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CHEMICAL MODIFICATION OF NEAMINE*

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ABSTRACT

The aminocyclitol antibiotic neamine has been modified by changing the configuration of one or two hydroxyl groups of the aminocyclitol moiety to elucidate the relationship between configuration and antimicrobial activity. 5-Epi-, 6-epi-, and 5,6-diepineamine have been prepared and their antimicrobial activity has been determined against several micro-organisms.

INTRODUCTION

In connection with the preceding paper[2], the stereochemistry of one or two hydroxyl groups of the 2-deoxystreptamine moiety of neamine has been inverted in order to elucidate the relationship between the configuration of the hydroxyl group and antimicrobial activity.

Inversion of stereochemistry of the hydroxyl group at C-2″ of kanamycin[3] and gentamicin[4] X_2 has afforded antibiotics active against adenylating strains of bacteria. 3′-Epiparomamine[5], 3′-epigentamicin[6], and 4′-epigentamicin[7] have been prepared to prevent inactivation by a phosphorylating enzyme[8].

As the inversion of stereochemistry of a hydroxyl group of an aminocyclitol moiety of an antibiotic has never been described, except for a biological conversion with epistreptamine in the case of hybrimycins[9], and a chemical modification of spectinomycin to 7-epispectinomycins[10], we have attempted to prepare 5-epi-, 6-epi-, and 5,6-diepi-neamine to elucidate the relationship between stereochemistry of the hydroxyl group on the 2-deoxystreptamine moiety of neamine and the antimicrobial activity.

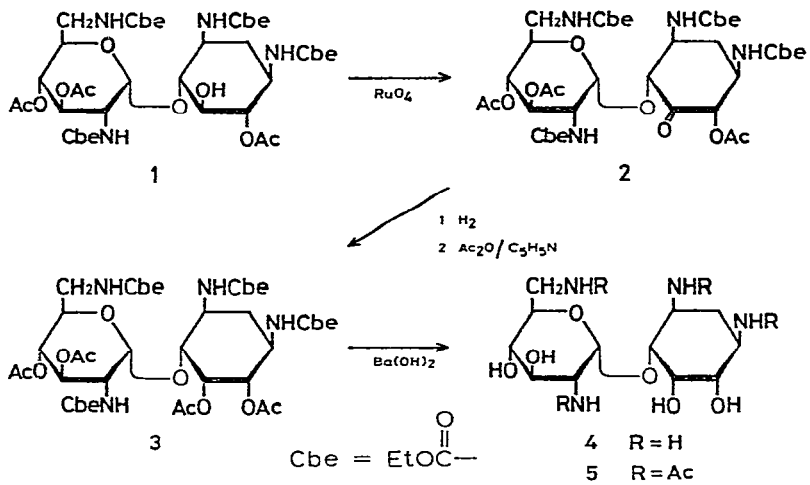
RESULTS AND DISCUSSION

Oxidation of 6,3′,4′-tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[11] (1) with ruthenium tetraoxide afforded 1D-4-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2,6-

*Part IV of this series. For a preliminary report see ref. 1.

diethoxycarbonylamido-α-D-glucopyranosyl)-6-*O*-acetyl-1,2,3-trideoxy-1,3-diethoxycarbonylamido-*neo*-inosose-5 (**2**). Compound **2** was characterized by converting it into the (2,4-dinitrophenyl)hydrazone.

Catalytic hydrogenation of **2** in the presence of platinum oxide, followed by acetylation, gave the 5-epineamine derivative (**3**) in 52% yield. Hydrolysis of **3** in aqueous barium hydroxide and subsequent purification by column chromatography on Amberlite CG-50 (NH_4^+) resin gave 5-epineamine (**4**) in 82% yield. The structure of **4** was confirmed by degradation in 8.8M hydrobromic acid whereby the known[12] penta-*N*,*O*-acetyl-2-deoxy-*neo*-inosadiamine-1,3 was isolated in 61% yield.

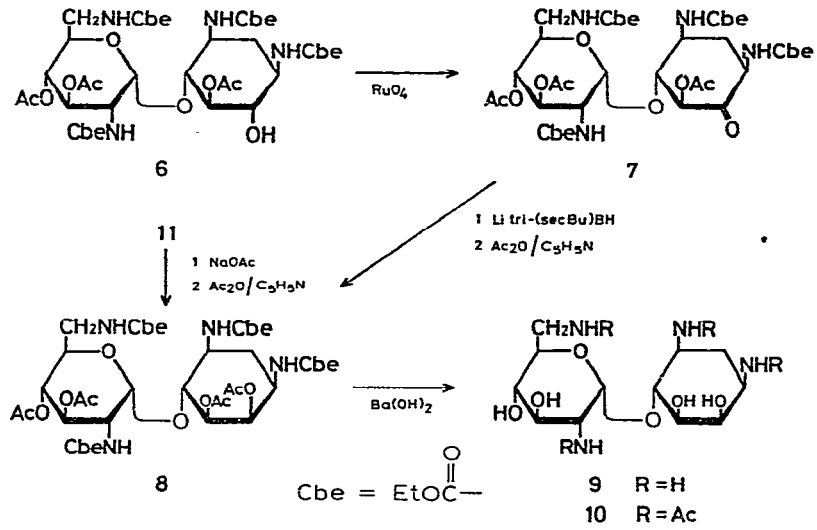


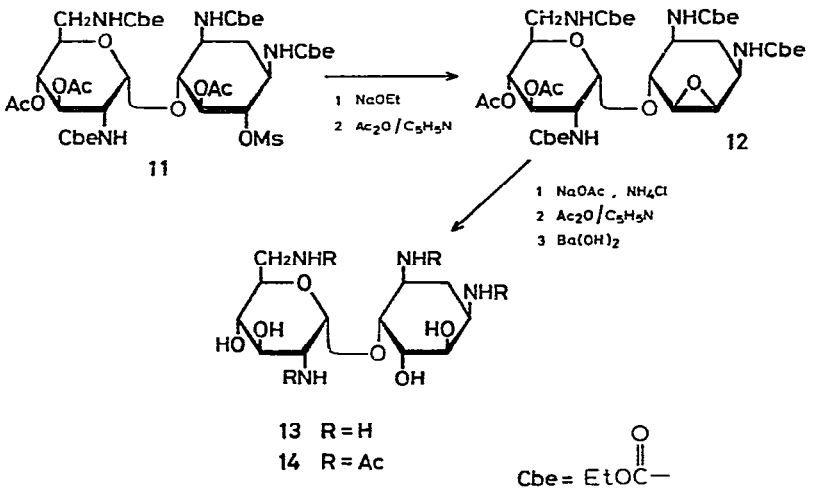
Oxidation of 5,3′,4′-tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[11] (**6**) with ruthenium tetraoxide gave the corresponding 6-oxo compound (**7**). Reduction of **7** with lithium tris(2-butyl)borohydride[13] afforded the 6-epineamine derivative **8** in 31% yield. Compound **8** was also prepared, in 56% yield, by nucleophilic displacement of 5,3′4′-tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonyl-6-*O*-mesylneamine[14] (**11**) with sodium acetate.

Hydrolysis of **8** in aqueous barium hydroxide gave 6-epineamine (**9**). The structure of **9** was confirmed by a degradation study analogous to that already described, and led to 1L-penta-*N*,*O*-acetyl-2-deoxy-*epi*-inosadiamine-1,3 (ref. 15).

Finally, when **11** was treated with ethanolic sodium ethoxide and subsequently acetylated, the corresponding 5,6-anhydride (**12**) was obtained in 44% yield. Nucleophilic ring-opening of the epoxide with acetate ion, followed by hydrolysis in aqueous barium hydroxide, gave 5,6-diepineamine (**13**) in 22% yield.

The structure of **13** was established by isolating the optically active 1L-2-deoxy-*allo*-inosadiamine-1,3 dihydrochloride from a degradation mixture of **13** in 8.8M hydrobromic acid. The configuration of the aminocyclitol obtained was established





by its ^{1}H-n.m.r. spectrum with the aid of spin–spin decoupling, which showed that the conventional *trans*-diaxial opening of the epoxide ring had occurred.

Antimicrobial activities were determined by a paper-disk method and the results are listed in Table I. Compound **4** exhibits activity comparable with that of the parent neamine, and it is active against kanamycin-resistant strains. Compounds **9** and **13** showed less activity as compared with neamine.

TABLE I

ANTIMICROBIAL ACTIVITIES OF **4**, **9**, AND **13**

Compound	*Diameter of inhibition zone (mm), determined by the paper-disk method*					
Concentration 1 mg/ml	Staphylococcus aureus *6538P*	Bacillus subtilis *ATCC 6633*	Escherichia coli *K-12*	Mycobacterium smegmatis *ATCC 607*	Klebsiella[a] pneumoniae *7*	Escherichia[a] coli *ML-1629*
4	20.7	31.4	33.0	27.4	12.6	11.2
9	0	20.6	29.8	18.4	0	0
13	0	20.4	19.8	0	0	0
Neamine	22.4	30.1	31.8	30.0	0	0

[a]Kanamycin-resistant strains.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes and are uncorrected. Solutions were evaporated under diminished pressure. Optical rotations were measured with a Japan Spectroscopic DIP-SL polarimeter. ^{1}H-N.m.r. spectra were recorded at 60 MHz with a Varian A-60D spectrometer in chloroform-*d* or deuterium oxide with tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard. The peak positions are given in δ values. I.r. spectra were recorded for potassium bromide disks with a Hitachi–Perkin–Elmer 225 spectrophotometer. Acetylation was performed conventionally with acetic anhydride in pyridine. T.l.c. was carried out on Wakogel B-10 (Wako Pure Chemical Co. Ltd.) plates. Silica gel (Wakogel C-300) was employed for column chromatography. Elemental analyses were performed by Mr. Saburo Nakada.

*1*D-*4*-O-(*3,4-Di*-O-*acetyl-2,6-dideoxy-2,6-diethoxycarbonylamido*-α-D-*glucopyranosyl*)-*6*-O-*acetyl-1,2,3-trideoxy-1,3-diethoxycarbonylamido*-neo-*inososе-5* (**2**). — To a solution of 6,3′,4′-tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[11] (**1**, 1.01 g) in dichloromethane (3 ml), a solution of ruthenium tetraoxide in carbon tetrachloride (50 ml), that had been prepared conventionally with ruthenium dioxide (0.65 g) and sodium metaperiodate (2.5 g), was added with stirring. After 3 h at room temperature, isopropyl alcohol (5 ml) was added to the solution to decompose the excess of oxidant. The mixture was filtered and the filtrate evaporated to give 910 mg (90%) of **2** as an amorphous powder; m.p. 130–136°, $[\alpha]_D^{21}$ +64.3° (*c* 1.7, chloroform).

Compound **2** (118 mg) was treated with (2,4-dinitrophenyl)hydrazine (118 mg) in ethanol (38 ml) in the presence of three drops of conc. hydrochloric acid overnight at room temperature. The solution was evaporated and the residue was purified by column chromatography with 20:1 (v/v) chloroform–ethanol. Fractions showing a single spot at R_F 0.30 in t.l.c. in the same solvent were combined and evaporated to give 57 mg (39%) of the corresponding (2,4-dinitrophenyl)hydrazone; m.p. 125–131°, $[\alpha]_D^{23}$ +64.6° (*c* 1.4, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.26 (t, 12, *J* 7.5 Hz, $4CO_2CH_2CH_3$), 2.01 (*s*, 3, OAc), 2.06 (s, 3, OAc), 2.31 (s, 3, OAc).

Anal. Calc. for $C_{36}H_{50}N_8O_{20}$: C, 47.26; H, 5.51; N, 12.25. Found: C, 47.41; H, 5.42; N, 12.00.

*5,6,3',4'-Tetra-*O*-acetyl-1,3,2',6'-tetra-*N*-ethoxycarbonyl-5-epineamine* (**3**). — Compound **2** (625 mg) was hydrogenated in methanol (10 ml) in the presence of platinum oxide (30 mg) and a drop of acetic acid under hydrogen for 15 h in a Parr apparatus. The catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography with 30:1 (v/v) chloroform–ethanol. Fractions showing a single spot at R_F 0.34 in t.l.c. in 20:1 (v/v) chloroform–ethanol were combined and evaporated. The residue was acetylated to give 342 mg (52%) of **3**; m.p. 123–129°, $[\alpha]_D^{19}$ +60.8° (*c* 1.5, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.95 (s, 3, OAc), 1.99 (s, 6, 2O Ac), and 2.15 (s, 3, OAc).

Anal. Calc. for $C_{32}H_{50}N_4O_{18}$: C, 49.35; H, 6.47; N, 7.19. Found: C, 49.61; H, 6.65; N, 7.04.

From the fractions that showed a spot at R_F 0.27 in t.l.c. in the same solvent, **1** (261 mg) was recovered in 42% yield.

5-Epineamine (**4**). — A mixture of **3** (336 mg) and barium hydroxide octahydrate (2.5 g) in water (7 ml) was boiled for 9 h under reflux. Carbon dioxide was bubbled into the mixture and the precipitate was filtered off. The filtrate was evaporated and the residue was purified on a column of Amberlite CG-50 (NH_4^+) resin. After washing with water and 0.1M aqueous ammonia, the column was eluted with 0.3M aqueous ammonia to give 114 mg (82%) of **4**; m.p. 81–100°, $[\alpha]_D^{21}$ +119° (*c* 0.9, water); ν_{max}^{KBr} 1570 cm^{-1} (NH_2). The product showed a single spot at R_F 0.19 in t.l.c. in 5:8:10:7 (v/v) 28% ammonia–1-butanol–ethanol–water.

*1,3,2',6'-Tetra-*N*-acetyl-5-epineamine* (**5**). — Compound **4** (30 mg) was *N*-acetylated with acetic anhydride in methanol to give 39 mg (84%) of **5**; m.p. >270°, $[\alpha]_D^{19}$ +96.8° (*c* 0.6, water). ^{1}H-n.m.r. data (D_2O): δ 2.03 (s, 6, 2NAc), 2.08 (s, 6, 2NAc), and 5.05 (d, 1, *J* 3 Hz, H-1').

Anal. Calc. for $C_{20}H_{34}N_4O_{10}\cdot 0.5H_2O$: C, 48.09; H, 7.06; N, 11.22. Found: C, 47.82; H, 6.79; N, 11.12.

Degradation of **4** *in* 8.8M *hydrobromic acid.* — Compound **4** (50 mg) was boiled in 8.8M hydrobromic acid (2 ml) for 50 h under reflux and the solution evaporated. The residue was dissolved in water and made neutral with Dowex 1×2 (OH^-) resin. The solution was evaporated and the residue was purified on a column of Amberlite CG-50 (NH_4^+) resin. After washing with water and 0.1M aqueous ammonia, the column was eluted with 0.3M aqueous ammonia and the eluate was evaporated. The residue was acetylated and the product recrystallized from methanol to give 35 mg (61%) of penta-*N,O*-acetyl-2-deoxy-*neo*-inosadiamine-1,3, identical with an authentic sample[12]; m.p. 291-294° (dec). [lit.[12] m.p. 293–294° (dec)]. (Found: C, 51.72; H, 6.46; N, 7.62.).

*1*D*-4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2,6-diethoxycarbonamido-α-*D*-glucopyranosyl)-5-*O*-acetyl-1,2,3-trideoxy-1,3-diethoxycarbonamido*-scyllo-*inosose-6* (**7**). — 5,3',4'-Tri-*O*-acetyl-1,3,2',6'-tetra-*N*-ethoxycarbonylneamine[11] (**6**, 2.00 g) was oxidi-

zed with ruthenium tetraoxide as described in the preparation of **2**, to give 1.51 g (76%) of **7**; m.p. 119–120°, $[\alpha]_D^{20}$ +44.8° (*c* 1.1, chloroform).

Compound **7** (100 mg) was treated with (2,4-dinitrophenyl)hydrazine (102 mg) in ethanol in the presence of a few drops of conc. hydrochloric acid. The product was purified by a column chromatography with 30:1 (v/v) chloroform–ethanol. Fractions showing a single spot at R_F 0.68 in t.l.c. in 10:1 (v/v) chloroform–ethanol were combined and evaporated to give 36 mg (29%) of the corresponding (2,4-dinitrophenyl) hydrazone; m.p. 141–144°, $[\alpha]_D^{23}$ −53.5° (*c* 0.8 chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 2.00 (s, 3, OAc), 2.03 (s, 3, OAc), and 2.18 (s, 3, OAc).

Anal. Calc. for $C_{36}H_{50}N_8O_{20}$: C, 47.26; H, 5.51; N, 12.25. Found: C, 47.53; H, 5.54; N, 12.01.

*5,6,3′,4′-Tetra-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonyl-6-epineamine* (**8**). — (*a*) A solution of **7** (609 mg) in tetrahydrofuran (2 ml) was added to a solution of lithium tris(2-butyl)borohydride[13] (1 mmol) in tetrahydrofuran (1 ml) at −78° under nitrogen. After stirring for 2 h at −78°, the mixture was allowed to settle for 1 h at room temperature. To the mixture, 70% aqueous ethanol (0.7 ml) was added, and subsequently 6M sodium hydroxide (0.4 ml) and 30% hydrogen peroxide (0.5 ml) were added. To the mixture was added chloroform (30 ml), and the chloroform solution was washed with saturated sodium chloride solution. The solution was dried over anhydrous sodium sulfate, evaporated and then the residue was ecetylated. The product was purified by column chromatography with 20:1 (v/v) benzene–isopropyl alcohol. Fractions showing a single spot at R_F 0.55 in t.l.c. in 7:1 (v/v) benzene–isopropyl alcohol were combined and evaporated to give 81 mg (13%) of 5,6,3′,4′-tetra-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonylneamine[11].

Fractions showing a single spot at R_F 0.45 in t.l.c. in the same solvent were combined and evaporated to give 203 mg (31%) of **8**; m.p. 113–115°, $[\alpha]_D^{21}$ +76.7° (*c* 0.8, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.92 (s, 3, OAc), 1.99 (s, 3, OAc), 2.02 (s, 3, OAc), and 2.16 (s, 3, OAc).

Anal. Calc. for $C_{32}H_{50}N_4O_{18}$: C, 49.35; H, 6.47; N, 7.19. Found: C, 49.59; H, 6.29; N, 7.02.

(*b*) 5,3′,4′-Tri-*O*-acetyl-1,3,2′,6′-tetra-*N*-ethoxycarbonyl-6-*O*-mesylneamine[14] (**11**, 1.04 g) was heated with sodium acetate (3.0 g) in boiling, 60% aqueous 2-methoxyethanol (20 ml) for 70 h under reflux. The mixture was evaporated and the residue was acetylated. The product was purified by column chromatography with 40:1 (v/v) chloroform–ethanol. Fractions showing a single spot at R_F 0.63 in t.l.c. in 20:1 (v/v) chloroform–ethanol were combined and evaporated to give 561 mg (56%) of **8**.

6-Epineamine (**9**). — Compound **8** (1.32 g) was hydrolyzed in aqueous barium hydroxide and the hydrolyzate was purified as described in the preparation of **4**, to give 307 mg (56%) of **9**, m.p. 152–155°, $[\alpha]_D^{22}$ +89.9° (*c* 1.2, water); ν_{max}^{KBr} 1580 cm^{-1} (NH_2). The product showed a single spot at R_F 0.29 in t.l.c. in the same solvent as that described for **4**.

*1,3,2′,6′-Tetra-*N*-acetyl-6-epineamine* (**10**). — Compound **9** (43 mg) was *N*-

acetylated with acetic anhydride in methanol to give 53 mg (80%) of **10**; m.p. 201–203°, $[\alpha]_D^{21}$ +86.4° (*c* 1.1, water). ^{1}H-n.m.r. data (D_2O): δ 2.00 (s, 6, 2NAc), 2.03 (s, 3, NAc), 2.05 (s, 3, NAc), and 5.33 (d, 1, *J* 3 Hz, H-1′).

Anal. Calc. for $C_{20}H_{34}N_4O_{10}\cdot 0.5H_2O$: C, 48.09; H, 7.06; N, 11.22. Found: C, 47.72; H, 6.80; N, 11.00.

Degradation of **9** *in 8.8*M *hydrobormic acid.* — Compound **9** (67 mg) was boiled in 8.8M hydrobromic acid (4 ml) for 46 h under reflux. The product was treated as described for the degradation of **4** to give 60 mg (78%) of L-penta-*N,O*-acetyl-2-deoxy-*epi*-inosadiamine-1,3 (the DL form has been described[15]); m.p. 242–243°, $[\alpha]_D^{26}$ +14° (*c* 3.4, methanol); ^{1}H-n.m.r. data (D_2O): δ 1.93 (s, 3, NAc), 1.97 (s, 3, NAc), 2.02 (s, 3, OAc), 2.06 (s, 3, OAc), and 2.23 (s, 3, OAc).

Anal. Calc. for $C_{16}H_{24}N_2O_8$: C, 51.61; H, 6.50; N, 7.52. Found; C, 51.78; H, 6.46; N, 7.39.

D-6-O(3,4-Di-O-acetyl-2,6-dideoxy-2,6-diethoxycarbonamido-α-D-glucopyranosyl)-1,2-anydro-3,4,5-trideoxy-3,5-diethoxycarbonlamido-epi-*inositol* (**12**). — Compound **11** (600 mg) was suspended in M ethanolic sodium ethoxide (6 ml) overnight at room temperature to give a gelatinous product. Ethanol was added to the mixture, and the product was collected by filtration. The product was acetylated to give 218 mg (44%) of **12** as an amorphous powder; m.p. 116–118°, $[\alpha]_D^{20}$ +126° (*c* 1.1, pyridine); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.22 (t, 3, *J* 8 Hz, $CO_2CH_2CH_3$), 1.24 (t, 9, *J* 8 Hz, $3CO_2CH_2CH_3$), 2.00 (s, 3, OAc), and 2.02 (s, 3, *OA*c).

Anal. Calc. for $C_{28}H_{44}N_4O_{15}$: C, 49.70; H, 6.55; N, 8.28. Found: C, 49.75; H, 6.45; N, 8.09.

5,6-Diepineamine (**13**). — Compound **12** (1.25 g) was boiled under reflux for 40 h in 60% aqueous 2-methoxyethanol (18 ml) with sodium acetate (0.63 g) and ammonium chloride (0.24 g). The mixture was evaporated, and the residue was acetylated. The product was purified on an alumina column with chloroform to give a syrup that was hydrolyzed in aqueous barium hydroxide solution as described in the preparation of **4**, and the hydrolyzate was purified on a column of Amberlite CG-50 (NH_4^+) resin. After washing with water and 0.1M aqueous ammonia, the column was eluted with 0.3M aqueous ammonia to recover 61 mg (10%) of neamine. The column was successively eluted with 0.5M aqueous ammonia to give 129 mg (22%) of **13** as an amorphous powder; m.p. 110–129°, $[\alpha]_D^{20}$ +149° (*c* 1.2, water); ν_{max}^{KBr} 1580 cm^{-1} (NH_2). The product showed a single spot at R_F 0.25 in t.l.c. in the same solvent described for **4**.

1,3,2′,6′-Tetra-N-*acetyl-5,6-diepineamine* (**14**). — Compound **13** (46 mg) was acetylated with acetic anhydride in methanol to give 58 mg of **14**; m.p. >250°, $[\alpha]_D^{20}$ +135° (*c* 2.0, water). ^{1}H-n.m.r. data (D_2O): δ 2.06 (s, 3, NAc), 2.09 (s, 6, 2NAc), and 5.09 (d, 1, *J* 3.5 Hz, H-1′).

Anal. Calc. for $C_{20}H_{34}N_4O_{10}\cdot 0.5H_2O$: C, 48.09; H, 7.06; N, 11.22. Found: C, 48.16; H, 6.97; N, 11.15.

Degradation of **13** *in* 8.8M *hydrobromic acid.* — Compound **13** (67 mg) was boiled in 8.8M hydrobromic acid (5 ml) for 46 h under reflux. The mixture was

purified as described for **4**. The base was neutralized with diluted hydrochloric acid, and the solution was evaporated. The residue was recrystallized from aqueous ethanol to give 38 mg (78%) of 1L-2-deoxy-*allo*-inosadiamine-1,3 dihydrochloride as crystals; m.p. >250°, $[\alpha]^{20}$ +48.8° (*c* 1.9, water). ^{1}H n.m.r. data (D_2O): δ 1.98 (ddd, 1, H-2a), 2.30 (dddd, 1, H-2e), 3.53 (ddd, 1, H-1), 3.78 (ddd, 1, H-3), 4.03 (dd, 1, H-6), and 4.1–4.3 (m, 2, H-4,5); $J_{1,2e} = J_{2e,3} = 5$, $J_{1,2a} = J_{2a,3} = 12$, $J_{1,6}$ 10, $J_{2a,2e}$ −12, $J_{2e,4} \leq 1$, and $J_{3,4} = J_{5,6} = 2.5$ Hz.

Anal. Calc. for $C_6H_{14}N_2O_3 \cdot 2HCl$: C, 30.65; H, 6.86; N, 11.91; Cl, 30.16. Found: C, 30.38; H, 6.71; N, 11.76; Cl, 30.03.

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