), under the reaction conditions developed by Terashima *et al.*,[12] gave a 2:3 mixture of diastereoisomeric α-glycosides. Separation of the glycosides by preparative t.l.c. on silica gel followed by base hydrolysis provided the pure natural-type (9*S*, 11*S*)-α-glycoside (2) [24% yield based on

‡ The cycloaddition of (3a) was shown to proceed with the same regiochemistry as that of the parent anhydride (3c) in the reaction with 3-bromo-5-hydroxy-1,4-naphthoquinone.

(**13**), m.p. 114—118 °C, $[\alpha]_D^{25}$ + 37° (c 0.15, $CHCl_3$), $[\theta]_{320\ max}$ -1.4×10^3 (EtOH), mass spectrum (fast-atom bombardment), *m/z* 645 $(M - 1)^-$]. The stereochemistry of the glycoside linkage was determined from its 500 MHz n.m.r. and c.d. spectral data.

The D-ring indole analogue (**2**) shows inhibition activity against L-1210 cell growth (*in vitro*) comparable to that of (**1b**).

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