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Synthesis of 1,4-Diaminocyclitol Antibiotics. I. Synthesis of 4′-Hydroxyfortimicin D

Kazuaki KANAI, Itsuki SAKAMOTO, Yasunobu MIYAMOTO, Seiichiro OGAWA,* and Tetsuo SUAMI†
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223
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The 4′-hydroxy analog of fortimicin D has been synthesized by condensation of 4-*O*-acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl chloride with a partially protected aminocyclitol, 1,2:4,5-di-*N*,*O*-carbonylfortamine B, followed by deprotection.

Fortimicins are isolated from a fermentation broth of *Micromonospora olivoasterospora*,[1,2] and belong to members of 1,4-diaminocyclitol antibiotics. The structural features of the antibiotics are pseudo-disaccharides consisting of the aminocyclitol, fortamine, and the diamino sugar, 6-epipurpurosamine B. As a member of anitibiotic fortimicin-group, sporaricins,[3] istamycins,[4] sannamycins,[5] SF-2052,[6] and SF-1854[7] have been known. A number of chemical modifications has extensively been carried out, and the relationship between the structure and antimicrobial activity has gradually been made clear. However, most studies have been centered around the aminocyclitol moiety.[8] Therefore, in order to elucidate the role of the diamino sugar moiety in the antimicrobial activity, we have undertaken a modification of the amino sugar moiety.

We now describe a chemical synthesis of the 4′-hydroxy analog (**17**) of fortimicin D.[9] The synthesis involved preparation of the glycosyl chloride, 4-*O*-acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,6-trideoxy-α-*ribo*-hexopyranosyl chloride (**8**) and condensation of **8** with the partially protected aminocyclitol, 1,2:4,5-di-*N*,*O*-carbonylfortamine B (**9**).[10,11]

Results and Discussion

The glycosyl chloride **8** has been prepared by the following sequence. Methyl 2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**3**)[12–15] was obtained in high yield (80%, 2 steps) from methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**1**)[6] by modified Barton's deoxygenation reaction.[17] Catalytic hydrogenation of methyl 2-acetamido-6-azido-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside (**4**),[18] which was accessible from **3**, gave the 6-amino derivative **5** as an acetate form in 84% yield. Hydrolysis of **5** in refluxing 2 M†† hydrochloric acid solution gave the 2,6-diamino sugar **6**, which was converted into 1,4-di-*O*-acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,6-trideoxy-D-*ribo*-hexopyranose (**7**, 55%) by treatment with 2,4-dinitrofluorobenzene and triethylamine, followed by acetylation. The chloride **8** was obtained as yellow crystals (54%) by chlorination of **7** with 15% HCl–dioxane and acetyl chloride.

Condensation of **9** with **8** in dioxane in the presence of silver trifluoromethanesulfonate afforded 28% yield of the condensate **10** as an anomeric mixture, which was directly used for the following step. *O*-Deacetylation of **10** with 0.02 M sodium hydroxide gave two products (**11**, 5% based on **9**) and (**12**, 11%). The ^{1}H NMR spectrum of **11** revealed the presence of the anomeric proton of the α-D-glycoside as a doublet at δ 5.62 (J=4.5 Hz). The spectrum of **12** showed a doublet at δ 5.15 (J=7.5 Hz) attributable to the anomeric proton of the β-D-glycoside. Removal of the dinitrophenyl group of **11** with Amberlite IRA-400 (OH^-) resin, followed by hydrolysis in refluxing 1 M sodium hydroxide solution gave, in 76% yield, 4′-hydroxyfortimicin KE (**13**), which was characterized by conversion into the hepta-*N*,*O*-acetyl derivative (**14**). Selective *N*-benzyloxycarbonylation of **13** with *N*-(benzyloxycarbonyloxy)succinimide gave 1,2′,6′-tris[*N*-(benzyloxycarbonyl)]-4′-hydroxyfortimicin KE (**15**) in 50% yield. Tetrakis[*N*-(benzyloxycarbonyl)] derivative of 4′-hydroxyfortimicin D (**16**) was obtained in 67% yield by introduction of *N*-(benzyloxycarbonyl)-glycyl group into methyl amino group at C-4 of **15** with *N*-[*N*-(benzyloxycarbonyl)glycyloxy]succinimide and triethylamine. Hydrogenolysis of **16** in ethanol containing 0.1 M hydrochloric acid in the presence of

Table 1. Antimicrobial Activity of **17** and Fortimicin A[a]

Test Organisms	**17**	Fortimicin A
Streptococcus faecalis KY4280	>100	3.1
Pseudomonas aeruginosa KY4276	50	3.1
Staphylococcus aureus KY4279	6.3	<0.05
Escherichia coli KY4271	25	0.39
Bacillus subtilis KY4273	3.1	0.1
Shigella sonnei KY4281	50	0.78
Klebsiella pneumoniae KY4275	6.3	<0.05

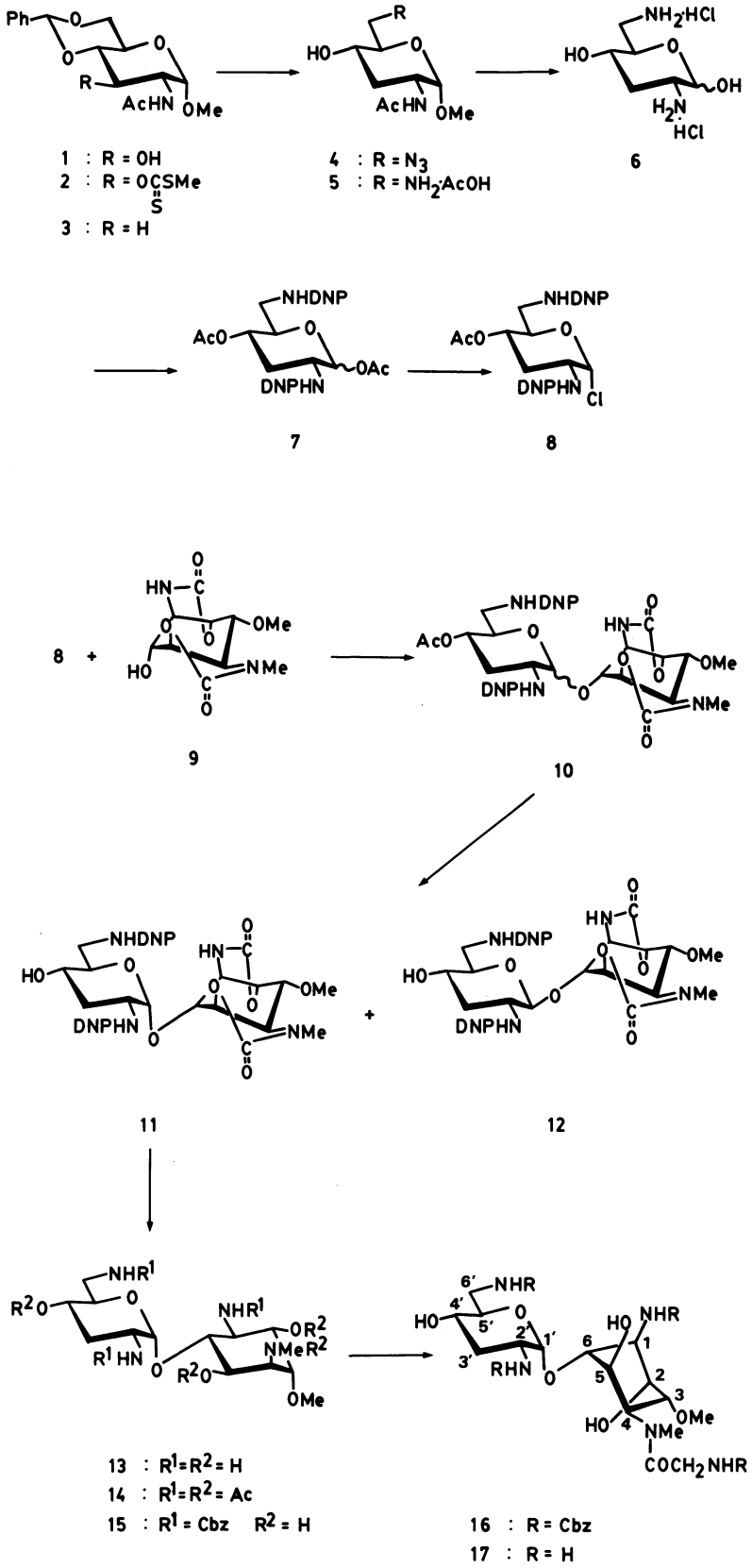
a) Minimum inhibitory concentration in μg ml^{-1}.

† Present address: Department of Chemistry, Faculty of Science and Technology, Meisei University, Hodokubo, Hino, Tokyo 191.

†† 1 M=1 mol dm^{-3}.

10% palladium on charcoal gave 4′-hydroxyfortimicin D (**17**) as the hydrochloride.

The minimum inhibitory concentrations of **17** against seven organisms were compared with those of fortimicin A (Table 1). Antimicrobial activity of **17** was lower than that of fortimicin A.



Experimental

General Procedures. Melting points were determined in capillary-tubes and are uncorrected. Optical rotations were measured on a JASCO DIP-4 polarimeter. IR and Mass spectra were recorded on Hitachi HPL-225 spectrophotometer and Hitachi M-80 and M-80A (SIMS) spectrometers, respectively. ^{1}H NMR spcetra with TMS or DSS as internal standard were recorded on Varian EM-390 (90 MHz). TLC and column chromatography were performed on Silica Gel 60F-254 (E. Merck) and Wakogel C-200, C-300 or Kieselgel 60, respectively. Concentration were carried out under reduced pressure below 40 °C.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-[methylthio(thiocarbonyl)]-α-D-glucopyranoside (2). To a solution of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[16] (28.5 g) in *N*,*N*-dimethylformamide (400 ml), a suspension of 60% sodium hydride (5.40 g) in *N*,*N*-dimethylformamide (10 ml) and catalytic amount of imidazole were added. After stirring for 1 h at 50 °C, carbon disulfide (54 ml) was added to the mixture. After 15 min, methyl iodide (40 ml) was added and stirring was continued for 30 min. The mixture was then poured into ice water (500 ml) and extracted with chloroform (300 ml). The extracts were washed with 0.1 M hydrochloric acid, saturated aqueous $NaHCO_3$ and water, and dried. After evaporation of the solvent, the residue was crystallized from ethanol to afford **2** (29.1 g, 81%): Mp 182—183 °C; $[\alpha]_D^{14}$ −23.8° (*c* 0.93, chloroform); IR (KBr) 1665, 1520 (NHC=O), 1200 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.92 (3H, s, NAc), 2.54 (3H, s, SMe), 3.41 (3H, s, OMe), 4.75 (1H, d, *J*=3.5 Hz, H-1), 5.53 (1H, s, C<u>H</u>C_6H_5), 5.90 (1H, d, *J*=9 Hz, NH), 6.31 (1H, t, *J*=9 Hz, H-3), 6.92—7.53 (5H, m, phenyl).

Found: C, 52.51; H, 5.56; N, 3.35; S, 15.26%. Calcd for $C_{18}H_{23}NO_6S_2$: C, 52.28; H, 5.61; N, 3.39; S, 15.51%.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*ribo*-hexopyranoside (3). To a boiling solution of **2** (30 g) in toluene (750 ml), a solution of *n*-Bu_3SnH (38.8 ml) in toluene (62 ml) and catalytic amount of α, α′-azobisisobutyronitrile were added under nitrogen atmosphere. After 5 min, the mixture was cooled and concentrated to give a gelatinous residue, which was chromatographed on silica gel with chloroform–acetone (1:1). The fractions [R_f 0.38; toluene–acetone (3:1)] were concentrated to afford **3** (22.2 g, 99%) as an amorphous solid: Mp 248—249 °C; $[\alpha]_D^{16}$ +54.5° (*c* 1.27, chloroform), Lit.[14] mp 245 °C, $[\alpha]_D$ +55.5° (*c* 0.95).

Found: C, 62.38; H, 7.02; N, 4.55%. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56%.

Methyl 2-Acetamido-6-amino-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside Acetate (5). A solution of methyl 2-acetamido-6-azido-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside (**4**)[18] (2.62 g) in methanol (25 ml) containing acetic acid (0.1 ml) was hydrogenated with Raney nickel in the initial hydrogen pressure of 3.4 kg cm^{-2} for 17 h. The catalyst was filtered and the filtrate was concentrated to a residue, which was washed with ether to give **5** (2.52 g, 84%) as a white powder: Mp 150 °C; $[\alpha]_D^{22}$ +115° (*c* 0.65, methanol); ^{1}H NMR (CD_3OD) δ=1.97 (3H, s, NAc), 3.47 (3H, s, OMe), 4.64 (1H, d, *J*=3.3 Hz, H-1).

Found: C, 47.21; H, 7.75; N, 10.23%. Calcd for $C_9H_{18}N_2O_4 \cdot CH_3COOH$: C, 47.47; H, 7.97; N, 10.07%.

1,4-Di-*O*-acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,6-trideoxy-D-*ribo*-hexopyranose (7). A solution of **5** (9.52 g) in 2 M hydrochloric acid (200 ml) was refluxed for 4 h. The mixture was concentrated and the residue was dissolved in methanol (100 ml) and acetone (70 ml). 2,4-Dinitrofluorobenzene (17.9 g) and triethylamine (26.9 ml) were added to it under ice cooling and the mixture was stirred for 12 h at room temperature. The mixture was concentrated to half volume and partitioned between ethyl acetate (200 ml) and water (200 ml). The organic layer and the extracts (400 ml) were combined and dried. After concentration, the residue was chromatographed on silica gel with toluene–acetone (5:1) as an eluent to afford the *N*-(2,4-dinitrophenyl) derivative of **6** (14.7 g, 68%) as a yellow powder: Mp 138—139.5 °C; $[\alpha]_D^{19}$ +19.1° (*c* 1.1, acetone); IR (KBr) 1520, 1335 (NO_2) cm^{-1}. To a solution of the powder (14.6 g) in pyridine (150 ml), acetic anhydride (56 ml) was added under ice cooling and the mixture was stirred for 13 h at room temperature. The reaction solution was concentrated and the residue gave **7** (7.11 g) as a yellow powder upon addition of ethyl acetate. An additional crop of **7** (6.72 g, total yield 55%) was obtained by chromatography of the mother liquor on silica gel using toluene–acetone (8:1): Mp 190 °C (decomp); $[\alpha]_D^{25}$ +14.3° (*c* 0.34, chloroform); IR (KBr) 1745 (ester), 1525, 1340 (NO_2) cm^{-1}; ^{1}H NMR (pyridine-d_5) δ=2.12 and 2.26 (each 3H, s, OAc), 5.30 (1H, dt, *J*=5 Hz, 10 Hz, H-4), 6.63 (1/4H, d, *J*=8.5 Hz, H-1), 6.66 (3/4H, d, *J*=3.5 Hz, H-1).

Found: C, 45.55; H, 3.92; N, 14.46%. Calcd for $C_{22}H_{22}N_6O_{13}$: C, 45.68; H, 3.83; N, 14.53%.

4-*O*-Acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl Chloride (8). A solution of **7** (4.0 g) in 15% HCl–dioxane (175 ml) containing acetyl chloride (10 ml) was stirred at 50 °C for 4 h. The mixture was concentrated, and the residue was washed with ether and recrystallized from chloroform to afford **8** (2.10 g, 54%): Mp 127 °C (decomp); $[\alpha]_D^{17}$ +86.0° (*c* 1.66, acetone); ^{1}H NMR (acetone-d_6) δ=2.10 (3H, s, OAc), 4.80 (1H, ddt, *J*=4 Hz, 9 Hz, 12 Hz, H-2), 5.10 (1H, dt, *J*=4.5 Hz, 11.5 Hz, H-4), 6.54 (1H, d, *J*=4 Hz, H-1), 7.27 and 7.46 (each 1H, d, *J*=9 Hz, H-3 of DNP), 8.26 (2H, dd, *J*=3 Hz, 9 Hz, H-5 of DNP × 2), 8.98 (2H, d, *J*=3 Hz, H-6 of DNP × 2).

Found: C, 43.10; H, 3.60; N, 14.88; Cl, 6.45%. Calcd for $C_{20}H_{19}N_6O_{11}Cl$: C, 43.29; H, 3.45; N, 15.15; Cl, 6.39%.

4′-*O*-Acetyl-1,2:4,5-di-*N*,*O*-carbonyl-2′,6′-bis[*N*-(2,4-dinitrophenyl)]-fortimicin KE and -1′-epifortimicin KE (10). 1,2:4,5-Di-*N*,*O*-carbonylfortamine B (**9**)[10,11] (404 mg) was dissolved in freshly distilled dioxane (16 ml) at 100 °C. After the solution had been cooled to room temperature, **8** (1.95 g) and silver trifluoromethanesulfonate (990 mg) were added, and the mixture was stirred under argon atmosphere in the dark for 66 h. An insoluble material was filtered and washed with acetone. The filtrate was concentrated and the residual product was purified by a column chromatography using toluene–acetone (5:1). Fractions [R_f 0.33, toluene–acetone (5:2)] were concentrated to give the anomeric mixture of **10** (342 mg, 28%) and the aglycon **9** (200 mg) recovered.

1,2:4,5-Di-*N*,*O*-carbonyl-2′,6′-bis[*N*-(2,4-dinitrophenyl)]-4′-hydroxyfortimicin KE (11) and -1′-epi-4′-hydroxyfortimicin KE (12). To a solution of **10** (342 mg) in acetone (30 ml) and methanol (30 ml), 0.02 M sodium hydroxide (20 ml) was added and the mixture was stirred for 5 min. The mixture

was neutralized with Amberlite IR-120 (H^+) resin and concentrated. The residue was purified by chromatography with chloroform–acetonitrile (5:1). Fractions [R_f 0.46, chloroform–acetonitrile (3:1)] were concentrated to give **11** (58 mg, 5% based on **9**): Mp 163—167 °C; $[\alpha]_D^{23}$ +0.83° (*c* 0.84, acetone); IR (KBr) 1760 (cyclic carbamate), 1620, 1590 (aromatic), 1335 (NO_2) cm^{-1}; ^1H NMR (acetone-d_6) δ=2.86 (3H, s, NMe), 3.54 (3H, s, OMe), 5.62 (1H, d, *J*=4.5 Hz, H-1′).

Found: C, 45.49; H, 4.12; N, 14.98%. Calcd for $C_{28}H_{30}N_8O_{16}$: C, 45.78; H, 4.12; N, 15.25%.

The fractions (R_f 0.37) gave **12** (122 mg, 11% based on **9**): Mp 180—184 °C; $[\alpha]_D^{23}$ −32.2° (*c* 0.90, acetone); IR (KBr) 1760, 1620, 1590, 1335 cm^{-1}; ^1H NMR (acetone-d_6) δ=2.86 (3H, s, NMe), 3.48 (3H, s, OMe), 5.15 (1H, d, *J*=7.5 Hz, H-1′).

Found: C, 45.52; H, 4.17; N, 14.99%. Calcd for $C_{28}H_{30}N_8O_{16}$: C, 45.78; H, 4.12; N, 15.25%.

4′-Hydroxyfortimicin KE (13). A mixture of **11** (80 mg) in acetone (10 ml), methanol (10 ml) and water (5 ml), and Amberlite IRA-400 (OH^-) resin (2 ml) was stirred overnight. The resin was filtered and the filtrate was concentrated and the residue was partitioned between ethyl acetate (20 ml) and water (20 ml). The organic layer was washed with water (20 ml) and the aqueous layers were concentrated to give a syrup of *N*-de(2,4-dinitrophenyl)ated derivative of **11** (67 mg). To a refluxing solution of 1 M sodium hydroxide (10 ml), a solution of the syrup (67 mg) in water was added and the mixture was stirred for 1 h. The mixture was cooled to room temperature and neutralized with 1 M hydrochloric acid. After concentration, the residue was chromatographed on a column of Amberlite CG-50 (NH_4^+, 40 ml) resin with 0—0.16 M aq ammonia with gradient increase in concentration. Fractions [R_f 0.41, isopropyl alcohol–chloroform–concd aq ammonia (4:1:2)] were collected and concentrated to give 4′-hydroxyfortimicin KE **13** (29 mg, 76%): $[\alpha]_D^{17}$ +19.1° (*c* 0.43, water); ^1H NMR (D_2O) δ=2.72 (3H, s, NMe), 3.43 (3H, s, OMe).

1,4,2′,6′-Tetra-*N*-acetyl-2,5-di-*O*-acetyl-fortimicin KE (14). Compound **13** was acetylated in the usual way to give **14**: $[\alpha]_D^{17}$ +84.9° (*c* 0.85, methanol); IR (KBr) 1740 (ester), 1650 (NHC=O) cm^{-1}; ^1H NMR (CD_3OD) δ=1.89, 1.94, 1.96, 2.02, 2.05, 2.08 and 2.11 (each 3H, s, NAc×4 and OAc×3), 3.02, and 3.10 (3H in total, each s, NMe), 3.40 (3H, s, OMe).

Found: *m/z*, 645.2979. Calcd for $C_{28}H_{45}N_4O_{13}$: M+1, 645.2979.

1,2′,6′-Tris[*N*-(benzyloxycarbonyl)]-4′-hydroxyfortimicin KE (15). To a solution of **13** (29 mg) in water–methanol (1:2, 5 ml), *N*-(benzyloxycarbonyloxy)succinimide (64 mg) was added under ice cooling. After stirring for 3 h at 0 °C, the mixture was stirred for 20 h at room temperature. The mixture was concentrated, and the residue was extracted with chloroform (40 ml) and dried. After concentration, the residue was purified by preparative TLC with toluene–ethanol (4:1) to give **15** (31 mg, 50%): $[\alpha]_D^{21}$ +16.8° (*c* 0.30, methanol); ^1H NMR ($CDCl_3$) δ=2.30 (3H, s, NMe), 3.41 (3H, s, OMe), 5.06 (6H, s, benzyl×3), 5.28 (1H, d, *J*=3.8 Hz, H-1′), 7.31 (15H, s, phenyl×3).

Found: C, 59.89; H, 6.42; N, 7.21%. Calcd for $C_{38}H_{48}N_4O_{12}\cdot 2/3H_2O$: C, 59.68; H, 6.50; N, 7.33%.

1,2′,6′-Tris[*N*-(benzyloxycarbonyl)]-4-[*N*-[*N*-(benzyloxycarbonyl)glycyl]]-4′-hydroxyfortimicin KE (16). To a solution of **15** (18 mg) in dioxane (1.5 ml), *N*-[*N*-(benzyloxycarbonyl)-glycyloxy]succinimide (19 mg) and triethylamine (0.02 ml) were added and the mixture was stirred at 60 °C for 12 h. The mixture was cooled to room temperature and concentrated to give a residue which was extracted with chloroform (40 ml). The extract was dried and concentrated to the residue, which was purified by preparative TLC with toluene–ethanol (6:1) to give **16** (15 mg, 67%): $[\alpha]_D^{27}$ +53.0° (*c* 0.63, chloroform); ^1H NMR ($CDCl_3$) δ=2.82 (3H, s, NMe), 3.22 (3H, s, OMe), 5.07 (8H, s, benzyl×4), 7.32 (20H, s, phenyl×4).

Found: C, 60.86; H, 6.09; N, 7.16%. Calcd for $C_{48}H_{57}N_5O_{15}$: C, 61.07; H, 6.09; N, 7.42%.

4′-Hydroxyfortimicin D (17). To a solution of **16** (13.8 mg) in ethanol (3 ml), a mixture of 0.1 M hydrochloric acid (0.6 ml) and water (0.5 ml) was added. The mixture was hydrogenated in the presence of 10% palladium on charcoal (23 mg) at an initial hydrogen pressure of 3.4 kg cm^{-2} for 6 h. After removal of the catalyst, the filtrate was concentrated to afford a white solid of **17** (8.0 mg, quant.) as the hydrochloride: $[\alpha]_D^{22}$ +42.5° (*c* 0.4, water); ^1H NMR (D_2O) δ=3.13 (3H, s, NMe), 3.48 (3H, s, OMe), 4.10 (2H, bs, $COC\underline{H}_2NH_2$), 5.48 (1H, d, *J*=4.8 Hz, H-1′). MS (SIMS) Found: *m/z*, 408. Calcd for $C_{16}H_{34}N_5O_7$: M+1, 408.

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