Synthesis of a Potent Rhodomycin, Oxaunomycin, and Its Analogs

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Oxaunomycin (3) and its regioisomer (6) were synthesized by employing regioselective glycosidations of the C-7 hydroxyl group of 10-*O*-acetyl-β-rhodomycinone (16) and the C-10 hydroxyl group of the C-7,9-*O*-phenylboronate (14), respectively, in the presence of trimethylsilyl trifluoromethanesulfonate. Under the Königs–Knorr conditions, 16 was also glycosidated to provide a fluoro sugar analog (7).

Keywords anthracycline antibiotic; oxaunomycin; β-rhodomycinone; regioselective glycosidation; total synthesis

The anthracycline antibiotics, such as daunomycin (**1**) and adriamycin (**2**), are powerful antitumor agents in the treatment of a wide range of human cancers.[1] Although a group of rhodomycins which are structurally similar to **1** and **2** is also known,[2] their clinical applicability had been limited until quite recently because of their strong toxicities.[3] Since the discoveries of new, less toxic rhodomycins such as oxaunomycin (**3**),[4] betaclamycin A,[5] and distrisarubin B,[6] they have been attracting considerable interest as candidate antitumor agents. For example, **3** was found to be about 100-fold more active than **2** against leukemic L-1210 cultures.[4] Although many asymmetric syntheses of anthracyclinones have been accomplished,[7] quite few studies have been reported on the asymmetric syntheses of rhodomycinones.[8] Recently, Krohn and Hamann reported the synthesis of β-rhodomycinone (**5**) by incorporation of (*S*)-α-hydroxybutyric acid.[9] Independently, we have communicated an asymmetric synthesis of γ-rhodomycinone (**4**) using a regioselective coupling reaction of new chiral AB and CD building blocks[10] and we achieved the first total synthesis of oxaunomycin (**3**) from **4** through a regioselective glycosidation of the C-7 hydroxyl group of **5**.[11] We now present a full account of the regioselective glycosidation and syntheses of a 10-*O*-daunosaminyl regioisomer (**6**) and an analog (**7**) containing a 2′-fluoro sugar in place of daunosamine.

γ-Rhodomycinone (**4**) was converted to β-rhodomycinone (**5**) by a similar method to Krohn and Hamann's.[9] The 10-*O*-trifluoroacetate (**8**), prepared from **4** and trifluoroacetic anhydride, was transformed into the C-7 bromide (**9**) by treatment with bromine under irradiation with a daylight lamp. When the bromide (**9**) was treated with 0.1 N NaOH in 1,2-dimethoxyethane (Krohn's procedure),

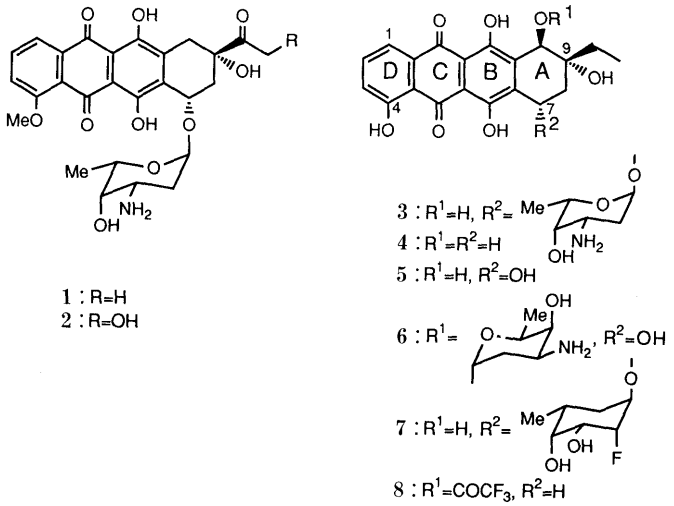

Fig. 1

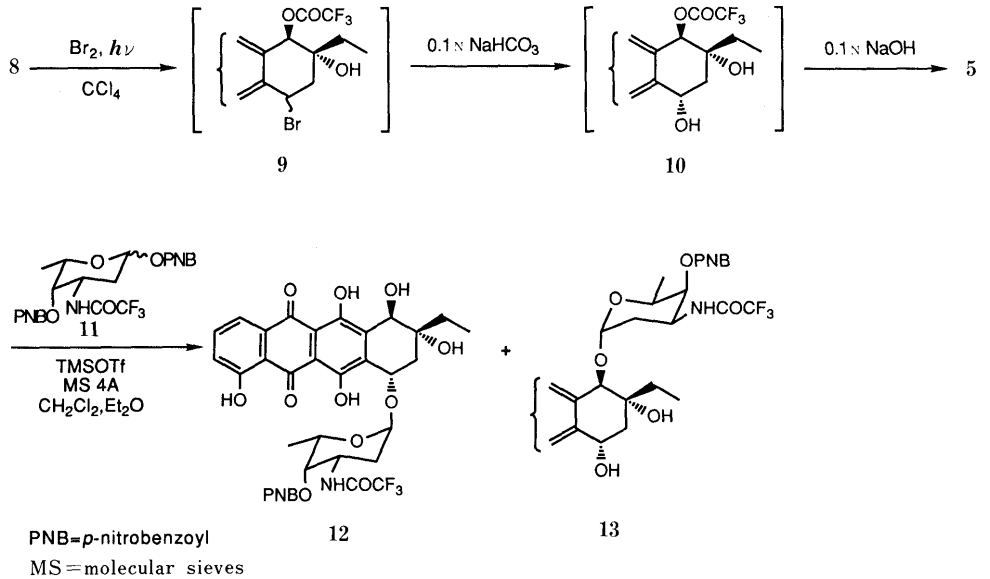

Chart 1

it gave **5** in a poor yield (38%).[12,13] On the other hand, **9** was treated with 0.1 N $NaHCO_3$ in ether to give the 7,9-*cis*-diol (**10**), which on deacylation with 0.1 N NaOH afforded **5** in 70% overall yield from **8**. This product was identical with natural β-rhodomycinone.[14]

For the total synthesis of **3**, the regiochemistry of glycosidation must be controlled. Thus, direct glycosidation of **5** with the 1,4-bis(*O*-*p*-nitrobenzoyl)-L-daunosamine derivative (**11**) using trimethylsilyl trifluoromethanesulfonate (TMSOTf) and molecular sieves 4A in a mixed solvent of anhydrous dichloromethane and anhydrous ether at −15 °C,[15] resulted in an inseparable mixture (2:1) of the C-7 and C-10-*O*-glycosides (**12** and **13**) in 50% yield (Chart 1).

Regioselective glycosidation of the C-7 hydroxyl group of **5** was accomplished by the use of the C-10-*O*-acetylated compound (**16**). The *cis*-phenylboronate (**14**), readily prepared from **5** and phenylboric acid in trifluoroacetic acid (TFA) and benzene,[16] was acetylated with isopropenyl acetate in the presence of a catalytic amount of concentrated H_2SO_4 to give the 10-*O*-acetyl compound (**15**) in 95% yield. The protecting group in **15** was removed by treatment with 2-methylpentane-2,4-diol and acetic acid to afford the desired 10-*O*-acetyl-β-rhodomycinone

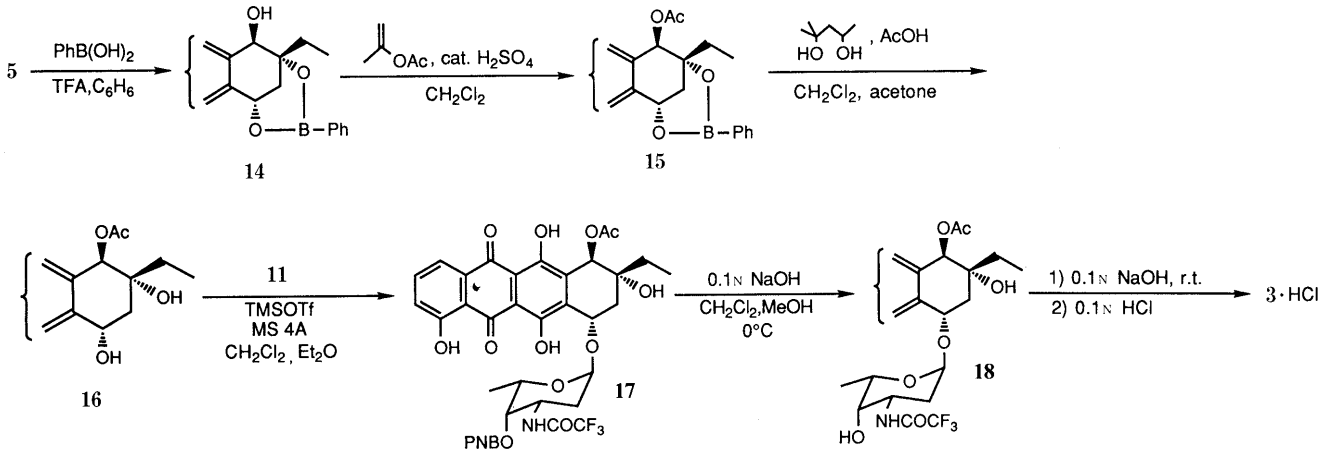

Chart 2

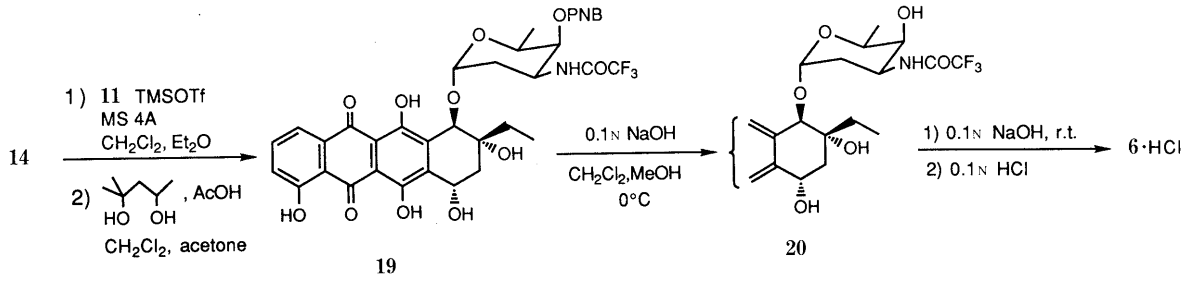

Chart 3

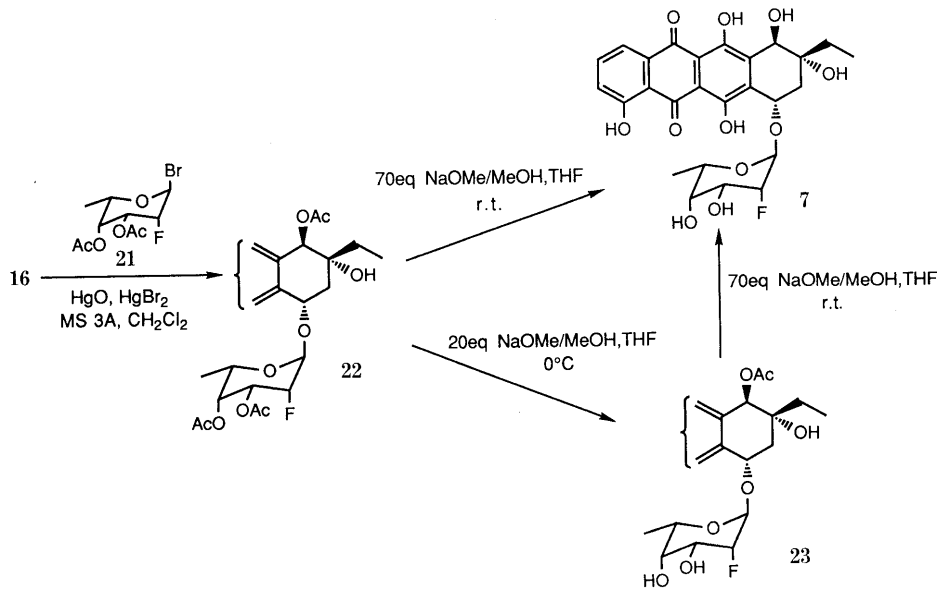

Chart 4

(**16**) in 95% yield. Glycosidation of **16** with the L-daunosamine derivative (**11**) by the same procedure as described for the glycosidation of **5** gave the C-7-*O*-α-glycoside (**17**) in 82% yield. The glycoside (**17**) was deprotected with 1 eq amount of 0.1 N NaOH at 0 °C in dichloromethane–MeOH to give the 4'-hydroxyl compound (**18**), which was further treated with 0.1 N NaOH at room temperature followed by treatment with dilute HCl to afford oxaunomycin·HCl (**3**·HCl) in 81% yield from **17**. This sample was identical with natural oxaunomycin·HCl (Chart 2).[14]

Similarly, the regioisomeric glycoside of **3**·HCl was obtained by direct glycosidation of **14**. Thus, condensation of **14** with **11** followed by deboronation gave the β-rhodomycinone 10-*O*-glycoside derivative (**19**) in 56% yield. The glycoside (**19**) was saponified in two steps *via* **20** to give the desired regioisomer (**6**) as its hydrochloride in 81% yield (Chart 3).

Next, we synthesized an oxaunomycin analog (**7**) in which the daunosamine residue was replaced by 2,6-dideoxy-2-fluoro-α-L-talopyranose, because much attention has recently been focused on the antitumor activities of anthracycline analogs containing a sugar which has an axial 2'-fluoro substituent.[17] Regioselective C-7-*O*-glycosidation of **16** with the protected sugar derivative (**21**) under Königs–Knorr conditions afforded the corresponding glycoside (**22**) in 48% yield. This triacetate was deprotected by treatment with a large excess of NaOMe/MeOH–tetrahydrofuran (THF) at room temperature to give the desired glycoside (**7**) in 62% yield. Alternatively, **7** was obtained from **22** in a stepwise manner. The triacetate (**22**) was treated with NaOMe/MeOH–THF at 0 °C to give the 10-*O*-monoacetate (**23**), which was further treated with an excess of NaOMe/MeOH–THF at room temperature to yield the desired oxaunomycin analog (**7**) containing a 2'-fluoro sugar in 71% yield from **22** (Chart 4).

The preparation of other oxaunomycin analogs by the use of this synthetic method and biological testing for activity against tumor cells are in progress.

Experimental

All melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using a 10 cm cell. Infrared (IR) absorption spectra were recorded on a JASCO HPIR-102 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a JEOL JNM-GX500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS-D300 (for electron impact (EI)- and exact MS) or a JEOL HX-100 [for fast atom bombardment mass spectra (FAB-MS)] mass spectrometer. E. Merck pre-coated thin layer chromatography (TLC) plates, silica gel 60 F_{254} were used for preparative TLC.

10-*O*-Trifluoroacetyl-γ-rhodomycinone (8) Trifluoroacetic anhydride (2 ml) was added to a solution of **4** (25 mg, 0.067 mmol) in dry CH_2Cl_2 (20 ml) at 10 °C and the mixture was stirred at room temperature for 3 h, then concentrated *in vacuo*. To this residue, a mixture of CH_2Cl_2 (30 ml) and saturated aqueous $NaHCO_3$ (15 ml) was added. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from a mixture of hexane–Et_2O to afford **8** (24 mg, 76%) as red crystals, mp 213—217 °C, lit.[18] mp 198 °C. $[\alpha]_D^{25}$ −294° (c=0.057, $CHCl_3$). IR ($CHCl_3$) ν: 3670, 1780, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (t, 3H, J=7.3 Hz, H-14×3), 1.65, 1.75 (each sextet, 2H, J=7.3 Hz, H-13×2), 1.83 (ddd, 1H, J=13.5, 11.5, 6.1 Hz, H-8), 2.10 (ddt, 1H, J=13.5, 6.1, 1.7 Hz, H-8), 2.89 (ddd, 1H, J=19.5, 11.5, 6.1 Hz, H-7), 3.11 (ddd, 1H, J=19.5, 6.1, 1.7 Hz, H-7), 6.24 (d, 1H, J=1.2 Hz, H-10), 7.31 (dd, 1H, J=8.0, 1.2 Hz, H-3), 7.71 (t, 1H, J=8.0 Hz, H-2), 7.88 (dd, 1H, J=8.0, 1.2 Hz, H-1), 12.15 (s, 1H, OH-4), 12.69 (s, 1H, OH-6), 13.56 (s, 1H, OH-11). Exact MS Calcd for $C_{22}H_{17}F_3O_8$: 466.0872. Found: 466.0871.

β-Rhodomycinone (5) A solution of **8** (19 mg, 0.041 mmol) in CCl_4 (30 ml) was treated with two drops of Br_2 and the mixture was irradiated for 30 min with a 100 W daylight lamp. The solvent was evaporated to dryness *in vacuo* and the residue was dissolved in Et_2O (20 ml). Then 0.1 N $NaHCO_3$ (20 ml) was added dropwise to the solution at 5 °C. The mixture was stirred for 15 min at 5 °C, then the organic layer was separated. The organic phase was treated with 0.1 N NaOH (2 ml) at 5 °C. After the mixture had been stirred for 5 min, 1% aqueous HCl (1.5 ml) was added. The ether layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (CH_2Cl_2 : Et_2O=4 : 1) to give **5** (11 mg, 70%) as red crystals, mp 227—230 °C (natural **5**[14] mp 228—231 °C, lit.[9] mp 195 °C, lit.[13] mp 224—225 °C). $[\alpha]_D^{25}$ +111° (c=0.047, $CHCl_3$) [natural **5**[14] $[\alpha]_D^{25}$ +111° (c=0.058, $CHCl_3$), lit.[9] $[\alpha]_D^{20}$ +335° (c=0.012, $CHCl_3$: MeOH=1 : 1)]. IR (KBr) ν: 3350, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (t, 3H, J=7.3 Hz, H-14×3), 1.79, 1.80 (each sextet, 2H, J=7.3 Hz, H-13×2), 2.15 (dd, 1H, J=15.0, 4.2 Hz, H-8), 2.21 (dt, 1H, J=15.0, 1.5 Hz, H-8), 2.68 (br, 1H, OH-10), 3.27 (br s, 1H, OH-9), 3.51 (br, 1H, OH-7), 4.88 (s, 1H, H-10), 5.22 (br, 1H, $\nu_{1/2}$=10.0 Hz, H-7), 7.34 (dd, 1H, J=7.5, 1.2 Hz, H-3), 7.73 (t, 1H, J=7.5 Hz, H-2), 7.89 (dd, 1H, J=7.5, 1.2 Hz, H-1), 12.10 (s, 1H, OH-4), 12.85 (s, 1H, OH-6), 13.56 (s, 1H, OH-11).

10-*O*-Trifluoroacetyl-β-rhodomycinone (10) Compound **8** (18 mg, 0.038 mmol) was brominated, then hydroxylated with 0.1 N $NaHCO_3$ as described above. The organic phase obtained was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to preparative TLC (CH_2Cl_2 : Et_2O=9 : 1) to afford a mixture of **10** and **5** (5 : 1, 6 mg) and pure **5** (4 mg). The spectral data of **10** were abstracted from those of the mixture of **10** and **5**. IR ($CHCl_3$) ν: 3660, 1780, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7.3 Hz, H-14×3), 1.57, 1.72 (each sextet, 2H, J=7.3 Hz, H-13×2), 2.05 (dd, 1H, J=15.2, 4.9 Hz, H-8), 2.40 (dt, 1H, J=15.2, 1.5 Hz, H-8), 3.49 (br, 1H, OH), 3.79 (br s, 1H, OH), 5.34 (br s, 1H, $\nu_{1/2}$=9.0 Hz, H-7), 6.34 (d, 1H, J=1.5 Hz, H-10), 7.34 (dd, 1H, J=8.0, 1.2 Hz, H-3), 7.74 (t, 1H, J=8.0 Hz, H-2), 7.89 (dd, 1H, J=8.0, 1.2 Hz, H-1), 11.99 (s, 1H, OH-4), 12.79 (s, 1H, OH-6), 13.32 (s, 1H, OH-11). FAB-MS (negative) m/z: 481 $[(M-H)^-]$.

7,9-*O*-Phenylboronyl-β-rhodomycinone (14) Under a nitrogen atmosphere, a mixture of **5** (150 mg, 0.39 mmol), phenylboric acid (60 mg, 0.49 mmol), TFA (17.7 ml), and dry benzene (39 ml) was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 ml) and extracted with CH_2Cl_2 (50 ml×2). The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give crude **14**. Recrystallization from $CHCl_3$–hexane afforded a pure sample of **14** (172 mg, 95%) as red crystals, mp 274—275 °C. $[\alpha]_D^{25}$ +501° (c=0.10, $CHCl_3$). IR ($CHCl_3$) ν: 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (t, 3H, J=7.3 Hz, H-14×3), 1.85, 2.13 (each sextet, 2H, J=7.3 Hz, H-13×2), 2.19 (ddd, 1H, J=14.5, 3.0, 1.2 Hz, H-8), 2.29 (dd, 1H, J=14.5, 1.8 Hz, H-8), 2.97 (br d, 1H, J=3.0 Hz, OH-10), 4.98 (br d, 1H, J=3.0 Hz, H-10), 5.68 (br t, 1H, J=3.0 Hz, H-7), 7.25—7.40 (m, 4H, phenyl protons and H-3), 7.71 (t, 1H, J=8.0 Hz, H-2), 7.7—7.85 (m, 2H, phenyl protons), 7.87 (d, 1H, J=8.0 Hz, H-1), 12.16 (s, 1H, OH-4), 12.79 (s, 1H, OH-6), 13.60 (s, 1H, OH-11). Exact MS Calcd for $C_{26}H_{21}BO_8$: 472.1328. Found: 472.1308.

10-*O*-Acetyl-7,9-*O*-phenylboronyl-β-rhodomycinone (15) Two drops of concentrated H_2SO_4 (d=1.84) were added to a solution of **14** (148 mg, 0.314 mmol) and isopropenyl acetate (0.2 ml, 1.82 mmol) in CH_2Cl_2 (20 ml) at room temperature with stirring. After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (40 ml), and extracted with CH_2Cl_2 (50 ml×2). The extract was dried over Na_2SO_4 and concentrated *in vacuo*. Recrystallization of the residue from $CHCl_3$–hexane gave **15** (153 mg, 95%) as red crystals, mp 250—251 °C. $[\alpha]_D^{25}$ +317° (c=0.10, $CHCl_3$). IR ($CHCl_3$) ν: 1740, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (t, 3H, J=7.3 Hz, H-14×3), 1.67, 2.05 (each sextet, 2H, J=7.3 Hz, H-13×2), 2.10 (s, 3H, $COCH_3$), 2.20 (dd, 1H, J=4.0, 2.4 Hz, H-8), 2.35 (ddd, 1H, J=14.0, 2.4, 1.2 Hz, H-8), 5.75 (br t, 1H, J=2.4 Hz, H-7), 6.35 (d, 1H, J=1.2 Hz, H-10), 7.25—7.40 (m, 4H, phenyl protons and H-3), 7.70 (t, 1H, J=8.0 Hz, H-2), 7.7—7.85 (m, 2H, phenyl protons), 7.87 (d, 1H, J=8.0 Hz, H-1), 12.13 (s, 1H, OH-4), 12.81 (s, 1H, OH-6), 13.41 (s, 1H, OH-11). Exact MS Calcd for $C_{28}H_{23}BO_9$: 515.1433. Found: 515.1418.

10-*O*-Acetyl-β-rhodomycinone (16) A mixture of **15** (140 mg, 0.272 mmol), 2-methyl-2,4-pentanediol (1 ml), AcOH (0.1 ml), CH_2Cl_2 (7 ml), and acetone (7 ml) was stirred at room temperature for 12 h. The reaction

mixture was poured into a mixture of CH_2Cl_2 (100 ml) and saturated aqueous $NaHCO_3$ (40 ml). The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was washed with pentane (20 ml × 3) and recrystallized from $CHCl_3$–hexane to give **16** (115 mg, 95%) as red crystals, mp 259—260 °C. $[\alpha]_D^{25}$ −60° (c=0.05, $CHCl_3$). IR ($CHCl_3$) ν: 1730, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (t, 3H, J=7.3 Hz, H-14×3), 1.56, 1.75 (each sextet, 2H, J=7.3 Hz, H-13×2), 2.03 (dd, 1H, J=15.3, 4.9 Hz, H-8), 2.05 (s, 3H, $COCH_3$), 2.36 (d, 1H, J=15.3 Hz, H-8), 3.36 (s, 1H, OH-9), 3.63 (d, 1H, J=4.9 Hz, OH-7), 5.27 (dt, 1H, J=4.9, 1.2 Hz, H-7), 6.27 (d, 1H, J=1.2 Hz, H-10), 7.30 (d, 1H, J=8.0 Hz, H-3), 7.70 (t, 1H, J=8.0 Hz, H-2), 7.85 (d, 1H, J=8.0 Hz, H-1), 12.06 (s, 1H, OH-4), 12.87 (s, 1H, OH-6), 13.37 (s, 1H, OH-11). *Anal.* Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71. Found: C, 61.34; H, 4.55.

10-*O*-Acetyl-4′-*O*-*p*-nitrobenzoyl-3′-*N*-trifluoroacetyloxaunomycin (17) Under a nitrogen atmosphere, TMSOTf (0.02 ml, 0.11 mmol) was added to a stirred solution of molecular sieves 4A (150 mg) and **11** (30 mg, 0.055 mmol) in dry CH_2Cl_2 (6 ml) and dry Et_2O (2 ml) at −40 °C. The mixture was stirred at −5 °C for 1 h and then cooled to −15 °C, and a solution of **16** (18 mg, 0.042 mmol) in dry CH_2Cl_2 (5 ml) was added to it. After being stirred for 4 h under the same conditions, the mixture was poured into a vigorously stirred mixture of AcOEt (15 ml) and saturated aqueous $NaHCO_3$ (3 ml). The organic layer was separated, and the aqueous layer was extracted with AcOEt (10 ml). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by preparative TLC (CH_2Cl_2) gave **17** (28 mg, 82%) as red crystals, mp 181—185 °C (CH_2Cl_2–CCl_4). $[\alpha]_D^{25}$ −81° (c=0.026, $CHCl_3$). IR ($CHCl_3$) ν: 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (t, 3H, J=7.0 Hz, H-14×3), 1.28 (d, 3H, J=6.3 Hz, H-6′×3), 1.51, 1.79 (each sextet, 2H, J=7.0 Hz, H-13×2), 2.04 (s, 3H, $COCH_3$), 2.02—2.19 (m, 3H, H-8 and H-2′×2), 2.42 (d, 1H, J=15.3 Hz, H-8), 3.53 (s, 1H, OH-9), 4.46 (m, 1H, H-3′), 4.51 (q, 1H, J=6.3 Hz, H-5′), 5.23 (br d, 1H, J=3.0 Hz, $\nu_{1/2}$=8.5 Hz, H-7), 5.50 (br s, 1H, H-4′), 5.65 (br s, 1H, H-1′), 6.28 (s, 1H, H-10), 6.40 (br d, 1H, J=7.4 Hz, NH-3′), 7.31 (d, 1H, J=7.9 Hz, H-3), 7.72 (t, 1H, J=7.9 Hz, H-2), 7.87 (d, 1H, J=7.9 Hz, H-1), 8.28, 8.33 (2d, 2H each, J=8.0 Hz, $C_6H_4NO_2$), 12.04 (s, 1H, OH-4), 12.86 (s, 1H, OH-6), 13.39 (s, 1H, OH-11). FAB-MS (negative) m/z: 802 (M^-).

10-*O*-Acetyl-3′-*N*-trifluoroacetyloxaunomycin (18) A solution of **17** (15 mg, 0.019 mmol) in CH_2Cl_2 (1 ml) and MeOH (10 ml) was treated with 0.1 N NaOH (0.2 ml) at 0 °C. The mixture was stirred for 30 min under the same conditions, then AcOH (0.01 ml) was added. The resulting mixture was partitioned between AcOEt (15 ml) and brine (3 ml). The separated organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by preparative TLC (CH_2Cl_2 : AcOEt = 5 : 1) gave **18** (11.4 mg, 92%) as red crystals, mp 147—151 °C ($CHCl_3$–CCl_4). $[\alpha]_D^{25}$ +155° (c=0.01, $CHCl_3$). IR ($CHCl_3$) ν: 1720, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (t, 3H, J=7.5 Hz, H-14×3), 1.32 (d, 3H, J=6.1 Hz, H-6′×3), 1.49 (sextet, 1H, J=7.5 Hz, H-13), 1.75—1.87 (m, 2H, H-13, H-2′), 2.00—2.08 (m, 2H, H-8, H-2′), 2.04 (s, 3H, $COCH_3$), 2.38 (d, 1H, J=15.2 Hz, H-8), 3.57 (s, 1H, OH-9), 3.66 (br d, 1H, J=6.1 Hz, H-4′), 4.19 (m, 1H, H-3′), 4.30 (q, 1H, J=6.1 Hz, H-5′), 5.17 (br d, 1H, J=4.3 Hz, $\nu_{1/2}$=7.9 Hz, H-7), 5.46 (d, 1H, J=3.6 Hz, H-1′), 6.29 (s, 1H, H-10), 6.62 (br d, 1H, J=8.0 Hz, NH-3′), 7.33 (d, 1H, J=8.0 Hz, H-3), 7.73 (t, 1H, J=8.0 Hz, H-2), 7.92 (d, 1H, J=8.0 Hz, H-1), 12.11 (s, 1H, OH-4), 12.86 (s, 1H, OH-6), 13.46 (s, 1H, OH-11). FAB-MS (negative) m/z: 653 (M^-).

Oxaunomycin Hydrochloride (3·HCl) Compound **18** (4 mg, 0.006 mmol) was added to 0.1 N NaOH (3 ml) at room temperature and the mixture was stirred at 40 °C for 1 h. The solution was acidified with 0.1 N HCl (3.1 ml) and extracted with $CHCl_3$ (5 ml). The aqueous layer was added to saturated aqueous $NaHCO_3$ (4 ml) and extracted with $CHCl_3$ (5 ml × 3). The extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: MeOH = 85 : 15) to give a dark red product. This was taken up in EtOH (1 ml) and treated with a drop of 0.1 N HCl at 0 °C. The solution was evaporated to dryness *in vacuo*. The crystals obtained were triturated with $CHCl_3$ and collected by suction to give **3**·HCl (3 mg, 88%), mp 208—210 °C. $[\alpha]_D^{25}$ +98° (c=0.012, EtOH). The synthetic material was identical with an authentic sample of the natural product,[14] which has mp 209—211 °C, $[\alpha]_D^{25}$ +100° (c=0.013, EtOH). IR (KBr) ν: 3300, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.99 (t, 3H, J=7.3 Hz, H-14×3), 1.16 (d, 3H, J=7.0 Hz, H-6′×3), 1.58 (sextet, 1H, J=7.3 Hz, H-13), 1.62—1.70 (m, 2H, H-13 and H-2′), 1.88 (dt, 1H, J=12.8, 3.3 Hz, H-2′), 1.98 (d, 1H, J=14.7 Hz, H-8), 2.08 (dd, 1H, J=14.7, 5.0 Hz, H-8), 3.57 (br d, 1H, J=4.3 Hz, H-4′), 4.20 (q, 1H, J=7.0 Hz, H-5′), 4.59 (d, 1H, J=7.3 Hz, H-10), 4.86 (d, 1H, J=5.0 Hz, $\nu_{1/2}$=8.1 Hz, H-7), 5.29 (d, 1H, J=3.3 Hz, H-1′), 7.44 (dd, 1H, J=7.3, 1.8 Hz, H-3), 7.72—7.89 (m, 2H, H-1, H-2), 12.03 (br, 1H, OH-4), 12.87 (br, 1H, OH-6), 13.59 (br, 1H, OH-11). FAB-MS (negative) m/z: 515 (free base, M^-).

10-*O*-(4′-*O*-*p*-Nitrobenzoyl-3′-*N*-trifluoroacetyl-α-L-daunosaminyl)-β-rhodomycinone (19) Under a nitrogen atmosphere, TMSOTf (0.03 ml, 0.155 mmol) was added to a stirred solution of molecular sieves 4A (170 mg) and **11** (40 mg, 0.074 mmol) in dry CH_2Cl_2 (3 ml) and dry Et_2O (1 ml) at −40 °C. The mixture was stirred at −5 °C for 1 h and then cooled to −15 °C, and a solution of **14** (20 mg, 0.052 mmol) in dry CH_2Cl_2 (5 ml) was added to it. After being stirred for 5 h under the same conditions, the mixture was poured into a vigorously stirred mixture of AcOEt (15 ml) and saturated aqueous $NaHCO_3$ (3 ml). The organic layer was separated, and the aqueous layer was extracted with AcOEt (10 ml). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in a mixture of 2-methyl-2,4-pentanediol (0.15 ml), AcOH (0.1 ml), CH_2Cl_2 (4 ml), and acetone (4 ml). After being stirred for 20 h at room temperature, the reaction mixture was poured into a mixture of CH_2Cl_2 (15 ml) and saturated aqueous $NaHCO_3$ (7 ml). The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was washed with pentane (10 ml × 2). Purification of the residue obtained was achieved by preparative TLC (CH_2Cl_2) to give **19** (22 mg, 56%) as red crystals, mp 200—203 °C (CH_2Cl_2–CCl_4). $[\alpha]_D^{25}$ +60° (c=0.023, $CHCl_3$). IR ($CHCl_3$) ν: 1730, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (t, 3H, J=7.3 Hz, H-14×3), 1.23 (d, 3H, J=6.7 Hz, H-6′×3), 1.75—1.89 (m, 3H, H-13×2 and H-2′), 2.00 (dt, 1H, J=12.9, 3.3 Hz, H-2′), 2.20 (d, 1H, J=14.7 Hz, H-8), 2.30 (dd, 1H, J=14.7, 4.9 Hz, H-8), 3.35 (br, 1H, OH), 3.57 (br, 1H, OH), 4.32 (q, 1H, J=6.7 Hz, H-5′), 4.50 (m, 1H, H-3′), 5.01 (s, 1H, H-10), 5.27 (br s, 1H, $\nu_{1/2}$=11.0 Hz, H-7), 5.42 (br s, 1H, H-4′), 5.66 (d, 1H, J=3.3 Hz, H-1′), 6.27 (br d, 1H, J=7.3 Hz, NH-3′), 7.32 (d, 1H, J=8.0 Hz, H-3), 7.72 (t, 1H, J=8.0 Hz, H-2), 7.88 (d, 1H, J=8.0 Hz, H-1), 8.25, 8.30 (2d, 2H each, J=9.3 Hz, $C_6H_4NO_2$), 12.02 (s, 1H, OH-4), 12.87 (s, 1H, OH-6), 13.73 (s, 1H, OH-11). FAB-MS (negative) m/z: 760 (M^-).

10-*O*-(3′-*N*-Trifluoroacetyl-α-L-daunosaminyl)-β-rhodomycinone (20) A sample of **19** (12 mg, 0.016 mmol) was debenzoylated as described for **18** to afford **20** (9 mg, 93%) as red crystals, mp 154—157 °C ($CHCl_3$–CCl_4). $[\alpha]_D^{25}$ +294° (c=0.05, $CHCl_3$). IR ($CHCl_3$) ν: 1720, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (t, 3H, J=7.3 Hz, H-14×3), 1.29 (d, 3H, J=6.1 Hz, H-6′×3), 1.62—1.67 (m, 3H, H-13, H-2′×2), 1.82 (sextet, 1H, J=7.3 Hz, H-13), 2.17 (d, 1H, J=15.0 Hz, H-8), 2.30 (dd, 1H, J=15.0, 5.0 Hz, H-8), 3.26 (br, 1H, OH), 3.53 (br, 1H, OH), 3.59 (br s, 1H, H-4′), 4.14 (q, 1H, J=6.1 Hz, H-5′), 4.23 (m, 1H, H-3′), 4.97 (s, 1H, H-10), 5.27 (br d, 1H, J=5.0 Hz, $\nu_{1/2}$=6.0 Hz, H-7), 5.47 (d, 1H, J=3.6 Hz, H-1′), 6.63 (br d, 1H, J=8.5 Hz, NH-3′), 7.33 (d, 1H, J=8.0 Hz, H-3), 7.72 (t, 1H, J=8.0 Hz, H-2), 7.89 (d, 1H, J=8.0 Hz, H-1), 12.05 (s, 1H, OH-4), 12.89 (s, 1H, OH-6), 13.70 (s, 1H, OH-11). FAB-MS (negative) m/z: 611 (M^-).

10-*O*-(α-L-Daunosaminyl)-β-rhodomycinone Hydrochloride (6·HCl) A sample of **20** (3.1 mg, 0.005 mmol) was detrifluoroacetylated as described for **3**·HCl to afford **6**·HCl (2.4 mg, 87%) as red crystals, mp 184—185 °C. $[\alpha]_D^{25}$ +350° (c=0.01, EtOH). IR (KBr) ν: 3400, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.00 (t, 3H, J=7.3 Hz, H-14×3), 1.13 (d, 3H, J=6.0 Hz, H-6′×3), 1.41 (dd, 1H, J=12.5, 4.3 Hz, H-2′), 1.66 (sextet, 1H, J=7.3 Hz, H-13), 1.73 (sextet, 1H, J=7.3 Hz, H-13), 1.80 (dt, 1H, J=12.5, 4.3 Hz, H-2′), 1.94 (d, 1H, J=14.7 Hz, H-8), 2.07 (dd, 1H, J=14.7, 4.5 Hz, H-8), 3.55 (br d, 1H, J=4.9 Hz, H-4′), 3.89 (q, 1H, J=6.0 Hz, H-5′), 4.83 (s, 1H, H-10), 5.02 (br s, 1H, $\nu_{1/2}$=9.0 Hz, H-7), 5.31 (br d, 1H, J=3.0 Hz, H-1′), 7.44 (d, 1H, J=8.0 Hz, H-3), 7.83—7.90 (m, 2H, H-1, H-2), 12.01 (br, 1H, OH-4), 12.80 (br, 1H, OH-6), 13.70 (br, 1H, OH-11). FAB-MS (negative) m/z: 515 (free base, M^-).

10-*O*-Acetyl-7-*O*-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-2′-fluoro-α-L-talopyranosyl)-β-rhodomycinone (22) Under a nitrogen atmosphere, a mixture of **16** (24.2 mg, 0.057 mmol), yellow HgO (49 mg, 0.23 mmol), $HgBr_2$ (20.5 mg, 0.057 mmol), and molecular sieves 3A (300 mg) in dry CH_2Cl_2 (10 ml) was stirred for 30 min at room temperature. A solution of **21** (32.2 mg, 0.103 mmol) in dry CH_2Cl_2 (3 ml) was added, and the mixture was stirred for 48 h in the dark. After filtration with the aid of $CHCl_3$, the organic solution was washed with aqueous 30% KI and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by preparative TLC (CH_2Cl_2 : Et_2O = 5 : 1) gave **22** (18 mg, 48%) as red crystals, mp 161—164 °C ($CHCl_3$–hexane). $[\alpha]_D^{25}$ +108° (c=0.20, $CHCl_3$). IR ($CHCl_3$) ν: 1740, 1600 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.06 (t, 3H, J=7.3 Hz, H-14×3), 1.29 (d, 3H, J=6.7 Hz, H-6′×3), 1.51, 1.78 (each sextet, 2H, J=7.3 Hz, H-13×2), 2.04, 2.06, 2.19 (3s, 3H each, $OCOCH_3$×3), 2.08 (dd, 1H, J=15.3, 4.3 Hz, H-8), 2.43 (d, 1H, J=15.3 Hz, H-8), 3.03 (s, 1H, OH-9), 4.38 (q, 1H, J=6.7 Hz, H-5′), 4.59 (br d, 1H, J=49.5 Hz, H-2′), 4.97 (dt, 1H, J=32.3, 3.1 Hz, H-3′), 5.21—5.25 (m, 2H, H-7, H-4′), 5.61 (dd, 1H, J=9.8, 1.1 Hz, H-1′), 6.28 (s, 1H, H-10), 7.34 (dd, 1H, J=8.5, 1.3 Hz, H-3), 7.74 (t, 1H, J=8.5 Hz, H-2), 7.91 (dd, 1H, J=8.5, 1.3 Hz, H-1), 12.09 (s, 1H, OH-4), 12.88 (s, 1H, OH-6), 13.42 (s, 1H, OH-11). FAB-MS (negative) m/z: 660 (M^-).

10-*O*-Acetyl-7-*O*-(2′,6′-dideoxy-2′-fluoro-α-L-talopyranosyl)-β-rhodomycinone (23) A solution of **22** (16 mg, 0.024 mmol) in MeOH (1 ml) and THF (1 ml) was treated with 28% NaOMe/MeOH (0.11 ml, 0.53 mmol) at 0 °C and the mixture was stirred for 15 min at the same temperature. The reaction was quenched with AcOH (0.05 ml) at 0 °C, then water (30 ml) and AcOEt (30 ml) were added to the mixture with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with AcOEt (30 ml×2). The extracts were combined, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: MeOH = 96 : 4) to give **23** (11 mg, 85%) as red crystals, mp 256—259 °C ($CHCl_3$–Et_2O). $[\alpha]_D^{25}$ +20° (c=0.16, $CHCl_3$). IR ($CHCl_3$) ν: 3560, 1740, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (t, 3H, J=7.3 Hz, H-14×3), 1.40 (d, 3H, J=6.7 Hz, H-6′×3), 1.50, 1.78 (each sextet, 2H, J=7.3 Hz, H-13×2), 1.90 (dd, 1H, J=11.6, 6.0 Hz, OH-4′), 2.04 (s, 3H, $OCOCH_3$), 2.08 (dd, 1H, J=15.3, 4.3 Hz, H-8), 2.43 (d, 1H, J=15.3 Hz, H-8), 2.90 (d, 1H, J=11.0 Hz, OH-3′), 3.17 (s, 1H, OH-9), 3.55—3.70 (m, 2H, H-3′, H-4′), 4.22 (q, 1H, J=6.7 Hz, H-5′), 4.62 (dd, 1H, J=48.5, 1.5 Hz, H-2′), 5.22 (br d, 1H, J=4.3 Hz, $\nu_{1/2}$=7.9 Hz, H-7), 5.57 (br d, 1H, J=10.4 Hz, H-1′), 6.27 (d, 1H, J=1.2 Hz, H-10), 7.34 (d, 1H, J=8.0 Hz, H-3), 7.74 (t, 1H, J=8.0 Hz, H-2), 7.90 (d, 1H, J=8.0 Hz, H-1), 12.08 (1H, s, OH-4), 12.88 (1H, s, OH-6), 13.42 (1H, s, OH-11). FAB-MS (negative) m/z: 576 (M^-).

7-*O*-(2′,6′-Dideoxy-2′-fluoro-α-L-talopyranosyl)-β-rhodomycinone (7) A solution of **23** (9 mg, 0.016 mmol) in MeOH (0.5 ml) and THF (0.5 ml) was treated with 28% NaOMe/MeOH (0.22 ml, 1.1 mmol) at 0 °C and the mixture was stirred for 30 min at room temperature. The reaction was quenched with AcOH (0.1 ml) at 0 °C, then water (30 ml) and AcOEt (30 ml) were added to the mixture with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with AcOEt (30 ml×2). The extracts were combined, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$: MeOH = 95 : 5) to give **7** (7 mg, 84%) as red crystals, mp > 300 °C ($CHCl_3$–Et_2O). $[\alpha]_D^{25}$ +101° (c=0.035, $CHCl_3$). IR (KBr) ν: 3430, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (t, 3H, J=7.3 Hz, H-14×3), 1.41 (d, 3H, J=6.7 Hz, H-6′×3), 1.78 (sextet, 1H, J=7.3 Hz, H-13), 1.83—1.94 (m, 2H, H-13, OH-4′), 2.20 (dd, 1H, J=15.3, 4.3 Hz, H-8), 2.28 (d, 1H, J=15.3 Hz, H-8), 2.71 (d, 1H, J=3.1 Hz, OH-10), 2.90 (d, 1H, J=10.4 Hz, OH-3′), 3,18 (s, 1H, OH-9), 3.55—3.70 (m, 2H, H-3′ and H-4′), 4.23 (q, 1H, J=6.7 Hz, H-5′), 4.60 (br d, 1H, J=48.5 Hz, H-2′), 4.92 (d, 1H, J=3.1 Hz, H-10), 5.19 (dd, 1H, J=4.3, 2.8 Hz, H-7), 5.59 (dd, 1H, J=10.0, 1.2 Hz, H-1′), 7.36 (dd, 1H, J=8.0, 1.2 Hz, H-3), 7.75 (t, 1H, J=8.0 Hz, H-2), 7.92 (dd, 1H, J=8.0, 1.2 Hz, H-1), 12.12 (s, 1H, OH-4), 12.90 (s, 1H, OH-6), 13.60 (s, 1H, OH-11). FAB-MS (negative) m/z: 534 (M^-).

Direct Saponification of 22 to 7 Direct deacetylation of **22** (14 mg, 0.021 mmol) was performed under the same conditions as described for transforming **23** to **7**. Purification was achieved by preparative TLC to give **7** (7 mg, 62%) as red crystals.

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