A Regiospecific and Flexible Approach for the Synthesis of (±)-Daunomycinone and (±)-11-Deoxydaunomycinone

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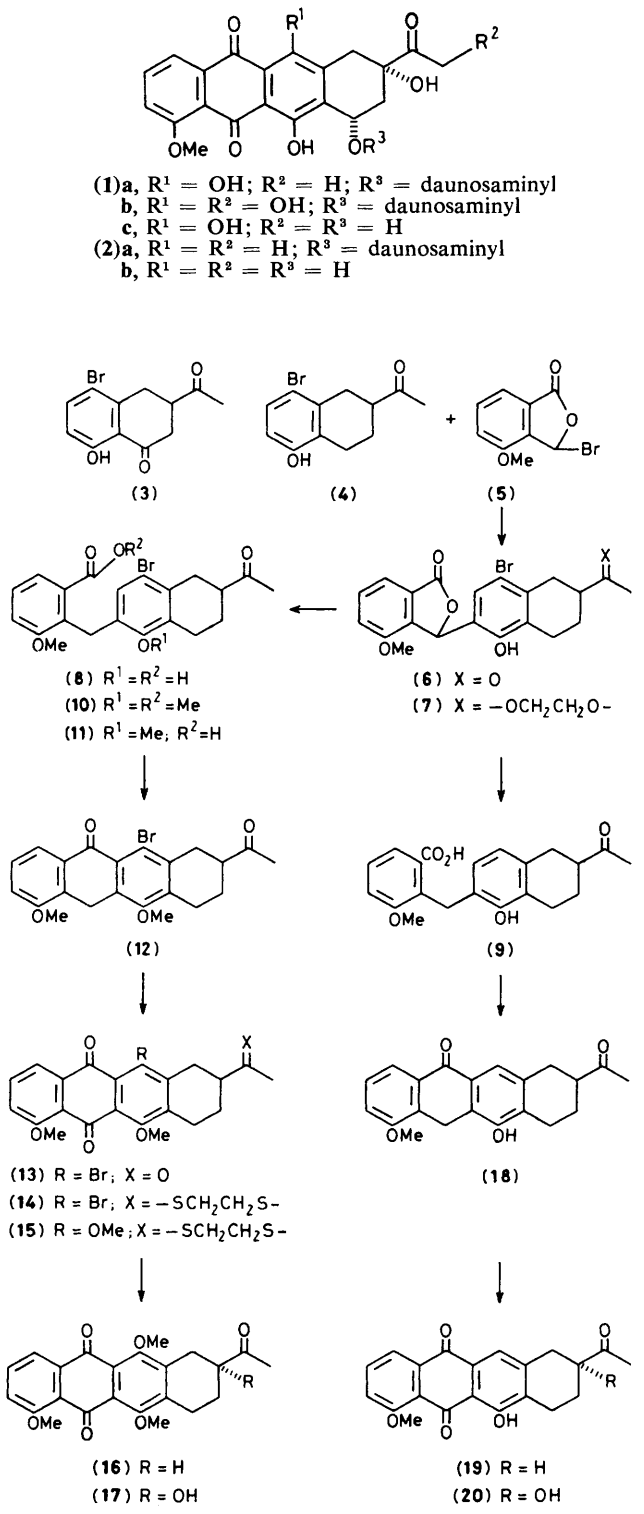
A flexible and regiospecific synthesis of (±)-daunomycinone and (±)-11-deoxydaunomycinone is described starting from a common synthon, 2-acetyl-8-bromo-5-hydroxy-1,2,3,4-tetrahydronaphthalene-4-one.

The clinical efficacy of daunomycin (**1a**) and adriamycin (**1b**) in the treatment of human tumours has stimulated the search for improved anthracycline antibiotics with better therapeutic indices, and has resulted in the isolation of 11-deoxydaunomycin (**2a**).[1] Novel methods of synthesis of these and other related aglycones directly involved in the intercalation process



Scheme 1

with DNA have led to a regiospecific synthesis of (±)-daunomycinone (**1c**)[2] and (±)-11-deoxydaunomycinone (**2b**)[3] but their large-scale synthesis may prove to be uneconomic. We report here an expeditious, regiospecific, and flexible approach to both (±)-daunomycinone (**1c**) and (±)-11-deoxydaunomycinone (**2b**), which is sufficiently versatile for the synthesis of other analogues. This method is conceptually different from previous approaches and does not involve expensive reagents and reactions which are difficult to scale-up.

Our strategy makes use of the key synthon (**3**) which was reported recently by us in a seven-step synthesis from *m*-cresol[3d] to give the desired daunomycinone and 11-deoxydaunomycinone (Scheme 1).

The requisite AB synthon (**3**) was converted into the acetyl compound (**4**)† (m.p. 131 °C, 90% yield) by protecting the acetyl carbonyl group (ethylene glycol, toluene-*p*-sulphonic acid, C_6H_6, reflux 6 h), followed by Wolff–Kishner reduction ($H_2NNH_2{\cdot}H_2O$, KOH, 160—165 °C, 4 h; acid work-up). Condensation of (**4**) with 3-bromo-4-methoxyphthalide (**5**)[4] ($SnCl_4$, CH_2Cl_2, room temp., 4 h) resulted in the formation of (**6**)† in 85% yield (m.p. 142—143 °C, decomp.). The ethylene acetal (**7**) [prepared from (**6**) in 95% yield] was reduced with zinc dust in ethanolic KOH (20%, 80 °C, 4.5 h; acid work-up) to the bromo-acid (**8**) (75%). Alternatively, heating (**7**) with zinc dust in aqueous KOH (20%, 100 °C, 6 h; acid work-up) gave (**9**) (70%, m.p. 156—157 °C). Compound (**8**) was used in the synthesis of (±)-daunomycinone (**1c**), while (**9**) was utilised for (±)-11-deoxydaunomycinone (**2b**) (Scheme 1).

The bromo-acid (**8**) was permethylated (Me_2SO_4, K_2CO_3, acetone) to give (**10**), which was hydrolysed to give (**11**) (83%, m.p. 200—201 °C). Compound (**11**) was cyclised by treatment with $(CF_3CO)_2O$ in CH_2Cl_2 at room temp. for 12 h to give the anthrone (**12**) (80%, m.p. 154—155 °C). Oxidation of (**12**) (Jones reagent, acetone, room temp., 2 h) gave (**13**)† (65%, m.p. 181—182 °C). The acetyl carbonyl group in (**13**) was protected ($HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, $CHCl_3$, room temp., 1 h) to afford (**14**) (90%, m.p. 223—225 °C), which was converted into (**15**) by displacing the bromine by a methoxy-group (NaOMe–pyridine–Cu_2Cl_2, room temp., 6 h). Dethioacetalization of (**15**) [$HgCl_2$–HgO, aq. MeCN (80%), reflux, 1 h] and chromatographic purification of the products (silica gel, benzene) resulted in the isolation of orange crystals of 7,9-dideoxydaunomycinone dimethyl ether (**16**)† [55% from (**13**), m.p. 185—186 °C], which was identical with the product prepared by a different procedure.[5] Conversion of (**16**) into 7-deoxydaunomycinone dimethyl ether (**17**) and subsequently into (±)-daunomycinone (**1c**) has been reported by many groups.[6]

The acid (**9**) was converted into (±)-11-deoxydaunomycinone (**2b**) by the following sequence of reactions. Cyclisation of (**9**) (HF, 5—10 °C, 4 h) afforded the anthrone (**18**)† (75%, m.p. 204 °C). Oxidation of (**18**) (Jones reagent, acetone, room temp., 0.5 h) led to the tetrahydronaphthecene quinone (**19**)† (70%, m.p. 224—226 °C). Hydroxylation of the tertiary carbon (C-9) to give (**20**) as orange plates, m.p. 209—211 °C (lit.[3b] m.p. 210—211 °C), was accomplished by the standard procedure adopted by Sih *et al.*[2a] The conversion of (**20**) into (±)-11-deoxydaunomycinone (**2b**) has been reported.[3a,e]

Our work represents a flexible, yet simple, synthesis of (±)-daunomycinone and (±)-11-deoxydaunomycinone.

† All compounds gave satisfactory elemental analyses and spectroscopic data; ^{1}H n.m.r.: δ(CD_3COCD_3), (**6**), 1.83 (m, 2H), 2.23 (s, 3H), 2.87 (m, 5H), 3.86 (s, 3H), 6.60 (s, 1H), 6.66 (s, 1H), and 7.20—7.73 (m, 3H); (**13**), 1.73 (m, 2H), 2.26 (s, 3H), 2.73—3.13 (m, 5H), 3.93 (s, 3H), 4.06 (s, 3H), and 7.23—7.73 (m, 3H); (**16**), 1.83 (m, 2H), 2.26 (s, 3H), 2.73—3.23 (m, 5H), 3.86 (s, 3H), 3.90 (s, 3H), 4.03 (s, 3H), and 7.20—7.77 (m, 3H); (**18**), 1.93 (m, 2H), 2.27 (s, 3H), 2.91 (m, 5H), 4.00 (br. s, 5H, OMe and anthrone CH_2), 5.06 (s, 1H, OH), 7.10 (dd, *J* 8 and 1.5 Hz, 1H), 7.44 (t, 1H), 7.82 (s, 1H), and 7.94 (dd, *J* 8 and 1.5 Hz, 1H); (**19**), 1.80 (br. s, 2H), 2.26 (s, 3H), 2.53—2.97 (m, 5H), 4.10 (s, 3H), 7.30 (dd, *J* 8 and 1.5 Hz, 1H), 7.43 (s, 1H), 7.73 (t, 1H), 7.93 (dd, *J* 8 and 1.5 Hz, 1H), and 13.37 (s, 1H, OH).

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