Syntheses of Lividomycin B Analogues, 5-*O*-[3-*O*-(6-Amino-6-deoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-3′-deoxyparomamine and 5-*O*-[2-*O*-(6-Amino-6-deoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]-3′-deoxyparomamine

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The preparation of lividomycin B analogues, the title pseudotetrasaccharides, is described. Condensation of 6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-L-idopyranosyl chloride with 4′,6′-di-*O*-benzoyl-5-*O*-(5-*O*-benzoyl-β-D-ribofuranosyl)-3,2′-bis(*N*-benzyloxycarbonyl)-1-*N*:6-*O*-carbonyl-3′-deoxyparomamine was followed by deblocking and reduction of the azido groups. Structure determinations and the antibacterial activities of the products are described.

Lividomycin B[1] is an amino glycoside antibiotic which belongs to a pseudotetrasaccharide. Since its pseudotrisaccharide[2] portion (**5**; B-A-C portion of lividomycin B) has almost no antibacterial activity, it is suggested that the fourth sugar (D portion) plays an important role in exhibiting the antibacterial activity of lividomycin B. Until now, however, variation of the D portion has rarely been studied. A lividomycin B analogue,[3] which has 2-amino-2-deoxy-α-D-glucopyranose as the fourth sugar, was reported and found to show much less antibacterial activity than lividomycin B having the 2,6-diamino-2,6-dideoxy-β-L-idopyranose. As the continuation of this work, the present study was performed. Since it appeared that the 6-amino group on the β-L-idopyranose portion of lividomycin B would have an important role in its activity, we undertook to synthesize a lividomycin B analogue having 6-amino-6-deoxy-β-L-idopyranose instead of the diamino sugar. This synthesis was carried out by condensation of a protected idopyranosyl halide (**4**) with a pseudotrisaccharide derivative (**8**), leading to the desired glycoside (**14**) and an isomer (**13**).

6-Azido-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-L-idofuranose[4] (**1**) was prepared from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose *via* 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-L-idofuranose[5] through 6 steps. Conversion of the furanose (**1**) to the corresponding pyranose was carried out by treating **1** with 95% formic acid and the crude product was treated with α-bromotoluene in the presence of a base to give benzyl 6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-β-L-idopyranoside (**2**). Acidic hydrolysis of **2** gave the free sugar (**3**). Reaction of **3** with thionyl chloride gave the corresponding glycosyl chloride (**4**), which was used without purification.

The pseudotrisaccharide[2] (**5**) obtained from lividomycin B by cleavage[6] of the 2,6-diamino-2,6-dideoxy-L-idopyranose portion was treated with benzyl chloroformate to give 1,3,2′-tris(*N*-benzyloxycarbonyl) derivative (**6**). Treatment of **6** with sodium hydride in *N*,*N*-dimethylformamide, a procedure producing cyclic carbamate developed by Umezawa, Tsuchiya, and Ikeda,[7] gave 3,2′-bis(*N*-benzyloxycarbonyl)-1,6-carbamate (**7**). Structural proof of the five-membered carbamate was obtained from the presence of an absorption peak at 1770 cm^{-1} [8] in its IR spectrum. Treatment of **7** with phenylboronic acid (1 mol equiv. for **6**), followed by benzoylation and removal of the phenylboronate protecting group[9] gave 4′,6′,5″-tri-*O*-benzoyl derivative (**8**) as the main product with the minor 5″-*O*-benzoyl derivative (**9**). The structure of **8** was confirmed by the result of periodate oxidation, and the structure of **9**, by the formation of its 4′,6′:2″,3″-di-*O*-isopropylidene derivative (**10**). This suggests that the intermediary boronate was mainly formed between 2″- and 3″-hydroxyls, and between 4′- and 6′-hydroxyls in a minor extent.

Condensation of the glycosyl chloride (**4**) with the protected pseudotrisaccharide (**8**) was carried out in benzene in the presence of mercury(II) cyanide to give

Table 1. The ^{13}C chemical shifts[a] of lividamine (LA), pseudotrisuccharide (**5**), lividomycin B (LVB), **13** and **14** (all as free bases)

Carbon	LA	5	LVB	13	14
1′	100.8	99.2	99.4	97.4[e]	98.8[l]
2′	49.8	50.1	50.1	49.8	50.0
3′	35.7	35.1	35.4[c]	34.2	34.7
4′	65.4	65.4	65.5	65.1	65.3
5′	74.3	74.3	74.3	74.3	74.3
6′	61.6	61.6	61.6	61.5	61.5
1	51.1	51.1	51.2	51.2[f]	51.1[j]
2	36.3	36.4	35.5[c]	36.0	36.1
3	50.4	51.1	51.2	50.9[f]	51.0
4	88.0	85.4	85.3	86.4	85.5
5	76.7	83.3[b]	82.1[d]	83.1[g]	83.0[k]
6	78.2	78.3	78.5	78.4	78.0
1″		109.6	109.5	108.7	109.5
2″		75.7	74.8	82.9[g]	74.8
3″		70.5	77.1	70.5[h]	77.1
4″		83.8[b]	83.9[d]	81.9[g]	82.1[k]
5″		62.6	62.0	62.4	62.0
1‴			99.8	99.0[e]	99.8[l]
2‴			53.6	70.8[h]	70.5[l]
3‴			71.5	70.1[h]	69.9[l]
4‴			69.4	69.7[h]	69.4[l]
5‴			74.3	74.0	74.3
6‴			41.0	41.5	41.7

a) In ppm downfield from TMS calculated as $\delta^{TMS}=\delta^{dioxane}+67.4$ ppm. b—l) Figures indicated by the same character may be interconvertible.

2″-*O*- (**11**, 43%) and 3″-*O*-(6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-β-L-idopyranosyl) derivatives (**12**, 19%). Debenzoylation and cleavage[7] of the carbamate groups of the condensation products (**11** and **12**) were carried out with dilute barium hydroxide. Further treatment with sodium metal in liquid ammonia resulted in debenzylation, de(benzyloxycarbonyl)ation and the reduction of the azido into an amino group simultaneously to give the final products (**13** and **14**).

The structures of **13** and **14** were confirmed as follows. The molecular rotations ($[\alpha]_D \times MW/100$) of the final products (**13** : +340; **14** : +310) showed comparative values with that of lividomycin B (+360), but greater than that of **5** (+200), indicating that the contributions of the L-idopyranose moiety of **13** and **14** for their rotations are both positive (*ca.* +120). Since the molecular rotations of α-L- and β-L-idopyranosides are roughly estimated[10] −190 and +100, respectively, it is shown that the L-idopyranoses of **13** and **14** are coupled to the pseudotrisaccharide portion (**5**) with the desired β-L-anomeric configuration. The positions at which the β-L-idopyranose was attached were decided by the ^{13}C-NMR spectra. At first, carbon chemical shifts of lividamine[11] were assigned on the basis of comparison of the data with those of neamine[12] and paromomycin[12] (Table 1); the shifts of pseudotrisaccharide (**5**) were then assigned by comparison of the data with those of lividamine just obtained and paromomycin;[12] finally

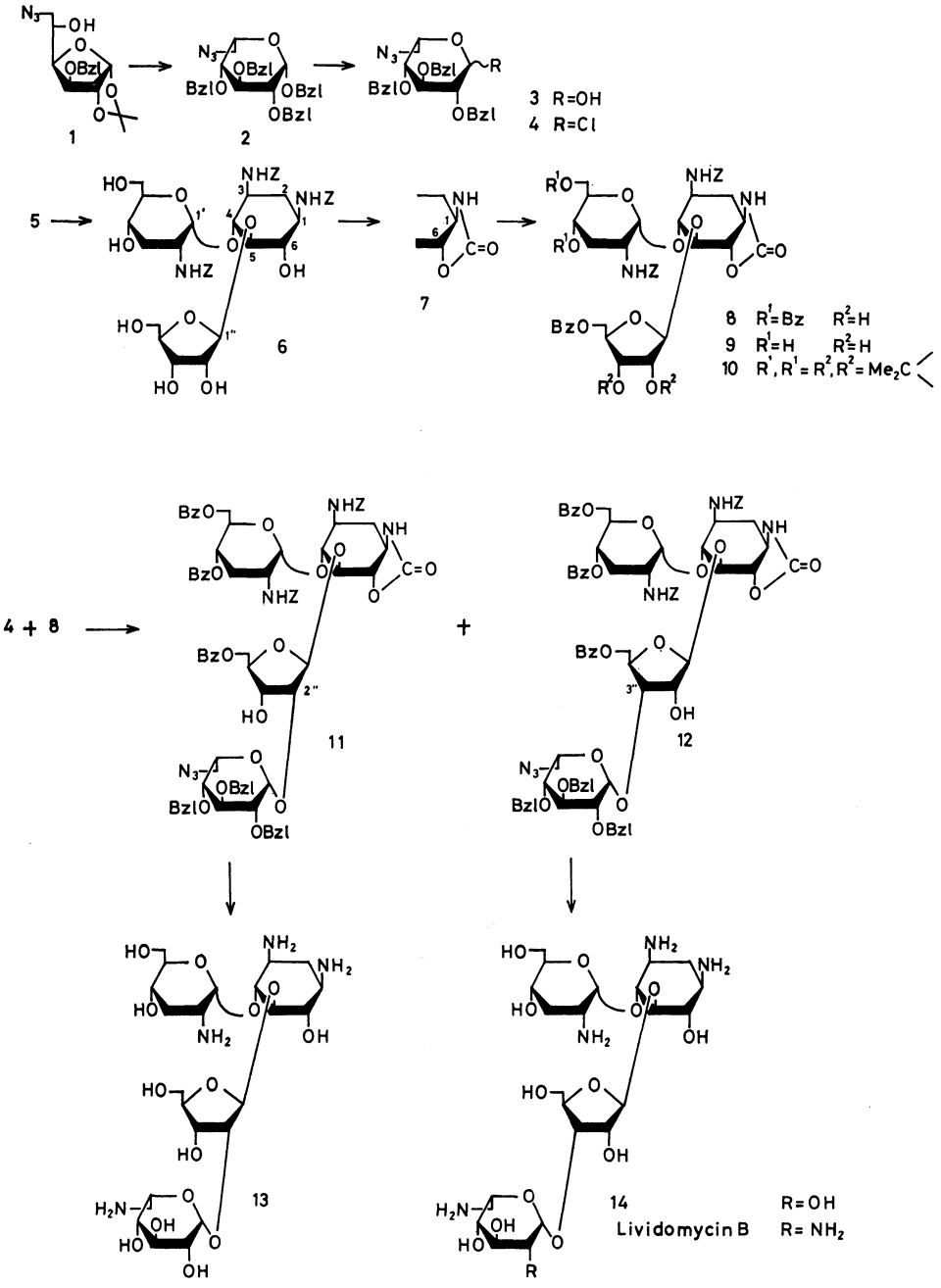

Table 2. Antibacterial spectra of **13**, **14**, and lividomycin B (LVB)

Test organisms[a]	Minimal inhibitory concentration/μg cm^{-3}		
	13	**14**	LVB
Staphylococcus aureus 209P	12.5	6.25	0.78
Bacillus subtilis NRRL B-558	12.5	1.56	1.56
Klebsiella pneumoniae PCI 602	25	6.25	3.12
Salmonella typhi T-63	12.5	6.25	1.56
Escherichia coli K-12	100	25	6.25
Escherichia coli K-12 ML 1629	>100	>100	>100
Escherichia coli K-12 W677	25	3.12	1.56
Pseudomonas aeruginosa A3	100	50	12.5
Mycobacterium smegmatis ATCC 607[b]	6.25	12.5	0.78

a) Agar dilution streak method (nutrient agar, 37 °C, 18 h). b) 48 h.

the shifts of lividomycin B were assigned on the basis of comparison of the data with those of **5** and paromomycin. Shift-assignments of **14** were next made by comparison of the data with that of lividomycin B just obtained. The sole discrepancy in shift-value between **14** and lividomycin B observed was that for C-2‴ at which a hydroxyl group is attached in **14** instead of the amino group in lividomycin B. Downfield shift[13] (6.6 ppm) of C-3″ from the corresponding position of **5** also supported that glycosylation occurred at the 3″-hydroxyl. Compound **14** was, therefore, decided to be 3″-*O*-glycosyl compound. Shift-assignments of **13** were made on the basis of the data of **14**. The chemical shift at 82.9 ppm of **13** can reasonably be assigned to that of C-2″; the shift-difference (7.2 ppm) of the C-2″ between **13** and **5** indicates that **13** is a 2″-*O*-glycosyl isomer.

Antibacterial spectra of **13** and **14** were shown in Table 2 with that of lividomycin B. The results show that **14** has weaker antibacterial activity than that of lividomycin B, and that the position isomer **13** is less active than **14**. This result shows that an important factor with respect to structure-activity relationships in the ring D is the number and location of amino functions, affecting the binding of the antibiotics with bacterial ribosomes. It is noteworthy that the isomer (**13**) does not loss activity against bacteria in spite of the introduction of the D ring at another position of the ribose.

Experimental

^{1}H-NMR spectra were recorded at 90 MHz with a Varian EM-390 spectrometer. ^{13}C-NMR spectra were recorded on a Varian XL-100 spectrometer with Varian 620-L data processing system (25.2 MHz) in deuterium oxide solution containing dioxane as internal reference. Thin-layer chromatography (TLC) was performed on DC-Fertigplatten Kieselgel 60 F_{254} (E. Merck). For column chromatography, silica gel (Wakogel C-200) was used.

*Benzyl 6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-β-*L*-idopyranoside (**2**).* A solution of **1** (3.00 g) in 95% formic acid (100 ml) was kept at room temperature for 4 h. Evaporation *in vacuo* followed by several coevaporations with toluene gave a residue, which was dissolved in DMF (60 ml). To the solution cooled to 0 °C, α-bromotoluene (5.8 ml. *ca* 3 mol equiv. for **1**), barium oxide (7.26 g) and $Ba(OH)_2 \cdot 8H_2O$ (15 g, powdered) were added and the mixture was stirred overnight at the temperature. Addition of benzene (100 ml) gave precipitates which were removed by centrifugation. Concentration of the solution and the washings (the solid was washed with benzene) combined gave a residue. Column chromatography of the residue with benzene–ethyl acetate (100 : 1) gave a syrup of **2**, 2.90 g (57%), $[\alpha]_D^{24}$ +101° (*c* 1, chloroform).

^{1}H-NMR ($CDCl_3$): δ 3.53 (1H dd, $J_{1,2}$ 2 Hz, $J_{2,3}$ 5 Hz, H-2), and 4.85 (1H d, H-1); IR (KBr): 2100 cm^{-1} (N_3).

Found: C, 72.35; H, 6.31; N, 7.37%. Calcd for $C_{34}H_{35}N_3O_5$: C, 72.19; H, 6.24; N, 7.43%.

*6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-*L*-idopyranose (**3**).* To a solution of **2** (1.70 g) in acetic acid (93 ml) was added 2 M† sulfuric acid (8.5 ml) and the solution was kept at 80 °C for 3 h. Ice–water (200 g) was introduced and the mixture was extracted with chloroform. The organic solution was washed with sodium hydrogencarbonate solution, water, dried over sodium sulfate and concentrated. The residue was purified by a short column of silica gel with benzene–ethyl acetate (10 : 1) to give a colorless syrup, 1.24 g (86%), $[\alpha]_D^{24}$ +6.5° (*c* 1, chloroform); IR(KBr): 2100 cm^{-1} (N_3).

Found: C, 68.40; H, 6.26; N, 8.88%. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.21; H, 6.11; N, 8.84%.

*6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-*L*-idopyranosyl Chloride (**4**).* Compound **3** (700 mg) was dissolved in thionyl chloride (7 ml) and the solution was kept at room temperature for 3 h. Evaporation followed by several coevaporations *in vacuo* with dry toluene gave a surup (730 mg).

^{1}H-NMR ($CDCl_3$): δ 5.84 (*ca.* 0.3H d, *J* 3 Hz, α-L-isomer), and 6.16 (*ca.* 0.7 H slightly broadened s, β-L-isomer).

*1,3,2′-Tris(*N*-benzyloxycarbonyl)-3′-deoxy-5-*O*-(β-*D*-ribofuranosyl)paromamine (**6**).* To a cold (−5°C) solution of **5** (4.44 g as the base) in aqueous methanol (1: 1, 50 ml), anhydrous sodium carbonate (4.0 g) and benzyl chloroformate (6.2 g) were added and the solution was kept at 0 °C for 1 h and then at room temperature for 2 h. Concentration followed by addition of water gave a solid, which was thoroughly washed with ether to give a solid, 7.47 g (88%), $[\alpha]_D^{24}$ +27° (*c* 1, methanol).

Found: C, 58.31; H, 6.05; N, 5.13%. Calcd for $C_{41}H_{50}N_3O_{16}$: C, 58.56; H, 5.99; N, 5.00%.

*3,2′-Bis(*N*-benzyloxycarbonyl)-1-*N*:6-*O*-carbonyl-3′-deoxy-5-*O*-(β-*D*-ribofuranosyl)paromamine (**7**).* To a cold (0 °C) solution of **6** (8.0 g) in dry DMF (80 ml), 50% oily sodium hydride (0.6 g as net NaH) was added and the mixture was stirred vigorously for 4 h at the cold. Acetic acid (6.4 ml) was added and the solution was concentrated *in vacuo*. Extraction of the resulting residue with dioxane followed by concentration of the dioxane solution gave a solid, which was chromatographed with chloroform–methanol (8 : 1→ 6 : 1). Starting material (**6**) (1.66 g, 21%) and **7** (4.11 g, 59%) were eluted in this order. **7**: $[\alpha]_D^{24}$ +34° (*c* 1, methanol); R_f 0.24 (TLC with $CHCl_3$–MeOH=6 : 1; **6**: R_f 0.38); IR(KBr): 1770 (cyclic carbamate), and 1710 cm^{-1} (urethane carbonyl).

Found: C, 55.37; H, 6.02; N, 5.43%. Calcd for $C_{34}H_{43}N_3O_{15}$: C, 55.66; H, 5.91; N, 5.73%.

*4′,6′-Di-*O*-benzoyl-5-*O*-(5-*O*-benzoyl-β-*D*-ribofuranosyl)-3,2′-bis(*N*-benzyloxycarbonyl)-1-*N*:6-*O*-carbonyl-3′-deoxyparomamine (**8**).* To a solution of **7** (3.16 g) in dry pyridine (120 ml), phenylboronic acid (527 mg, 1 mol equiv. for **7**) was added and the solution was kept at room temperature for 2 h. To the solution cooled in an ice-bath, benzoyl chloride (7.3 g)

† 1 M=1 mol dm^{-3}.

was added and the solution was kept at room temperature for 2 h. The solution showed a major spot at R_f 0.7 (4′,6′,5″-tri-*O*-benzoyl-2″,3″-boronate derivative), on TLC with chloroform–methanol (10 : 1). After addition of water (2 ml) followed by stirring for 1 h, 1,3-propanediol (1.5 ml) was added and the solution was kept at room temperature overnight. Concentration gave a residue, which was dissolved in chloroform. The solution was washed with 1 M aqueous potassium hydrogensulfate, aqueous sodium hydrogencarbonate, and water, dried over sodium sulfate and concentrated. The residue showed, on TLC with chloroform–methanol (10 : 1), spots of R_f 0.9 (slight, penta-*O*-benzoyl derivative?), 0.43 (slight, another tri-*O*-benzoyl derivative?), 0.38 (major, **8**), 0.22 (minor **9**) and 0.1 (slight, **7**). The residue was chromatographed on a silica-gel column with chloroform–methanol (50: 1→30: 1→15: 1→8: 1→5: 1) as developer to give a solid of **8**, 2.00 g (44%), R_f (0.38 TLC with 10 : 1 chloroform–methanol) and a solid of **9**, 0.84 g (23%), R_f 0.22 (TLC).

8: $[\alpha]_D^{24}$ +48° (*c* 1, chloroform).

Found: C, 63.36; H, 5.35; N, 4.03%. Calcd for $C_{55}H_{55}N_3O_{18}$: C, 63.15; H, 5.26; N, 4.02%.

9: $[\alpha]_D^{24}$ +29° (*c* 1, chloroform).

Found: C, 58.46; H, 5.76; N, 4.77%. Calcd for $C_{41}H_{47}N_3O_{16}$: C, 58.78; H, 5.62; N, 5.02%.

Periodate Oxidation of **8**. To a solution of **8** (10 mg) in ethanol (0.5 ml) was added sodium periodate (5 mg) and the solution was kept at room temperature for 2 h. On checking by TLC with chloroform–methanol (10 : 1), the solution showed a single spot R_f 0.60 (*cf.* **8** : R_f 0.38).

*5-O-(5-O-Benzoyl-2,3-O-isopropylidene-β-*D*-ribofuranosyl)-3,2′-bis(*N*-benzyloxycarobnyl)-1-*N*:6-O-carbonyl-3′-deoxy-4′,6′-O-isopropylideneparomamine (**10**)*. A mixture of **9** (50 mg), anhydrous *p*-toluenesulfonic acid (18 mg), and 1,1-dimethoxypropane (1 ml) in DMF (5 ml) was kept at room temperature overnight. Addition of aqueous saturated sodium hydrogencarbonate solution (1 ml) followed by concentration of the mixture gave a residue. Extraction of the residue with chloroform followed by silica gel chromatography of the extracts with benzene–ethyl acetate–triethylamine (1 : 1 : 0.02) gave a solid of **10**, which was reprecipitated from chloroform–hexane, 44 mg (80%), $[\alpha]_D^{25}$ +19° (*c* 1, chloroform): IR(KBr): 1775, and 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.28, 1.34, 1.42 and 1.46 (each 3H s, Ip).

Found: C, 61.43; H, 5.94; N, 4.61%. Calcd for $C_{47}H_{55}N_3O_{16}$: C, 61.50; H, 6.04; N, 4.58%.

*5-O-[2-O-(6-Azido-2,3,4-tri-O-benzyl-6-deoxy-β-*L*-idopyranosyl)-5-O-benzoyl-β-*D*-ribofuranosyl]-4′,6′-di-O-benzoyl-3,2′-bis(*N*-benzyloxycarbonyl)-1-*N*:6-O-carbonyl-3′-deoxyparomamine (**11**) and 5-O-[3-O-(6-azido-2,3,4-tri-O-benzyl-6-deoxy-β-*L*-idopyranosyl)-5-O-benzoyl-β-*D*-ribofuranosyl]-4′,6′-di-O-benzoyl-3,2′-bis(*N*-benzyloxycarbonyl)-1-*N*:6-O-carbonyl-3′-deoxyparomamine (**12**)*. A mixture of **4** (553 mg), **8** (205 mg), mercury (II) cyanide (308 mg, dried at 75 °C under 1 Torr (1 Torr≈133.32 Pa) pressure for 3 h), and Drierite (610 mg, dried at 250 °C for 3 h) in dry benzene (10 ml) was stirred overnight at room temperature. Chloroform (50 ml) was added, filtered, and the organic solution was washed with aqueous saturated sodium hydrogencarbonate and water, dried over sodium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (50 g) with chloroform–methanol (60 : 1) to give a mixture of major products (352 mg). The mixture was separated by preparative TLC (Kieselgel 60 PF_{254}, E. Merck) with chloroform–methanol (30 : 1) to give a solid of **11**, 140 mg (43%, R_f 0.35 on TLC with chloroform–methanol=30 : 1) and **12**, 85 mg (19%, R_f 0.32), with minor products (48 mg, R_f 0.30, a mixture of α-L-isomers?).

11: $[\alpha]_D^{24}$ +51° (*c* 1, chloroform); IR(KBr): 2100 (N_3), 1780, and 1725 cm^{-1}.

Found: C, 65.68; H, 5.48; N, 5.53%. Calcd for $C_{82}H_{82}N_6O_{22}$: C, 65.51; H, 5.46; N, 5.59%.

12: $[\alpha]_D^{24}$ +42° (*c* 1, chloroform); IR (KBr): 2100, 1780, and 1725 cm^{-1}.

Found: C, 65.55; H, 5.44; N, 5.43%.

*5-O-[2-O-(6-Amino-6-deoxy-β-*L*-idopyranosyl)-β-*D*-ribofuranosyl]-3′-deoxyparomamine (**13**)*. To a solution of **11** (145 mg) in dioxane (9 ml) was added 0.03 M barium hydroxide solution (2 ml) and the mixture was stirred at 60 °C for 30 min. After introduction of carbon dioxide, the mixture was centrifuged, and the solid was washed thoroughly with dioxane. The solution and the washings combined were concentrated to give a residue. The residue was dissolved in tetrahydrofuran–methanol (1 : 1) and the solution was passed through a column of Sephadex LH-20. The elution was concentrated and the solid was dried thoroughly. A solution of the solid in tetrahydrofuran (3 ml) was adedd to a solution of sodium metal (*ca.* 200 mg) in liquid ammonia (*ca.* 9 ml, −50 °C) and the deep-blue solution was kept at the temperature for 1 h. Addition of water until the solution became colorless, followed by gradual warming to room temperature, and evaporation under diminished pressure, gave a residue. An aqueous solution of the residue was poured onto a column of Dowex 50W×2 (NH_4^+) resin, and the column was washed with water, then eluted with 2 M aqueous ammonia. Ninhydrin-positive fractions were collected and evaporated. The residue was chromatographed on a column of CM-Sephadex C-25 (NH_4^+) with aqueous ammonia (0→0.08 M, gradually changed) to give a solid of **13**, 30 mg (42% as dicarbonate), $[\alpha]_D^{26}$ +47° (*c* 1, water).

^{1}H-NMR (D_2O containing DCl; pD *ca.* 1); δ 1.7—2.7 (4H, H-2,3′), 5.17 (1H d, $J_{1''',2'''} \simeq 1.5$ Hz, H-1‴), 5.43 (1H br s, H-1″), and 5.60 (1H d, $J_{1',2'}$ 3.5 Hz, H-1′).

Found: C, 41.85; H, 6.90; N, 7.69%. Calcd for $C_{23}H_{44}N_4O_{14}\cdot 2H_2CO_3$: C, 41.43; H, 6.68; N, 7.73%.

*5-O-[3-O-(6-Amino-6-deoxy-β-*L*-idopyranosyl)-β-*D*-ribofuranosyl]-3′-deoxyparomamine (**14**)*. Compound **12** (145 mg) was treated similarly as described for **13** to give a solid of **14**, 35 mg (50% as dicarbonate), $[\alpha]_D^{26}$ +42° (*c* 0.7, water).

^{1}H-NMR (D_2O containing DCl; pD *ca.* 1): δ 1.7—2.7 (4H, H-2,3′), 5.07 (1H d, $J_{1''',2'''} \simeq 1.5$ Hz, H-1‴), 5.38 (1H br s, H-1″), and 5.62 (1H d, $J_{1',2'}$ 3.5 Hz, H-1′).

Found: C, 41.16; H, 6.96; N, 7.56%. Calcd for $C_{23}H_{44}N_4O_{14}\cdot 2H_2CO_3$: C, 41.43; H, 6.68; N, 7.73%.

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