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ANTHRACYCLINONES IV* A SYNTHETIC APPROACH TOWARDS RHODOMYCINONES

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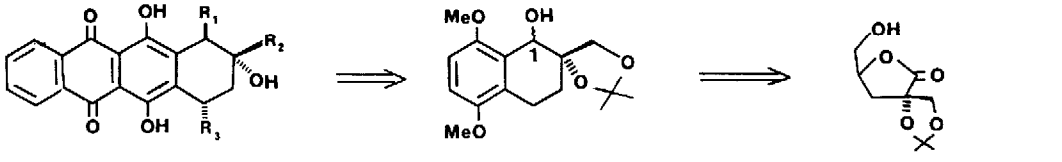
Abstract: *A precursor of 4-deoxy-γ and β-rhodomycinones has been synthesized from α-D-isosaccharino-lactone via annelation of quinone monoacetals with the anion of 3-cyano-isobenzofuranone.*

Considerable efforts have been made to synthesize enantiomerically pure anthracyclinones [1], especially in the case of 4-demethoxy daunorubicin and doxorubicin which are more potent and less toxic[2] than the parent compounds and are not available by a fermentation process[3]. Some other 4-demethoxy anthracyclines also appear promising. We previously reported the synthesis of aglycon analogs of daunomycinone from the chiral synthon, α-D-isosaccharino-lactone[4-6]. In the course of our study on the synthesis of potentially active anthracyclines we are now interested by the synthesis of 4-deoxy analogs of γ-rhodomycinone 1 and β-rhodomycinone[7] 2.

Interestingly, for our purpose, the tetralin intermediate 4, already prepared[6] from α-D-isosaccharino-lactone during the synthesis of 4-demethoxy-9-deacetyl-9-hydroxymethyl-daunomycinone 3 seemed to be (figure 1) a good precursor for the target molecules but the C-1 configuration of 4 had to be controlled.



	R_1	R_2	R_3
1	OH	C_2H_5	H
2	OH	C_2H_5	OH
3	H	CH_2OH	OH

4

α D-isosaccharino lactone

Figure 1

Thus intramolecular cyclization of 5 with $SnCl_4$ as catalyst was reinvestigated (figure 3) and a mixture of tetralin derivatives 4a and 4b, easily separated by chromatography, was obtained in a 5:1 ratio. The 1-R configuration of the major isomer, 4a, was deduced from comparison of the CD curves of 4a and 4b with the CD curve of the model A (figure 2), the structure of which being earlier assigned[6] by ^1H NMR and confirmed by further transformation into anthracyclinone and comparison with known aglycones.

* Part III: see reference[6].

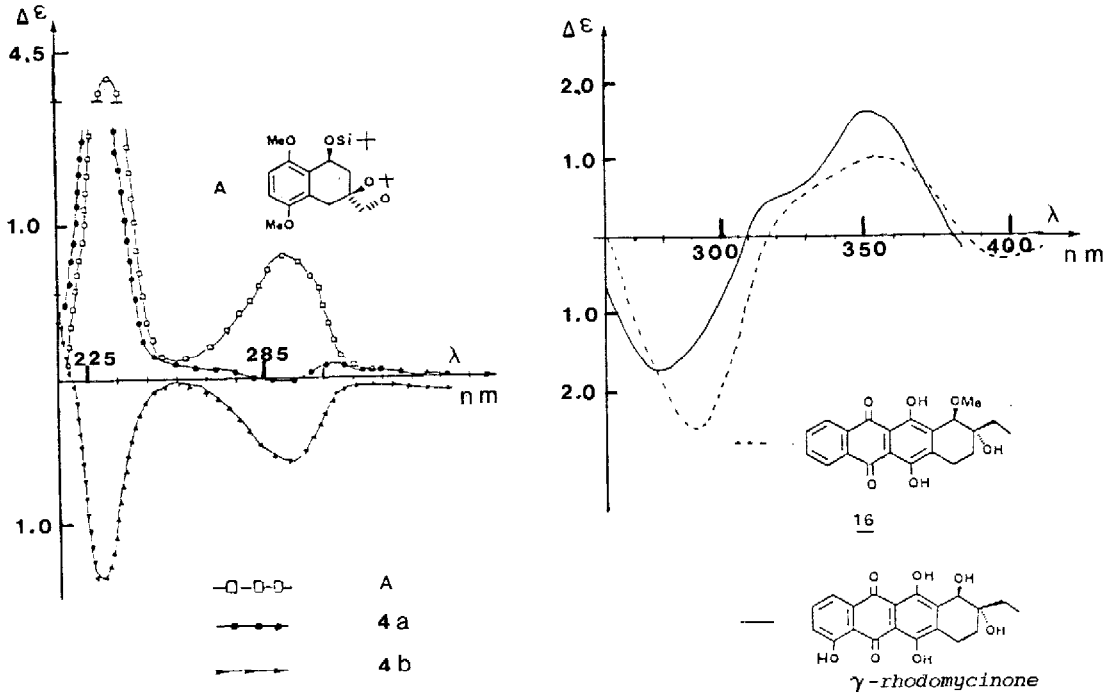


Figure 2. CD curves of 4a, 4b, A, 16 and γ-rhodomycinone.

The high stereocontrol observed in favor of the anti isomer (1R, 2R) can be explain as follows (figure 3): the familiar chelate Cram "cyclic model" of asymmetric induction is not followed [8,9], and the observed preference may be attributed to the presence of the β-alkoxy function which allow such an efficient complexation of metal tin in the arrangement B that the system has nothing to gain from the anti Cram chelate A which is so characteristic of the α-alkoxy carbonyl aldehydes. The result is consistent with a report of Mukaiyama[10] concerning the Lewis acid assisted addition of furyl lithium to a closely related system (glyceraldehyde) where an enhancement of the antiselectivity was also observed.

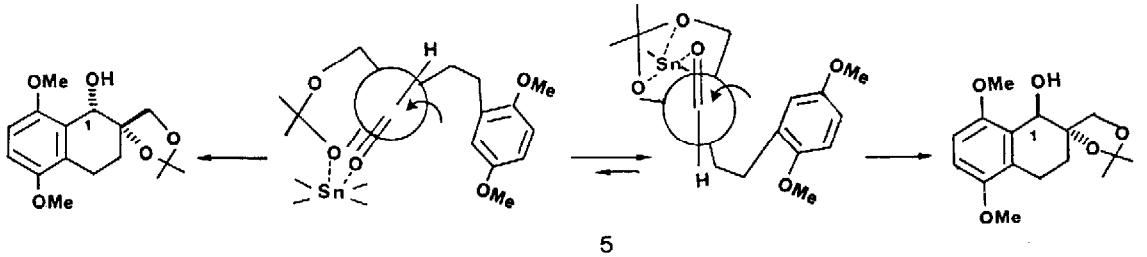


Figure 3

The right configuration of 4a (mp 94°C, $(\alpha)_D$ - 60°)[11] being well established, the next step consisted in the transformation of the hydroxymethyl side-chain into an ethyl. Thus, after protection of the benzylic alcohol as a methyl ether (MeI, DMSO, KOH), hydrolysis of the acetal ring of 6 (mp 55°C, $(\alpha)_D$ - 62°) was carried out in the presence of 80% aqueous AcOH to afford the diol 7 (syrup, $(\alpha)_D$ - 68°) in 85% overall yield for the two steps. Mesylation of 7 (MsCl, pyridine, 65%) followed by treatment of compound 8 (mp 112°C, $(\alpha)_D$ - 57°) with Me_2CuLi in ether at 0°C afforded the ethyl derivative 9 (syrup, $(\alpha)_D$ - 71°) in 76% yield.

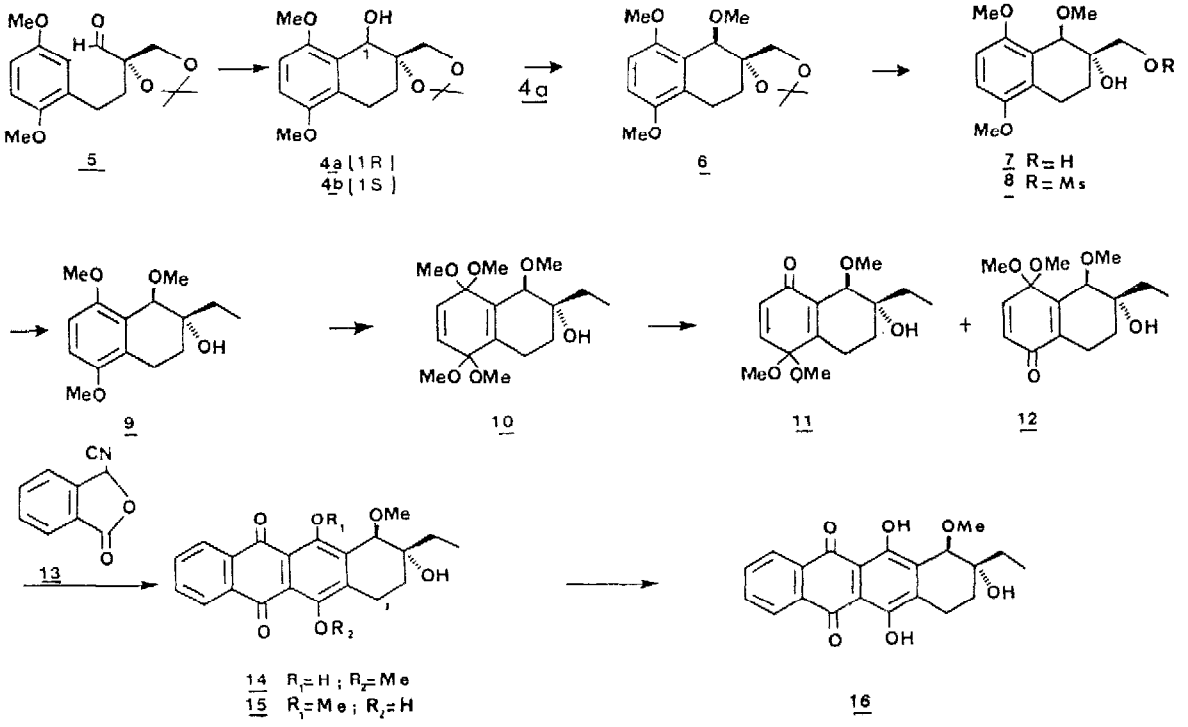


Figure 4

The tetralin 9 was subjected to anodic oxidation[12] to yield the quinone bisketal 10, immediately hydrolyzed in aqueous AcOH in quinone monoketals 11 and 12 (66%)[13]. By annelating this mixture with the anion of 3-cyano-1(3H)-isobenzofuranone 13 by the known procedure[14], the anthracyclinones 14 and 15 were produced in 50% overall yield and a 3:1 ratio. Separation of these compounds could be achieved by chromatography but this mixture was inconsequential for the following step. Deprotection of the phenol ethers was realized by treatment of the crude mixture with boron trichloride at -78°C and gave the anthracyclinone 16[15] (mp 170°C, $(\alpha)_D$ + 83°, c 0.07) in 98% yield. The CD curve of 16 was superposable to the curve of γ rhodomycinone[16] as shown in figure 2.

Cleavage of the C-1 methyl ether of 16 proved to be rather difficult since 16 was unaffected by treatment with reagents such as Me_2BBr[17], Me_3SiI[18], CF_3COOH[19] or EtSH, $AlBr_3$[20]. Due to these difficulties, a more suitable protecting group such as a methylthiomethyl ether[21] must be used whereas introduction of a benzylic alcohol at C-4 should give a new aglycone suitably protected for regioselective glycosylations. Both attempts are now under investigation.

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11. All compounds were characterized by IR and ^1H NMR spectroscopy. $(\alpha)_D$ were measured in $CHCl_3$ solution, c = 1. For new compounds, adequate analysis and mass spectroscopic data have been obtained. Compound 4: δ 6.47 (s, 2H, Ar), 4.57 (s, 1H, H-1), 4.16 (d) and 3.78 (d) (AB, J = 9 Hz, H-2'), 3.56 (s, OMe), 3.52 (s, OMe), 2.81-2.48 (m, 3H, H-4 and OH), 1.80 (m, 2H, H-3), 1.21 (s, 3H, Me), and 1.14 (s, 3H, Me); DCI/NH_3 ($C_{16}H_{22}O_5$) m/z 312 ($M + NH_4^+$), 295 ($M + H^+$), 294, 277, 254, 236.

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13. The ratio was deduced from the ratio of anthracyclinones obtained in the next step.

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15. Compound 16: ^1H NMR: δ 13.72 (s, OH) and 13.41 (s, OH), 8.22 (m, 2H, Ar), 7.68 (m, 2H, Ar), 4.40 (s, 1H, H-10), 3.75 (s, 3H, OMe), 2.97 (dd, 1H) and 2.78 (m, 1H) (ABX, J = 18, J' = J" = 8 Hz, CH_2-7), 2.04-1.86 (m, CH_2-8), 1.85-1.74 (q, J = 8 Hz, CH_2-CH_3), 1.08 (t, CH_2-CH_3); DCI/NH_3 ($C_{21}H_{20}O_6$) m/z 396 ($M + NH_4^+$), 369 ($M + H^+$), 354, 337, 210.

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