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ANTHRACYCLINES AND RELATED SUBSTANCES 4. A NOVEL REGIO- AND STEREOSELECTIVE TOTAL SYNTHESIS OF 7-EPIDAUNOMYCINONE AND DAUNOMYCINONE

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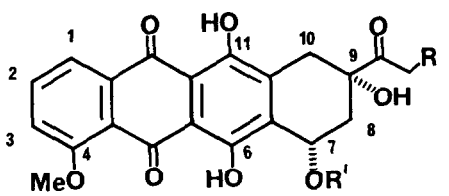
Abstract Daunomycinone 2a has been synthesized by a novel regio- and stereoselective route that establishes the tetracyclic framework and the C-7 oxygen in naphthacenol 5c via a double Friedel-Crafts acylation

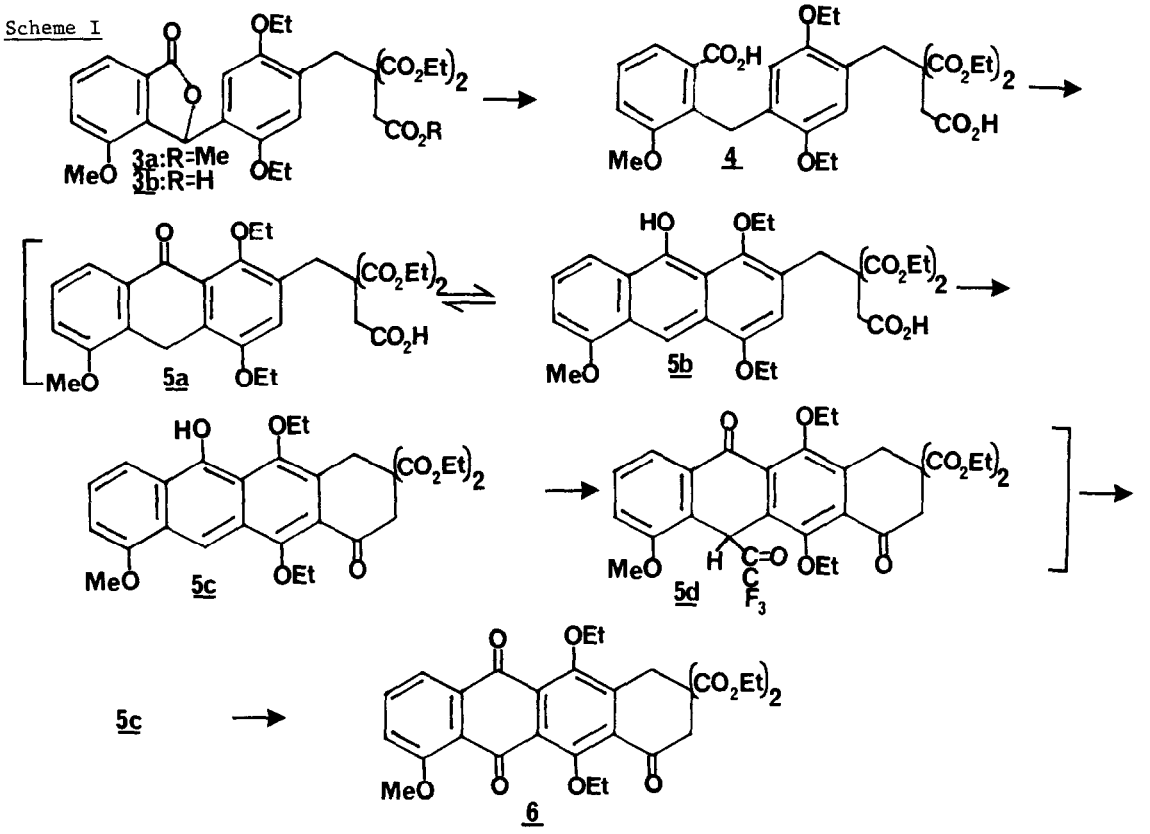
The clinical importance of the anthracycline antitumor agents adriamycin 1b and daunomycin 2b has led to a substantial number of total syntheses of their aglycones,[1] 1a and 2a, respectively Several of these have successfully addressed one of the major problems posed by these systems, namely the regiochemistry.[2] A second problem in the synthesis of daunomycinone is the introduction of the C-7 oxygen[3] which in most cases has been accomplished by a chemically-difficult last step



1 : R = OH
2 : R = H
a : R' = H
b R' = daunosamine

Previously[2c] we reported that lactone 3b can be converted to 7,9-dideoxydaunomycinone in an efficient, regiocontrolled process. We now report a total synthesis of daunomycinone from intermediate 3a that establishes the tetracyclic ring system in one step(DB→DCBA) via a novel

Scheme I



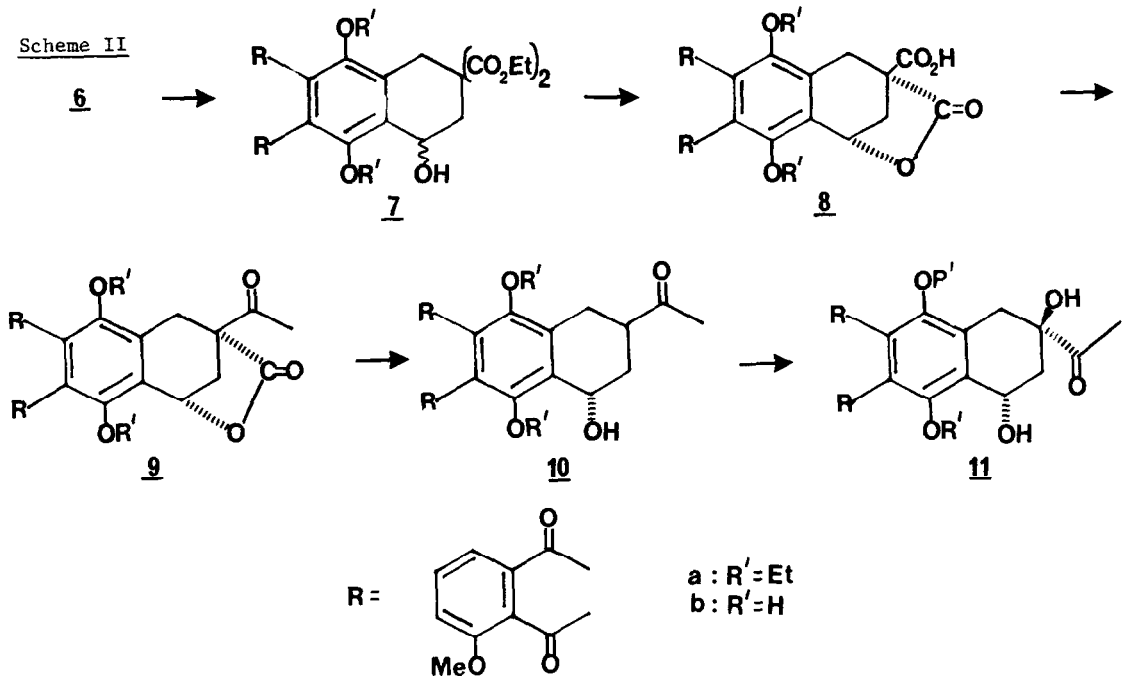
Friedel-Crafts double cyclization reaction and incorporates the C-7 oxygen atom [4] In addition, it allows control of A ring stereochemistry, a feature missing from many previous approaches.

Lactone 3a was selectively hydrolyzed($NaOH/MeOH/THF/H_2O$/reflux/4 days) to give monoacid 3b as white needles in 78% yield,[5] which was then reduced(CF_3CO_2H/Et_3SiH/ 24 hr) to diacid 4(83%).

The critical reaction involves intermediate 4 whose diethoxy aromatic ring can be acylated at either of the two free aromatic carbon atoms. Based on our previous work[2,6] we anticipated that diacid 4 would first cyclize to give the anthrone 5a. Tautomerization to the anthracenol 5b could be expected to render the B ring susceptible to acylation by the other acid moiety These expectations were fully borne out Treatment of 4 with $CF_3CO_2H/(CF_3CO)_2O$ showed, after 5 min, primarily species 5a(δ 4.06, $-OCH_3$). Tautomerization of anthrone 5a to anthracenol 5b was half-complete after 1 hr(δ 3.97, $-OCH_3$), and some 5d was in evidence(δ 6.50, H-5) at the same time After 6 hr the NMR spectrum[7] shows only pure 5d, bicarbonate workup afforded anthracenol 5c(100%) as a fluorescent orange oil. The structure of 5d as a 5-trifluoroacetyl derivative is supported by the chemical shift of the proton at C-5, as well as by precedent.[8]

In practice a one-pot sequence commencing with 4 was carried out by double cyclization ($CF_3CO_2H/(CF_3CO)_2O$/18 hr) followed by immediate oxidation(CrO_3/HOAc/acetone/0°/30 min) to afford 6 as orange blades in 46% yield after recrystallization.

Scheme II



The functionalization of the A ring is outlined in Scheme II. Reduction(BH_3/RT/30 min) of 6 afforded the C-7 alcohol 7a as a yellow solid(79%), which upon hydrolysis(NaOH/THF/48 hr) and lactonization(($(CF_3CO)_2O$) gave lactone-acid 8a in 85% yield. This was then converted to methyl ketone 9a($SOCl_2$,CH_2N_2;HI)[9] in 78% yield from 8a.

Hydrolytic decarboxylation(NaOH/H_2O/THF/12 hr) of 9a led stereoselectively to trans ketone 10a(78%). We believe that this result is due to complexation of water by the C-7 hydroxyl group which delivers a proton to the α-face of the intermediate enol.[10] The relative stereochemistry of 10a is evident from the splitting of the Ψ-equatorial proton at C-7 [11] This hydroxy ketone was shown to have the 'natural' stereochemistry in the A ring by de-ethylation($AlCl_3$/$PhNO_2$) to give 10b, whose NMR spectrum was identical with that reported in the literature.[12]

Hydroxylation(t-BuOK/t-BuOH/DMF/O_2/$(EtO)_3P$/-40°/15 min)[13] of methyl ketone 10a gave 40% of only trans diol 11a after chromatography and recrystallization The selectivity of this step may reflect either steric control or neighboring group participation by the C-7 hydroxyl group. In either case, the net result is the transfer of relative stereochemistry from C-7 to C-9 [14]

Selective de-ethylation[15](dry $AlCl_3$/$PhNO_2$/2 hr) of 11a afforded 7-epidaunomycinone[3c] 11b in 64% yield. The physical characteristics of a synthetic sample matched those recorded in the literature[16] and also the spectra of an authentic sample. Because 7-epidaunomycinone has been epimerized to daunomycinone[3b] in high yield, the synthesis of 11b constitutes a formal total synthesis of the latter substance

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14 Introduction of chirality at C-7 via asymmetric reduction would thus allow establishment of an optically pure stereocenter at C-7 and subsequently, at C-9 This possibility is being explored in an attempt to develop a direct synthesis of optically active daunomycinone.

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