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AN EFFICIENT SYNTHESIS OF OPTICALLY ACTIVE 4-DEMETHOXY ANTHRACYCLINONES

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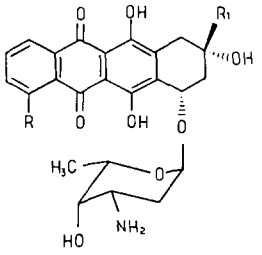
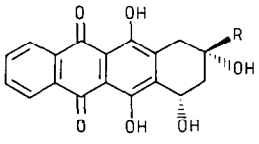
Summary : Optically active 4-demethoxy-anthracyclinones were synthezised in few steps from lactose as chiral precursor of ring A and from leucoquinizarine as precursor of rings B, C and D.

The total synthesis of naturally occuring anthracyclines, daunorubicin 1 and adriamycin 2 and of related structural analogs has been the subject of intense studies over the last decade[1]. Recent findings indicate that the 4-demethoxy derivative 3 of daunorubicin 1 is 5 to 10 times more potent than 1[2] and of equivalent efficacy [3], and that substitution of the acetyl side chain of daunorubicin by a CH_2OH group, as in 4 does not appreciably alter biological activity.[4]



1 R = OCH_3 R_1 = $COCH_3$
2 R = OCH_3 R_1 = $COCH_2OH$
3 R = H R_1 = $COCH_3$
4 R = OCH_3 R_1 = CH_2OH

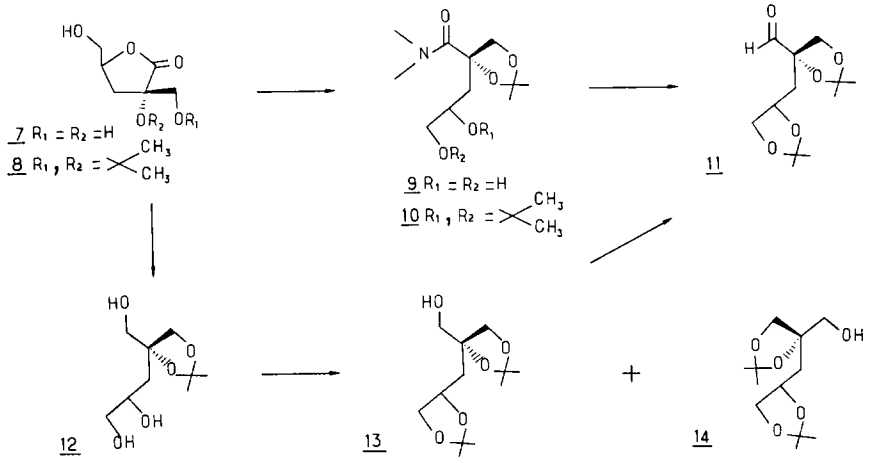


5 R = $COCH_3$
6 R = CH_2OH

Based upon these observations we have prepared the anthracycline analog 6 (4-demethoxy-9-deacetyl-9-hydroxymethyl daunomycinone)[5] which possesses both these structural modifications. Our objective was to prepare 6 in optically active form by a route which a) avoids the introduction of the hydroxy groups at C-9 and/or at C-7 at a late stage in the synthesis, and b) could be scaled up to a preparative level. For these reasons we chose the readily available and abundant sugar derivative α-D-isosaccharino-1,4-lactone 7 as the precursor of the

ring A synthon 11, and leucoquinizarine 15 as the precursor of rings B, C and D.

α-D-isosaccharino-1,4-lactone 7 was prepared by the reaction of lactose with calcium hydroxyde[6] and its vicinal diol system was protected as an isopropylidene, giving 8[7]. At first, we examined the reductive ring opening of the acetonide 8 by reaction with LAH or BH_3-Me_2S[8]. Under both conditions the triol 12 was obtained in 94-98 % yield. Unfortunately subsequent acetalation of 12 (acetone-HCl or 2,2-dimethoxypropane-TsOH-DMF) led to the formation of the two diastereoisomeric di-O-isopropylidenes 13 and 14 in nearly equal proportions. As the quaternary center C-2 (corresponding to C-9 in 6) was essentially racemized during this process[9], this route was abandoned.

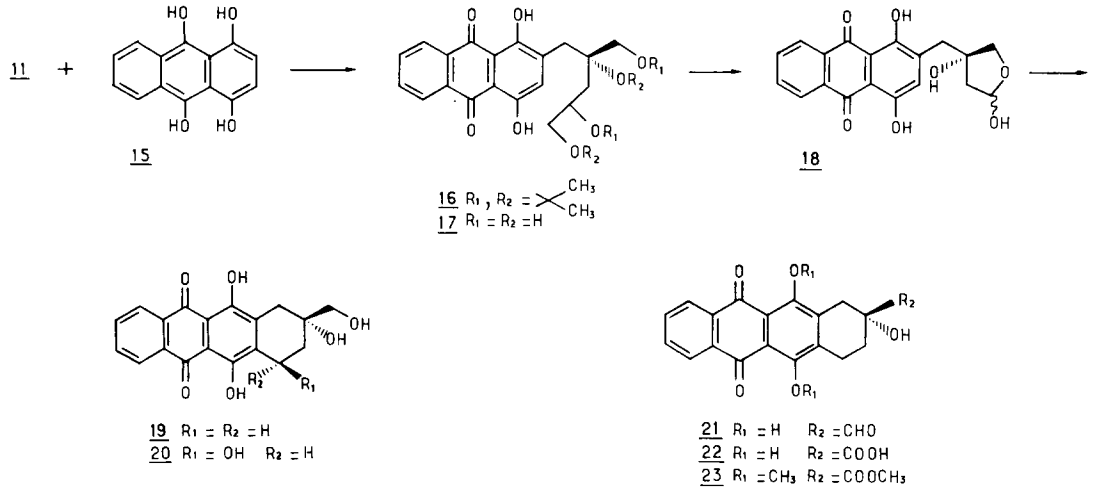


Acetonide 8 was successfully transformed into aldehyde 11 in three steps, 1) Reaction of 8 with Me_2NH in $CHCl_3$ gave the amido derivative 9 (syrup, $(\alpha)_D$ -27° (c 1, $CHCl_3$)[10] ; 2) Compound 9 was converted to its O-isopropylidene derivative 10 (syrup, $(\alpha)_D$ -30° (c 1, $CHCl_3$)) ; 3) Partial reduction[11] of the amide function of 10 with LAH at -40°C gave aldehyde 11 (syrup $(\alpha)_D$ -53° (c 1, $CHCl_3$)) : (overall yield from 8 to 11 ≈ 50 %).

Condensation of compound 11 with leucoquinizarine 15 under Lewis conditions[12] (piperidinium acetate, iPrOH) led to the adduct 16 (m.p. 130°C, hexane-acetone, $(\alpha)_D$ -70° (c 0.15, dioxane)) in 75 % yield. After acidic hydrolysis (THF-MeOH-H_2O-HCl) of the acetal (98 % yield) regiospecific cleavage of the terminal vicinal diol of tetrol 17 (m.p. 90-92°C, $(\alpha)_D$ +12°5 (c 0.08, dioxane)) was achieved by treating 17 with one molar equivalent of sodium periodate. As deduced from the i.r. and n.m.r. spectra, the aldehydo derivative 18 exists in its hemiacetal form (m.p. 95-100°C, hexane-acetone, $(\alpha)_D$ +78° (c 0.05, dioxane)).

Under Marschalk conditions[13] (sodium dithionite-NaOH), at room temperature 18 gave exclusively the 7-deoxy anthracyclinone 19 (m.p. 235-238°C, $(\alpha)_D$ -32° (c 0.06, dioxane))[14] in 80 % yield. However, when this reaction was performed at 0°C, two other anthracyclinones were obtained in equal amounts which could be separated by chromatography on silica gel. The trans derivative 7(R), 9(S) 20 obtained in 35 % yield was eluted first (m.p. 210-212°, $(\alpha)_D$ -108° (c 0.05, THF)) and its structure unambiguously established by n.m.r. and mass spectra[15]. Further

elution gave the corresponding cis derivative 7(S), 9(S), 6 in 35 % yield (m.p. 230°C, $(\alpha)_D$ +95° (c 0.05, THF))[16].



Oxidation of the 7-deoxy aglycone (N-chlorosuccinimide-Me_2S-Et_3N)[17] afforded the unstable aldehyde 21 which was immediatly oxidized (sulfamic acid-$NaClO_2$)[18] into 22 and methylated (Me_2SO_4-K_2CO_3) to give 23 identical in all respects (m.p., i.r., n.m.r., $(\alpha)_D$) with the (R)(-)Methyl-2-hydroxy-5,12-dimethoxy -6,11-dioxo-1,2,3,4,6,11-hexahydronaphtacene-2 carboxylate as previously described by Terashima et al.[19].

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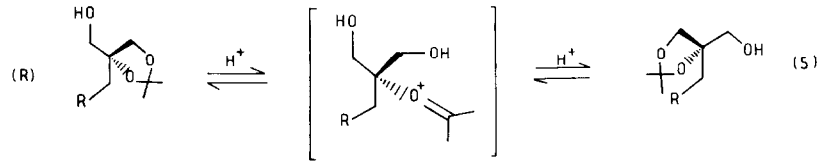
9 The mechanism of formation of 13 and 14 in acidic medium can be explained as indicated below :



10 I.r. and n.m.r. spectra were in agreement with assigned structures as well as analytical and/or mass spectral data.

11 The formation of only small amounts (≃ 10%)of the corresponding alcohol 13 can be explained by the fact that the reaction sequence is stopped at the amino alcohol stage as already observed with various hindered N,N-disubstituted amides : E. Mosettig, Organ. Reactions, 8, 210 (1954).

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14 N.m.r. (pyridine-d_5, 400 MHz) : δ 8.39 (2H, m) and 7.75 (2H, m) (ArH) ; 4.09 (2H, s, CH_2O) ; 3.44 (1H, d) and 3.21 (1H, d) (J = 19, 1-H) ; 3.39-3.11 (4H, m, 4-H and 2 OH) ; 2.30 (1H, m) and 2.08 (1H,m, 3-H). Mass spectrum (E.I.) : m/z 340 (M^+, 100 %) ; 308 (M-31, 88 %), and 291 (M-31-18, 68 %).

15 N.m.r. (pyridine-d_5, 400 MHz) :δ 8.39 (2H, m) and 7.75 (2H, m) (ArH) ; 5.86 (1H, t, J = J' = 6, 1-H) ; 4.28 (1H, d) and 4.21 (1H, d) (J = 10, 5, CH_2O) ; 3.60 (1H, d) and 3.39 (1H, d)(J = 18, 4-H) ; 2.77 (1H, m, J = 13.5 ; J'= 6 ; J''=1, 2e-H) and 2.67 (1H, dd, J = 13.5 ; J'=6.5, 2a-H). Mass spectrum (E.I.) m/z 356 (M^+, 20 %), 338 (M-18, 27 %), 320 (M-18-18, 13%),307 (M-18-31, 100%), 279 (32 %).

16 N.m.r.(pyridine-d_5, 400 MHz) : δ 8.37 (2H, m) and 7.73 (2H, m)(ArH); 5.63 (1H, broad s,1-H), 4.11 (1H, d) and 4.06 (1H, d) (J = 11, CH_2O) ;3.67 (1H, dd, J = 18.5 ; J'=2, 4a-H) and 3.24 (1H, d, J = 18.5,4e-H), 2.72 (1H, m, J = 14 ; J'= J''=2, 2e-H) and 2.30 (1H, dd, J = 14 ; J'= 4.5, 2a-H). Mass spectrum (E.I.) : m/z 356 (M^+, 55 %), 338 (M-18, 100 %), 320 (M-18-18, 68 %), 307 (M-18-31, 88 %), 279 (60 %).

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