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Synthesis on 1,4-Diaminocyclitol Antibiotics. II. Synthesis of 7′-Propylfortimicin A[1]

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7′-Propylfortimicin A has been synthesized by a condensation of newly prepared 1-*O*-acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,4,6,7,8,9,10-octadeoxy-L-*lyxo*-decopyranose with 2,5-di-*O*-benzoyl-1,4-bis-*N*-(methoxycarbonyl)fortamine B, followed by deprotection.

Since fortimicin A was discovered by Nara et al. in 1977,[2] its chemical modifications have extensively been studied.[3,4] In continuation of our study on modification of the diamino sugar moiety,[5] an extension of its sidechain would be of interest in connection with increase in its hydrophobic nature. We now describe the synthesis of 7′-propylfortimicin A (**17**).

Results and Discussion

1-*O*-Acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,4,6,7,8,9,10-octadeoxy-L-*lyxo*-decopyranose (**9**) has been prepared from the known methyl 2-acetamido-2,3,4-trideoxy-α-D-*erythro*-hexopyranoside (**1**)[6] as shown in Scheme.

Treatment of **1** with *p*-toluenesulfonyl chloride in pyridine gave the tosylate **2** in 76% yield. Displacement of the tosyloxy group with sodium iodide, followed by treatment with sodium nitrite in *N,N*-dimethylformamide and dimethyl sulfoxide, afforded the nitro derivative **4** in 48% yield. The nitro aldol reaction of **4** with butyraldehyde was effected in the presence of CsF in acetonitrile for 5 h at room temperature and the product was successively acetylated with acetic anhydride and BF_3 etherate to give **5** as a diastereoisomeric mixture. The reaction using KF instead of CsF resulted in a poor yield. Hydrogenation of **5** with sodium borohydride in dimethyl sulfoxide afforded a mixture of methyl 2-acetamido-2,3,4,6,7,8,9,10-octadeoxy-6-nitro-α-D-*ribo* and -β-L-*lyxo*-decopyranoside (**6**) in 41% yield based on **4**. Catalytic hydrogenation of **6** with Raney nickel in methanol, followed by *N*-acetylation with acetic anhydride, gave two products (**7**, 57% and **8**, 19%) after chromatography.

The stereochemistry at C-6 in **7** and **8** has been established by the values of specific rotations, and chemical shifts of C-7 in ^{13}C NMR spectra. The values of the specific rotations of **7** and **8**, together with those of methyl 2,6-di-*N*-acetyl-α-purpurosaminide B[7] and -6-*epi*-α-purpurosaminide B[6,8] are shown in Table 1.

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From these data, we could assume that the values of specific rotations of the compounds with α-D-*ribo* configuration are more dextrorotatory than those of the corresponding β-L-*lyxo* isomers. In the ^{13}C NMR spectra on **7** and **8**, the signal of C-7 of **8** shifted upfield by 1.99 ppm compared to that of **7**. Chmielewski et al. observed this upfield shift for the related compounds, and assumed that it was due to the antiperiplanar arrangement of C-7/C-6/C-5/O-5.[9,10] In addition, the ^1H NMR spectrum of **8** revealed the H-5 signal (δ 3.60) with 6 Hz splitting, the dihedral angle around H-5 and H-6 being about 60°. The stereochemistry at C-6 of **7** and **8** has thus been confirmed as shown in Scheme.

Hydrolysis of **7** with 2 M†† hydrochloric acid, followed by successive *N*-(2,4-dinitrophenyl)ation and

Table 1. Specific Rotations of **7** and **8**

	7	**8**	a	b
$[\alpha]_D$	+43.4°	+147°	+62.5°	+185.7°

a: Methyl 2,6-di-*N*-acetyl-6-*epi*-α-purpurosaminide B.[7]
b: Methyl 2,6-di-*N*-acetyl-α-purpurosaminide B.[7]

Table 2. ^{13}C NMR Chemical Shifts[a] of **7** and **8**

	7	**8**
C-1	99.539	99.441
C-2	49.769	49.623
C-3	24.933	25.201
C-4	28.144	28.120
C-5	70.494	71.273
C-6	53.223	53.734
C-7	32.352	30.358
C-8	29.628	29.384
C-9	23.546	23.546
C-10	14.376	14.351
OMe	55.364	55.169
$\underline{C}OCH_3$	173.220	172.928
	172.782	172.758
$CO\underline{C}H_3$	22.525	22.598
	22.525	22.525

a) In parts per million downfield from TMS.

†† 1 M=1 mol dm^{-3}.

O-acetylation gave **9** in 26% yield. On the other hand, the aglycon, 2,5-di-*O*-benzoyl-1,4-bis[*N*-(methoxycarbonyl)]fortamine B (**12**), has been prepared from fortimicin B in the following way. Treatment of fortimicin B with methyl chloroformate in aqueous acetone gave 1,4,2′,6′-tetrakis[*N*-(methoxycarbonyl)]-fortimicin B (**10**) in 98% yield. Benzoylation of **10** with benzoyl chloride in pyridine afforded 65% yield of the 2,5-dibenzoate (**11**), which was hydrolyzed with acetic acid containing 2 M hydrochloric acid to give the aglycon **12** in 79% yield. Judging from the ^{1}H NMR data, **12** is assumed to adopt the skew-boat form as depicted in Scheme. However, the conformations of the fortamine moieties in pseudo-disaccharides could not be deduced by analogy with these results.

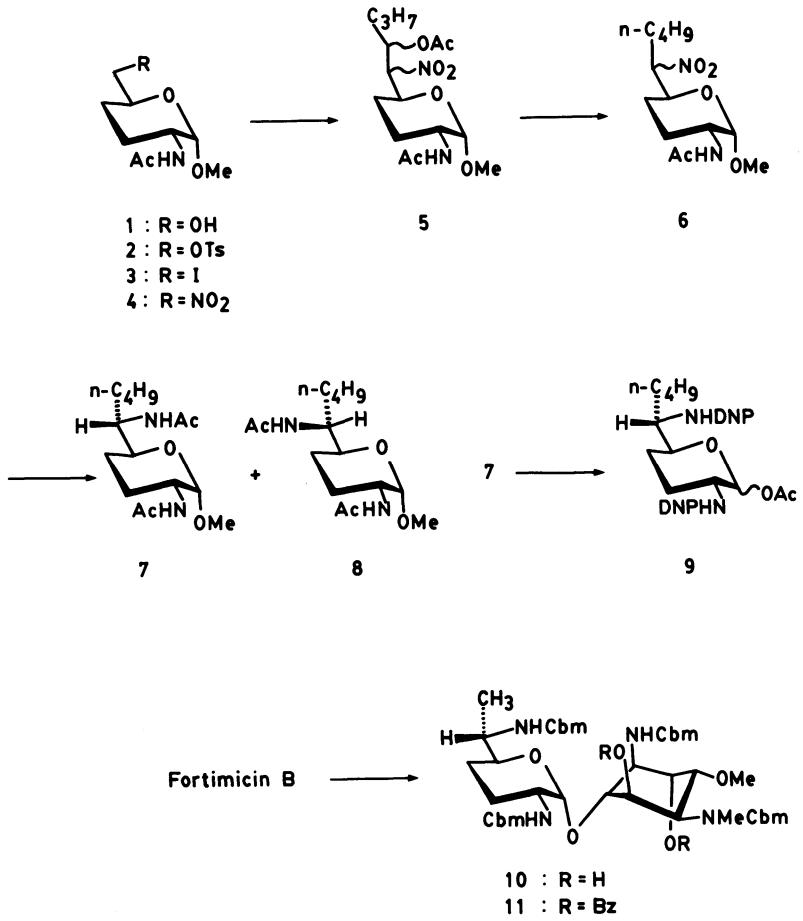
Condensation of **9** with **12** in 1,2-dichloroethane in the presence of trimethylsilyl trifluoromethanesulfonate under argon gave single compound **13** in 49% yield. The ^{1}H NMR spectrum of **13** exhibited the signal of H-1′ (δ 5.28) with a small coupling constant ($J_{1',2'}$=3 Hz), supporting that the anomeric proton is equatorial of the α-D-glycoside. Hydrolysis of **13** in refluxing aqueous dioxane with barium hydroxide, followed by removal of the dinitrophenyl group with Amberlite IRA-400 (OH^-) resin, afforded 7′-propylfortimicin B (**14**) in 68% yield. The tris[*N*-(benzyloxycarbonyl)] derivative **15** was prepared in 60% yield by treatment of **14** with *N*-(benzyloxycarbonyloxy)succinimide. Treatment of **15** with *N*-[*N*-(benzyloxycarbonyl)glycyloxy]succinimide and triethylamine gave 1,4,2′,6′-tetrakis[*N*-(benzyloxycarbonyl)] derivative **16** in 86% yield. Catalytic hydrogenation of **16** in the presence of 10% palladium on charcoal gave quantitatively the free base, which was characterized as crystalline 7′-propylfortimicin A disulfate (**17**).

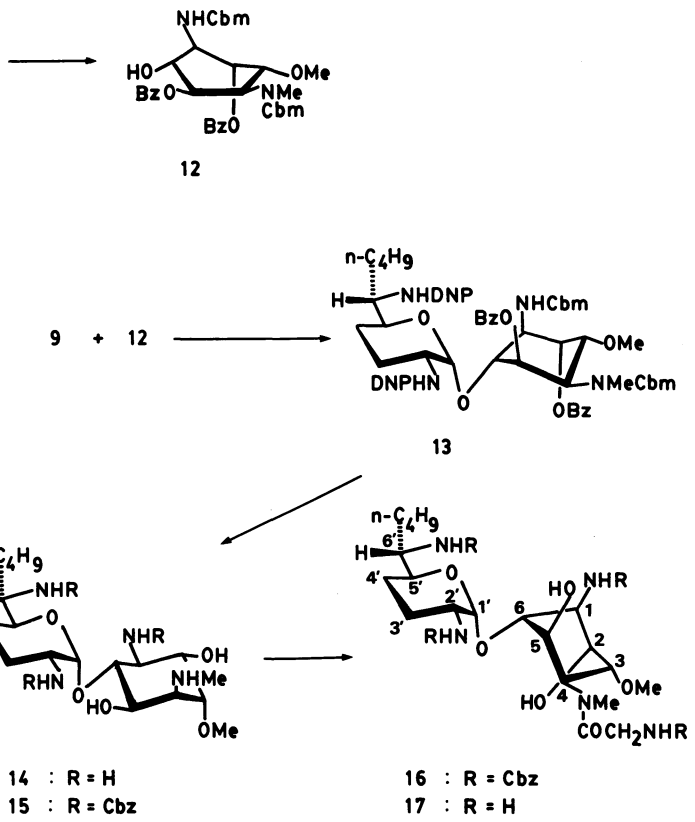
Table 3. Antimicrobial Activity of **17** and Fortimicin A[a)]

Test Organisms	**17**	Fortimicin A
Streptococcus faecalis KY4280	12.5	12.5
Pseudomonas aeruginosa KY4276	50.0	12.5
Staphylococcus aureus KY4279	0.4	0.4
Escherichia coli KY4271	1.6	1.6
Bacillus subtillis KY4273	0.4	0.4
Shigella sonnei KY4281	3.1	6.3
Klebsiella pneumoniae KY4275	0.4	0.4

a) Minimum inhibitory concentration in $\mu g\,ml^{-1}$.

The minimum inhibitory concentration of **17** was compared with those of fortimicin A (Table 3). 7′-propylfortimicin A (**17**) exhibited almost similar activity to that of fortimicin A against many micro organisms except *Pseudomonas*.





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 spectra with TMS or DSS as internal standard were recorded on Varian EM-390 (90 MHz) or JEOL FX-200 (200 MHz), and ^{13}C NMR spectra with TMS on JEOL FX-200 (50 MHz). TLC and column chromatography were performed on Silica Gel 60F-254 (E. Merck) and Kieselgel 60. Organic solutions were concentrated under reduced pressure below 40 °C.

Methyl 2-Acetamido-2,3,4-trideoxy-6-*O*-tosyl-α-D-*erythro*-hexopyranoside (2). To a solution of methyl 2-acetamido-2,3,4-trideoxy-α-D-*erythro*-hexopyranoside (**1**)[6] (1.03 g) in pyridine (20 ml), *p*-toluenesulfonyl chloride (2.50 g) was added under ice cooling and the mixture was poured into ice water (200 ml) and the solution was extracted with chloroform (200 ml). The extract was washed successively with 1 M hydrochloric acid (100 ml), saturated aqueous $NaHCO_3$ (100 ml) and water (100 ml), and dried. After concentration, the residue was chromatographed on silica gel with toluene–ethanol (10:1) to give **2** (1.38 g, 76%). Recrystallization from ethyl acetate–pentane afforded an analytical sample: Mp 98—99 °C; $[\alpha]_D^{20}$ +68.3° (*c* 1.29, chloroform); IR (KBr) 1355, 1170 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.39—2.05 (4H, m, H-3,4), 1.91 (3H, s, NAc), 2.43 (3H, s, Me of tosyl), 3.31 (3H, s, OMe), 4.50 (1H, d, *J*=3 Hz, H-1), 5.66 (1H, d, *J*=9 Hz, NH), 7.34 and 7.80 (each 2H, d, *J*=8.5 Hz, tosyl).

Found: C, 53.96; H, 6.44; N, 4.10; S, 8.71%. Calcd for $C_{16}H_{23}NO_6S$: C, 53.77; H, 6.49; N, 3.92; S, 8.97%.

Methyl 2-Acetamido-2,3,4,6-tetradeoxy-6-nitro-α-D-*erythro*-hexopyranoside (4). To a stirred solution of **2** (897 mg) in 2-butanone (30 ml), sodium iodide (1.50 g) was added and the mixture was refluxed for 2.5 h. The mixture was cooled to room temperature, and the solid was filtered. The filtrate was concentrated to dryness and was diluted with ethyl acetate (150 ml). The solution was washed successively with 30% aqueous sodium thiosulfate (100 ml) and water (100 ml), and dried. Evaporation of the solvent gave crude **3** (738 mg). To a solution of **3** (738 mg), without purification, in *N*,*N*-dimethylformamide (2 ml) and dimethyl sulfoxide (8 ml), sodium nitrite (938 mg) and phloroglucinol dihydrate (1.12 g) were added and the mixture was stirred for 6 d at room temperature. To the mixture, ice water (30 ml) was added and the mixture was extracted with chloroform (100 ml). The extract was washed with water (150 ml) and dried. After concentration, the residue was recrystallized from chloroform–petroleum ether to afford **4** (274 mg, 48% based on **2**): Mp 169 °C (decomp); $[\alpha]_D^{20}$ +138° (*c* 0.78, methanol); IR (KBr) 1545, 1365 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.89 (3H, s, NAc), 3.31 (3H, s, OMe), 4.51 (1H, d, *J*=3 Hz, H-1).

Found: C, 46.48; H, 6.78; N, 11.77%. Calcd for $C_9H_{16}N_2O_5$: C, 46.55; H, 6.94; N, 12.06%.

Methyl 2-Acetamido-2,3,4,6,7,8,9,10-octadeoxy-6-nitro-α-D-*ribo*- and β-L-*lyxo*-decopyranoside (6). To a solution of **4** (1.55 g) in acetonitrile (15 ml), butyraldehyde (1.20 ml) and CsF (1.01 g) were added and the mixture was stirred for 5 h at room temperature. The mixture was partitioned between ethyl acetate (20 ml) and water (20 ml). The aqueous layer

was extracted with ethyl acetate (40 ml) and the organic layer and the extract were combined, and dried. After evaporation of the solvent, a crude syrup of the condensation product (1.91 g) was obtained. To a solution of the condensate (1.91 g) in acetic anhydride (20 ml), BF_3 etherate (3 ml) was added under ice cooling. After stirring for 1 h at 0 °C, the mixture was poured into ice water (200 ml) and the solution was extracted with chloroform (300 ml). The extracts were washed successively with saturated aqueous $NaHCO_3$ (600 ml) and water (200 ml), and dried. After concentration, the residue was chromatographed on silica gel with ethyl acetate–2-butanone (10:1). Fractions [R_f 0.66, chloroform–methanol (10:1)] gave **5** (951 mg) as a syrup: IR ($CHCl_3$) 1740 (ester), 1665, 1560 (NHC=O), 1510, 1370 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.95 (3H, s, NAc), 2.11 (3H, s, OAc), 3.38 and 3.40 (3H in total, each s, OMe), 4.57 (1H, d, J=3 Hz, H-1), 5.26 (1H, m, H-7), 5.72 (1H, d, J=9 Hz, NH). The fractions [R_f 0.55, chloroform–methanol (10:1)] recovered **4** (359 mg).

To a solution of **5** (951 mg) in dimethyl sulfoxide (10 ml), a suspension of sodium borohydride (250 mg) in dimethyl sulfoxide (5 ml) was added. After stirring for 1 h at room temperature, the mixture was acidified with Amberlite IR-120 (H^+) resin and partitioned between dichloromethane (100 ml) and water (100 ml). The aqueous layer was extracted with dichloromethane (200 ml). The organic layer and the extracts were combined and washed with water (200 ml), and dried. After concentration, the residue was recrystallized from chloroform–petroleum ether to afford **6** (484 mg). Chromatography of the mother liquor on silica gel with ethyl acetate–2-butanone (10:1) gave an additional crop of **6** (310 mg, total yield 41% based on **4**): Mp 110 °C (decomp); $[\alpha]_D^{27}$ +124° (c 1.0, methanol); ^1H NMR ($CDCl_3$) δ=0.91 (3H, m, H-10), 1.17—2.19 (10H, m, H-3,4,7,8,9), 1.96 (3H, s, NAc), 3.33 and 3.38 (3H in total, each s, OMe), 4.54 (1H, d, J=3 Hz, H-1), 5.70 (1H, d, J=9 Hz, NH).

Found: C, 54.23; H, 8.17; N, 9.46%. Calcd for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72%.

Methyl 2,6-Diacetamido-2,3,4,6,7,8,9,10-octadeoxy-β-L-*lyxo*-decopyranoside (7) and α-D-*ribo*-decopyranoside (8). A solution of **6** (730 mg) in methanol (10 ml) was hydrogenated in the presence of Raney nickel at an initial hydrogen pressure of 3.4 kg cm^{-2} for 18 h. After removal of the catalyst, the filtrate was concentrated. The residue was treated with acetic anhydride (4 ml) in methanol (10 ml) for 2 h. The mixture was concentrated and was chromatographed on silica gel with toluene–ethanol (10:1). Fractions [R_f 0.45, toluene–ethanol (3:1)] gave **7** (434 mg, 57%) as an amorphous solid: Mp 224—225.5 °C; $[\alpha]_D^{22}$ +43.4° (c 1.0, methanol); ^1H NMR (CD_3OD) δ=0.90 (3H, t, J=7 Hz, H-10), 1.32 (4H, m, H-8,9), 1.43—1.89 (6H, m, H-3,4,7), 1.92 and 1.98 (each 3H, s, NAc), 3.38 (3H, s, OMe), 3.74 (1H, dt, J=3.5 Hz, 10 Hz, H-5), 3.86 (1H, dt, J=3.5 Hz, 7 Hz, H-6), 3.88 (1H, ddd, J=3.5 Hz, 5.5 Hz, 12 Hz, H-2), 4.61 (1H, d, J=3.5 Hz, H-1).

Found: C, 59.89; H, 9.24; N, 9.08%; m/z, 300.2041. Calcd for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.40; N, 9.33%; M^+, 300.2047.

The fractions [R_f 0.41, toluene–ethanol (3:1)] gave **8** (143 mg, 19%): Mp 252.5—254 °C; $[\alpha]_D^{22}$ +147° (c 0.86, methanol); ^1H NMR (CD_3OD) δ=0.90 (3H, t, J=7 Hz, H-10), 1.27—1.83 (10H, m, H-3,4,7,8,9), 1.92 and 1.94 (each 3H, s, NAc), 3.36 (3H, s, OMe), 3.60 (1H, ddd, J=2 Hz, 6 Hz, 11 Hz, H-5), 3.76 (1H, ddd, J=3 Hz, 6 Hz, 10 Hz, H-6), 3.88 (1H, ddd, J=3.5 Hz, 6.5 Hz, 10.5 Hz, H-2), 4.60 (1H, d, J=3.5 Hz, H-1).

Found: C, 59.70; H, 9.21; N, 8.94%; m/z, 301.2121. Calcd for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.40; N, 9.33%; M+1, 301.2125.

1-*O*-Acetyl-2,6-bis(2,4-dinitrophenylamino)-2,3,4,6,7,8,9,10-octadeoxy-L-*lyxo*-decopyranose (9). A stirred solution of **7** (430 mg) in 2 M hydrochloric acid (10 ml) was refluxed for 23 h. The mixture was cooled to room temperature and concentrated, and dried in vacuum. To a solution of the residue in methanol (15 ml) containing 2,4-dinitrofluorobenzene (0.38 ml), triethylamine (0.8 ml) was added dropwise under ice cooling. After stirring for 1 h at 0 °C, the mixture was partitioned between ethyl acetate (50 ml) and water (30 ml). The aqueous layer was extracted with ethyl acetate (80 ml), and the organic layer and the extract were combined and dried. After concentration, the residue was treated with acetic anhydride (5 ml) in pyridine (10 ml) for 4 h at room temperature. The mixture was poured into ice water (100 ml) and the solution was extracted with dichloromethane (200 ml). The extract was successively washed with 1 M hydrochloric acid (200 ml) and water (200 ml), and dried. After concentration, the residue was chromatographed on silica gel with toluene–2-butanone (50:1—30:1) to afford **9** (218 mg, 26% based on **7**) as yellow syrup: $[\alpha]_D^{24}$ −42.4° (c 1.0, chloroform); ^1H NMR ($CDCl_3$) δ=1.99 and 2.25 (3H in total, each s, OAc), 5.65 (1/4H, d, J=9 Hz, H-1β), 6.35 (3/4H, d, J=3 Hz, H-1α), 6.91 and 7.31 (each 1H, d, J=11 Hz, H-3 of DNP), 8.24 and 8.33 (each 1H, dd, J=3 Hz, 11 Hz, H-5 of DNP), 8.48 and 8.86 (each 1H, d, J=10 Hz, NH-2,6), 9.10 and 9.15 (each 1H, d, J=3 Hz, H-6 of DNP).

Found: m/z, 576.1823. Calcd for $C_{24}H_{28}N_6O_{11}$: M^+, 576.1814.

1,4,2′,6′-Tetrakis[*N*-(methoxycarbonyl)]fortimicin B (10). To a solution of fortimicin B (5.80 g) in aqueous acetone (1:1, 200 ml), anhydrous sodium carbonate (5.29 g) and methyl chloroformate (7.85 ml) were added and the mixture was stirred for 20 min under ice cooling. The mixture was concentrated and the residue was partitioned between water (150 ml) and chloroform (150 ml). The aqueous layer was extracted with chloroform (250 ml), and the organic layer and the extract were combined and dried. After concentration, the residue was washed with petroleum ether to give **10** (9.50 g, 98%): Mp 85—92 °C; $[\alpha]_D^{19}$ +63.5° (c 1.21, chloroform); ^1H NMR ($CDCl_3$) δ=1.08 (3H, d, J=6 Hz, H-7′), 3.62, 3.65, 3.70, and 3.75 (each 3H, s, Cbm), 3.00 (3H, s, NMe), 3.42 (3H, s, OMe), 4.84 (1H, d, J=3 Hz, H-1′).

2,5-Di-*O*-benzoyl-1,4,2′,6′-tetrakis[*N*-(methoxycarbonyl)]-fortimicin B (11). To a solution of **10** (1.0 g) in pyridine (10 ml), benzoyl chloride (1.2 ml) was added and the mixture was stirred for 65 h at 60 °C. After cooling to room temperature, the mixture was poured into ice water (100 ml). The mixture was extracted with ethyl acetate (200 ml) and the extract was washed successively with 1 M hydrochloric acid (100 ml), saturated aqueous $NaHCO_3$ (100 ml), and water (100 ml), and dried. After concentration, the residue was chromatographed on silica gel with chloroform–methanol (40:1). Fractions [R_f 0.58, chloroform–methanol (20:1)] were concentrated and the residue was crystallized from ether–chloroform–petroleum ether to give **11** (890 mg, 65%): Mp 115—121 °C; $[\alpha]_D^{27}$ +13.4° (c 1.19, chloroform); ^1H NMR ($CDCl_3$) δ=1.09 (3H, d, J=6 Hz, H-7′), 2.92 (3H, s,

NMe), 3.49 (3H, s, OMe), 3.55, 3.64, 3.67, and 3.77 (each 3H, s, Cbm), 5.04 (1H, d, J=3 Hz, H-1′).

Found: C, 56.13; H, 6.04; N, 6.98%. Calcd for $C_{37}H_{48}N_4O_{15}$: C, 56.34; H, 6.13; N, 7.10%.

2,5-Di-*O*-benzoyl-1,4-bis[*N*-(methoxycarbonyl)]fortamine B (12). A solution of **11** (890 mg) in acetic acid (4 ml) containing 2 M hydrochloric acid (1 ml) was stirred for 4 h at 80 °C. After cooling to room temperature, the mixture was diluted with water (20 ml). The mixture was extracted with dichloromethane (100 ml) and the extract was washed successively with saturated aqueous $NaHCO_3$ (200 ml), brine (100 ml) and water (100 ml), and dried. After concentration, the residue was chromatographed on silica gel with chloroform–methanol (99:1). Fractions [R_f 0.32, chloroform–methanol (50:1)] gave **12** (476 mg, 79%). Recrystallization from ether–petroleum ether afforded an analytical sample: mp 104—113 °C; $[\alpha]_D^{22}$ +18.0° (c 0.65, chloroform); ^{1}H NMR ($CDCl_3$) δ=3.00 (3H, s, NMe), 3.29 (1H, bs, OH-6), 3.48 (3H, s, OMe), 3.60 and 3.64 (each 3H, s, Cbm), 4.04 (1H, dd, J=3 Hz, 8 Hz, H-3), 4.28 (2H, m, H-1,6), 4.97 (1H, dd, J=5 Hz, 8 Hz, H-4), 5.29 (1H, d, J=8 Hz, NH-1), 5.69 (1H, dd, J=5 Hz, 7 Hz, H-5), 5.78 (1H, dd, J=3 Hz, 7 Hz, H-2), 7.40—7.62 (6H, m, benzoyl), 7.98—8.10 (4H, m, benzoyl).

Found: C, 58.66; H, 5.69; N, 5.16%. Calcd for $C_{26}H_{30}N_2O_{10}$: C, 58.86; H, 5.70; N, 5.28%.

2,5-Di-*O*-benzoyl-2′,6′-bis[*N*-(2,4-dinitrophenyl)]-1,4-bis-[*N*-(methoxycarbonyl)]-7′-propylfortimicin B (13). To a mixture of **9** (218 mg), **12** (200 mg), and powdered molecular sieve 4A (200 mg) in 1,2-dichloroethane (5 ml) was added trimethylsilyl trifluoromethanesulfonate (0.07 ml) and the mixture was stirred for 2 h under argon. The mixture was diluted with dichloromethane (40 ml) and an insoluble material was filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (40 ml) and water (40 ml), and dried. After concentration, the residue was chromatographed on silica gel eluting with toluene–2-butanone (50:1—20:1) to give **13** (195 mg, 49%): Mp 127—132 °C; $[\alpha]_D^{27}$ + 0.8° (c 0.4, chloroform); ^{1}H NMR ($CDCl_3$) δ=2.82 (3H, s, NMe), 3.43 (3H, s, OMe), 3.52 and 3.64 (each 3H, s, Cbm), 3.70 (2H, m, H-2′,6′), 3.95 (1H, m, H-1), 4.09 (1H, dd, J=3 Hz, 10 Hz, H-3), 4.54 (1H, m, H-6), 4.88 (1H, m, H-4), 5.18 (1H, d, J=9 Hz, NH-1), 6.28 (1H, d, J=3 Hz, H-1′), 5.44 (1H, m, H-5), 5.77 (1H, m, H-2), 6.86 and 7.02 (each 1H, d, J=9 Hz, H-3 of DNP), 7.22—7.66 (6H, m, benzoyl), 7.88 and 8.16 (each 2H, d, J=8.5 Hz, bezoyl), 8.16 and 8.28 (each 1H, dd, J=3 Hz, 9 Hz, H-5 of DNP), 8.64 (2H, m, NH-2′,6′), 9.12 and 9.14 (each 1H, d, J=3 Hz, H-6 of DNP).

Found: C, 54.65; H, 5.20; N, 10.88%. Calcd for $C_{48}H_{54}N_8O_{19}$: C, 55.07; H, 5.20; N, 10.70%.

7′-Propylfortimicin B (14). A stirred solution of **13** (204 mg) in aqueous dioxane (1:2, 15 ml) containing barium hydroxide octahydrate (3.80 g) was refluxed for 14 h. The mixture was cooled to room temperature and the solid was filtered. Carbon dioxide was introduced to the filtrate and an insoluble material was filtered. After concentration, the residue was treated with Amberlite IRA-400 (OH^-) resin (13 ml) in a mixture of water (10 ml), methanol (15 ml) and acetone (15 ml). After stirring for 15 h, the resin was filtered, and the filtrate was neutralized with 1% H_2SO_4. After concentration of the solution, the residue was chromatographed on a column of Amberlite CG-50 (NH_4^+) resin (35 ml) with 0—0.20 M aq ammonia with gradient increase in concentration. Fractions [R_f 0.60, isopropyl alcohol–chloroform–concd aq ammonia (4:1:1)] gave **14** (51 mg, 68%): $[\alpha]_D^{27}$ +8.6° (c 1.54, water); IR (KBr) 3350, 2930, 1570, 1460, 1370, 1090 cm^{-1}; ^{1}H NMR (D_2O) δ=0.89 (3H, m, H-10′), 1.20—1.90 (10H, m, H-3′,4′,7′,8′,9′), 2.40 (3H, s, NMe), 2.82—2.96 (2H, m, H-2′,6′), 3.01 (1H, t, J=9.5 Hz, H-1), 3.11 (1H, dd, J=4 Hz, 4.5 Hz, H-4), 3.48 (3H, s, OMe), 3.53 (1H, t, J=9.5 Hz, H-6), 3.69 (1H, t, J=4 Hz, H-3), 3.72 (1H, dd, J=4 Hz, 9.5 Hz, H-2), 3.82 (1H, m, H-5′), 4.01 (1H, dd, J=4.5 Hz, 9.5 Hz, H-5), 5.16 (1H, d, J=3 Hz, H-1′).

Found: C, 52.80; H, 9.14; N, 13.29%; m/z, 391. Calcd for $C_{18}H_{38}N_4O_5 \cdot 1/2H_2CO_3$: C, 52.71; H, 9.32; N, 13.29%; M+1, 391.

1,2′,6′-Tris[*N*-(benzyloxycarbonyl)]-7′-propylfortimicin B (15). To a solution of **14** (49 mg) in aqueous methanol (1:2, 6 ml), *N*-(benzyloxycarbonyloxy)succinimide (97 mg) was added under ice cooling and the mixture was stirred for 3 h at 0 °C, and stirring was continued for 23 h at room temperature. After addition of 5% aqueous $NaHCO_3$ (10 ml) to the solution, the mixture was extracted with chloroform (30 ml) and the extract was dried. After concentration, the residue was chromatographed on silica gel with chloroform–methanol (30:1) to give **15** (59 mg, 60%): $[\alpha]_D^{27}$ +11.4° (c 1.66, chloroform); ^{1}H NMR ($CDCl_3$) δ=2.26 (3H, s, NMe), 3.39 (3H, s, OMe), 5.00 (6H, bs, benzyl × 3), 7.27 (15H, s, phenyl × 3).

1,2′,6′-Tris[*N*-(benzyloxycarbonyl)]-4-[*N*-[*N*-(benzyloxycarbonyl)glycyl]]-7′-propylfortimicin B (16). To a solution of **15** (57 mg) in dioxane (5 ml), *N*-[*N*-(benzyloxycarbonyl)-glycyloxy]succinimide (27 mg) and triethylamine (0.01 ml) were added and the mixture was stirred for 13 h at 60 °C. After cooling to room temperature, 5% aqueous $NaHCO_3$ (20 ml) was added to the mixture and the mixture was extracted with chloroform (30 ml). The extract was washed with water (30 ml), and dried. After concentration, the residue was chromatographed on silica gel with chloroform–methanol (50:1) to give **16** (62 mg, 86%): $[\alpha]_D^{25}$ +21.2° (c 1.16, chloroform); ^{1}H NMR ($CDCl_3$) δ=2.78 (3H, s, NMe), 3.27 (3H, s, OMe), 4.78 (1H, d, J=3 Hz, H-1′), 5.06 (8H, s, benzyl × 4), 7.31 (20H, s, phenyl × 4).

Found: C, 63.46; H, 6.65; N, 6.87%. Calcd for $C_{52}H_{66}N_5O_{14}$: C, 63.40; H, 6.75; N, 7.11%.

7′-Propylfortimicin A (17). A solution of **16** (53 mg) in methanol (5 ml) was hydrogenated in the presence of 10% palladium on charcoal (50 mg) at an initial hydrogen pressure of 3.4 kg cm^{-2} for 4 h. The catalyst was removed and the solution was concentrated. The residue was dissolved in water and passed through a column of Amberlite IRA-400 (OH^-) resin using water as an eluent. Fractions [R_f 0.39, isopropyl alcohol–chloroform–concd aq ammonia (4:1:1)] were collected and the solution was adjusted to pH 5 with 1% H_2SO_4. The mixture was concentrated to a residue, which was recrystallized from methanol–acetone to give **17** (25 mg, 70%) as the disulfate: $[\alpha]_D^{25.5}$ +63.5° (c 0.47, water); IR (KBr) 3430, 2920, 1485, 1110, 1030 cm^{-1}; ^{1}H NMR (D_2O) δ=0.92 (3H, t, J=7 Hz, H-10′), 1.41, 1.65, and 2.02 (10H in total, each m, H-3′,4′,7′,8′,9′), 3.16 (3H, s, NMe), 3.52 (3H, s, OMe), 4.88 (1H, dd, J=2 Hz, 12 Hz, H-4), 5.33 (1H, d, J=3.5 Hz, H-1′).

Found: C, 35.72; H, 7.04; N, 9.80%; m/z, 448. Calcd for $C_{20}H_{41}N_5O_6 \cdot 2H_2SO_4 \cdot 2H_2O$: C, 35.35; H, 7.27; N, 10.30%; M+1, 448.

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