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SYNTHESIS OF 7′-(3-HYDROXYPROPYL)FORTIMICIN A AND 6′-EPIFORTIMICIN A*

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ABSTRACT

1,10-Di-*O*-acetyl-2,3,4,6,7,8,9-heptadeoxy-2,6-bis(2,4-dinitrophenylamino)-L-*lyxo*-decopyranose (**7**) and -D-*ribo*-decopyranose (**8**) have been prepared from methyl 2-acetamido-2,3,4,6-tetradeoxy-6-nitro-α-D-*erythro*-hexopyranoside *via* a nitro aldol reaction with 4-[(tetrahydropyranyl)oxy]butanal in the presence of cesium fluoride, and their configurations at C-6 have been established by conversion of the precursor of **8**, namely, methyl 2,6-diacetamido-10-*O*-acetyl-2,3,4,6,7,8,9-heptadeoxy-α-D-*ribo*-decopyranoside, into the known methyl 2,6-diacetamido-2,3,4,6,7,8,9,10-octadeoxy-α-D-*ribo*-decopyranoside. The title fortimicin A derivatives, 7′-(3-hydroxypropyl)fortimicin A and 6′-epifortimicin A, have been synthesized by condensation of compound **7** and **8**, respectively, with 2,5-di-*O*-benzoyl-1,4-bis[*N*-(methoxycarbonyl)]fortamine B, followed by deprotection and introduction of a glycyl group. Their antimicrobial activities have been found to be weak compared to that of fortimicin A.

INTRODUCTION

The 1,4-diaminocyclitol antibiotic fortimicin A, isolated[2] from a fermentation broth of *Micromonospora olivoasterospora*, exhibits potent antibacterial activity against both Gram-positive and -negative bacteria. A great number of fortimicin derivatives have so far been synthesized; however, most of the chemical modifications have centered around the 1,4-diaminocyclitol moiety.

In order to elucidate the role of the diamino sugar moiety, namely, 6-epipurpurosamine B, in the antimicrobial activity, we have synthesized several 7′-substituted fortimicin A derivatives[3,4]. Since 7′-propylfortimicin A demonstrated antimicrobial activity similar to that of fortimicin A, except for *Pseudomonas*, we

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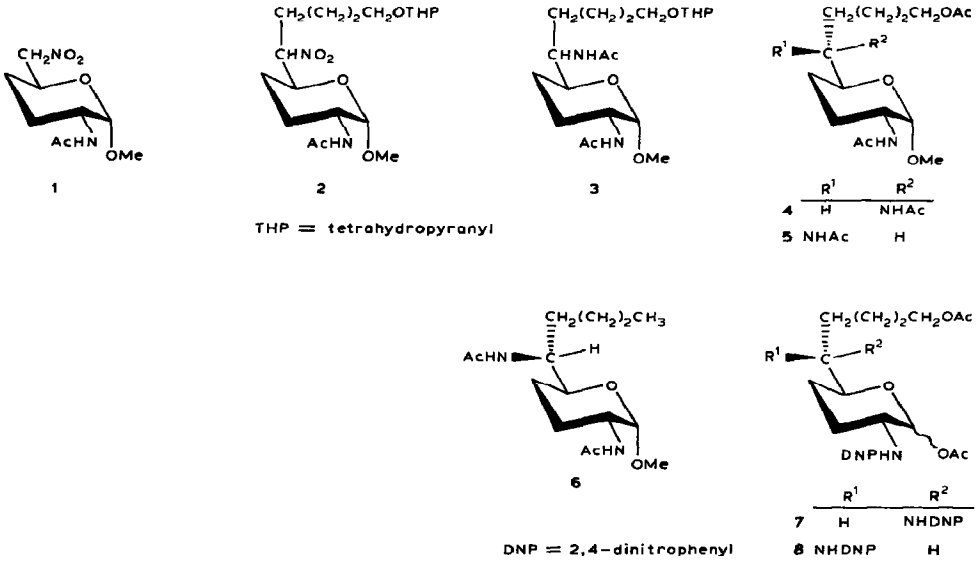
deduced that introduction of a hydroxyl group into the terminal propyl group of 7′-propylfortimicin A would be of interest.

We describe here the synthesis and biological activities of 7′-(3-hydroxypropyl)fortimicin A (**18**) and 6′-epifortimicin A (**19**).

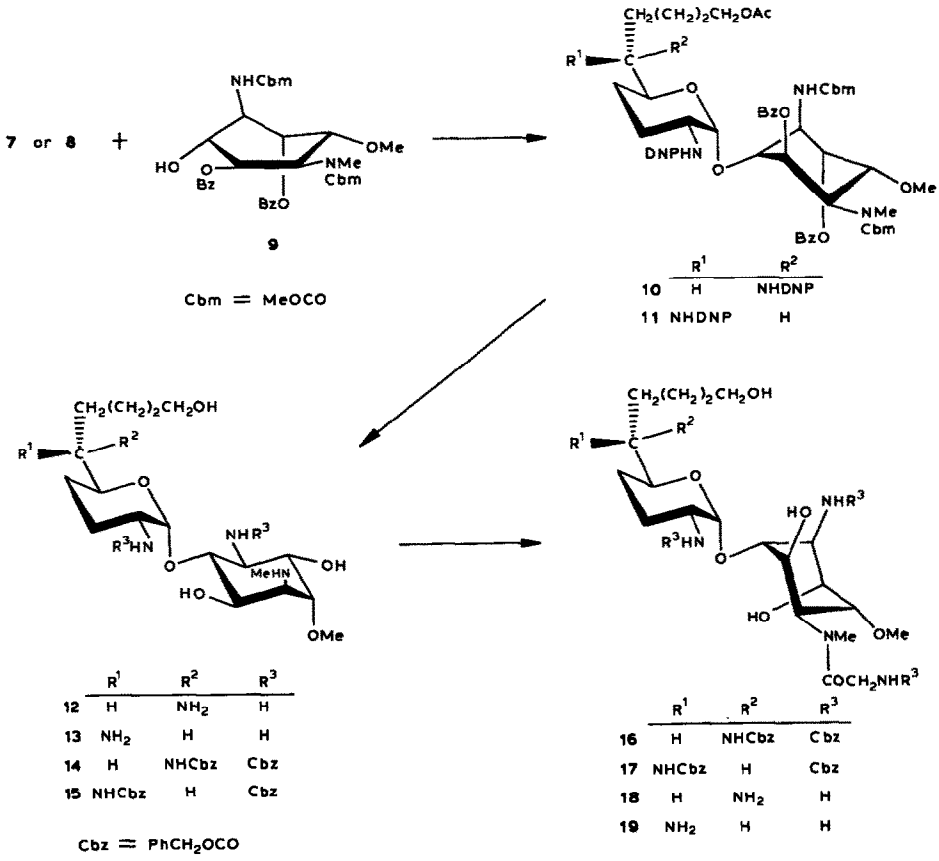


RESULTS AND DISCUSSION

A mixture of methyl 2-acetamido-2,3,4,6,7,8,9-heptadeoxy-6-nitro-10-*O*-tetrahydropyranyl-β-L-*lyxo*- and -α-D-*ribo*-decopyranoside (**2**) was obtained by nitro aldol reaction of compound **1** (ref. 3) with 4-[(tetrahydropyranyl)oxy]butanal[5] in the presence of cesium fluoride, followed by deoxygenation in the usual way. Catalytic hydrogenation of **2** with Raney nickel, followed by acetylation gave the 2,6-diacetamido derivative **3** as a mixture of isomers.

Removal of the tetrahydropyranyl group of **3**, followed by acetylation gave two products, the acetates **4** (34%) and **5** (29%), respectively. Replacement of the tetrahydropyranyl group with the acetyl group thus facilitated the chromatographic separation of this isomeric mixture. The specific rotation of compound **5**, having the D-*ribo* configuration was more dextrorotatory than that of the L-*lyxo* compound **4**. Correlated to the previously reported diacetamido derivatives[3,4] these results indicated the configuration of C-6 of **4** and **5**. Furthermore, the stereochemistry at C-6 was verified by conversion of **5** into the known[3] compound **6**. The conversion product was identical to an authentic sample in all respects, except that the $[\alpha]_D$ values differed by 43 degrees.

Hydrolysis of **4** in refluxing 2M hydrochloric acid, followed by *N*-(2,4-dinitro-



phenyl)ation in the usual way, and acetylation of the product gave compound **7**.

Condensation of **7** and **9** (ref. 3) in 1,2-dichloroethane in the presence of trimethylsilyl trifluoromethanesulfonate under argon gave the single condensate **10** in 35% yield. The anomeric configuration was supported by the ^{1}H-n.m.r. spectrum of 7′-(3-hydroxypropyl)fortimicin B (**12**), which was obtained by hydrolysis of the condensate **10** with barium hydroxide in aqueous 1,4-dioxane, followed by treatment with Amberlite IRA-400 (OH^-) resin. In the ^{1}H-n.m.r. spectrum of **12**, the signal due to H-1′ (δ 5.14) was a doublet, with 3 Hz splitting, corresponding to the anomeric proton of the α-D-glycoside.

The conformation of **9** could be assumed to adopt a skew form judging from the ^{1}H-n.m.r. data[3]; however, those of aminocyclitol moieties of pseudo-disaccharides could not be deduced by analogy with these data.

Selective *N*-(benzyloxycarbonyl)ation of the amino groups at C-1, 2′, and 6′, followed by introduction of a *N*-(benzyloxycarbonyl)glycyl group onto the 4-(methylamino) group gave the tetrakis[*N*-(benzyloxycarbonyl)] derivative (**16**).

Finally, hydrogenation of **16** with 10% palladium-on-charcoal in methanol,

TABLE I

ANTIMICROBIAL ACTIVITY[a]

Test organisms	**18**	**19**	*7′-Propyl-fortimicin A*[3]	*Fortimicin A*
Streptococcus faecalis KY4280	>50	>100	6.3	13
Pseudomonas aeruginosa KY4276	>50	>100	50	13
Staphylococcus aureus KY4279	3.1	1.6	0.1	0.2
Escherichia coli KY4271	25	13	1.6	3.1
Bacillus subtilis KY4273	3.1	1.6	0.2	0.2
Shigella sonnei KY4281	>50	13	1.6	3.1
Klebsiella pneumoniae KY4275	3.1	1.6	0.2	0.2

[a]Minimum inhibitory concentration in μg/mL.

followed by treatment with AG1-X2 (SO_4^{2-}) resin, gave 7′-(3-hydroxypropyl)-fortimicin A (**18**) as the sulfate.

7′-(3-Hydroxypropyl)-6′-epifortimicin A (**19**) was prepared, starting from **5**, in a manner similar to that described for the preparation of **18** from **4**.

The minimum inhibitory concentrations of **18** and **19** are listed, together with those of 7′-propylfortimicin A and fortimicin A[6], in Table I. Compounds **18** and **19** exhibited weak activity, compared to those of 7′-propylfortimicin A and fortimicin A, against many micro-organisms.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes and are uncorrected. Optical rotations were measured with a Jasco DIP-4 polarimeter. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 (90 MHz) spectrometer, using Me_4Si as the internal standard, and a JEOL FX-200 (200 MHz) for D_2O solutions (external sodium 4,4-dimethyl-4-silapentane-1-sulfonate). A high-resolution mass spectrum was recorded with a Hitachi M-80 spectrometer and secondary-ion mass spectra with an M-80A instrument. Column chromatography was performed on Wakogel C-300 (Wako Pure Chemical Co., Ltd.), and t.l.c. on Kieselgel 60F-254 (E. Merck), with detection by charring with sulfuric acid. Organic solutions were dried with anhydrous Na_2SO_4. Evaporation was performed under diminished pressure below 40°.

*Methyl 2-acetamido-2,3,4,6,7,8,9-heptadeoxy-10-O-(tetrahydropyranyl)-6-nitro-β-*L*-lyxo- and -α-*D*-ribo-decopyranoside* (**2**). — To a solution of compound **1** (ref. 3); (1.0 g, 4.31 mmol) and 4-[(tetrahydropyranyl)oxy]butanal[5] (1.50 g, 8.31 mmol) in acetonitrile (16 mL) was added cesium fluoride (0.65 g, 4.28 mmol), and the mixture was stirred for 4.5 h. The mixture was extracted with ethyl acetate, and the extract was washed with water, dried, and evaporated. The residue, crude condensate (1.66 g), was dissolved in chloroform (10 mL), and the mixture was treated with acetic anhydride (10 mL), pyridine (1 mL) and 4-(dimethylamino)pyridine

(0.2 g, 1.63 mmol) for 0.5 h at room temperature. The mixture was extracted with chloroform (30 mL) and the extract was successively washed with saturated aqueous sodium hydrogencarbonate (50 mL) and water (50 mL), dried, and evaporated. The residue was dissolved in dimethyl sulfoxide (20 mL) and sodium borohydride (0.38 g, 10.0 mmol) was added. After stirring for 0.5 h at room temperature, the mixture was acidified with Amberlite IRA-120 (H^+) resin, extracted with dichloromethane, and the extract washed with water, dried, and concentrated. Column chromatography (1:5 acetone–toluene) gave **2** (648 mg, 39%) as a solid; $[\alpha]_D^{22}$ +93.4° (*c* 0.95, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 5.68 (d, 1 H, $J_{2,NH}$ 9 Hz, NH), 3.36 and 3.31 (each s, 3 H in total, OMe), and 1.92 (s, 3 H, NAc).

Anal. Calc. for $C_{18}H_{33}N_2O_7$: *m/z* 389.2286 $(M + H)^+$. Found: *m/z* 389.2288.

*Methyl 2,6-di(acetamido)-2,3,4,6,7,8,9-heptadeoxy-10-*O*-(tetrahydropyranyl)-β-*L*-lyxo- and -α-*D*-ribo-decopyranoside* (**3**). — Compound **2** (1.71 g, 4.41 mmol) was hydrogenated in methanol (12 mL) in the presence of Raney nickel at an initial hydrogen pressure of 345 kPa (Parr apparatus) for 18 h. The catalyst was removed and the filtrate evaporated. The residue (1.70 g) was treated with acetic anhydride (3.3 mL) in methanol (35 mL), and the product was purified by chromatography on silica gel with 30:1 chloroform–methanol to afford **3** (1.46 g, 83%) as a solid; $[\alpha]_D^{25}$ +86.4° (*c* 1.02, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.83 (bd, 2 H, *J* 10 Hz, 2 NH), 3.33 (s, 3 H, OMe), and 2.00 (s, 6 H, 2 NAc).

Anal. Calc. for $C_{20}H_{36}N_2O_6$: C, 59.98; H, 9.06; N, 6.99. Found: C, 59.90; H, 8.84; N, 6.92.

*Methyl 2,6-di(acetamido)-10-*O*-acetyl-2,3,4,6,7,8,9-heptadeoxy-β-*L*-lyxo-decopyranoside* (**4**) *and -α-*D*-ribo-decopyranoside* (**5**). — A solution of **3** (1.46 g, 3.46 mmol) in a mixture of dichloromethane (30 mL) and methanol (3 mL) containing boron trifluoride etherate (1.54 mL, 12.5 mmol) was stirred for 2 h under ice-cooling. The mixture was made neutral with Amberlite IRA-400 (OH^-) resin, and evaporated. The residue (1.27 g) was treated with acetic anhydride (2.4 mL) in pyridine (20 mL) for 1 h. After concentration, the residue was chromatographed on silica gel with 30:1 chloroform–methanol to give, first, compound **4** (438 mg, 34%), as a white powder, R_F 0.55 (10:1 chloroform–methanol); m.p. 186–188°, $[\alpha]_D^{23}$ +40.4° (*c* 1.05, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 4.61 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 3.40 (s, 3 H, OMe), 2.01, 1.98 and 1.93 (each s, 3 H, OAc and 2 NAc).

Anal. Calc. for $C_{17}H_{30}N_2O_6$: C, 56.97; H, 8.44; N, 7.82. Found: C, 56.96; H, 8.39; N, 7.63.

Further elution afforded **5** (379 mg, 29%), obtained as a white powder, R_F 0.52 (10:1 chloroform–methanol); m.p. 208–210°, $[\alpha]_D^{23}$ +123° (*c* 0.98, methanol); ^{1}H-n.m.r. (CD_3OD): δ 4.63 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 3.37 (s, 3 H, OMe), 2.02, 1.95 and 1.93 (each s, 3 H, OAc and 2 NAc).

Found: C, 56.82; H, 8.31; N, 7.46.

*Methyl 2,6-di(acetamido)-2,3,4,6,7,8,9,10-octadeoxy-α-*D*-ribo-decopyranoside* (**6**). — Compound **5** (50 mg, 0.14 mmol) was treated with M methanolic sodium methoxide (0.5 mL) in methanol (5 mL) at room temperature for 0.5 h. The

mixture was made neutral with Amberlite IR-120 (H^+), and evaporated. The residue (32 mg) was treated with *p*-toluenesulfonyl chloride (85 mg, 0.22 mmol) in pyridine (5 mL) for 24 h. The mixture was extracted with dichloromethane and the extract was successively washed with M hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The residue was roughly purified by preparative t.l.c. with 1:5 ethanol–toluene, to give the tosylate (27 mg), which was treated with sodium iodide (42 mg, 0.28 mmol) in refluxing butanone (4 mL) for 3 h, insoluble material filtered off, and the filtrate extracted with ethyl acetate. The extract was washed with 30% aqueous sodium thiosulfate, dried, and evaporated. The residue was hydrogenated as described for the preparation of compound **3**. Column chromatography (1:10 ethanol–toluene) gave **6** (8 mg, 30% based on **5**), as a solid; m.p. 252–253°, $[\alpha]_D^{25}$ +104° (*c* 0.39, methanol), lit.[3] m.p. 252.5–254°, $[\alpha]_D^{22}$ +147° (*c* 0.86, methanol).

*1,10-Di-*O*-acetyl-2,3,4,6,7,8,9-heptadeoxy-2,6-bis(2,4-dinitrophenylamino)-*L*-lyxo-decopyranose* (**7**). — A solution of **4** (438 mg, 1.22 mmol) in 2M hydrochloric acid (20 mL) was refluxed for 3 h. After evaporation, the residue was treated with fluoro-2,4-dinitrobenzene (0.32 mL, 2.56 mmol) and triethylamine (1.8 mL, 12.9 mmol) in methanol (20 mL) for 12 h. The mixture was then evaporated, and the residue was chromatographed on silica gel (1:4 acetone–toluene), to give the *N*-(2,4-dinitrophenyl)ated derivative (224 mg, 33% based on **4**), which was treated with acetic anhydride (1.5 mL) in pyridine (5 mL) for 11 h. Column chromatography (1:20 2-butanone–toluene) gave **7** (234 mg, 32% based on **4**). Recrystallization from acetone–2-propanol gave an analytical sample, m.p. 80–82°, $[\alpha]_D^{25}$ −58.7° (*c* 0.51, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 9.10 (d, 2 H, *J* 3 Hz, H-3 of DNP × 2), 8.82 and 8.53 (each d, 1 H, *J* 9 Hz, 2,6-NH), 7.05 and 6.95 (each d, 1 H, *J* 10 Hz, H-5 of DNP), 6.34 (d, 3/4 H, $J_{1,2}$ 4 Hz, H-1α), 2.23 and 2.03 (each s, 3 H, OAc).

Anal. Calc. for $C_{26}H_{30}N_6O_{13}$: C, 49.21; H, 4.77; N, 13.24. Found: C, 48.99; H, 4.70; N, 13.03.

*7'-(3-Acetoxypropyl)-2,5-di-*O*-benzoyl-2',6'-bis*[N-*(2,4-dinitrophenyl)*]*-1,4-bis*[N-*(methoxycarbonyl)*]*fortimicin B* (**10**). — To a solution of **7** (234 mg, 0.39 mmol) and **9** (210 mg, 0.40 mmol) in freshly distilled 1,2-dichloroethane (5 mL) in the presence of powdered molecular sieve 4A (260 mg) was added trimethylsilyl trifluoromethanesulfonate (0.1 mL, 0.52 mmol) and the mixture was stirred for 4 h at room temperature under argon, diluted with dichloromethane (50 mL), and insoluble material filtered off. The filtrate was successively washed with saturated aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residue was chromatographed on silica gel with 1:8 2-butanone–toluene, to afford **10** (146 mg, 35%) as a yellow powder: m.p. 135–140° (from acetone–2-propanol), $[\alpha]_D^{25}$ −7.4° (*c* 0.86, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 9.13 and 9.10 (each d, 1 H, *J* 3 Hz, H-3 of DNP), 7.90 (m, 2 H, benzoyl), 7.67–7.38 (m, 6 H, benzoyl), 7.05 and 6.87 (each d, *J* 9 Hz, H-5 of DNP), 3.64 and 3.53 (each s, 3 H, Cbm), 3.45 (s, 3 H, OMe), 2.83 (s, 3 H, NMe), and 1.92 (s, 3 H, OAc).

Anal. Calc. for $C_{50}H_{56}N_8O_{21}$: C, 54.35; H, 5.11; N, 10.14. Found: C, 53.61; H, 5.08; N, 9.68.

7′-(3-Hydroxypropyl)fortimicin B (**12**). — A solution of **10** (146 mg, 0.13 mmol) in a mixture of 1,4-dioxane (12 mL) and water (3 mL) in the presence of barium hydroxide octahydrate (3.0 g, 9.51 mmol) was refluxed for 8.5 h. Insoluble material was filtered off, and carbon dioxide was passed into the filtrate. The precipitate was filtered off, the filtrate evaporated, and a solution of the residue in a mixture of methanol (15 mL), acetone (15 mL) and water (7 mL) was stirred in the presence of Amberlite IRA-400 (OH^-) resin (20 mL) for 17 h. After concentration, the residue was chromatographed on a column of Amberlite CG-50 (NH_4^+) resin (20 mL) with 0–1.0M aqueous ammonia (with gradient increase in concentration), to give **12** (24 mg, 44%) as a solid; $[\alpha]_D^{23}$ +7.4° (*c* 0.86, methanol); ^{1}H-n.m.r. (CD_3OD): δ 5.14 (d, $J_{1',2'}$ 3 Hz, H-1′), 3.46 (s, 3 H, OMe), and 2.40 (s, 3 H, NMe); e.i.-m.s.: *m/z* 407 $(M + H)^+$.

1,2′,6′-Tris[N-*(benzyloxycarbonyl)*]-*7′-(3-hydroxypropyl)fortimicin B* (**14**). — To a solution of **12** (24 mg, 58 μmol) in a mixture of methanol (2 mL) and water (1 mL) was added *N*-[(benzyloxycarbonyl)oxy]succinimide (44 mg, 0.18 mmol) under ice cooling and the mixture was stirred for 1.5 h at 0°; stirring was continued for 18 h at room temperature. The mixture was poured into 5% aqueous sodium hydrogencarbonate (20 mL), and extracted with chloroform (30 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with 50:1 chloroform–methanol, to give **14** (25 mg, 52%) as a solid; $[\alpha]_D^{23}$ +7.7° (*c* 1.19, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.33 (s, 15 H, 3 phenyl), 5.06 (bs, 6 H, 3 benzyl), 3.41 (s, 3 H, OMe), and 2.35 (s, 3 H, NMe).

1,2′,6′-Tris[N-*(benzyloxycarbonyl)*]-*4-*{N-[N-*(benzyloxycarbonyl)glycyl*]}-*7′-(3-hydroxypropyl)fortimicin B* (**16**). — A solution of **14** (25 mg, 31 μmol) in 1,4-dioxane (2.5 mL) containing *N*-{[*N*-(benzyloxycarbonyl)glycyl]oxy}succinimide (11 mg, 37 μmol) and triethylamine (0.005 mL, 36 μmol) was stirred for 22 h at 45°. The product was purified as described for the preparation of **14** to give **16** (18 mg, 60%) as a solid; $[\alpha]_D^{22}$ +21.1° (*c* 0.85, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.34 (s, 20 H, 4 phenyl), 5.06 (s, 8 H, 4 benzyl), 4.80 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 3.29 (s, 3 H, OMe), and 2.80 (bs, 3 H, NMe).

Anal. Calc. for $C_{52}H_{65}N_5O_{15}$: C, 62.45; H, 6.55; N, 7.00. Found: C, 62.33; H, 6.84; N, 6.14.

7′-(3-Hydroxypropyl)fortimicin A (**18**). — A solution of **16** (4.3 mg, 4 μmol) in methanol (0.5 mL) containing 0.1M hydrochloric acid (0.07 mL) was hydrogenated in the presence of 10% palladium-on-charcoal (3 mg) under a hydrogen atmosphere for 1 h. The catalyst was removed and the solution was evaporated. The residue was dissolved in water and the solution was passed through a column of AG1-X2 (SO_4^{2-}) resin (1 mL). The fractions containing **18**, R_F 0.24 (4:1:1 2-propanol–chloroform–conc. aqueous ammonia), were evaporated to afford white solid **18** as the sulfate (2.4 mg); $[\alpha]_D^{20}$ +39.1° (*c* 0.12, water); ^{1}H-n.m.r. (200 MHz, D_2O): δ 5.29 (d, $J_{1',2'}$ 3 Hz, H-1′), 3.52 (s, 3 H, OMe), and 3.16 (s, 3 H, NMe); e.i.-m.s.: *m/z* 464 $(M + H)^+$.

*1,10-Di-*O*-acetyl-2,3,4,6,7,8,9-heptadeoxy-2,6-bis(2,4-dinitrophenylamino)-*

D-ribo-*decopyranoside* (**8**). — A solution of **5** (379 mg, 1.06 mmol) in 2M hydrochloric acid (20 mL) was refluxed for 3 h. After evaporation, the residue was treated with fluoro-2,4-dinitrobenzene (0.28 mL, 2.23 mmol) and triethylamine (1.5 mL, 10.8 mmol) in methanol (15 mL) for 13 h. The product was purified as described for the preparation of **7**, to give the *N*-(2,4-dinitrophenyl)ated derivative (274 mg, 47% based on **5**), which was then treated with acetic anhydride (3 mL) in pyridine (10 mL) for 1 h. The product was purified by chromatography on silica gel with 1:5 butanone–toluene to afford **8** (288 mg, 46% based on **5**) as a yellow syrup; $[\alpha]_D^{21}$ −64.5° (*c* 1.19, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 9.04 and 9.03 (each d, 1 H, *J* 3 Hz, H-3 of DNP), 8.59 and 8.50 (each d, 1 H, *J* 9 Hz, 2′,6′-NH), 8.22 and 8.20 (each dd, 1 H, *J* 3 Hz, 11 Hz, H-5 of DNP), 7.16 and 7.03 (each d, 1 H, *J* 11 Hz, H-6 of DNP), 6.23 (d, 4/5 H, $J_{1,2}$ 3 Hz, H-1α), 5.62 (d, 1/5 H, $J_{1,2}$ 9 Hz, H-1β), 2.20 and 2.01 (each s, 3 H, OAc).

*7′-(3-Acetoxypropyl)-2,5-di-*O*-benzoyl-2′,6′-bis*[N-*(2,4-dinitrophenyl)*]*-1,4-bis*[N-*(methoxycarbonyl)*]*-6′-epifortimicin B* (**11**). — To a solution of **8** (76 mg, 0.07 mmol) and **9** (68 mg, 0.07 mmol) in freshly distilled 1,2-dichloroethane (0.5 mL) in the presence of powdered molecular sieve 4A (20 mg) was added trimethylsilyl trifluoromethanesulfonate (25 μL, 0.13 mmol) and the mixture was stirred for 2.5 h at room temperature under argon. The product was purified as described for the preparation of **10**, to afford **11** (66 mg, 48%) as a yellow solid; $[\alpha]_D^{25}$ −5.4° (*c* 0.86, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 9.13 and 9.06 (each d, 1 H, *J* 3 Hz, H-3 of DNP), 5.20 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 3.67 and 3.55 (each s, 3 H, Cbm), 3.46 (s, 3 H, OMe), 2.86 (s, 3 H, NMe), and 1.97 (s, 3 H, OAc).

Found: C, 53.87; H, 5.09; N, 9.74.

7′-(3-Hydroxypropyl)-6′-epifortimicin B (**13**). — A solution of **11** (66 mg, 0.06 mmol) in a mixture of 1,4-dioxane (4 mL) and water (2 mL) in the presence of barium hydroxide octahydrate (1.2 g, 3.80 mmol) was refluxed for 9 h. The product was purified as described for the preparation of **12** to give **13** (20 mg, 83%) as a solid; $[\alpha]_D^{23}$ +13.5° (*c* 1.01, methanol); ^{1}H-n.m.r. (CD_3OD): δ 4.95 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 3.44 (s, 3 H, OMe), 2.37 (s, 3 H, NMe).

Anal. Calc. for $C_{18}H_{38}N_4O_6 \cdot 0.5\ H_2CO_3$: C, 50.79; H, 8.99; N, 12.81. Found: C, 51.04; H, 8.95; N, 12.02.

1,2′,6′-Tris[N-*(benzyloxycarbonyl)*]*-7′-(3-hydroxypropyl)-6′-epifortimicin B* (**15**). — To a solution of **13** (48 mg, 0.12 mmol) in a mixture of methanol (4 mL) and water (2 mL) was added *N*-[(benzyloxycarbonyl)oxy]succinimide (90 mg, 0.36 mmol) under ice-cooling and the mixture was stirred for 6.5 h at 0°; stirring was continued for 6.5 h at room temperature. The product was purified as described for the preparation of **14**, to give **15** (39 mg, 42%) as a solid; $[\alpha]_D^{23}$ +30.7° (*c* 1.42, chloroform); ^{1}H-n.m.r. (CD_3OD): δ 7.35 (s, 15 H, 3 phenyl), 5.06 (bs, 6 H, 3 benzyl), 3.40 (s, 3 H, OMe), and 2.33 (s, 3 H, NMe).

1,2′,6′-Tris[N-*(benzyloxycarbonyl)*]*-4-*{N-[N-*(benzyloxycarbonyl)glycyl*]}*-7′-(3-hydroxypropyl)-6′-epifortimicin B* (**17**). — A solution of **15** (8 mg, 0.01 mmol) in 1,4-dioxane (0.5 mL) containing *N*-{[*N*-(benzyloxycarbonyl)glycyl]oxy}suc-

cinimide (3.6 mg, 0.01 mmol) and triethylamine (2 μL, 0.01 mmol) was stirred for 18 h at 60°. The product was purified as described for the preparation of **16** to give **17** (7.4 mg, 75%) as a solid; $[\alpha]_D^{21}$ +44.7° (*c* 1.06, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.34 (s, 20 H, 4 phenyl), 5.10 (s, 8 H, 4 benzyl), 3.26 (s, 3 H, OMe), and 2.85 (s, 3 H, NMe).

Found: C, 62.51; H, 6.68; N, 6.82.

7′-(3-Hydroxypropyl)-6′-epifortimicin A (**19**). — A solution of **17** (7.4 mg, 7 μmol) in methanol (0.5 mL) containing 0.1M hydrochloric acid (0.1 mL) was hydrogenated in the presence of 10% palladium-on-charcoal (5 mg) under a hydrogen atmosphere for 1.5 h. The product was purified as described for the preparation of **18**, to give white solid **19** (3.4 mg) as the sulfate; R_F 0.26 (4:1:1 2-propanol–chloroform–conc. aqueous ammonia; $[\alpha]_D^{21}$ +31.4° (*c* 0.15, water); ^{1}H-n.m.r. (200 MHz, D_2O): δ 5.32 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 4.93 (dd, 1 H, $J_{3,4}$ 12, $J_{4,5}$ 3 Hz, H-4), 3.58 (s, 3 H, OMe), and 3.18 (s, 3 H, NMe); e.i.-m.s.: *m/z* 464 $(M + H)^+$.

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