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Anthracyclinones VI[1]. DIASTEREOSELECTIVE SYNTHESIS OF 7,10-DIHYDROXY-4-DEMETHOXY-ANTHRACYCLINONES

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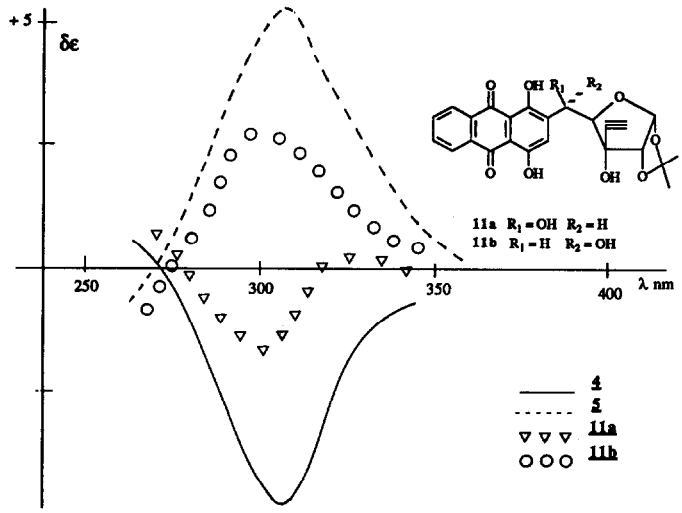
Abstract: *The total synthesis of two new enantiomerically pure anthracyclinones **9** and **10** from leucoquinizarin **2** and chiral aldehyde **3** readily obtained from α-D-isosaccharinolactone, is described. The stereochemical results are discussed.*

We have previously reported [2] an efficient synthesis of **1** from leucoquinizarin **2** and the chiral aldehyde **3** in which the initial C-C bond was formed by an intermolecular Marschalk[3] or Lewis[4] reaction and the second one by an intramolecular Marschalk condensation.

Pursuing our interest in the synthesis of new enantiomerically pure anthracyclinones by this anthraquinone approach, we report the preparation of **9** and **10** in order to investigate the influence of the configuration of the benzylic hydroxyl group of 1-hydroxyalkyl anthraquinones on the stereochemical result of the intramolecular Marschalk cyclization. The reinvestigation of the first aldol condensation (**2** + **3**) under milder conditions, using DBU in THF as reported by Shaw *et al.*[5], provided a 75/25 mixture of *anti* and *syn* isomers , **4** and **5**[6] separated by column chromatography (CH_2Cl_2:MeOH, 99.9:0.1) in 55% overall yield. CD spectra of **4** and **5** were compared with those of compounds **11a** and **11b**[5], the absolute configuration of **11a** having been already determined by X-ray chromatography[7]. These comparisons suggest the configuration to be S at C-1 for (+)-diastereoisomer **4** and R for the (-) diastereoisomer **5**. Careful examination of this reaction showed that the diastereoselectivity and the overall yield could not be improved when DMF was used as solvent (ratio 4/5 = 60/40) or when DBN instead of DBU was used as the base (ratio = 65/35).

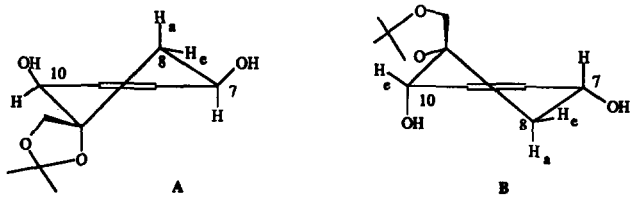
Since among the anthracycline analogs having an α or β substituent (OH,OMe,COOMe..) at this position, only the latters retain antitumor activity[8], it was of interest to obtain predominantly the *syn* isomer **5**. We therefore explored the reduction of the chiral α,β-dialkoxy anthraquinoyl ketone **6** [mp 98-100°C; [α]D + 15° (c 0.02, THF)], prepared in 83% yield by Corey oxidation [9] of the mixture **4** and **5**, using a variety of hydride reducing agents. A major consideration in this study was to avoid reduction of the quinone system. Unidentified products were obtained in the reaction of **6** with L-selectride and $PhMe_2SiH$[10] probably resulting from preferential reduction of the more accessible quinone carbonyl group. Reduction with $NaBH_4$ or $NaBH_3CN$ gave the desired alcohols in 72-74% yields, respectively, but with low diastereoselectivity in favour of 1R isomer **5** (**4**:**5** = 36/64 and 33/67, respectively).



We next examined the reaction of **6** with $Zn(BH_4)_2$[11] in the hope of obtaining a good level of stereocontrol through chelation as in the case of reduction of chiral α,β-dialkoxy ketones[12]. Unfortunately, under all conditions (time, temperature) studied, overreduction products were produced.

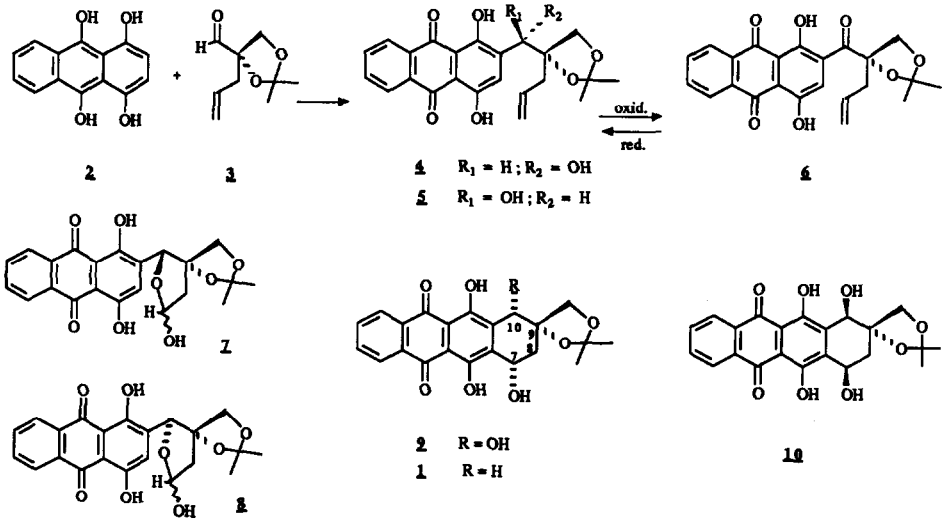
A satisfactory result was obtained , however, using $Zn(BH_4)_2$.1.5 DMF complex [13] which afforded **4** and **5** in 20/80 ratio and 62% overall yield. This stereoselectivity could be interpreted as the result of a chelation control in which the reagent complexes both the keto group and the oxygen of the α-alkoxy group and this interpretation is consistent with a Cram cyclic model previously proposed for nucleophilic addition to (R)-2,3-O-isopropylidene D-glyceraldehyde[14].

Reaction of 4 with OsO_4-$NaIO_4$ produced in quantitative yield the aldehyde derivative **7** which exists in its hemiketal form as shown by examination of its IR and ^1H NMR spectra. Intramolecular cyclization was then carried out under Marschalk conditions[3] with NaOH-$Na_2S_2O_4$ in THF-MeOH (1:1) at -20°C for 5 mn giving, with high stereoselectivity, the anthracyclinone (7S,10S) **9** in 81% yield. The same sequence of reactions provided the anthracyclinone (7R,10R) **10** with only traces of a less polar isomer (7S,10R) in 57% yield when **8** obtained from **5** ($NaIO_4$-OsO_4) was used as starting material. Determination of the configuration of **9** and **10** was deduced from their 270 MHz ^1H NMR spectra[15]. Thus examination of the spectrum of **10** shows that there is a trans-diaxial coupling for 7-H (J = 10 Hz) with 8a-H but also coupling data indicate that the ring A exists in the twisted-chair conformation **A** since a long range coupling was observed between 10e-H and 8e-H. Indeed the signal at δ 2.39 (dd) assigned to the equatorial proton 8e-H exhibits three coupling constants (13, 7, and 1 Hz) which were in full agreement with those previously reported by Krohn for the (+)4-deoxy-7-epi-α1-rhodomycinone[16]. The ^1H NMR of **9** also indicate a twisted-chair conformation, i.e. **B**, in which 7-H occupies an axial position in agreement with the coupling constants between 7-H and 8-H (J = 7.6, J' = 6.5 Hz).



A B

The formation of **9** and **10** is no doubt attributable to the existence of an equilibrium[17] in THF-MeOH between the cyclic hemiacetals and their corresponding γ-hydroxy-aldehydes. Whereas the stereochemical outcome of the Marschalk cyclization with α-hydroxy-aldehyde units present in alkyl anthraquinones can be rationalized in terms of chelation *versus* non-che



2 **3** **4** $R_1 = H; R_2 = OH$ **5** $R_1 = OH; R_2 = H$ **6** **7** **8** **9** R = OH **1** R = H **10**

lation control[18], under the same conditions, the cyclization of the β,γ-dihydroxy aldehyde unit led to a complex mixture of products[19]. This is likely due to the presence of free β-hydroxyl group . Since in the case of **7** and **8**, the β-hydroxyl group is protected as an isopropylidene derivatives, our results show that the diastereoselectivity is dictated by the configuration of the benzylic OH group. We are unable to propose a transition state model to explain the stereochemical results since no information is available concerning the conformations of the phenoxyde salts of the γ -hydroxy aldehyde anthraquinones **7** and **8** .

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6. Ratio determined by ^{1}H 270 MHz NMR. *Compound* **4**: Syrup, $[\alpha]_D$ +220° (c 0.02, THF ^{1}H NMR ($CDCl_3$): δ 13.62 and 12.82 (2s, 2 x 1H, OH phenols), 8.36 and 7.86 (2m, 2 x 2H, Ar), 7.67 (s, 1H, 1Ar), 5.86 (m, 1H, 4-H), 5.31 (d, 1H, J= 4 Hz, 1-H), 5.08 (m, 2H, 5-H), 4.41 (d, 1H, J= 9 Hz) and 3.90 (2d,2 x 1H, J= 9 and 4 Hz, 2'-CH_2), 2.55 (dd, 1H, J= 15 Hz, J'= 7 Hz) and 2.14 (dd,J'= 8 Hz, 3-H), 1.52 , 1.44 (2s, 2 x 3H, CMe_2); DCI/NH_3: m/z 411 (M + H^+); *Compound* **5**: Syrup, [α]D - 235° (c 0.02, THF); ^{1}H NMR: d 13.55 and 12.77 (2s, 2 x 1H, OH phenols), 8.34 and 7.85 (2m, 2 x 2H, Ar), 7.53 (s, 1H, Ar), 5.96 (m, 1H, 4-H), 5.25 (m, 2H, 5-H), 5.19 (s, 1H, 1-H), 4.07 and 3.85 (2d, 2 x 1H, J =10 Hz, 2'-CH_2), 2.72 (dd, 1H, J= 14, J'= 9 Hz) and 2.48 (dd, J'= 9 Hz, 3-H),1.44,1.32 (2s, 2 X 3H, CMe_2); DCI/NH_3: m/z 411 (M+H^+).
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15. *Compound* **9**: Syrup, $[\alpha]_D$ + 50° (c 0.01, THF); ^{1}H NMR: δ 13.66 and 13.61 (2s, 2x 1H) (OH, phenols), 8.32 and 7.86 (2m, 2 x 2H, Ar), 5.09 (dd, 1H, J= 7.6, J' = 6.3 Hz, 7a-H), 4.92 (d, 1H, J = 1Hz, 10e-H), 4.34 (bs, 1H, OH exch. D_2O), 3.87 (s, 2H, 13-H), 3.53 (bs, 1H, OH, exch. D_2O), 2.62 (dd, 1H, J= 13.7, J' = 7.6 Hz, 8a-H), 2.16 (ddd, 1H, J = 13.7, J' = 6.3, J" = 1 Hz, 8e-H), 1.56 and 1.52 (2s, 2x3H, (CMe_2); DCI/NH_3 : m/z 413 (M + H^+). *Compound* **10**: m.p. 254-256°C; $[\alpha]_D^{20}$ - 60° (c 0.02, THF); ^{1}H NMR: δ 13.72 and 13.55 (2s, 2x1H, OH phenols), 8.33 and 7.86 (2m, 2 x 2H, Ar), 5.28 (dd, 1H, J = 10, J' = 7 Hz, 7a-H) , 4.85 (d, 1H, J = 1 Hz, 10e-H), 4.37 (d, 1H, J = 9.5 Hz) and 3.97(d, 1H, J=9.5 Hz) (AB, 13-H), 4.22 (bs, 1H, OH, exch. D_2O),3.74(s,1H, OH exch. D_2O), 2.39 (ddd, 1H, J = 13, J'= 7, J"= 1Hz, 8e-H), 2.22 (dd,1H,J = 13, J' = 10 Hz, 8a-H), 1.44 and1.36 (2s, 2 x 3H) (CMe_2); DCI/NH_3: m/z 413 (M+H^+).
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