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A SIMPLE AND REGIOSPECIFIC SYNTHESIS OF (±) 11-DEOXYDAUNOMYCINONE

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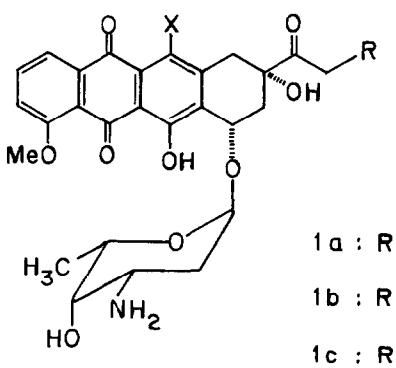
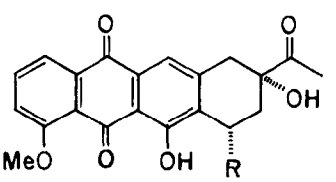
A convenient method for the synthesis of 11-deoxyanthracyclinones is described.

The anthracycline antibiotics, daunomycin (1a) and adriamycin (1b) have enjoyed clinical effectiveness in the treatment of a wide variety of human cancers.[1] However, their main disadvantage of having irreversible cardiomyopathy[2] have prompted the search for new compounds that show decreased side effects and/or increased antitumor activity. This has resulted in the isolation of new anthracycline antibiotics lacking a hydroxyl group at 11-position [11-deoxydaunomycin (1c) and 11-deoxyadriamycin (1d) etc.] having better therapeutic index than daunomycin and adriamycin.[3] Although many elegant approaches for the total synthesis of the aglycones of daunomycin and its 4-demethoxy analogue have been developed,[4] only two recent reports have appeared on the synthesis of 7,11-dideoxydaunomycinone (2a)[5] and 11-deoxydaunomycinone (2b)[6] respectively. Recently we have communicated a general regiospecific synthesis of 11-deoxyanthracyclinones involving the Diels-Alder reaction,[7] and now we report a simple and more practical approach for the large scale preparation of 11-deoxyanthracyclinones.



1a : R=H; X=OH
1b : R=X=OH
1c : R=X=H
1d : R=OH; X=H



2a: R = H
2b: R = OH

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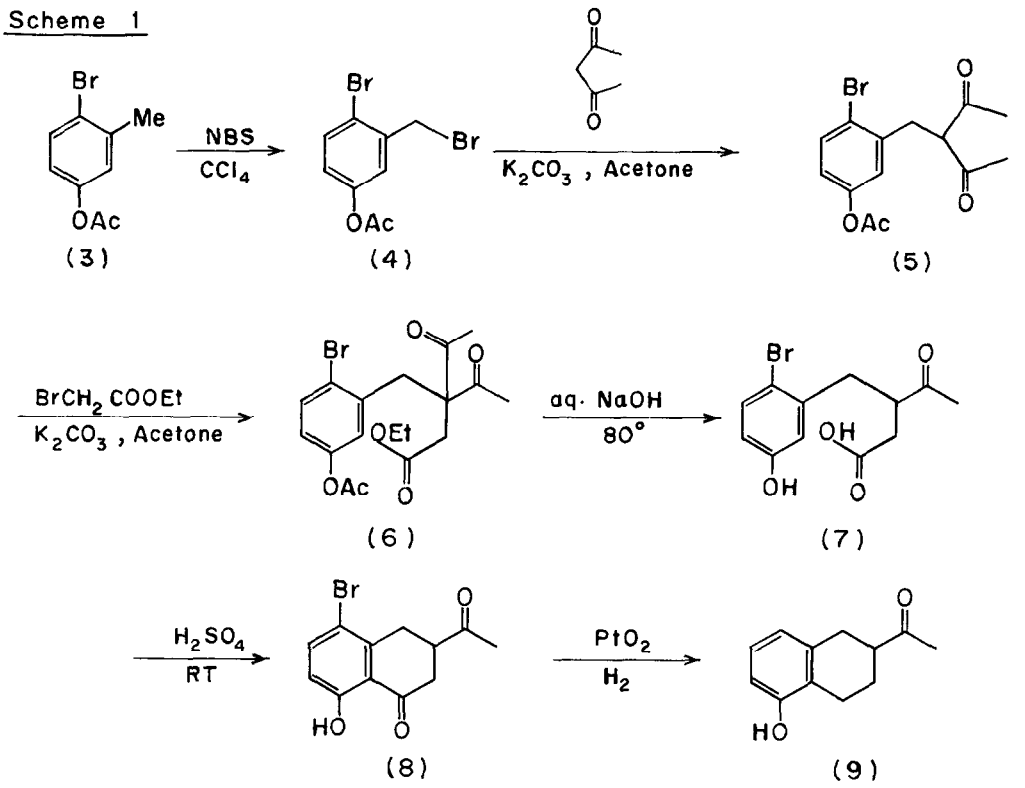
Our present synthetic strategy centered upon the concept of constructing AB ring, utilizing inexpensive intermediates and reagents and condensing a D-ring unit to form the anthracyclinone system (11), which can be transformed to (±) 11-deoxydaunomycinone (2b).

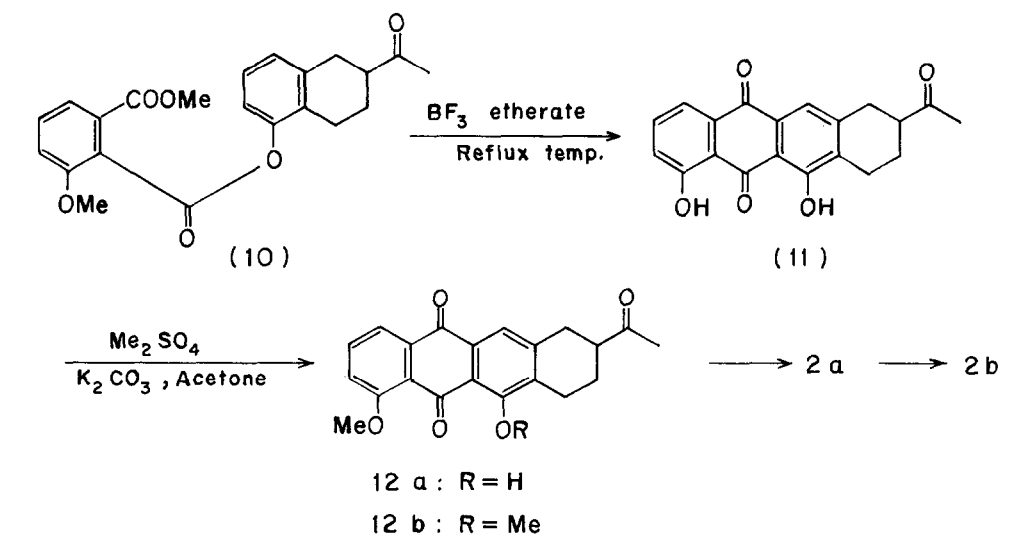
The requisite AB synthon (9) is made from m-cresol in eight steps as shown in scheme 1. 4-Bromo-m-cresol[8] is acetylated (Ac_2O, pyridine, RT) to give 3, which is then brominated (NBS, CCl_4, 6 hr, reflux) to afford 3-acetoxy-6-bromobenzyl bromide (4) in 80% yield. Condensation of 4 with acetyl acetone in presence of potassium carbonate in acetone at room temp (48 hr) gave 5 in 70% yield.[9] [m.p. 114-115°, PMR 2.00 (s, 6H, 2Ac), 2.20 (s, 3H, OAc), 3.6 (d, 2H, $ArCH_2$), 6.6 to 7.5 (m, 3H, Ar-H)]. Alkylation of 5 with ethyl bromoacetate (K_2CO_3, Acetone, RT) gave 6 in 75% yield [m.p. 68-69°, PMR 1.20 (t, 3H, $CH_2\underline{CH_3}$), 2.10 (s, 6H, 2Ac), 2.26 (s, 3H, OAc), 2.90 (s, 2H, CH_2-), 3.50 (s,2H, $ArCH_2$), 4.00 (q, 2H, $O\underline{CH_2}$-CH_3), 6.70-7.4 (m, 3H, ArH)]. Saponification (10% NaOH 80°, 6hr) of 6 followed by acidification afforded the desired acid 7 (m.p. 144°), which on treatment with conc. H_2SO_4 at room temperature is smoothly converted to 2-acetyl-8-bromo-5-hydroxy-1,2,3,4-tetrahydro-4-naphthelenone (8) in 75% yield [m.p. 108-109°; PMR 2.2 (s, 3H, Ac), 2.7 to 3.2 (m, 5H, $(CH_2)_2$ and CH), 6.8 (d, J=8 Hz,6-H), 7.4 (d, J=8 Hz, 7-H), 12.76 (s, 1H, OH)][10]. Hydrogenation of 8 (PtO_2, EtOH, 6 hr, RT) afforded 2-acetyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene 9 in 60% yield together with a small quantity of the corresponding α-hydroxyethyl tetralin.

Condensation of 2-carbomethoxy-6-methoxy-benzoyl chloride (prepared from 3-methoxyphthalic acid-1-methyl ester[11] with $SOCl_2$ and catalyst DMF) with 9 (pyridine, benzene, 6 hr, RT) gave the benzoyl ester (10) in 80% yield (m.p. 125-26°). Fries rearrangement of the ester 10 by subjecting it in BF_3-etherate at reflux temp for 20 min afforded directly 9,-11-dideoxycarminomycinone (11) in 40% yield after purification over silica gel column [orange crystals, m.p. 238-41°; IR(nujol) 1700, 1680, 1630 cm^{-1}. PMR 1.97 (m, 2H, $-CH_2$-), 2.27 (s, 3H, $COCH_3$), 2.7-3.1 (m, 5H), 7.3-7.9 (m, 4H, Ar-H), 12.77 and 12.93 (2s, chelated OH). Methylation of 11 (DMS 1.5 eq., K_2CO_3, Acetone) gave a mixture (1:1) of mono and dimethyl ethers (12a and 12b) together with trace quantities of the starting material,

Scheme 1



Scheme 2



12 a : R = H

12 b : R = Me

and were separated by silica gel chromatography (solvent Benzene-acetone). [12a: PMR 1.80 (s, 2H, $-CH_2-$), 2.31 (s, 3H, Ac), 2.29 (m, 1H), 2.8-3.1 (m, 4H), 4.10 (s, 3H, OMe), 7.26-8.05 (m, 4H, ArH), 13.37 (s, 1H, OH). 12b: PMR 1.8 (m, 2H, CH_2), 2.27 (s, 3H, Ac), 2.3 (m, 1H), 2.7 to 3.1 (m, 4H), 3.9 (s, 3H, OMe), 4.1 (s, 3H, OMe), 7.20-8.0 (m, 4H, ArH)].

As the conversion of 12a to 11-deoxydaunomycinone (2b) has already been described,[6] we consider that our present approach can in effect constitute a total synthesis of 2b.[12]

References and Notes

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9. All compounds gave satisfactory elemental analysis and spectroscopic data.

10. Compound 8 serves as a common synthon for the total synthesis of all antitumor anthracyclinones. The regiospecific synthesis of daunomycinone utilizing 8 will be communicated shortly.

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