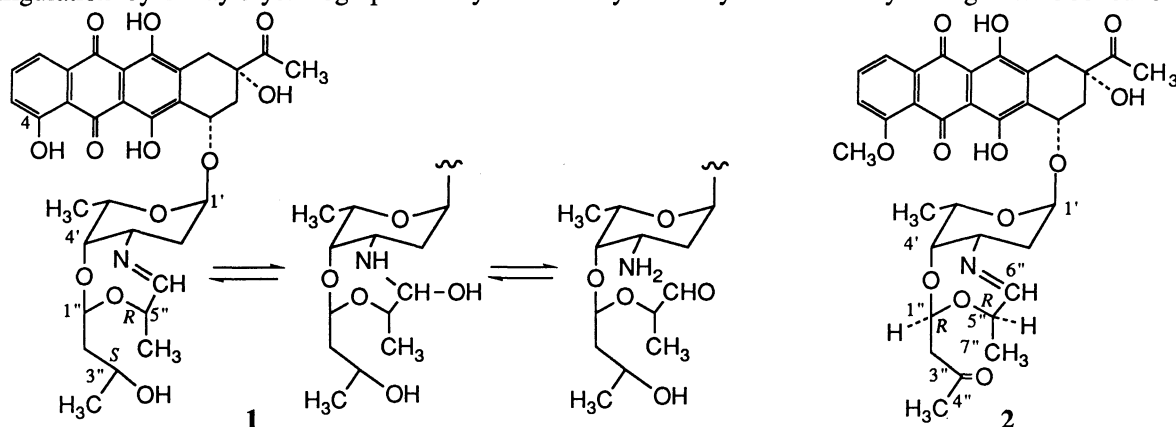


Synthesis of 3''-Dehydro-4-*O*-methylbarminomycin II Having an Eight-membered
Acetal-azomethine Ring

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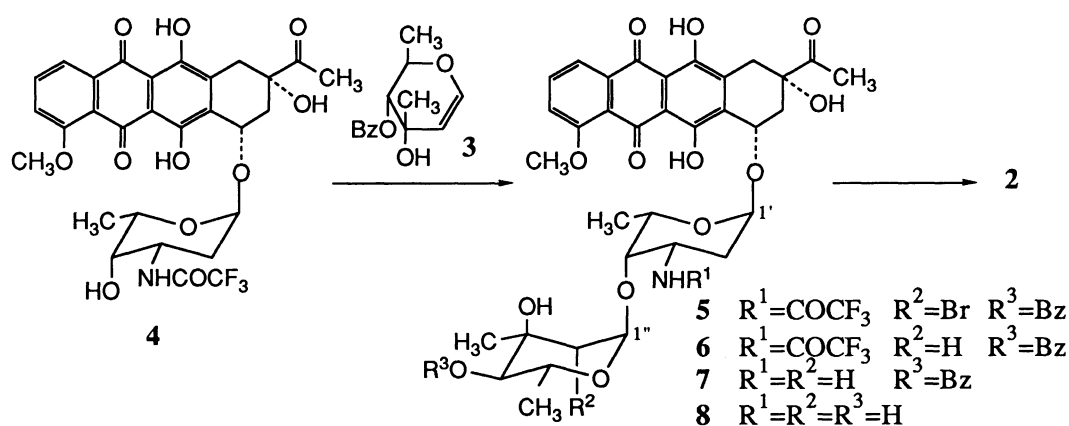
Barminomycin I and II, an extremely potent antitumor anthracyclines, have a unique eight-membered azomethine or carbinolamine structure. (1''*R*, 5''*R*)-3''-Dehydro-4-*O*-methylbarminomycin II was first synthesized through the hypothetical biogenetic intermediate.

Barminomycins I and II^{1,2)} (**1**), are new type of anthracycline antibiotics having 4'-*O*-substituent with acetal and aldehyde functions and show the equilibrium involving the eight-membered azomethine and carbinolamine. The stereochemistries at C-3'' and C-5'' of **1** were determined, but C-1'' position was not yet. Takahashi,³⁾ however, described that C-1'' position of baumycins B1 and B2 having a similar 4'-*O*-substituent was *R*-configuration by X-ray crystallographic analysis. The cytotoxicity of barminomycins against P388 leukemia



cells is more than 500 times stronger than that of doxorubicin (adriamycin). Because of their activity and unique eight-membered structure, the synthesis of the analogue of **1**, (1''*R*, 5''*R*)-3''-dehydro-4-*O*-methylbarminomycin II (**2**) has been attempted starting from daunorubicin (daunomycin). The interesting 4'-*O*-side chain was presumed to be produced from 4'-*O*-glycoside (**8**) by the biologically oxidative cleavage of vicinal diol. Based on this hypothetical biogenesis, the synthetic way for **2** was designed.

Glycal (**3**) was prepared from methyl 4-*O*-benzoyl-2,6-dideoxy-3-*C*-methyl- α -D-ribo-hexopyranoside⁴⁾ according to Tatsuta's method.⁵⁾ Stereoselective glycosidation of *N*-trifluoroacetyl-daunomycin (**4**) with **3** (NBS/CH₃CN,⁶⁾ 0 °C, 4 h, 62%) gave 4'-*O*-(4-*O*-benzoyl-2-bromo-2,6-dideoxy-3-*C*-methyl- α -D-altropyranosyl)-3'-*N*-trifluoroacetyl-daunomycin (**5**) and no β -anomer, along with a trace of 9-*O*-glycoside. In ¹H NMR spectrum of **5**, an anomeric proton of C-1'' position appeared at δ 5.02 as a doublet with *J*=3 Hz.⁷⁾ It showed the α -linkage at C-1''. Debromination of **5** with *n*-Bu₃SnH (AIBN/benzene, 60 °C, 28 h, 49%) gave **6**. The practical removal of 3'-*N*-trifluoroacetyl group in anthracyclines having 4'-*O*-substituent has not been known



yet. Usual deprotection of trifluoroacetyl group under alkaline condition always gave the complicated products. This problem was overcome by the treatment of **6** with sodium hydroxide in two layers (saturated aq NaCl contained 1 mol dm^{-3} NaOH/ CHCl_3 with vigorous stirring, room temp, 2 h) to give **7** in quantitative yield, which was hydrolyzed (10% aq $\text{K}_2\text{CO}_3/\text{MeOH}$, 0°C , 18 h, 30%) to afford **8**,⁸⁾ the important precursor for **2**. Finally, periodate oxidation of **8** ($\text{NaIO}_4/\text{MeOH-H}_2\text{O}$, room temp, 24 h) provided **2** as the equilibrium mixture. The addition of 10% acetic acid to the reaction mixture, followed by extraction with CHCl_3 gave cyclized imine **2**⁹⁾ in 10% yield. Thus, we have devised the synthesis of **2** starting from glycal **3** and *N*-trifluoroacetyl-daunomycin (**4**) through the hypothetical biogenetic intermediate **8**.

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- 7) **5**: Mp $128\text{--}136^\circ\text{C}$ (decomp); $[\alpha]_D^{+82}$; FABMS m/z 949 and 951 (M^+); ^1H NMR (CDCl_3) δ 1.30 (3H, *d*, $J=6.5$ Hz, 6''-H), 1.36 (3H, *d*, $J=6.5$ Hz, 6'-H), 1.46 (3H, *s*, 3''a-H), 3.84 (1H, *br s*, 4'-H), 4.05 (3H, *s*, OCH_3), 4.20 (1H, *d*, $J=3$ Hz, 2''-H), 4.34 (1H, *m*, 3'-H), 4.45 (1H, *dq*, $J=9.5$ and 6.5 Hz, 5''-H), 5.02 (1H, *d*, $J=3$ Hz, 1''-H), 5.31 (1H, *d*, $J=9.5$ Hz, 4''-H), and 5.55 (1H, *br d*, $J=3.5$ Hz, 1'-H).
- 8) **8**: Mp $199\text{--}200^\circ\text{C}$ (decomp); $[\alpha]_D^{+220}$; FABMS m/z 672 (MH^+); ^1H NMR (CD_3OD) δ 1.26 (3H, *s*, 3''a-H), 1.27 (3H, *d*, $J=6$ Hz, 6''-H), 1.36 (3H, *d*, $J=6.5$ Hz, 6'-H), 1.77 (1H, *dd*, $J=15$ and 4 Hz, 2''-H), 1.86 (1H, *br dd*, $J=12.5$ and 4 Hz, 2'-H_{eq}), 2.02 (1H, *dt*, $J=12.5$ and 3.5 Hz, 2'-H_{ax}), 2.09 (1H, *br d*, $J=15$ Hz, 2''-H), 3.03 (1H, *d*, $J=9.5$ Hz, 4''-H), 3.62 (1H, *m*, 3'-H), 3.64 (1H, *br s*, 4'-H), 4.15 (1H, *m*, 5''-H), 4.30 (1H, *br q*, $J=6.5$ Hz, 5'-H), 4.8 (behind HOD signal, 1''-H), 5.47 (1H, *br d*, $J=3.5$ Hz, 1'-H).
- 9) **2**: FABMS: m/z 652 (MH^+), ^1H NMR ($\text{DMSO}-d_6$) δ 1.16 (3H, *d*, $J=6.5$ Hz, 6''-H), 1.29 (3H, *d*, $J=7.0$ Hz, 7''-H), 1.57 (1H, *br t*, 2'-H_{ax}), 1.71 (1H, *br d*, 2'-H_{eq}), 2.13 (2H, *br d*, $J=4.5$ Hz, 8-H), 2.25 (3H, *s*, 14-H), 2.43 (3H, *s*, 4''-H), 2.95 (2H, *ABq*, $J=18$ Hz, 10-H), 3.72 (1H, *br s*, 4'-H), 3.99 (3H, *s*, OCH_3), 4.26 (1H, *q*, $J=6.5$ Hz, 5'-H), 4.94 (1H, *t*, $J=4.5$ Hz, 7-H), 5.2 (1H, *m*, 5''-H), 5.23 (1H, *br s*, 1'-H), 5.93 (1H, *br d*, 1''-H), 7.55 (1H, *br s*, 6''-H), 7.67 (1H, *m*, 3-H), and 7.93 (2H, *m*, 1 and 2-H).

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