A Convenient AB-Ring Segment for β-Rhodomycinone, β-Isorhodomycinone, α_2-Rhodomycinone, and α-Citromycinone using a Novel Oxygenation Reaction

Charles E. Coburn, D. Keith Anderson, and John S. Swenton*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, U.S.A.

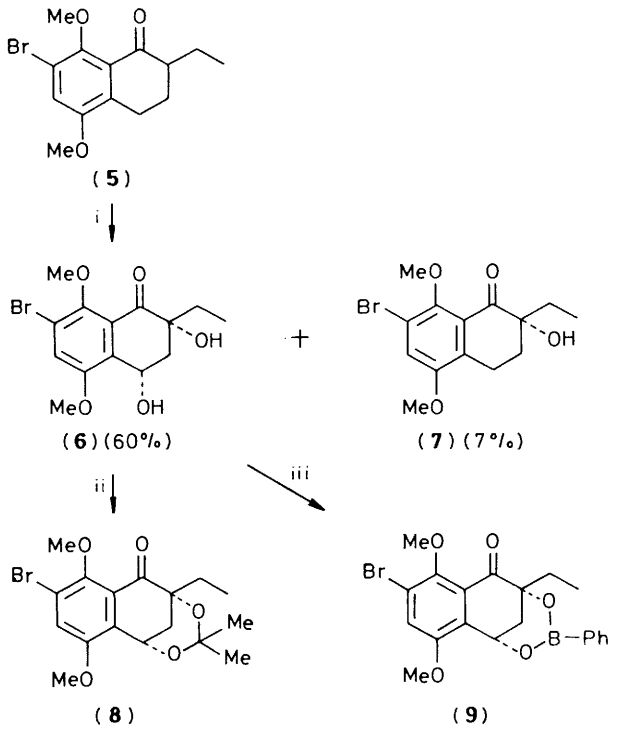
An unusual bishydroxylation of 2-ethyl-5,8-dimethoxy-7-bromo-1-tetralone gives an AB-ring segment suitable for elaboration to certain anthracyclinones.

The anthracyclinones[1] (**1**)—(**4**) have the interesting trihydroxy-substitution pattern in the A-ring of the tetracyclic framework. Several synthetic methods have been devised to couple highly functionalized AB-ring systems to a CD-ring segment to form daunomycinone-type anthracyclinones.[2] Such a synthetic approach could be equally applicable to other anthracyclinones if suitably substituted AB-ring systems were available. We report here a short stereoselective route to an AB-ring system having the A-ring substitution pattern of the anthracyclinones (**1**)—(**4**).

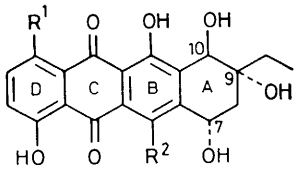
When the tetralone[3] (**5**) (10 g) was oxygenated at −15 °C in a mixture of dimethylformamide, t-butyl alcohol, triethyl phosphite, and potassium t-butoxide (80 ml, 45 ml, 12.5 ml, and 17.9 g, respectively), a major and a minor product were isolated by silica gel chromatography. The minor product, m.p. 117—118 °C, was identified as the expected hydroxy-ketone (**7**). When (**7**) was subjected to the oxygenation conditions, it was converted into (**6**). The major product, m.p. 107.5—110 °C, is assigned as structure (**6**) on the basis of the evidence outlined below. Mass spectral and combustion analytical data showed the formula of this major product to be $C_{14}H_{17}O_5Br$. The ^{13}C n.m.r. spectrum of (**6**) showed signals at δ 7.1, 29.7, 40.8, 56.1, 62.0, 62.5, 76.4, 119.0, 119.8, 125.2, 133.0, 149.7, 153.2, and 199.1 p.p.m., the signals at δ 76.4 and 62.5 corresponding to the tertiary and secondary C-OH. The ^1H n.m.r. spectrum [δ 0.80 (t, *J* 8 Hz, 3 H), 1.43—1.70 (m, 2 H), 2.03 (dd, *J* 9.0, 13.5 Hz, 1 H), 2.70 (dd, *J* 6.8, 13.5 Hz, 1 H), 3.90 (s, 3 H), 3.93 (s, 3 H), 5.10 (dd, *J* 6.8, 9.0 Hz, 1 H), and 7.28 (s, 1 H)] in $CDCl_3$ (D_2O washed) showed an ABX pattern for the methylene group and the benzylic proton as well as the other absorptions expected for structure (**6**). To establish that no structural rearrangement occurred during the oxygenation, (**6**) was reduced with a zinc–copper couple to 2-ethyl-5,8-dimethoxy-7-bromo-1-naphthol.

Having established the basic substitution pattern of (**6**), the *cis*-1,3-diol stereochemistry was proven by forming cyclic derivatives with 2-methoxypropene and phenylboronic acid under mild conditions. Thus, reaction of (**6**) at 0 °C with 2-methoxypropene[4] gave the dimethylmethylenedioxy-compound (**8**), m.p. 119—121 °C, in quantitative yield, while reaction with phenylboronic acid[2c] at room temp. gave (**9**), m.p. 90–91 °C, in 96% yield. Thus, the oxygenation reaction of (**5**) not only incorporates two key oxygen groups at the eventual C-7 and C-9 positions of what will be the A-ring of the anthracyclinone but also establishes the proper relative stereochemistry at these two centres (Scheme 1).

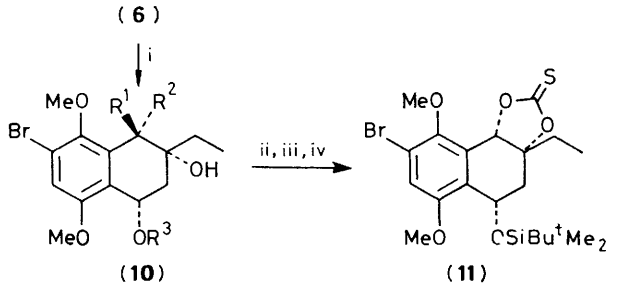
Finally, there remained reduction of the carbonyl to give the *trans*-C-9–C-10 stereochemistry of the A-ring of the anthracyclinones. Reduction of (**6**) with lithium borohydride in toluene gave (**10a**) (78%), m.p. 128–129 °C, and (**10b**) (16%), as a glass which were easily separable by silica gel chromatography. The minor product was established as having the all-*cis*-stereochemistry, (**10b**), by first selectively blocking the less hindered benzylic hydroxy-group with



Scheme 1. *Reagents:* i, $KOBu^t$, $(EtO)_3P$, O_2; ii, *p*-$MeC_6H_4SO_3H$, $MeC(OMe)=CH_2$; iii, *p*-$MeC_6H_4SO_3H$, $PhB(OH)_2$.



(**1**) R^1 = H, R^2 = OH: β-rhodomycinone
(**2**) R^1 = R^2 = OH: β-isorhodomycinone
(**3**) R^1 = OH, R^2 = H: α_2-rhodomycinone
(**4**) R^1 = R^2 = H: α-citromycinone



a; R^1 = OH, R^2 = R^3 = H
b; R^1 = R^3 = H, R^2 = OH

Scheme 2. *Reagents:* i, $LiBH_4$, toluene, ii, NaH, iii, CS_2, iv, MeI.

t-butyldimethylsilyl chloride [(**10c**), R^1 = H, R^2 = OH, R^3 = $SiBu^tMe_2$, m.p. 110–112 °C] and then reaction of this product as shown in Scheme 2 to obtain the thiomethylene-dioxy-compound (**11**), m.p. 143.3–143.5 °C. While the major product (**10a**) selectively reacted to give (**10d**) (R^1 = OH, R^2 = H, R^3 = $SiBu^tMe_2$, m.p. 168–169 °C), no cyclic thio-compound could be formed. This reaction sequence then affords (**10a**) stereoselectively in two steps from tetralone (**5**) in 47% overall yield. This triol, suitably protected, should prove valuable in the synthesis of the anthracyclinones (**1**)—(**4**).

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