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CHIRAL POOL SYNTHESIS OF TETRALIN AS AB RING SEGMENT, PRECURSOR OF ANTHRACYCLINES.

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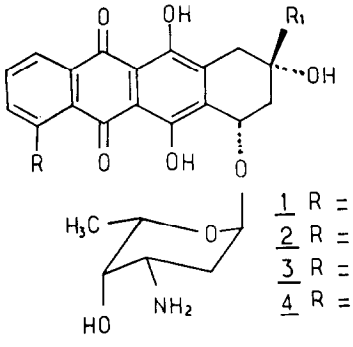
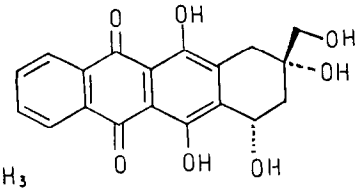
Summary : *A practical synthesis of chiral tetralin 6, an anthracycline precursor, is described, starting from the readily available α-D-isosaccharino-1,4 lactone.*

The anthracycline antibiotics daunorubicin 1 and doxorubicin 2 are clinically useful drugs for the treatment of a broad spectrum of human cancers[1]. Considerable efforts over the last ten years have focused on synthetic routes to the corresponding aglycones, daunomycinone and adriamycinone[2] and more recently towards the synthesis of their 4-demethoxy analogs[3] since structure-activity relationships have indicated that the unnatural anthracyclines 3 and 4 displayed improved chemotherapeutic properties[4]. The fact that only the 7(S) anthracyclines are biologically active explains that much effort has been expended in the preparation of chiral aglycones[3,5]. Very recently, we have reported a brief and regiospecific synthesis of the chiral anthracyclinone 5 following the DCB + A strategy[6]. We have been also engaged in another project aimed at a new total synthesis of anthracyclinone 5 and



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 = H R_1 = $COCH_2OH$



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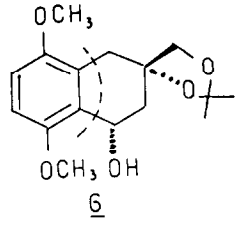

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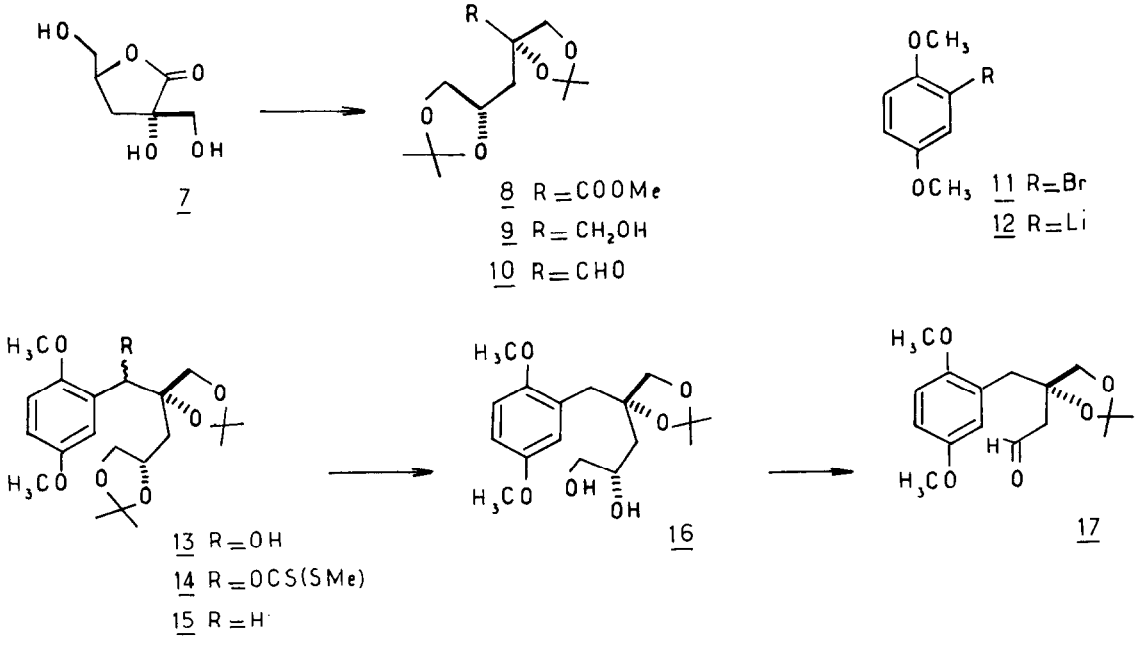
Figure 1

also new chromophore-modified analogs designed to provide information on the molecular basis of cardiotoxicity. The new convergent approach reported herein involves assembly of an appropriately substituted tetralin unit ; the later holds a pivotal

position to follow the classical AB + CD strategy to elaborate both anthracyclinones[7], and heteroanthracyclinones[8]. The bond dissection depicted on figure 1 takes advantage of maximum convergence and the synthesis involves an ortho alkylation of dimethoxybenzene with chiral aldehyde 10 and, after suitable transformations, ring closure of the adduct.

This aldehyde, previously synthesized[6] in five steps from α-D-isosaccharinolactone 7 as chiral template, is now best obtained by a modified process. Acidic ring opening[9] of lactone 7 (MeOH, 2,2-dimethoxypropane, Amberlyst 15 ion-exchange resin, 36h, R.T.) affords the ester 8 (syrup, $[\alpha]_D^{20}$= -17°)[10] in 75 % yield. Reduction of 8 (LAH, THF, reflux for 16h) followed by oxidation of the alcohol derivative 9 gives the desired aldehyde 10 (from 8 to 10 : overall yield 70 %). Addition of the aryl lithium compound 12 prepared from bromodimethoxybenzene[11] 11 (nBuLi, THF, -78°C) on the aldehyde 10 results in the formation of the diastereoisomeric adducts 13 (65-70 % yield). After formation of the dithiocarbonate esters 14 (HNa, CS_2, MeI, 0° to R.T.), radical deoxygenation[12] at the benzylic position (Bu_3SnH, AIBN, toluene, reflux, 12h) affords 15 in 86 % yield (syrup, $[\alpha]_D^{20}$= +5°). Regioselective hydrolysis of the terminal isopropylidene acetal (AcOH, MeOH, H_2O, 2:2:1, R.T., 36h), gives a mixture of the starting material 15 (56 %) and of the diol 16 (44 %, syrup, $[\alpha]_D^{20}$ = +13°), which are easily separated by chromatography on silica gel (hexane-CH_2Cl_2 1:1, then CH_2Cl_2). Oxidative cleavage of the glycol 16 ($NaIO_4$, MeOH, H_2O, R.T., 3h) gives the aldehyde 17 (97 %, syrup, $[\alpha]_D^{20}$= +4°).



Since our goal was to prepare an AB ring segment of anthracyclines where all the functionalities are present, instead of using a cold saturated solution of HCl on methylene chloride which would afford[8] the corresponding 1-chloro-1-deoxy tetralin analog to 6, we tried to perform the ring closure with Lewis acids. After a first attempt realized in the presence of $AlCl_3$ in CH_2Cl_2 at -78°C which gave a poor yield of a mixture of compounds not analyzed in detail, a better result was obtained with $SnCl_4$ on the same conditions (CH_2Cl_2, -78°C). This affords in a good yield (80 %) and in a stereospecific manner the tetralin 6 as a crystalline compound (m.p. 148°C, $[\alpha]_D^{20} = +31°$). The cis configuration 1(S), 3(S) of 6 was unambiguously established from n.m.r. data at 270 MHz in $CDCl_3$[14], the signal which appeared at δ 5.06 ppm as a broad singlet ($\nu_{1/2} \simeq 7$ Hz after D_2O exchange) being in full agreement with a pseudo-equatorial proton. This structure was fully supported by the chemical ionization mass spectrometry with NH_3 as reagent gas, which exhibits ions at m/z 312 ($M + NH_4^+$), 295 ($M + H^+$), 294 ($M^{+\cdot}$) and 277 ($M + H^+ - H_2O$).

The high stereoselectivity of the ring closure leading to the 1(S) isomer is noteworthy and examination of the two possible transition states A and B of 17 during this step shows that A is favored compared to B, since in the former, chelation can occur between aldehyde and oxygene of the tertiary alkoxy group as indicated on figure 2. Such an effect of chelation with $SnCl_4$ or $TiCl_4$ on diastereoselectivity has been already reported[15] during aldol condensation to β-alkoxy-aldehydes in dry CH_2Cl_2 at -78°C.

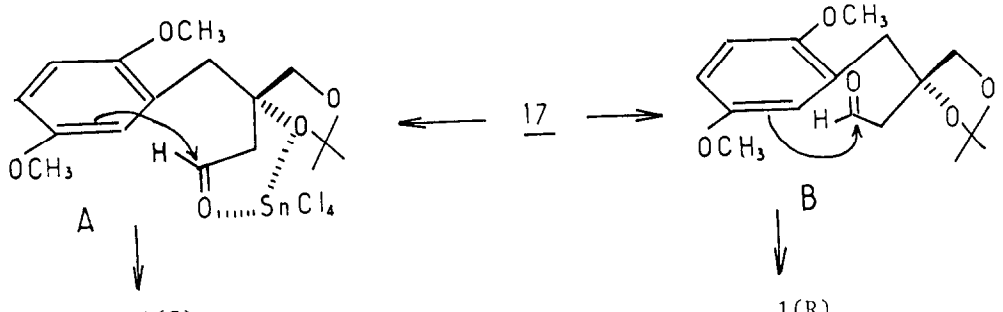


Figure 2

Protection of the benzylic alcohol of 6 and condensation with CD ring precursors[7] are now under investigation to afford new anthracyclines.

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10 Analytical data of the new compounds described here, including microanalyses, mass spectra and ^1H N.M.R. are in excellent agreement with the assigned structures ; $|\alpha|_D$ were measured in $CHCl_3$ (c = 1 to 2).

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14 Compound 6 : ^1H NMR : δ 6.64 ppm (s, 2H, arom.) ; 5.06 (m, 1H, 1-H, J = 9 Hz, J' = 6 ; J'' = 4) ; 4.16 (d, 1H, J = 9, OH ; disap. after D_2O exchange) ; 3.85 (s, 2H, 3'-H) ; 3.78 and 3.72 (2s, 6H, OCH_3) ; 3.03 (d, 1H, 4a-H) and 2.66 (d, 1H, 4b-H) (J = 18) ; 2.35 (dd, 1H, 2a-H, J = 14 ; J' = 4) and 1.98 (dd, 1H, 2b-H, J = 14 ; J' = 6) ; 1.43 and 1.36 (2s, 6H, isopropylidene).

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