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Synthesis of ara-Cadeguomycin. 2-Amino-3,4-dihydro-4-oxo-7-(β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic Acid

Kaoru Okamoto, Tadao Kondo,†,* and Toshio Goto*
Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University, Chikusa-ku, Nagoya 464
†Chemical Instrument Center, Nogoya University, Chikusa-ku, Nagoya 464
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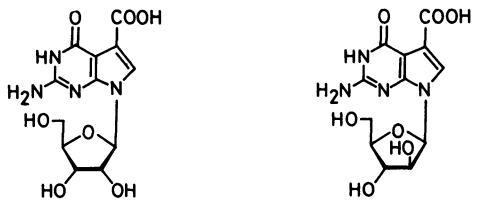
2-Amino-3,4-dihydro-4-oxo-7-(β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid, an analogue of cadeguomycin, has been synthesized via glycosylation of 3-methoxymethyl-5-methyl-2-methylthio-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride.

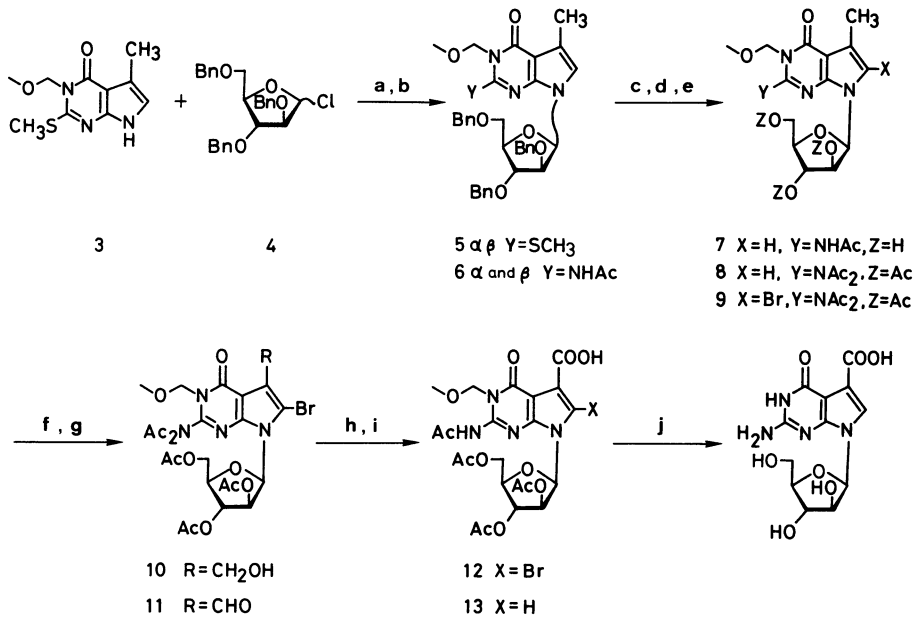
The arabinofuranosyl nucleosides such as ara-A[1] and ara-G[2] of naturally occurring purine and pyrimidine bases of nucleic acids have been synthesized to investigate their biological activities. It has been revealed that they act as inhibitors of ribonucleotide reductase or DNA polymerase.[3] 4-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (ara-tubercidin),[4] resists to deactivation by deaminases and shows antiviral activity. Recently, 2-amino-7-(β-D-arabinofuranosyl)-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (7-deaza-ara-G) was also synthesized[5] to avoid deactivation by the above reason. These properties of arabinofuranosyl nucleosides prompted us to synthesize the ara-analogue (**2**) of cadeguomycin (**1**), which was isolated from the culture broth of *Streptomyces hygroscopicus* IM7912T as a minor component concomitant with tubercidin.[6] Cadeguomycin (**1**) inhibits growth of IMC carcinoma and metastasis of Lewis lung carcinoma, and enhances cell-mediated immunity and macrophage activity,[7] but shows no significant antimicrobial activity against bacteria and fungi in contrast to tubercidin.[6]



Cadeguomycin (1) 2

Fig. 1.

As a base moiety for the synthesis of ara-cadeguomycin (**2**) we have chosen 3-methoxymethyl-5-methyl-2-methylthio-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**3**) which has been applied to the syntheses of cadeguomycin (**1**),[8] nucleoside Q, preQ$_0$, and preQ$_1$.[9] The glycosylation reaction of the base **3** with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (**4**), which was prepared from 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinofuranose according to the Fletcher's method,[10] was carried out in the same manner as the synthesis of cadeguomycin (**1**), etc.[8,9] Thus, treatment of **3** with **4** in the presence of sodium hydride in DMF gave **5αβ** as a 1:5 mixture of α and β isomer in 99% yield. The structural assignment of the anomers was achieved by comparison of chemical shifts of the anomeric protons in ^{1}H NMR spectra with those of known 7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one analogues.[5,11] Generally the anomeric proton signal of the β isomer appears in a low field (≈6.53 ppm) compared with that of the α isomer (≈6.27 ppm) and has a larger vicinal coupling constant (5.4 Hz) in contrast to the α isomer (3.9 Hz) in ^{1}H NMR spectra. As this glycosylation products, **5αβ**, could not be separated by the usual silica-gel column chromatography, the mixture was subjected to the next acetylamination reaction. The conversion of the 2-methylthio group of **5αβ** into an acetylamino group was carried out by the method which has been used for the synthesis of nucleoside Q.[12] Thus, the mixture was treated at 100 °C with acetamide anion generated by fusion of sublimed acetamide and sodium hydride to give a mixture of **6α** and **6β** in 64% yield. In this stage, the anomeric mixture **6αβ** was easily separated into β (53% yield) and α isomer (11% yield) by use of a silica-gel column. The protecting benzyl groups on the sugar moiety were changed to acetyl groups since the benzyl groups are intolerable to the subsequent allylic bromination. Debenzylation of **6β** was accomplished with 10% Pd–C under hydrogen atmosphere to give the triol **7** in 67% yield. Treatment of **7** with acetic anhydride and anhydrous pyridine gave the acetylated compound **8** in 99% yield. The compound **8** was brominated with *N*-bromosuccinimide (NBS) in benzene at room temperature to afford the bromide **9** in 99% yield. The bromide **9** was further brominated with NBS in carbon tetrachloride to give a dibromide, which was converted into the bromo alcohol **10** by hydrolysis with silver carbonate in dioxane–water. The overall yield from **8** was 76%. Without isolation of the bromide **9** direct conversion of **8** with 2 equivalents of NBS into **10** resulted in a low yield (ca. 30%). Oxidation of the bromo alcohol **10** with active manganese (IV) dioxide in acetonitrile caused partial deacetylation and, therefore, the product was reacetylated with acetic anhydride and pyridine to give the aldehyde **11** in 67% yield. Further oxidation of **11** with NBS[13] in carbon tetrachloride under irradiation by a reflecting photolamp at room temperature gave the acid bromide, which was hydrolyzed by addition of water and then deacetylated with aqueous ammonia to afford the



Scheme. 1. Reaction conditions: (a) NaH, DMF, 0°C, 2 h (97%); (b) NaH, CH_3CONH_2, 100°C, 40 min (64%); (c) 10% Pd-C/H_2, MeOH, rt, 7 h (67%); (d) Ac_2O, pyridine, rt, 1 h (99%); (e) NBS, benzene, rt, 30 min (99%); (f) NBS, benzoyl peroxide, K_2CO_3, CCl_4, reflux, 2 h; Ag_2CO_3, dioxane-water, rt, 1.5 h (76%); (g) MnO_2, CH_3CN, rt, 8 h (67%); (h) NBS, $h\nu$, K_2CO_3, CCl_4, rt, 45 min; 2M HCl (67%); (i) 10% Pd-C/H_2, MeOH-water, rt, 30 min (84%); (j) NH_4OH, MeOH, rt, 14 h; TFA-water (3/1), 70°C, 1 h (86%).

bromo carboxylic acid **12** in 64% yield. Finally, deprotection was accomplished stepwise. The compound **12** was debrominated with 10% Pd-C in the presence of potassium acetate giving the carboxylic acid **13** in 84% yield. Hydrolysis of **13** with aqueous ammonia in methanol followed by trifluoroacetic acid (TFA) afforded ara-cadeguomycin (**2**) in 86% yield, which was crystallized from ethanol-water to give pure ara-cadeguomycin (**2**).

Experimental

Melting points were determined on a Mitamura Riken flat-bulb thermometer with a heating metal block and uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. Nuclear magnetic resonance spectra (NMR) were recorded with a JEOL FX-200 instrument in the FT mode. Chemical shifts were expressed in δ values relative to tetramethylsilane as an internal standard unless otherwise noted. Coupling constants (J) were given in hertz (Hz) and splitting pattern abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of double doublets; br, broad; m, multiplet. Mass spectra (MS) were obtained on a JEOL DX-300 spectrometer. Infrared spectra (IR) were recorded on either a Shimadzu IR 435 or a JASCO A-3 spectrometer. Ultraviolet spectra (UV) were measured on a Hitachi 228 spectrometer. Optical rotations $[\alpha]_D$ were recorded on a JASCO DIP-181 digital polarimeter.

Analytical thin-layer chromatography (TLC) was done on precoated TLC glass sheets (silica gel 60F-254, layer thickness 0.25 mm) manufactured by E. Merck. Preparative silica-gel thick-layer chromatography was performed on 20×20 cm glass plates coated with silica gel PF-254 (E. Merck, Darmstadt). Column chromatography was performed with Merck silica gel 60 (70—230 mesh).

Glycosylation of the Base 3 with 4. Dry hydrogen chloride was bubbled into a solution of 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinofuranose[7] (5.8 g, 10.2 mmol) in dichloromethane (36 ml) at 0°C until no further *p*-nitrobenzoic acid precipitated. After standing for 2 h, the precipitate was filtered and washed with dichloromethane. The combined filtrates were evaporated in vacuo to give the halogenose **4** as a viscous syrup, which was dissolved in anhydrous DMF (5.5 ml). A mixture of **3** (1.8 g, 7.5 mmol) and sodium hydride (50% oil suspension, 0.45 g, 9.4 mmol) in anhydrous DMF (7.0 ml) was stirred for 0.5 h and to this was added above DMF solution of **4** at 0°C under argon atmosphere. The reaction mixture was allowed to warm to room temperature, stirred for 6 h, poured into ice-water, and extracted with ethyl acetate. The extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a viscous residue, which was applied to a silica-gel column and eluted with hexane-ethyl acetate (gradient elution from 3:1 to 2:1) to give 3-methoxymethyl-5-methyl-2-methylthio-7-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**5**$\alpha\beta$) (4.8 g, 99%) as a 1:5 mixture of α and β isomer (detected by ^{1}H NMR): UV (MeOH) 308 nm; ^{1}H NMR ($CDCl_3$)

δ=2.30 (d, J=1.0 Hz, β-CH_3-5), 2.36 (d, J=1.0 Hz, α-CH_3-5), 2.48 (s, α-CH_3S), 2.55 (s, β-CH_3S), 3.44 (s, β-CH_3O), 3.46 (s, α-CH_3O), 3.49—3.78 (m, α,β-H-5′), 4.0—4.7 (m, α,β-H-2′ and 3′, OCH_2Ph), 5.57 (br. s, OCH_2N), 6.27 (d, J=3.9 Hz, α-H-1′), 6.53 (d, J=5.4 Hz, β-H-1′), 6.70 (q, J=1.0 Hz, α-H-6), 6.82 (q, J=1.0 Hz, β-H-6), and 6.9—7.4 (m, ArH); IR (neat) 1685 (amide I), 1534 (amide II), and 1512 cm^{-1}; MS (EI) m/z 641 (M^+).

2-Acetylamino-3-methoxymethyl-5-methyl-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (6β) and Its α Isomer (6α). To a mixture of sodium hydride (50% oil suspension, 1.3 g) and acetamide (13 g, sublimed just before use) was added **5**$\alpha\beta$ (2.6 g, 4.1 mmol) and heated for 40 min at 100 °C under argon atmosphere. Excess acetamide was removed in vacuo and the residue was carefully acidified with acetic acid under ice-cooling and extracted with benzene. The extract was washed with water, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a syrup, which was chromatographed on a silica-gel column (hexane–ethyl acetate, gradient elution from 2:1 to 1:1). The more rapidly migrating zone was the isomer **6**α (0.3 g, 11%) and the slower, the isomer **6**β (1.4 g, 53%) as a viscous syrup; **6**α: UV (MeCN) 306 nm (ε 9580); $[\alpha]_D^{21}$ +23.6° (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=2.35 (3H, d, J=1.0 Hz, CH_3-5), 2.38 (3H, s, CH_3CON), 3.44 (3H, s, CH_3O), 3.60 (1H, dd, $J_{5',4'}$=5.1 Hz, $J_{5',5'}$=10.5 Hz, H-5′), 3.63 H, dd, $J_{5',4'}$=4.6 Hz, $J_{5',5'}$=10.5 Hz, H-5′), 4.15—4.28 (1H, m, H-4′), 4.35—4.66 (8H, m, H-2′ and 3′, 3×OCH_2Ph), 5.52 and 5.53 (2H, AB quartet, J=11.5 Hz, OCH_2N), 6.20 (1H, d, $J_{1',2'}$=3.9 Hz, H-1′), 6.77 (1H, q, J=1.0 Hz, H-6), 7.1—7.4 (15H, m, ArH), and 8.41 (1H, br. s, NH); IR (neat) 1685 (amide I) and 1570 (amide II) cm^{-1}; MS (EI) m/z 652 (M^+).

Found: C, 68.30; H, 6.15; N, 8.45%. Calcd for $C_{37}H_{40}N_4O_7$: C, 68.08; H, 6.18; N, 8.58%.

6β: UV (MeCN) 306 nm (ε 9660); $[\alpha]_D^{21}$ +45.8° (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=2.29 (3H, d, J=1.2 Hz, CH_3-5), 2.40 (3H, s, CH_3CON), 3.43 (3H, s, CH_3O), 3.70 (1H, dd, $J_{5',4'}$=4.4 Hz, $J_{5',5'}$=10.5 Hz, H-5′), 3.73 (1H, dd, $J_{5',4'}$= 4.2 Hz, $J_{5',5'}$=10.5 Hz, H-5′), 4.09 (1H, ddd, $J_{4',3'}$=5.4 Hz, $J_{4',5'}$=4.2 and 4.4 Hz, H-4′), 4.21 and 4.27 (2H, AB quartet, J=11.5 Hz, OCH_2Ph), 4.22 (1H, t, $J_{2',1'}$=$J_{2',3'}$=5.4 Hz, H-2′), 4.31 (1H, t, $J_{3',2'}$=$J_{3',4'}$=5.4 Hz, H-3′), 4.52 and 4.56 (2H, AB quartet, J=12.0 Hz, OCH_2Ph), 4.60 and 4.64 (2H, AB quartet, J=12.0 Hz, OCH_2Ph), 5.50 and 5.51 (2H, AB quartet, J=11.5 Hz, OCH_2N), 6.41 (1H, d, $J_{1',2'}$=5.4 Hz, H-1′), 6.91 (1H, q, J=1.2 Hz, H-6), 6.9—7.4 (15H, m, ArH), and 8.38 (1H, br. s, NH); IR (neat) 1692 (amide I) and 1575 (amide II) cm^{-1}; MS (FAB) m/z 653 (M+H).

Found: C, 68.21; H, 6.05; N,8.63%. Calcd for $C_{37}H_{40}N_4O_7$: C, 68.08; H, 6.18; N, 8.58%.

2-Acetylamino-3-methoxymethyl-5-methyl-7-(β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (7). A mixture of **6**β (1.2 g, 1.8 mmol) and 10% Pd–C (3.6 g) in methanol (50 ml) was stirred vigorously for 7 h at room temperature under hydrogen atmosphere. The catalyst was removed by filtration and washed well with methanol. The combined filtrates were evaporated in vacuo to give a syrup, which was chromatographed on a silica-gel column (chloroform–methanol, 5:1) to give a pale yellow syrup **7** (0.47 g, 67%): UV (MeCN) 305 nm (ε 7580); $[\alpha]_D^{21}$ +20.0° (c 0.1, MeOH); ^1H NMR (Acetone-d_6) δ=2.30 (3H, d, J=1.0 Hz, CH_3-5), 2.84 (3H, s, CH_3CON), 3.38 (3H, s, CH_3O), 3.83 (1H, ddd, $J_{5',4'}$=4.5 Hz, $J_{5',OH}$=5.1 Hz, $J_{5',5'}$=11.5 Hz, H-5′), 3.88 (1H, ddd, $J_{5',4'}$=4.5 Hz, $J_{5',OH}$=5.1 Hz, $J_{5',5'}$=11.5 Hz, H-5′), 3.95 (1H, q, $J_{4',3'}$=$J_{4',5'}$=4.5 Hz, H-4′), 4.16 (1H, ddd, $J_{2',1'}$=4.3 Hz, $J_{2',OH}$=7.5 Hz, $J_{2',3'}$=7.7 Hz, H-2′), 4.32 (1H, dd, $J_{3',2'}$=7.7 Hz, $J_{3',OH}$=$J_{3',4'}$=4.5 Hz, H-3′), 4.50 (1H, t, $J_{OH,5'}$=5.1 Hz, OH-5′), 4.70 (1H, d, $J_{OH,3'}$=4.5 Hz, OH-3′), 4.81 (1H, d, $J_{OH,2'}$=7.5 Hz, OH-2′), 5.52 and 5.55 (2H, AB quartet, J=10.8 Hz, OCH_2N), 6.34 (1H, d, $J_{1',2'}$=4.3 Hz, H-1′), 7.04 (1H, q, J=1.0 Hz, H-6), and 8.75 (1H, br. s, NH); IR (neat) 3370 (OH, NH) and 1675 (amide I) cm^{-1}; MS (FAB) m/z 383 (M+H).

Found: C, 50.03; H, 5.89; N, 14.91%. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65%.

2-Diacetylamino-3-methoxymethyl-5-methyl-7-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (8). A solution of **7** (350 mg, 0.92 mmol) in acetic anhydride (1.7 ml) and anhydrous pyridine (3.5 ml) was stirred for 1 h at room temperature under argon atmosphere. The solution was evaporated to a syrup, which was chromatographed on a silica-gel column (ethyl acetate–hexane, 2:1) and crystallized from hexane–ethyl acetate to give **8** (500 mg, 99%) as white crystals: Mp 169—170 °C; UV (MeCN) 305 nm (ε 8640); $[\alpha]_D^{22}$ +15.8° (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.85 (3H, s, CH_3COO), 2.14 (3H, s, CH_3COO), 2.17 (3H, s, CH_3COO), 2.31 (3H, s, CH_3CON), 2.41 (3H, d, J=1.0 Hz, CH_3-5), 2.45 (3H, s, CH_3CON), 3.42 (3H, s, CH_3O), 4.19 (1H, br. q, J=5.1 Hz, H-4′), 4.38 (1H, dd, $J_{5',4'}$=5.9 Hz, $J_{5',5'}$=11.7 Hz, H-5′), 4.44 (1H, dd, $J_{5',4'}$=4.6 Hz, $J_{5',5'}$=11.7 Hz, H-5′), 5.21 and 5.38 (2H, AB quartet, J=10.5 Hz, OCH_2N), 5.36—5.43 (2H, m, H-2′ and 3′), 6.48 (1H, d, $J_{1',2'}$=4.4 Hz, H-1′), and 6.85 (1H, q, J=1.0 Hz, H-6); IR (KBr) 1737 (COO), 1690 (amide I), and 1570 (amide II) cm^{-1}; MS (EI) m/z 550 (M^+).

Found: C, 52.33; H, 5.56; N, 10.14%. Calcd for $C_{24}H_{30}N_4O_{11}$: C, 52.36; H, 5.49; N, 10.18%.

6-Bromo-2-diacetylamino-3-methoxymethyl-5-methyl-7-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (9). To a solution of **8** (575 mg, 1.0 mmol) in benzene (75 ml) was added NBS (210 mg, 1.2 mmol) at room temperature. After stirring for 30 min, the solvent was removed and the residue was chromatographed on a silica-gel column (ethyl acetate–hexane, 3:2) to give a pale yellow syrup **9** (650 mg, 99%): UV (MeCN) 310 (ε 8380) and 269 nm (5390); $[\alpha]_D^{22}$ −61.4° (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.69 (3H, s, CH_3COO), 2.05 (3H, s, CH_3COO), 2.12 (3H, s, CH_3COO), 2.37 (3H, s, CH_3-5), 2.40 (3H, s, CH_3CON), 2.44 (3H, s, CH_3CON), 3.43 (3H, s, CH_3O), 4.14 (1H, ddd, $J_{4',3'}$=7.3 Hz, $J_{4',5'}$=3.4 and 7.6 Hz, H-4′), 4.25 (1H, dd, $J_{5',4'}$=7.6 Hz, $J_{5',5'}$=11.2 Hz, H-5′), 4.44 (1H, dd, $J_{5',4'}$=3.4 Hz, $J_{5',5'}$=11.2 Hz, H-5′), 5.28 and 5.34 (2H, AB quartet, J=10.5 Hz, OCH_2N), 5.50 (1H, t, $J_{2',1'}$=$J_{2',3'}$=7.3 Hz, H-2′), 6.26 (1H, t, $J_{3',2'}$= $J_{3',4'}$=7.3 Hz, H-3′), and 6.58 (1H, d, $J_{1',2'}$=7.3 Hz, H-1′); IR (neat) 1740 (COO), 1700, 1690 (amide I), and 1578 (amide II) cm^{-1}; MS (EI) m/z 628 and 630 (M^+).

Found: C, 45.71; H, 4.88; N, 9.12%. Calcd for $C_{24}H_{29}N_4O_{11}Br$: C, 45.80; H, 4.64; N, 8.90%.

6-Bromo-2-diacetylamino-5-hydroxymethyl-3-methoxymethyl-7-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-one (10). A mixture of **9** (650 mg, 1.0 mmol), NBS (210 mg, 1.2 mmol), anhydrous potassium carbonate (660 mg, 4.78 mmol), and benzoyl peroxide (20 mg) in carbon tetrachloride (60 ml) was refluxed with stirring for 2 h under argon atmosphere. The reaction mixture was cooled and the precipitate was removed through a glass filter and washed with carbon tetrachloride. The combined filtrates were

evaporated in vacuo to give a dibromide, which was dissolved in dioxane (40 ml) and water (14 ml). To this solution was added silver carbonate (800 mg, 2.9 mmol) and the mixture was stirred for 1.5 h at room temperature and filtered, and the filtrate was evaporated in vacuo to give a syrup, which was chromatographed on a silica-gel column (benzene–ethyl acetate, gradient elution from 1:1 to 2:3) to give **10** (507 mg, 76%) as a viscous syrup: UV (MeCN) 306 (ε 7290) and 269 nm (5830); $[\alpha]_D^{22}$ −44.7° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ= 1.72 (3H, s, CH_3COO), 2.05 (3H, s, CH_3COO), 2.12 (3H, s, CH_3COO), 2.41 (3H, s, CH_3CON), 2.45 (3H, s, CH_3CON), 3.44 (3H, s, CH_3O), 4.16 (1H, ddd, $J_{4',3'}$=7.3 Hz, $J_{4',5'}$=3.7 and 7.6 Hz, H-4'), 4.24 (1H, dd, $J_{5',4'}$=7.6 Hz, $J_{5',5'}$=11.3 Hz, H-5'), 4.44 (1H, dd, $J_{5',4'}$=3.7 Hz, $J_{5',5'}$=11.3 Hz, H-5'), 4.73 (2H, s, OCH_2-5), 5.32 and 5.40 (2H, AB quartet, J=10.4 Hz, OCH_2N), 5.53 (1H, t, $J_{2',1'}$=$J_{2',3'}$=7.3 Hz, H-2'), 6.25 (1H, t, $J_{3',2'}$=$J_{3',4'}$= 7.3 Hz, H-3'), and 6.58 (1H, d, $J_{1',2'}$=7.3 Hz, H-1'); IR (neat) 3450 (OH), 1740 (COO), 1710, and 1690 (amide I); MS (EI) *m/z* 644 and 646 (M^+).

Found: C, 44.36; H, 4.37; N, 8.35%. Calcd for $C_{24}H_{29}N_4O_{12}Br$: C, 44.66; H, 4.53; N, 8.68%.

6-Bromo-2-diacetylamino-5-formyl-3-methoxymethyl-7-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-one (11). To a solution of **10** (480 mg, 0.74 mmol) in acetonitrile (25 ml) was added active MnO_2 (7.0 g) in seven portions every 30 min with stirring. After stirring for further 5 h, the mixture was filtered through a Celite 545 bed and the solid was washed well with acetone. The combined filtrates were evaporated in vacuo and the resultant syrup, which was deacetylated partially, was treated with acetic anhydride (1.5 ml) and anhydrous pyridine (3.0 ml) for 0.5 h at room temperature. The mixture was condensed to a syrup, which was purified by chromatography on a silica-gel column (benzene–ethyl acetate, 1:1) to give a colorless syrup **11** (319 mg, 67%): UV (MeCN) 296 (ε 12530) and 239 nm (14280); $[\alpha]_D^{22}$ −57.6° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.72 (3H, s, CH_3COO), 2.05 (3H, s, CH_3COO), 2.14 (3H, s, CH_3COO), 2.42 (3H, s, CH_3CON), 2.47 (3H, s, CH_3CON), 3.46 (3H, s, CH_3O), 4.15—4.32 (2H, m, H-5'), 4.35—4.50 (1H, m, H-4'), 5.34 and 5.42 (2H, AB quartet, J=10.7 Hz, OCH_2N), 5.59 (1H, t, $J_{2',1'}$=$J_{2',3'}$=7.3 Hz, H-2'), 6.27 (1H, $J_{3',2'}$=$J_{3',4'}$=7.3 Hz, H-3'), 6.74 (1H, d, $J_{1',2'}$=7.3 Hz, H-1'), and 10.47 (1H, s, CHO); MS(EI) *m/z* 642 and 644 (M^+).

Found: C, 44.47; H, 4.41; N, 8.93%. Calcd for $C_{24}H_{27}N_4O_{12}Br$: C, 44.80; H, 4.32; N, 8.71%.

2-Acetylamino-6-bromo-3,4-dihydro-3-methoxymethyl-4-oxo-7-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine-5-carboxylic Acid (12). To a mixture of **11** 310 mg, 0.48 mmol) and anhydrous potassium carbonate (460 mg, 3.3 mmol) in carbon tetrachloride (70 ml) was added NBS (100 mg, 0.56 mmol). The mixture was irradiated by a 500 W reflecting photo-lamp with stirring for 45 min at room temperature. The mixture was cooled to 0°C and dioxane–water (3/1 v/v, 6 ml) was added to it. The reaction mixture was stirred for 30 min, acidified with 2 M HCl (1 M=1 mol dm^{-3}), and extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a syrup, which was treated with 28% aqueous ammonia (1 drop) in methanol (5 ml) for 5 min to hydrolyze the remaining *N,N*-diacetyl groups. After evaporation, the residual oil was purified by preparative silica-gel TLC (dichloromethane–methanol, 20:1) to give the bromo carboxylic acid **12** (190 mg, 64%) as a viscous syrup: UV (MeCN) 287 nm (ε 11650); $[\alpha]_D^{21}$ −71.4° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.78 (3H, s, CH_3COO), 2.07 (3H, s, CH_3COO), 2.14 (3H, s, CH_3COO), 2.38 (3H, s, CH_3CON), 3.51 (3H, s, CH_3O), 4.0—4.3 (2H, m, H-5'), 4.4—4.6 (1H, m, H-4'), 5.54 and 5.79 (2H, AB quartet, J=11.2 Hz, OCH_2N), 5.63 (1H, t, $J_{2',1'}$=$J_{2',3'}$=7.3 Hz, H-2'), 6.29 (1H, br. t, J=6.9 Hz, H-3'), 6.79 (1H, d, $J_{1',2'}$=7.3 Hz, H-1'), 8.40 (1H, br. s, NH), and 13.95 (1H, br, COOH); IR (neat) 1738 (COO), 1700 (sh, COOH), 1640 (amide I), and 1500 (amide II) cm^{-1}; MS (FAB) *m/z* 616 and 618 (M+H).

Found: C, 42.47; H, 4.13; N, 9.36%. Calcd for $C_{22}H_{25}N_4O_{12}Br$: C, 42.80; H, 4.08; N, 9.08%.

2-Acetylamino-3,4-dihydro-3-methoxymethyl-4-oxo-7-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic Acid (13). A mixture of **12** (150 mg, 0.24 mmol), 10% Pd-C (450 mg), and potassium acetate (1.2 g) in methanol (50 ml) was stirred vigorously for 30 min at room temperature under hydrogen atmosphere. The catalyst was filtered and washed with methanol. The combined filtrates were evaporated in vacuo and partitioned between chloroform and 1 M HCl. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a crude product, which was purified by preparative silica-gel TLC (dichloromethane–methanol, 20:1) to give a pale yellow viscous syrup **13** (110 mg, 84%): UV (MeCN) 297 (sh, ε 8990) and 281 nm (9180); $[\alpha]_D^{21}$ −10.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.90 (3H, s, CH_3COO), 2.17 (3H, s, CH_3COO), 2.20 (3H, s, CH_3COO), 2.51 (3H, s, CH_3CON), 3.51 (3H, s, CH_3O), 4.26 (1H, ddd, $J_{4',3'}$=4.4 Hz, $J_{4',5'}$=3.9 and 5.4 Hz, H-4'), 4.35 (1H, dd, $J_{5',4'}$=5.4 Hz, $J_{5',5'}$=11.7 Hz, H-5'), 4.46 (1H, dd, $J_{5',4'}$=3.9 Hz, $J_{5',5'}$=11.7 Hz, H-5'), 5.41 (1H, dd, $J_{3',2'}$=3.4 Hz, $J_{3',4'}$=4.4 Hz, H-3'), 5.47 (1H, dd, $J_{2',1'}$=4.9 Hz, $J_{2',3'}$=3.4 Hz, H-2'), 5.59 and 5.67 (2H, AB quartet, J=11.2 Hz, OCH_2N), 6.54 (1H, d, $J_{1',2'}$=4.9 Hz, H-1'), 7.89 (1H, s, H-6), 8.57 (1H, br. s, NH), and 13.17 (1H, br, COOH); IR (neat) 3310 (NH), 1750—1700 (COO), and 1654 (amide I) cm^{-1}; MS (FAB) *m/z* 539 (M+H).

Found: C, 49.28; H, 4.91; N, 10.26%. Calcd for $C_{22}H_{26}N_4O_{12}$: C, 49.07; H, 4.87; N, 10.40%.

2-Amino-3,4-dihydro-4-oxo-7-(β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic Acid (ara-cadeguomycin) (2). A solution of **13** (50 mg, 0.093 mmol) in 28% aqueous ammonia (2 ml) and methanol (2 ml) was stirred for 14 h at room temperature and evaporated in vacuo. The residue was heated for 1 h at 70°C in trifluoroacetic acid–water (3/1 v/v, 4 ml) and condensed to dryness, to which were added ethanol and water, and the precipitate was collected by filtration to give a crude material. Recrystallization from ethanol–water gave ara-cadeguomycin (**2**) (26 mg, 86%) as white crystals. A sample for analyses was obtained by purification with HPLC (Finepak SIL C_{18}; eluent: 30% methanol containing 1% acetic acid): Mp 240—255°C (decomp); UV (H_2O) 295 (ε 6890), 268 (7030), and 231 nm (16130); $[\alpha]_D^{26}$ +22.0° (*c* 0.1, DMSO); ^1H NMR (DMSO-d_6–D_2O, 2:1; internal standard: *t*-BuOH as 1.23 ppm) δ=3.78 (1H, dd, $J_{5',4'}$=5.4 Hz, $J_{5',5'}$=12.2 Hz, H-5'), 3.83 (1H, dd, $J_{5',4'}$=3.4 Hz, $J_{5',5'}$=12.2 Hz, H-5'), 3.93 (1H, ddd, $J_{4',3'}$=5.1 Hz, $J_{4',5'}$=3.4 and 5.4 Hz, H-4'), 4.20 (1H, t, $J_{3',2'}$=$J_{3',4'}$=5.1 Hz, H-3'), 4.30 (1H, t, $J_{2',1'}$=$J_{2',3'}$=5.1 Hz, H-2'), 6.32 (1H, d, $J_{1',2'}$=5.1 Hz, H-1'), and 7.84 (1H, s, H-6); IR (KBr) 3600—2200 (NH, OH, COOH), 1685 (COO, amide I), and 1654 (amide II) cm^{-1}; MS (FAB) *m/z* 327 (M+H).

Found: C, 44.15; H, 4.46; N, 17.02%. Calcd for $C_{12}H_{14}N_4O_7$:

C, 44.18; H, 4.32; N, 17.17%.

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