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FLEXIBLE SYNTHETIC ROUTE TO 6-DEOXY AND 11-DEOXYANTHRACYCLINONES

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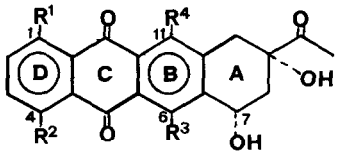
Summary: *The regiospecific synthesis of 6-deoxydaunomycinone 3 and 1-hydroxy-4-demethoxy-11-deoxydaunomycinone (4) is reported: the route allows the preparation of 6-deoxy or 11-deoxyanthracyclinones through the γ or δ lactones 6 and 11.*

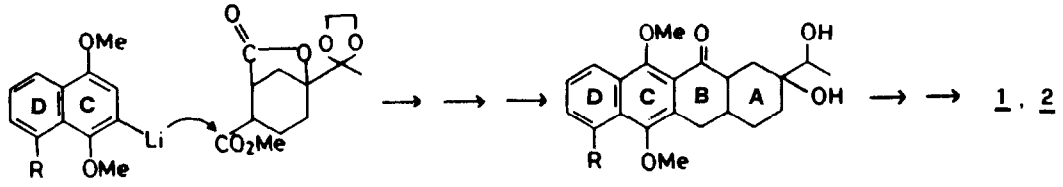
During the past few years the development of synthetic approaches to the antitumor anthracyclines has been a subject of extensive study and a number of elegant solutions to the regiochemical problem in the aglycone synthesis have been produced. As part of our continuing program aimed to the synthesis of daunomycin-doxorubicin analogues, we have sought routes that would be inherently flexible for the preparation of analogous structures differing in the substitution pattern of the anthraquinone moiety. We have recently developed a synthesis of 6-deoxyanthracyclinones[1], namely 4-demethoxy-6-deoxydaunomycinone (1) and 6-deoxy carminomycinone (2), based (Scheme I) on the nucleophilic attack of a 1,4-dimethoxynaphthalene derivative 5, formally representing the C-D rings of the tetracycle, on the ester carbonyl group of the cyclohexane derivative 6, the A-B rings precursor.



1 : $R^1 = R^2 = R^3 = H$; $R^4 = OH$
2 : $R^1 = R^3 = H$; $R^2 = R^4 = OH$
3 : $R^1 = R^3 = H$; $R^2 = OCH_3$; $R^4 = OH$
4 : $R^1 = R^3 = OH$; $R^2 = R^4 = H$

While the oxidative dealkylation of the intermediate 7 readily afforded the anthraquinone system of 1 and 2, such a procedure did not allow to preserve the O-methyl group at C-4, as required for the preparation of 6-deoxydaunomycinone (3). We now report our findings on the anthraquinone system formation using 7 ($R=OCH_3$) as intermediate for the preparation of 3 (see infra) and a convergent regiospecific synthesis of 11-deoxyanthracyclinones based on the assembly of synthones 5 and 11 in a fashion similar to the one leading to 6-deoxy derivatives. Indeed the attack of 5 ($R = OCH_3$)

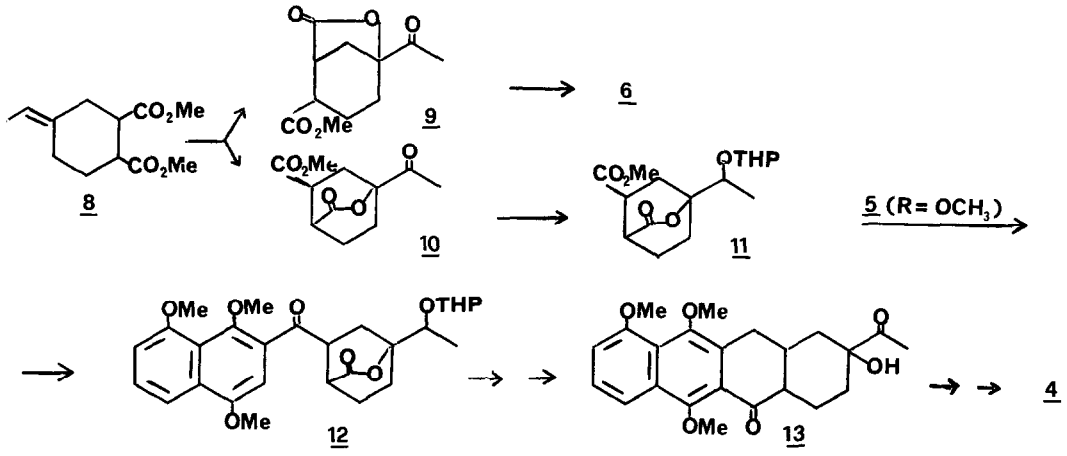
SCHEME I



5 6 7 R = H, OCH_3

on 11 (Scheme II) takes place, as observed for 6, only on the carbonyl of the ester function, to give, following the shown reaction sequence, the new 11--deoxyanthracyclinone 4. The main achievement of our approach resides in the high flexible synthetic scheme for the preparation of 6-deoxy or 11-deoxyanthracyclinones through the γ- or δ-lactones 6 and 11.

SCHEME II



Synthesis of (±) 1-hydroxy-4-demethoxy-11-deoxydaunomycinone (4)

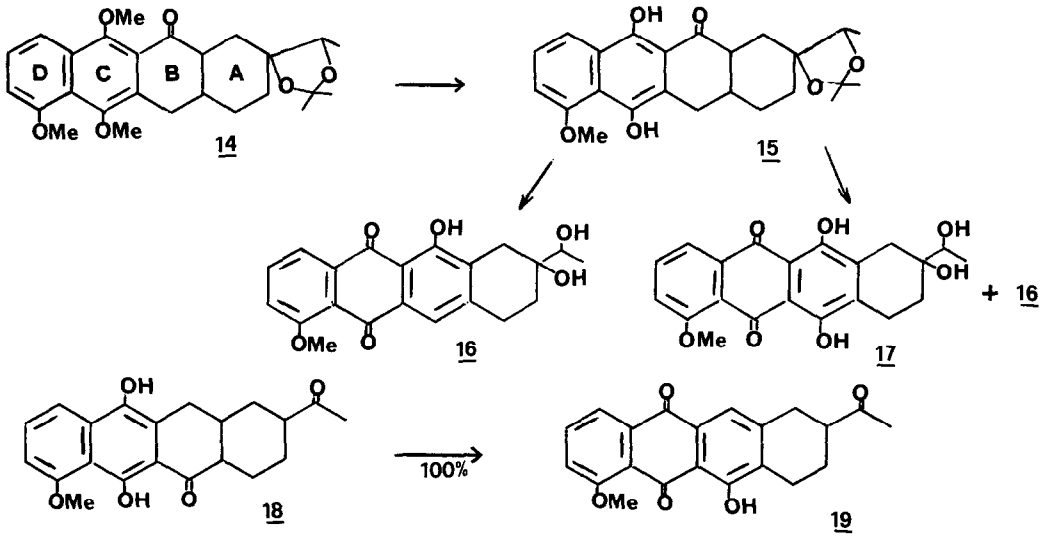
The procedure followed for the preparation of 6[1] has been utilized for obtaining the δ-lactone 11. Indeed the permanganate oxidation in acetic acid of the ester 8[1] and the treatment of the resulting α-hydroxy ketone isomers with a catalytic amount of p-toluensulfonic acid in refluxing toluene gave, after chromatographic separation, 9 and 10 in 36% and 24% overall yield[2] respectively. The six-membered lactone 10 was obtained in trace amounts when the cyclization was carried out in benzene. While 9 readily gave the ketal 6 by treatment with ethylene glycol and p-toluensulfonic acid, on the contrary 10, under the same conditions, afforded the corresponding hydroxyethylester. The protection of the ketone function in 10 was achieved by reduction with alumina supported $NaBH_4$[3] and protection of the corresponding alcohol as tetrahydropyranyl ether to give

11, as isomeric mixture (four products 1:1:1:1)[4] : (m/e = 312, M^+); [IR (film): 1760, 1740 cm^{-1}]; [^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.1-1.3 (4d, J = 6.5 Hz, 3H), 1.4-2.5 (m, 12H), 2.9-3.1 (m, 2H), 3.4-4.0 (m, 3H), 3.72 (s, 3H), 4.72 (m, 1H)]. The coupling reaction of 11 with 5 (R = OCH_3)[1] in tetrahydrofurane at -78°C afforded 12, as stereoisomeric mixture (four products 1:1:1:1) in 70% yield (m/e = 498, M^+); [IR ($CHCl_3$): 1750, 1670 cm^{-1}]; [^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.1-1.3 (4d, J = 6.5 Hz, 3H, $\underline{CH_3}$-CH), 1.5-2.4 (m, 12H, 6-CH_2-), 2.8-3.1 (m, 2H, 2-CH), 3.76,3.96,4.03 (3s, 9H, 3OCH_3), 3.5-4.3 (m, 3H, -$\underline{CH}$-CH_3, -CH_2-), 4.7-4.8 (m,1H), 6.86 (4s, 1H), 6.98 (d, J = 1.7 Hz, 1H), 7.48 (t, J = 2.7 Hz, 1H), 7.88 (d, J = 2.7 Hz, 1H)]. The reduction of the benzylic carbonyl group of 12 at -10°C with pyridine-borane complex[5] followed by alkaline hydrolysis, cyclization with $(CF_3CO)_2O$-CF_3COOH and oxidation of the secondary alcohol with DMSO, TEA-SO_3 afforded 13 in 45% overall yield. Dealkylation with $AlCl_3$ in nitrobenzene followed by the introduction of hydroxyl group at C-7, *via* reported homolytic bromination and solvolysis[1], afforded 4 in 20% overall yield, m.p. 209°-210°C [UV (MeOH) λmax: 228, 256, 290, 432 nm], [IR (CH_2Cl_2): 3420, 1705, 1660, 1625, 1605 cm^{-1}]; HRMS calc. [$C_{20}H_{16}O_7^+$]: 368.0896 (Found 368.0896); [^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.20 (dd, J = 14.6, 4.8 Hz, H-8_{ax}), 2.35 (ddd, J = 14.6, 2.3, 1.9 Hz, H-8_{eq}), 2.41 (s, $COCH_3$), 3.01 (dd, J = 18.0, 2.3 Hz, H-10_{eq}), 3.28 (d, J = 18.0 Hz, H-10_{ax}), 3.62 (d, OH-7), 4.57 (s, OH-9), 5.35 (ddd, J = 5.0, 4.8, 1.9 Hz, H-7), 7.33 (dd, J = 8.2, 1.2 Hz, H-2), 7.66 (s, H-11), 7.70 (dd, J = 8.2, 7.5 Hz, H-3), 7.84 (dd, J = 7.5, 1.2 Hz, H-4), 12.60 (s, OH-1), 13.33 (s, OH-6)].

Synthesis of 6-deoxydaunomycinone (3) (Scheme III)

The acetonide 14, obtained from 7 (R = OMe) by reaction with dimethoxypropane, when treated with 2.0 equiv. of ceric ammonium nitrate unexpectedly undergoes only the cleavage of the O-methyl groups on ring C without oxidation[6] to the quinone system 15. On the other hand the aromatization of ring B of 14 to the tetrahydronaphthacene intermediate, *via* bromination-dehydrohalogenation, before $Ce(NH_4)_2(NO_3)_6$ treatment, as reported for the synthesis of aklavin-type anthracyclinones[7], proceeded with exceedingly low yields. However the bromination-dehydrohalogenation reaction sequence (i: Br_2, CH_2Cl_2, 0°C; ii: TEA; iii: CF_3COOH) on substrate 15 afforded the desired anthraquinone derivative 16 from which 3[8] was obtained following the already reported procedure. It is worthnoting that while 18 has been converted quantitatively to 19 by heating (100°C) in dimethyl formamide in presence of oxygen[9], our intermediate 15, under the same conditions, gave a mixture of 16 and 17 (1:3) indicating a different reactivity towards oxidation of B ring in 15 and 18.

SCHEME III



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References and Notes

1. S. Penco, F. Angelucci, M. Ballabio, G. Barchielli, A. Suarato, E. Vanotti, A. Vigevani and F. Arcamone, *Tetrahedron, 40*, 4677 (1984).

2) All compounds gave mass, IR and ^{1}H-NMR spectra consistant with the assigned structures. Yields are unoptimized and mp uncorrected.

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4) Since the sp^3-hybridized carbons bearing the ester and lactone carbonyl groups, which become the bridging carbons in the tetracycle, are transformed to sp^2 centers at a later stage in the scheme, the presence of geometric isomers in 11 is without consequence allowing full utilization of products.

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8) The m.p. and ^{1}H-NMR are in agreement with that reported by R.K.Boeckman, Jr. and Seung Hoon Cheon, *J. Am. Chem. Soc., 105*, 4112 (1983).

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