Tetrahedron Letters,Vol.25,No.31,pp 3355-3358,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHETIC APPROACHES TO NEW ANTHRACYCLINES: 4,11-DIDEOXY-2-HYDROXY-β-RHODOMYCINONE AND ITS GLYCOSIDES

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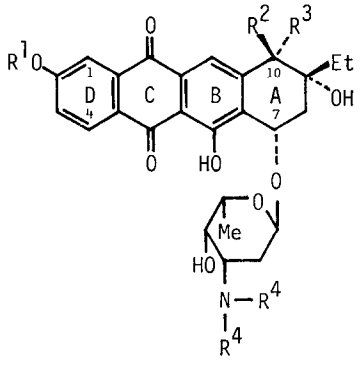
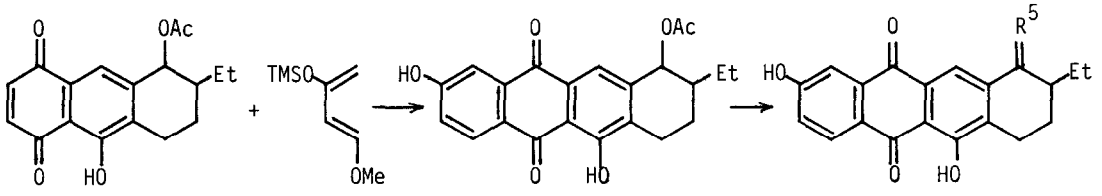
Summary: (±)-2-Acetoxy-4,11-dideoxy-10-oxo-β-rhodomycinone [(±)-6a] was synthesized from the tricyclic quinone (1) by a short efficient route in an overall yield of about 54%. Reaction of (±)-6a with protected daunosamine followed by reduction and deprotection provided the optically active α-glycosidated anthracycline (II) with the 7S,9R,10R-configuration. Furthermore, the amino and aromatic hydroxy groups of II were methylated.

In the preceding paper, we reported a total synthesis of racemic 2-hydroxyaklavinone using the functionallized tricyclic quinone (1)[1]. Availability of 1 as an 11-deoxyanthracycline precursor prompted us to synthesize new anthracyclines. New anthracycline antibiotics, 2-hydroxyaclacinomycin A[2] and 7-O-(cinerulosyl-2-deoxyfucosyl-rhodosaminyl)-β-rhodomycinone[3] have been reported recently. These antibiotics showed strong theraputic properties against leukemia L1210 in mice[4]. Thus a synthesis of hybrid analogs might give more potent drugs and provide information concerning the structure-activity relationships of anthracyclines. This communication describes a regio- and stereo-specific synthesis of β-rhodomycinone-related anthracyclinones and their daunosaminyl- (I,II) and rhodosaminyl glycosides (III, IV).



	R^1	R^2	R^3	R^4
I	H	=O		H
II	H	OH	H	H
III	H	OH	H	Me
IV	Me	OH	H	Me

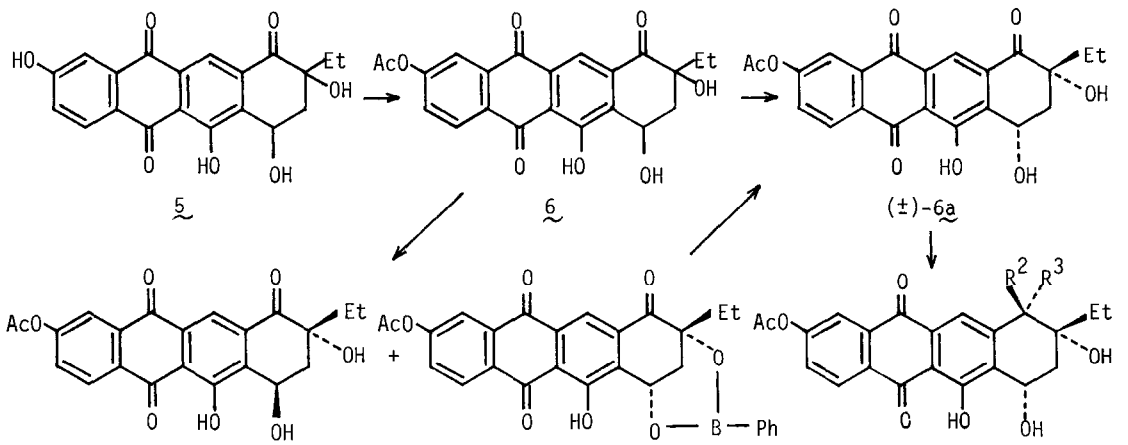
Cycloaddition of 1 and 1-methoxy-3-trimethylsiloxy-1,3-butabiene[5] in refluxing CH_2Cl_2 (followed by aromatization by air-bubbling in the presence of Et_3N) gave 2 exclusively (mp 276 ~279°C, 90%). Such orientation on Diels-Alder reaction has already been reported by Boeckmann[6]. Hydrolysis of 2 with 0.1N NaOH in MeOH afforded the triol 3 which was subjected to Jones oxidation to yield the key intermediate 4 (mp 238 ~ 243°C, 94% from 2).



1 2 3: R^5=H, OH
4: R^5=O

Hydroxylation of 4 at the C-7 and C-9 positions was stereospecifically achieved (O_2/^{t}BuOK/$P(OMe)_3$, ^{t}BuOH/DMF)[7], providing the tetraol 5 in 84% yield. To attain a high cis-: trans-diol ratio, the amount of ^{t}BuOK is critically important. The best result (cis:trans = 93:7) was obtained with 4 equiv. ^{t}BuOK and use of more than 4.5 equiv. of the base resulted in a poor ratio. The tetraol 5 was selectively acetylated into monoacetate 6 (82%) using $Ac_2O/B(OH)_3$/pyr. in THF. The cis-diol (±)-6a[8] (mp 187 ~191°C) was isolated by crystallization from $CHCl_3$/hexane. On the other hand, the treatment of the mixture 6 with phenylboronic acid in toluene gave, after chromatography, the benzene boronate (±)-7 (mp 267 ~272°C) and the trans-diol (±)-6b. The boronate (±)-7 was easily converted to (±)-6a (hexylene glycol/TsOH, $CHCl_3$).

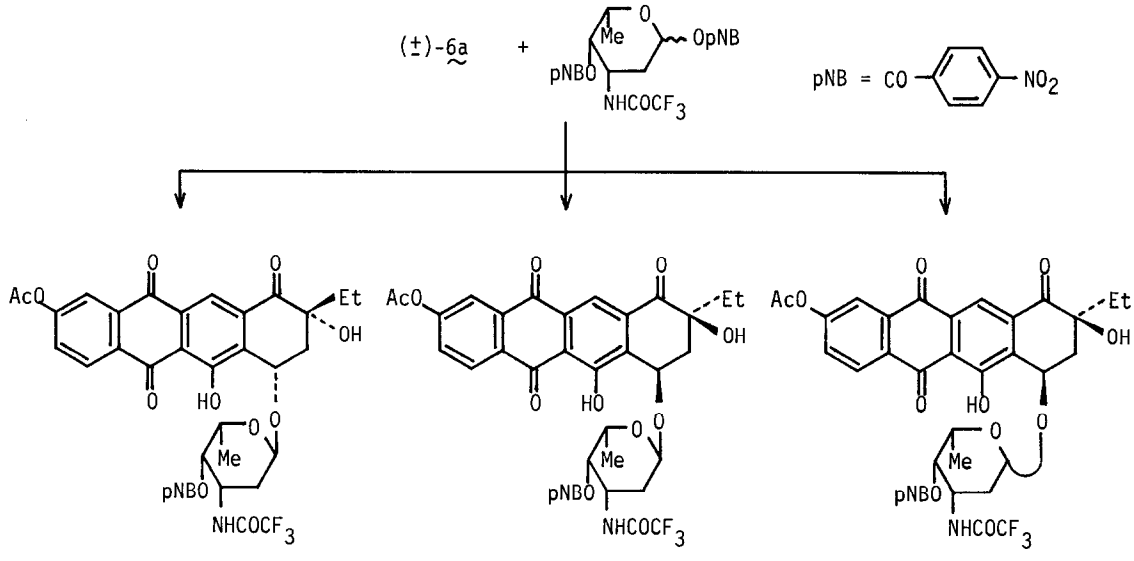
The carbonyl of (±)-6a was reduced with excess $NaBH_4$ in 20% dioxane/benzene to afford a 3:1 mixture of (±)-8a (mp 177 ~ 179°C) and (±)-8b in 76% combined yield.



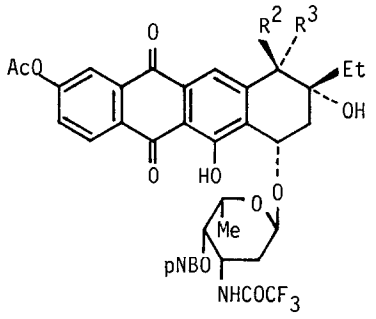
5 6 (±)-6a
(±)-6b (±)-7
(±)-8a: R^2=OH, R^3=H
(±)-8b: R^2=H, R^3=OH

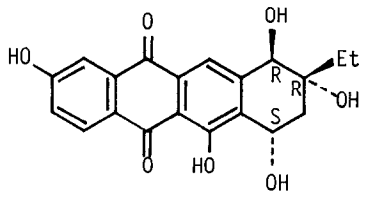
For the glycosidation reaction we chose (±)-6a, because (±)-8a required appropriate protection of the C-10 hydroxy group. Thus the anthracyclinone (±)-6a was allowed to react with 1,4-bis-O-p-nitrobenzoyl-3-N-trifluoroacetyldaunosamine[9] (2 equiv.) in the presence of $SnCl_4$[10] (0.5 equiv.) in CH_2Cl_2 at 23°C for 45 min. After chromatography, the desired α-glycoside 9 (mp 159 ~ 162°C, $[\alpha]_D^{25}$-100°/MeOH, 31.4%), its isomeric glycosides 10 (17%) and 11 (13.8%) were obtained, but no β-glycoside of 9 was seen. The α-configuration of the glycosidic linkage in 9 was readily confirmed by ^1H NMR (anomeric proton at δ5.70, doublet, J = 3.5Hz).

Deprotection of 9 with 0.1N NaOH in MeOH provided the keto anthracycline glycoside I (mp 187 ~ 192°C, dec., $[\alpha]_D^{24}$+49°/MeOH). $NaBH_4$ reduction of 9 in 20% dioxane/benzene gave a 72:28 steric mixture of the C-10 alcohols which were separated into the desired compound 12 (mp 161 ~164°C, 53%) and its C-10 epimer 13 on silics gel plates using 4:1 benzene:acetone.



9 10 11





14

12: R^2=OH, R^3=H

13: R^2=H, R^3=OH

The compound 12 was deprotected with 0.1N NaOH in MeOH, affording the daunosaminyl glycoside II (mp ~178°C, dec., $[\alpha]_D^{24}$+75°/MeOH, ~100%). When II was hydrolyzed with 0.1N HCl at 80°C for 1 hr, the optically pure anthracyclinone 14 ($[\alpha]_D^{24}$+309°/dioxane) was obtained. The CD-curve of 14 in dioxane was similar to that of β-rhodomycinone[11], indicating the 7S,9R, 10R-configuration of the ring A.

Finally, rhodosaminyl glycoside III[12] (mp ~205°C, dec., $[\alpha]_D^{24}$+136°/MeOH) was synthesized from II by reductive N-methylation[13] (37% formalin/$NaBH_3CN$/AcOH, CH_3CN). III was further methylated into 2-methoxyanthracycline IV (mp 152 ~ 156°C, NMR($CDCl_3$) δ2.24: NMe_2, 4.00: ArOMe) using diazomethane so that the relative effect of the 2-hydroxy group on antitumor activity could be obtained. The in vitro antitumor activity of the resulting glycosides will be reported elsewhere.

References and notes

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8. Proton resonances of the C-7 OH and C-9 OH of cis-diol (±)-6a were observed at δ4.15(d, J=2.5 Hz) and 3.76(s), while the corresponding signals of trans-diol (±)-6b shifted upper-field by 9.5 ppm and 2.3 ppm, respectively.
   (±)-6a: ν_{max}^{KBr} 1765, 1705, 1695, 1670, 1625 cm^{-1}; NMR($CDCl_3$) δ0.92(t, J=7, 3H), 1.45 ~ 1.9(m, 2H), 2.23(dd, J=9, 13.5, 1H), 2.40(s, 3H), 2.79(dd, J=6.6, 13.5, 1H), 3.76(s, 1H), 4.15(d, J=2.5, 1H), 5.40[m, 1H; dd (by irradiation at δ4.15), J=6.6, 9], 7.61(dd, J=2, 9, 1H), 8.08(d, J=2, 1H), 8.40(d, J=9, 1H), 8.46(s, 1H), 13.6(s, 1H).
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12. III: λ_{max}^{MeOH} 223, 272, 413 nm; ν_{max}^{KBr} 1665, 1620 cm^{-1}; NMR(3:1 $CDCl_3/CD_3OD$) δ1.06(t, J=7, 3H), 1.34(d, J=7, 3H), 1.5 ~ 2.9(m, 6H), 2.47(s, 6H), 5.10(m, 1H), 5.53(bs, W_H=6, 1H), 7.19(dd, J=2.5, 9, 1H), 7.56(d, J=2.5, 1H), 7.85(s, 1H), 8.16(d, J=9, 1H).
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(Received in Japan 16 April 1984)