

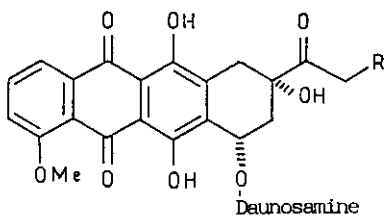
## TOTAL SYNTHESIS OF 7-HYDROXY-"9-OXA"-ANTHRACYCLINONE AND GLYCOSIDE DERIVATIVES

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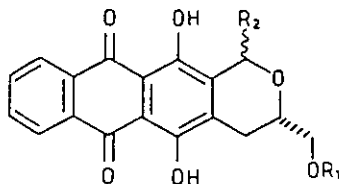
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**Abstract** - The racemic title aglycone was prepared in seven steps from quinizarin 5 and its resolution achieved after glycosidation with 3,4-di-O-acetyl-2-deoxy-L-fucose.

When compared to the strong antitumour activity of anthracyclines 1, the lack of significant biological (i.e. antibiotic and/or antitumour) activity of "9-oxa"-anthracyclines and "9-oxa"-anthracyclines of general structures 2 and 3<sup>1</sup> could be due either to the introduction of an oxygen atom at the 9-position in the A-ring of the molecule or to the change in the glycosidation position.



1 R = H, OH



2 R<sub>1</sub> = H ; R<sub>2</sub> = H, CH<sub>3</sub>

3 R<sub>1</sub> = Sugar ; R<sub>2</sub> = H, CH<sub>3</sub>

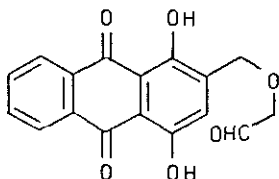
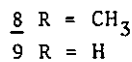
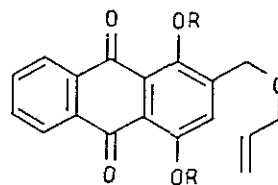
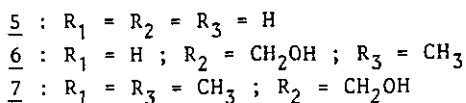
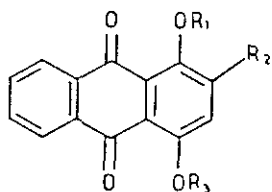
In order to establish clearly the origin of this lack of biological activity, it seemed of interest to achieve the synthesis of a simplified "9-oxa"-anthracycline (4a) bearing no side-chain at C-8 but a glycoside substituent at C-7 $\alpha$ .

The synthetic strategy to elaborate the tetracyclic anthracyclinone skeleton followed the classical A + BCD scheme previously used in our laboratory for the synthesis of both anthracycline<sup>2</sup> and "9-oxa"-anthracycline<sup>1</sup> derivatives. The

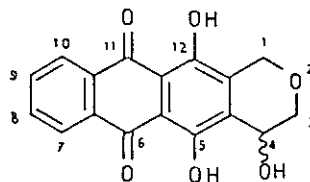
difficulties generally encountered in the synthesis of 4-hydroxyisochromans<sup>3</sup> corresponding to the AB rings segment of the molecule led us to use an intramolecular Marschalk reaction<sup>4</sup> during the last step of the synthesis of the aglycone, easily providing the hydroxy group at the required position.

Quinizarin (5) was converted in two steps into 1-hydroxy-2-hydroxymethyl-4-methoxy-9,10-anthraquinone (6) according to Krohn's procedure<sup>5</sup>. Methylation of 6 (Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, Me<sub>2</sub>CO, reflux, 48 h) led in almost quantitative yield to 2-hydroxymethyl-1,4-dimethoxy-9,10-anthraquinone (7)<sup>6</sup> (mp 180°C). Condensation of 7 with an excess of allyl bromide in strong alkaline medium (NaH, DMF, r.t., 2h) afforded the benzylic ether 8 (mp 174°C) in 77 % yield. Removal of the two methyl protective groups was then achieved by treatment with aluminum chloride under anhydrous conditions<sup>5</sup> (AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 10 min) to obtain 2-allyloxy-methyl-1,4-dihydroxy-9,10-anthraquinone (9) (mp 128-129°C) in 44 % yield. Upon ozonolysis (O<sub>3</sub> stream, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 15 min ; then addition of Me<sub>2</sub>S), 9 led in 87 % yield to the aldehyde 10 (mp 172°C), which was subjected to intramolecular alkylation under Marschalk conditions<sup>4</sup> to afford the required racemic (+)-4,5,12-trihydroxy-3,4-dihydro-1H-anthra[2,3-c]pyran-6,11-quinone (11) (mp 194°C) in almost quantitative yield.

Glycosidation of (+)-11 by 3,4-di-O-acetyl-2-deoxy-L-fucopyranosyl chloride<sup>8,9</sup> (yellow HgO, HgBr<sub>2</sub>, 4 Å molecular sieves, C<sub>6</sub>H<sub>6</sub>-CH<sub>2</sub>Cl<sub>2</sub>, r.t., 1 h)<sup>10,11</sup> finally led in 95 % overall yield to an equimolecular mixture of the two diastereoisomeric α-glycosides 4a (mp 228°C, [α]<sub>D</sub><sup>20</sup> = +77° (c = 0.05, CHCl<sub>3</sub>)<sup>12</sup> and 4b (mp 230°C, [α]<sub>D</sub><sup>20</sup> = -245° (c = 0.05, CHCl<sub>3</sub>)<sup>13</sup>, easily separated after column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>).

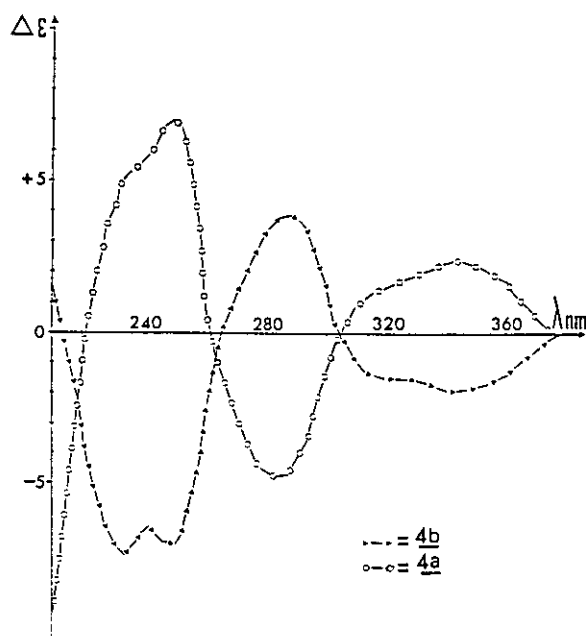
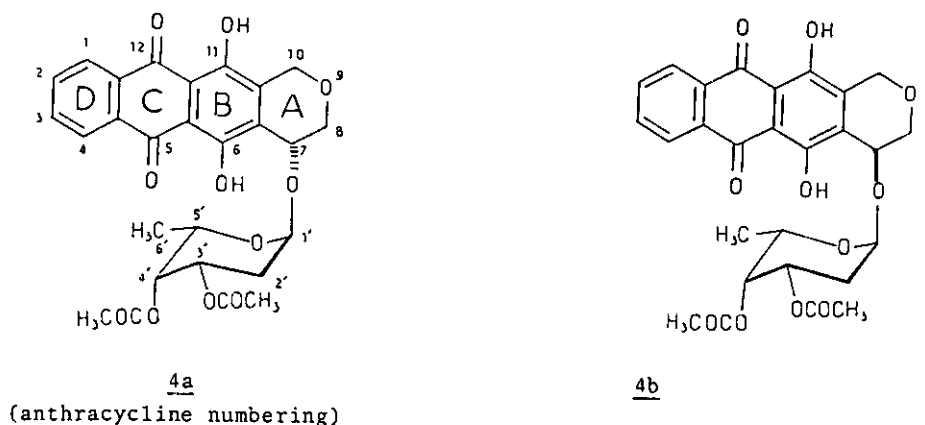


10



11  
(systematic numbering)

The absolute configuration at C-7 (anthracycline numbering) of these two compounds could be easily deduced from their cd curves (Scheme 1). Compound 4a with an  $\alpha$ -configuration at C-7 (7R) exhibited a negative maximum at 287 nm whereas 4b with a  $\beta$ -configuration at C-7 (7S) showed a positive maximum at the same wavelength<sup>14</sup>. Deacetylated glycosides corresponding to 4a and 4b show no significant antitumour activity.



Scheme 1

ACKNOWLEDGEMENTS

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5. K. Krohn and B. Behnke, *Chem. Ber.*, 1980, 113, 2994.
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7. (+)-4,5,12-Trihydroxy-3,4-dihydro-1H-anthra[2,3-c]pyran-6,11-quinone (11) :  $C_{17}H_{12}O_6$  ;  $^1H$  nmr (DMSO- $d_6$ , TMS) :  $\delta$  ppm : 13.28 and 12.99 (2 x 1H, 2s,  $D_2O$  exch., OH-5, OH-12), 8.25 (2H, m, H-7, H-10), 7.97 (2H, m, H-8, H-9) ; 5.50 (1H, dd,  $J = 6Hz$ ,  $J' = 1.5Hz$ , H-4), 4.88 (1H, d,  $J = 17Hz$ , H-1a), 4.63 (1H, d,  $J = 6Hz$ ,  $D_2O$  exch., OH-4), 4.52 (1H, d,  $J = 17Hz$ , H-1b), 4.00 (1H, d,  $J = 11Hz$ , H-3a), 3.68 (1H, dd,  $J = 11Hz$ ,  $J' = 1.5Hz$ , H-3b).
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12. 4a :  $C_{27}H_{26}O_{11}$  ;  $^1H$  nmr ( $CDCl_3$ , TMS) :  $\delta$  ppm : 13.45 and 13.10 (2 x 1H, 2s,  $D_2O$  exch., OH-6, OH-11), 8.24 (2H, m, H-1, H-4), 7.84 (2H, m, H-2, H-3), 5.60 (1H, d,  $J = 2Hz$ , H-1'), 5.26 (2H, m, H-7, H-3'), 5.09 (1H, d,  $J = 18Hz$ , H-10a), 4.76 (1H, narrow m, H-4'), 4.62 (1H, d,  $J = 18Hz$ , H-10b), 4.33 (1H, qd,  $J = 7Hz$ ,  $J' = 1Hz$ , H-5'), 4.24 (1H, d,  $J = 12Hz$ , H-8a), 3.75 (1H, dd,  $J = 12Hz$ ,  $J' = 1Hz$ , H-8b), 2.11 (3H, s, OAc), 2.05 (1H, m, H-2'a), 1.93 (3H, s, OAc), 1.91 (1H, m, H-2'b), 1.19 (3H, d,  $J = 7Hz$ ,  $CH_3$ -6').
13. 4b :  $C_{27}H_{26}O_{11}$  ;  $^1H$  nmr ( $CDCl_3$ , TMS) :  $\delta$  ppm : 13.57 and 13.09 (2 x 1H, 2s,  $D_2O$  exch., OH-6, OH-11), 8.35 (2H, m, H-1, H-4), 7.84 (2H, m, H-2, H-3), 5.40 (1H, d,  $J = 2Hz$ , H-1'), 5.25 (2H, m, H-7, H-3'), 5.15 (1H, d,  $J = 18Hz$ , H-10a), 5.01 (1H, narrow m, H-4'), 4.65 (1H, d,  $J = 18Hz$ , H-10b), 4.64 (1H, m, H-5'), 4.44 (1H, d,  $J = 13Hz$ , H-8a), 3.57 (1H, dd,  $J = 13Hz$ ,  $J' = 1Hz$ , H-8b), 2.16 (3H, s, OAc), 2.11 (1H, m, H-2'a), 1.93 (3H, s, OAc), 1.89 (1H, m, H-2'b), 1.20 (3H, d,  $J = 7Hz$ ,  $CH_3$ -6').
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