

STEREOSELECTIVE CONVERSION OF VALIENAMINE AND VALIDAMINE INTO VALIOLAMINE*

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ABSTRACT

Methods are described for the stereoselective conversion of valienamine (**2**) and validamine (**3**) into valioline (**1a**), a new pseudo-amino sugar isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* and which is a stronger α -D-glucosidase inhibitor than **2** and **3**. Treatment of the acyclic carbamates (**4**) of **2** with halogenation reagents led to ring closure to afford the halo cyclic carbamates (**6**), which were reductively dehalogenated and then hydrolyzed to give **1a**. Similar treatment of the exomethylene acyclic carbamate (**12**), derived from **3** via **8–11**, resulted in the formation of halo cyclic carbamates (**14a,b**), which were converted into **1a**. The synthesis of epivaliolamine (**1b**), the C-1 epimer of **1a**, starting from **2** and **3**, is also described.

INTRODUCTION

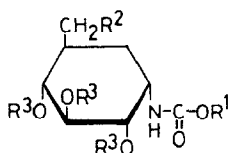
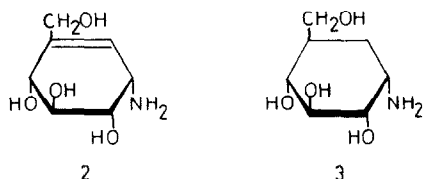
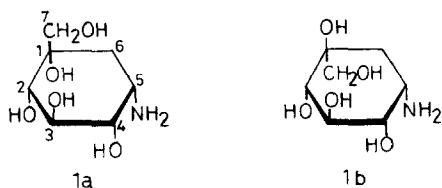
Valiolamine (**1a**) is a pseudo-amino sugar first isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus*. The structure of **1a** was proposed to be (1(OH),2,4,5/1,3)-5-amino-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol, mainly by spectrometric studies¹.

The purpose of this study was to obtain rigorous evidence of the *S* configuration at C-1 of **1a** and to provide a convenient route to **1a** in amounts large enough for preparation of semi-synthetic α -D-glucosidase inhibitors having **1a** as a key constituent. The inhibitory activity of **1a** against porcine intestinal disaccharidase [IC_{50}^{**} : 4.9×10^{-8} (Suc) and 2.2×10^{-6} (Mal)]¹ is significantly higher than that of such related pseudo-amino sugars as valienamine^{2,3} (**2**) [IC_{50}^{**} : 5.3×10^{-5} (Suc)

*Part of this work and related experimental results are disclosed in the following patent applications: Takeda Chemical Industries, Ltd., Jpn. Kokai Tokyo Koho JP 57-179,174 (1982) and 58-46,004 (1983) [Eur. Pat. Appl. EP 63,950 (1982); U.S. Pat. 4,446,319 (1984); Chem. Abstr. 98 (1983) 161113c].

** IC_{50} : Molar concentration required to give 50% inhibition against porcine sucrase (Suc) and porcine maltase (Mal).

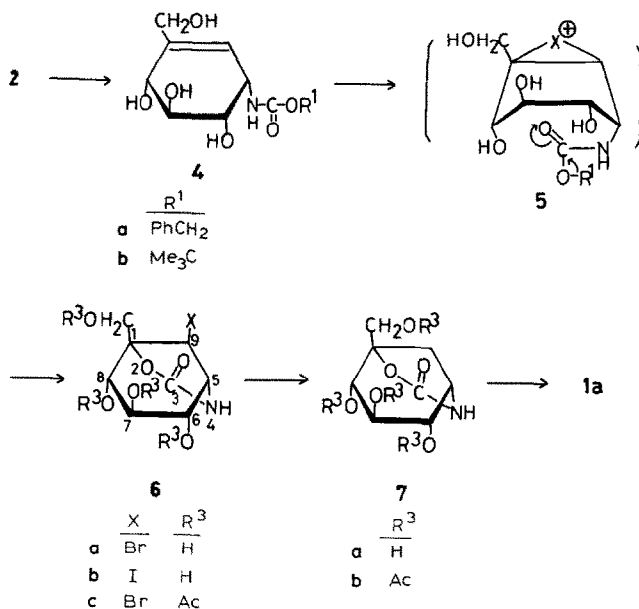
and 3.4×10^{-4} (Mal)], the core building-block of naturally occurring pseudo-oligosaccharide α -D-glucosidase inhibitors⁴, and validamine⁵ (**3**) [IC_{50}^{**} : 7.5×10^{-6} (Suc) and 1.1×10^{-4} (Mal)]¹. For this purpose, compounds **2** and **3**, which may be prepared on a large scale by microbiological degradation of validamycin A (ref. 6), were chosen as the starting materials.



	R^1	R^2	R^3
8	PhCH ₂	OH	H
9	PhCH ₂	OTs	H
10	PhCH ₂	OTs	Ac
11	PhCH ₂	I	Ac

RESULTS AND DISCUSSION

First, we describe a stereoselective conversion of **2** into **1a** (Scheme 1), which was also used to assign the absolute configuration at C-1 of **1a** as *S*. Acyclic carbamate derivatives of **2**, such as *N*-(benzyloxycarbonyl)valienamine (**4a**) and *N*-(*tert*-butoxycarbonyl)valienamine (**4b**), were treated with such halogenation reagents as bromine and iodine monochloride to afford the corresponding halo cyclic carbamates (**6**). This cyclization reaction is thought to proceed by a mechanism similar to halolactonization⁷, namely, by nucleophilic attack of a carboxylate anion (formed by release of the benzyl or *tert*-butyl moiety of the carbamates **4**) to a halonium ion (formed by addition of halogen to the carbon-carbon double bond), as shown in formula **5**. The halo cyclic carbamates **6** were dehalogenated reduc-

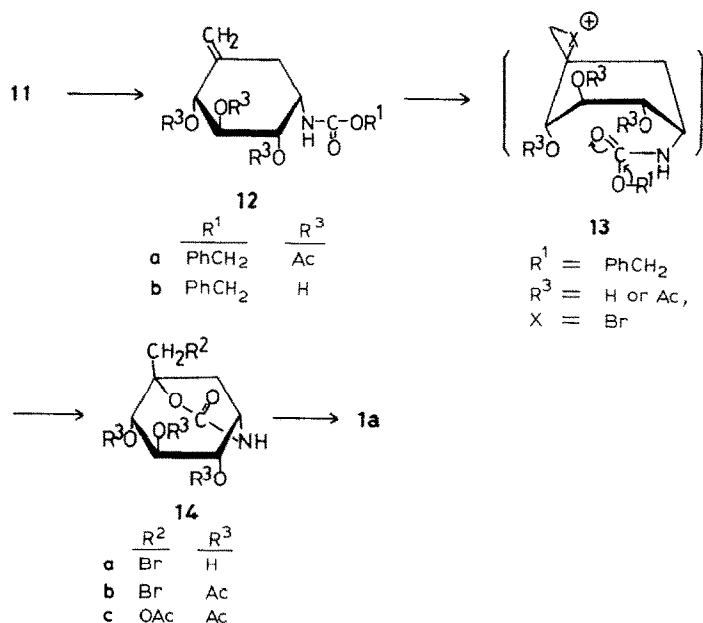


Scheme 1.

tively with sodium borohydride, and the resulting dehalogenated cyclic carbamates (**7**) were hydrolyzed to give **1a**.

Valiolamine was also obtained from **3** as shown in Scheme 2. Tri-*O*-acetyl-1L-(1,3,4/2,6)-4-[(benzyloxycarbonyl)amino]-6-*C*-(iodomethyl)-1,2,3-cyclohexanetriol (**11**) (prepared from **3** by a four-step sequence via **8**, **9**, and **10**) was treated with silver fluoride in pyridine to give tri-*O*-acetyl-1L-(1,3,4/2)-4-[(benzyloxycarbonyl)amino]-6-methylene-1,2,3-cyclohexanetriol (**12a**). Hydrolysis of **12a** with 5M ammonium hydroxide gave the *O*-deacetylated derivative (**12b**). The exomethylene derivatives **12b** and **12a** were treated with bromine to give 1-(bromoethyl)-6,7,8-trihydroxy-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (**14a**) and its tri-*O*-acetyl derivative (**14b**) respectively, presumably via a transient intermediate **13**. The bromomethyl derivative **14b** was treated with silver acetate in *N,N*-dimethylformamide to give the acetoxymethyl derivative (**14c**). Hydrolysis of **14a** and **14c** gave **1a**.

The cyclic carbamate structure of **6**, **7**, and **14** was supported by the following evidence: (i) the absence of vinyl proton and benzyl (or *tert*-butyl) proton signals in the n.m.r. spectra of **6**, **7**, and **14**; (ii) the absence of methylene proton signals in the n.m.r. spectra of **6** and the presence of methylene proton signals in the n.m.r. spectra of **7** (a proof of position of the halogenated carbon atom); (iii) the proton at C-8 [**6c**; 5.73 (d, 1 H, *J* 10 Hz): **7b**; 5.18 (d, 1 H, *J* 10 Hz)] couples only with the proton at C-7, and the proton at C-9 [**6c**; 4.65 (d, 1 H, *J* 4 Hz)] with the proton at C-5, and the methylene protons of the -CH₂O- group [**6c**; 4.17 and 4.33 (ABq, each 1 H, *J* 13 Hz): **7b**; 3.92 and 4.30 (ABq, each 1 H, *J* 12 Hz)] at C-1 couple only with



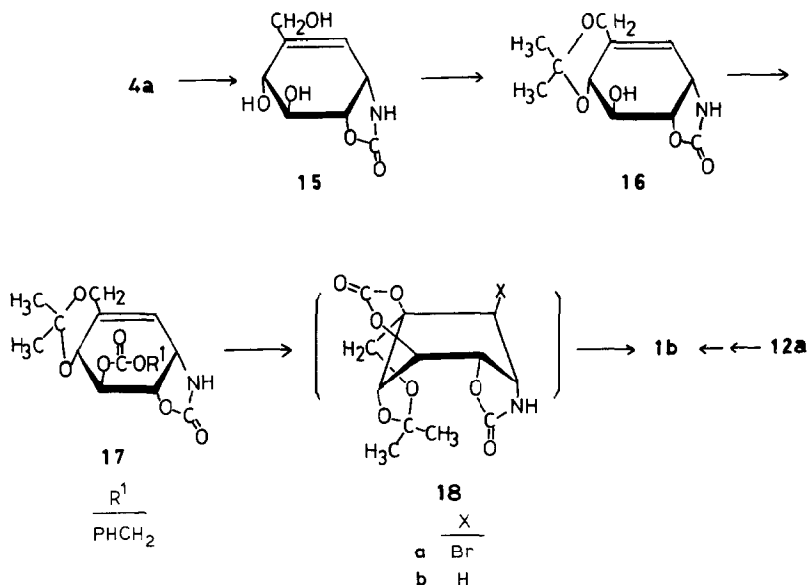
Scheme 2.

each other (*gem*-protons) (no proton at C-1); (iv) the presence of a six-membered cyclic amide band (1696 cm^{-1} in **6a**, 1669 cm^{-1} in **7a**, and 1691 cm^{-1} in **14a**) and the lack of an acyclic amide II band ($1500\text{--}1560\text{ cm}^{-1}$) in the i.r. spectra of **6**, **7**, and **14**; and (v) acetylation (acetic anhydride-pyridine) of **7a** gave the tetra-*O*-acetyl derivative **7b**, which was identical with **14c** derived from **3**. Thus, **7a** and **1a** were assigned as [1*S*-(*endo,exo,endo*)]-6,7,8-trihydroxy-1-(hydroxymethyl)-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane and (1*S*)-(1(OH),2,4,5/1,3)-5-amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol, respectively.

In addition, the configuration at C-9 of the 9-bromo derivative **6c** was elucidated, from the n.m.r. spectrum of **6c**, as compared with that of the dehalogenated derivative **7b**, as *S* on the basis of the downfield shifts of the H-6 and H-8 signals (0.67 and 0.55 p.p.m.), which indicates that H-6 and H-8 are in *syn*-axial relation with the C-9 bromine atom⁸.

Dihydroxylation of the exomethylene moiety of **12a** with osmium tetroxide⁹ in ethyl ether, followed by removal of the protecting groups, gave a 5-amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (**1b**) whose R_F value (0.42) was different from that of **1a** (0.30) in t.l.c. (silica gel; 4:1:1 1-propanol-acetic acid-water) and had less α -D-glucosidase inhibitory activity [IC_{50} : 4.7×10^{-4} (Suc) and 1.0×10^{-3} (Mal)] than **1a**. Judging from the foregoing synthetic route to **1b** from **12a**, it seemed most probable that **1b** is the C-1 epimer of **1a**, and the formation of **1b** may be explained by attack of osmium tetroxide from the less-hindered side of **12a**. In order to confirm the stereochemistry of **1b**, the following synthesis of **1b** from **2** was undertaken. The 2-*O*-(benzyloxycarbonyl) derivative (**17**) (prepared from **4a** by a three-step sequence via **15** and **16** was treated with bromine in acetonitrile to

produce the bromo cyclic carbonate intermediate (**18a**), followed by reductive debromination and hydrolysis to give **1b** as shown in Scheme 3. Therefore, **1b** was assigned as (1*R*)-(1(CH₂OH),2,4,5/1,3)-5-amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol and tentatively named epivaliolamine.



Scheme 3.

A series of *N*-substituted valioliamine derivatives has been synthesized using the **1a** thus obtained as starting material and these were screened by measuring their porcine sucrase-maltase inhibitory activity. Most of the *N*-substituted valioliamine derivatives tested were found to be more potent than the corresponding *N*-substituted valienamine and validamine derivatives^{10,11}. These findings will be reported elsewhere in detail.

EXPERIMENTAL

General methods. — Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter or a Jasco DIP-181 polarimeter. ¹H-N.m.r. spectra were recorded, with tetramethylsilane (Me₄Si) as the external standard in D₂O and as the internal standard in CDCl₃ and Me₂SO-*d*₆, with a Varian EM-390 spectrometer (90 MHz), unless noted that they were recorded with a Jeol JNM-GX400 spectrometer at 400 MHz, or with a Varian XL-100A spectrometer at 100 MHz (for decoupling experiments). ¹³C-N.m.r. spectra were recorded with a Varian XL-100A spectrometer at 25.2 MHz. I.r. spectra were recorded with a Hitachi 270-30 infrared spectrophotometer or a Jasco IRA-1 spectrometer. Mass spectra [SIMS

(Sputtered Ion Mass Spectra)] were recorded with a Hitachi M-80A mass spectrometer. Thin-layer chromatography (t.l.c.) was performed on pre-coated Kieselgel F₂₅₄ plates (Merck). Chromatography columns of silica gel were prepared with Kieselgel (70–230 mesh; Merck). Column chromatography was monitored by refractive index (with a Waters Differential Refractometer R-403) and/or u.v. (254 nm) detection (with a Uvicord II instrument). Ratios for mixtures of solvents are expressed by volume (v/v). Organic solvents were dried over anhydrous sodium sulfate before evaporation. Solutions were evaporated under diminished pressure by using a rotary evaporator.

1L-(1,3,4/2)-4-[(Benzyloxycarbonyl)amino]-6-C-(hydroxymethyl)-5-cyclohexene-1,2,3-triol [N-(benzyloxycarbonyl)valienamine] (**4a**). — A solution of benzyl chloroformate (170 mL) in toluene (500 mL) was added dropwise to a solution of valienamine (**2**, 100 g) and sodium hydrogencarbonate (100 g) in water (1 L) at 5–10° with stirring, followed by stirring at the same temperature for 1 h and at room temperature for 3 h. The mixture was kept for 2 h with the temperature <10°. The white, crystalline precipitate of **4a** was filtered off, washed with water and toluene, and dried under diminished pressure. The mother liquor and washings were combined. The aqueous layer was separated and washed with toluene, adjusted to pH 5–5.5 with 2M hydrochloric acid, and concentrated to ~400 mL. The concentrate was refrigerated overnight. A second crop of crystalline **4a** was filtered off, washed with cold water, and dried under diminished pressure; total yield, 146 g, $[\alpha]_D^{26} +125.4^\circ$ (c 1, water); ν_{\max}^{KBr} 1682 (C=O), 1548 cm⁻¹ (-NHCO-); ¹H-n.m.r. (Me₂SO-*d*₆ + D₂O): δ 3.35–3.85 (m, 3 H), 3.96 (broad s, 2 H), 4.15–4.38 (m, 1 H), 5.02 (s, 2 H, PhCH₂-) 5.47 (d, 1 H, *J* 4.5 Hz, 5-CH), and 7.33 (s, 5 H, C₆H₅-).

Anal. Calc. for C₁₅H₁₉NO₆: C, 58.24; H, 6.19; N, 4.53. Found: C, 58.38; H, 6.24; N, 4.54.

N-(tert-Butoxycarbonyl)valienamine (**4b**). — To a solution of **2** (10 g) in water (50 mL) was added 1,4-dioxane (50 mL) and *tert*-butyl S-(4,6-dimethylpyrimidin-2-yl)thiocarbonate (18.6 g). The mixture was stirred for 18 h at room temperature and then evaporated. The residue was dissolved in water (200 mL), and the solution was washed with ethyl acetate, concentrated to ~50 mL, and refrigerated overnight. The resulting crystals were filtered off and washed with cold water. The filtrate and washings were combined and applied to a column of MCI Gel CHP20P resin (150–300 μ m; a synthetic porous polymeric adsorbent, Mitsubishi Chem. Ind. Ltd., 400 mL). The column was washed with water and then eluted with a gradient of water–80% aqueous methanol. The eluate was concentrated and applied to a column of Amberlite CG-50 resin (H⁺, 550 mL). The column was eluted with water. The eluate was concentrated and then lyophilized to give the carbamate **4b** (12.5 g) as a white solid: $[\alpha]_D^{23} +128.2^\circ$ (c 1, water); ν_{\max}^{KBr} 1693 (C=O), 1515 cm⁻¹ (-NHCO-); ¹H-n.m.r. (D₂O): δ 1.58 (s, 9 H, *tert*-butyl), 3.6–4.05 (m, 2 H), 4.1–4.4 (m, 3 H), 4.45–4.65 (m, 1 H), and 5.87 (d, 1 H, *J* 4.5 Hz, 5-CH).

Anal. Calc. for C₁₂H₂₁NO₆: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.09; H, 7.93; N, 5.02.

9-Bromo-6,7,8-trihydroxy-1-(hydroxymethyl)-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (6a). — (a) *From 4a.* A solution of bromine (75 g) in methanol (450 mL) was added dropwise to a solution of **4a** (146 g) in methanol (1.2 L) at 0–5° with stirring, followed by stirring for 1 h at the same temperature. The mixture was evaporated, 1:10 ethanol–ethyl acetate (2.2 L) was added to the residue, and the mixture was refrigerated. The precipitated crystals were filtered off, washed successively with ethyl acetate and petroleum ether, and recrystallized from water to give the bromo cyclic carbamate **6a** (136 g); $[\alpha]_D^{24} +41.5^\circ$ (c 1, water); ν_{\max}^{KBr} 1696 cm^{-1} (C=O); $^1\text{H-n.m.r. (D}_2\text{O)}$: δ 3.66 (t, 1 H, J 9.3 Hz, 7-CH), 3.93 (t, 1 H, J 3.2 Hz, 5-CH), 3.95 and 4.14 (ABq, each 1 H, J 13 Hz, -CH₂O-), 4.18 (d, 1 H, J 9.3 Hz, 8-CH), 4.34 (dd, 1 H, J 3, 9.3 Hz, 6-CH), and ~ 4.75 (1 H, 9-CH, overlapped with HOD); $^{13}\text{C-n.m.r. (Me}_2\text{SO-}d_6)$: δ (from Me₄Si): 42.3(d), 54.7(d), 62.6(t), 71.5(d), 72.7(d), 73.7(d), 85.0(s), and 152.3(s).

Anal. Calc. for C₈H₁₂BrNO₆ · H₂O: C, 30.39; H, 4.46; Br, 25.28; N, 4.43. Found: C, 30.30; H, 4.54; Br, 25.41; N, 4.40.

(b) *From 4b.* A solution of bromine (1.8 g) in methanol (200 mL) was added dropwise to a solution of **4b** (2.8 g) in methanol (30 mL) with cooling in an ice-water bath, and the mixture was stirred for 1 h. The mixture was evaporated and the residue applied to a column of MCI Gel CHP20P resin (250 mL). The column was eluted with water and the eluate was concentrated and lyophilized to give a white solid (2.5 g). To obtain the anhydrous bromo cyclic carbamate **6a** (2.1 g), acetic acid (40 mL) was added to the white solid and the mixture was heated for 30 min at 80–90° and then kept overnight at room temperature; $[\alpha]_D^{24} +41.5^\circ$ (c 1, water); ν_{\max}^{KBr} 1695 cm^{-1} (C=O). The $^1\text{H-n.m.r.}$ spectrum of the halo cyclic carbamate obtained by method *b* was identical with that of the product obtained by method *a*.

Anal. Calc. for C₈H₁₂BrNO₆: C, 32.23; H, 4.06; Br, 26.81; N, 4.70. Found: C, 32.11; H, 4.19; Br, 26.67; N, 4.87.

6,7,8-Trihydroxy-1-(hydroxymethyl)-9-iodo-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (6b). — A solution of iodine monochloride (1.7 g) in acetonitrile (20 mL) was added dropwise to a solution of **4a** (3.1 g) in methanol (50 mL) at 0–5° with stirring, followed by stirring for 5 h at the same temperature and then for 15 h at room temperature. The mixture was evaporated and the residue partitioned between ethyl acetate and water. The aqueous layer was separated, washed with ethyl acetate, adjusted to pH 5 with saturated aqueous sodium hydrogencarbonate, and evaporated. The residue was applied to a column of MCI Gel CHP20P resin (250 mL). The column was eluted with water, and the eluate was evaporated. The residue was dissolved in hot water and refrigerated overnight to give the iodo cyclic carbamate **6b** (3.1 g) as crystals; $[\alpha]_D^{24} +37.5^\circ$ (c 1, water); ν_{\max}^{KBr} 1690 cm^{-1} (C=O); $^1\text{H-n.m.r. (D}_2\text{O)}$: δ 3.70 (t, 1 H, J 9.5 Hz, 7-CH), 3.92 (t, 1 H, J 3.5 Hz, 5-CH), 4.02 and 4.28 (ABq, each 1 H, J 15 Hz, -CH₂O-), 4.33 (d, 1 H, J 9.5 Hz, 8-CH), 4.53 (dd, 1 H, J 3.5, 9 Hz, 6-CH), and 4.79 (d, 1 H, J 3.5 Hz, 9-CH); $^{13}\text{C-n.m.r. (Me}_2\text{SO-}d_6)$: δ (from Me₄Si): 17.9(d), 55.8(d), 64.1(t), 72.6(d), 73.7(d), 74.1(d), 84.7(s), and 152.6(s).

Anal. Calc. for $C_8H_{12}INO_6 \cdot H_2O$: C, 26.46; H, 3.89; N, 3.86. Found: C, 26.57; H, 3.97; N, 3.96.

6,7,8-Triacetoxy-1-(acetoxymethyl)-9-bromo-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (6c). — A suspension of **6a** (1.0 g) in pyridine (10 mL) and acetic anhydride (5.0 mL) was stirred for 20 h at room temperature. The resulting, clear solution was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with M hydrochloric acid and saturated aqueous sodium hydrogencarbonate, and then evaporated. Ethyl ether was added to the residue, and the mixture was refrigerated to give **6c** (740 mg) as crystals, m.p. 226–228° (decomp.); ν_{\max}^{KBr} 1755, 1730 cm^{-1} ; $[\alpha]_D^{25} +57.7^\circ$ (c 1, methanol); 1H -n.m.r. ($CDCl_3$): δ 1.98, 2.03, 2.11, 2.24 (s, each 3 H, acetyl \times 4), 3.9–4.15 (m, 1 H, 5-CH), 4.17 and 4.33 (ABq, each 1 H, J 13 Hz, $-CH_2OAc$), 4.65 (d, 1 H, J 4 Hz, 9-CH), 5.36 (t, 1 H, J 10 Hz, 7-CH), 5.66 (dd, 1 H, J 2.5, 10 Hz, 6-CH), 5.73 (d, 1 H, J 10 Hz, 8-CH), and 7.92 (d, 1 H, J 6 Hz, $-CONH$ -).

Anal. Calc. for $C_{16}H_{20}BrNO_{10}$: C, 41.22; H, 4.32; Br, 17.14; N, 3.00. Found: C, 41.07; H, 4.21; Br, 17.05; N, 3.12.

6,7,8-Trihydroxy-1-(hydroxymethyl)-3-oxo-2-oxa-4-azabicyclo-[3.3.1]nonane (7a). — (a) *From 6a.* Sodium borohydride (55 g) was added to a solution of the bromo cyclic carbamate **6a** (100 g) in water (1.3 L) at room temperature with stirring. After stirring for 2 h at the same temperature, the mixture was adjusted to pH 6–7 with acetic acid and concentrated to \sim 800 mL. The concentrate was applied to a column of activated carbon (4.8 L), and the column was washed with water (5 L) and eluted with 50% aqueous methanol. The eluate was evaporated, methanol (350 mL) was added to the residue, and the solution was boiled under reflux for 10–20 min to remove a methanol-soluble byproduct. The mixture was refrigerated overnight. The resulting crystals were filtered off, washed with cold methanol, and dried under diminished pressure to give the cyclic carbamate **7a** (64 g); m.p. 254–255° (decomp.), $[\alpha]_D^{24} +36.4^\circ$ (c 1, water); ν_{\max}^{KBr} 1669 cm^{-1} ($C=O$); 1H -n.m.r. (D_2O): δ 2.07 (dd, 1 H, J 2, 15 Hz, 9-CH), 2.34 (dd, 1 H, J 5, 15 Hz, 9-CH), and 3.45–4.1 (6 H); ^{13}C -n.m.r. (D_2O): δ (from Me_4Si , reference 1,4-dioxane at 67.4): 25.6(t), 50.8(d), 64.0(t), 74.7(d), 75.2(d), 75.5(d), 85.0(s), and 156.8(s).

Anal. Calc. for $C_8H_{13}NO_6$: C, 43.83; H, 5.98; N, 6.39. Found: C, 43.81; H, 5.95; N, 6.55.

(b) *From 6b.* An aqueous solution (20 mL) of sodium borohydride (0.5 g) was added to an aqueous solution (50 mL) of the iodo cyclic carbamate **6b** (1.0 g) and the mixture was stirred for 2 h. The mixture was adjusted to pH 5 with acetic acid, and then evaporated. The residue was applied to a column of activated carbon (180 mL). The column was washed with water and then eluted with 50% aqueous methanol. The eluate was evaporated and 1:10 methanol–ethanol was added to the residue. The mixture was refrigerated to give **7a** (565 mg) as crystals. The m.p., $[\alpha]_D$, and i.r. and 1H -n.m.r. spectra of the crystals obtained by method *b* were identical with those obtained by method *a*.

Anal. Calc. for $C_8H_{13}NO_6$: C, 43.83; H, 5.98; N, 6.39. Found: C, 43.80; H, 5.94; N, 6.56.

6,7,8-Triacetoxy-1-(acetoxymethyl)-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (**7b**). — A suspension of **7a** (700 mg) in pyridine (5 mL) and acetic anhydride (2.5 mL) was stirred overnight at room temperature. The resulting solution was evaporated and the residue was extracted with ethyl acetate. The extract was washed with M hydrochloric acid and saturated aqueous sodium hydrogencarbonate, and then evaporated. Ethyl ether was added to the residue, and the mixture was refrigerated overnight to give **7b** (816 mg) as crystals; m.p. 173–174°, $[\alpha]_D^{25} + 60.4^\circ$ (c 1, methanol); $\nu_{\text{max}}^{\text{KBr}}$ 1753, 1708 cm^{-1} ; $^1\text{H-n.m.r.}$ (CDCl_3): δ 1.96, 2.00, 2.07, 2.25 (s, each 3 H, acetyl \times 4), 2.2 (2 H, 9- CH_2), 3.8–4.0 (m, 1 H, 5- CH), 3.92 and 4.30 (ABq, each 1 H, J 12 Hz, $-\text{CH}_2\text{O}-$), 4.99 (dd, 1 H, J 3, 10 Hz, 6- CH), 5.18 (d, 1 H, J 10 Hz, 8- CH), 5.38 (t, 1 H, J 10 Hz, 7- CH), and 7.95 (d, 1 H, J 5 Hz, $-\text{CONH}-$).

Anal. Calc. for $\text{C}_{16}\text{H}_{21}\text{NO}_{10}$: C, 49.61; H, 5.46; N, 3.62. Found: C, 49.57; H, 5.35; N, 3.50.

1L-(1,3,4/2,6)-4-[(Benzyloxycarbonyl)amino]-6-C-(hydroxymethyl)-1,2,3-cyclohexanetriol [N-(benzyloxycarbonyl)validamine] (**8**). — To a solution of validamine (**3**, 21 g) in water (250 mL) was added 1,4-dioxane (125 mL) and then benzyl chloroformate (22.5 mL) under ice-cooling. The solution was stirred for 1 h at 0–5° and then for 1 h at room temperature, adjusting to pH 7–7.5 with saturated aqueous sodium hydrogencarbonate. The mixture was adjusted to pH 5.5 with 2M hydrochloric acid and then concentrated to remove the organic solvent. Water (250 mL) was added to the concentrate, and the mixture was washed with ethyl acetate. The aqueous layer was concentrated and chromatographed on a column of Amberlite CG-50 (H^+ , 800 mL). The column was eluted with water, and the eluate was concentrated and then lyophilized to give **8** (31.8 g) as a white solid, $[\alpha]_D^{24} + 55.5^\circ$ (c 1, water); $\nu_{\text{max}}^{\text{KBr}}$ 1695 (C=O), 1536 cm^{-1} ($-\text{NHCO}-$); $^1\text{H-n.m.r.}$ (D_2O): δ 1.4–2.15 (m, 3 H), 3.25–3.85 (m, 5 H), 4.22 (1 H), 5.25 (s, 2 H, Ph-CH_2-), and 7.48 (s, 5 H, C_6H_5-).

Anal. Calc. for $\text{C}_{15}\text{H}_{21}\text{NO}_6$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.50; H, 6.81; N, 4.45.

1L-(1,3,4/2,6)-4-[(Benzyloxycarbonyl)amino]-6-C-(p-tolylsulfonyloxy-methyl)-1,2,3-cyclohexanetriol (**9**). — *p*-Toluenesulfonyl chloride (3.8 g) was added to a solution of **8** (6.0 g) in pyridine (60 mL) under cooling in an ice-water bath, and then the solution was stirred for 15 h at room temperature. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was separated, and the water layer was extracted with ethyl acetate. The combined organic layers were washed with M hydrochloric acid and then saturated aqueous sodium hydrogencarbonate, and evaporated. The residue was chromatographed on a column of silica gel (400 mL) that was eluted with ethyl acetate, and the eluate was evaporated. A 1:3 mixture (500 mL) of ethyl ether and petroleum ether was added to the residue, and the mixture was refrigerated overnight to give *N*-(benzyloxycarbonyl)-7-*O*-(*p*-tolylsulfonyl)validamine (**9**, 5.1 g); $^1\text{H-n.m.r.}$ ($\text{Me}_2\text{SO}-d_6$): δ 2.41 (s, 3 H), 5.00 (s, 2 H), 7.37 (s, 5 H), 7.45 (d, 2 H, J 8 Hz), and 7.76 (d, 2 H, J 8 Hz).

Anal. Calc. for $C_{22}H_{27}NO_8S$: C, 56.76; H, 5.85; N, 3.01; S, 6.89. Found: C, 57.08; H, 5.89; N, 3.38; S, 6.98.

1L-(1,3,4/2,6)-1,2,3-Tri-O-acetyl-4-[(benzyloxycarbonyl)amino]-6-C-(p-tolylsulfonyloxymethyl)-1,2,3-cyclohexanetriol (10). — A solution of the *p*-tolylsulfonyl derivative **9** (21 g) in pyridine (200 mL) and acetic anhydride (100 mL) was stirred for 16 h at room temperature. The mixture was evaporated, and a solution of the residue in ethyl acetate was washed with 2M hydrochloric acid and saturated aqueous sodium hydrogencarbonate, and then evaporated. A 1:4 mixture (1 L) of ethyl ether and petroleum ether was added to the residue, and the mixture was refrigerated overnight to give the tri-*O*-acetyl derivative **10** (26.2 g) as crystals, m.p. 80–81°, $[\alpha]_D^{24} +55.5^\circ$ (*c* 1, methanol); 1H -n.m.r. ($CDCl_3$): δ 1.92 (s, 6 H), 1.95 (s, 3 H), 2.44 (s, 3 H), 3.93 (d, 2 H, *J* 6 Hz), 4.1–4.4 (m, 1 H), 4.7–5.5 (m, 3 H), 5.09 (s, 2 H), 7.35 (d, 2 H, *J* 8 Hz), 7.36 (s, 5 H), and 7.76 (d, 2 H, *J* 8 Hz).

Anal. Calc. for $C_{28}H_{33}NO_{11}S$: C, 56.84; H, 5.62; N, 2.37; S, 5.42. Found: C, 56.69; H, 5.72; N, 2.39; S, 5.13.

1L-(1,3,4/2,6)-1,2,3-Tri-O-acetyl-4-[(benzyloxycarbonyl)amino]-6-C-(iodomethyl)-1,2,3-cyclohexanetriol (11). — A solution of the 1,2,3-tri-*O*-acetyl-7-*O*-tosyl derivative **10** (20 g) and sodium iodide (6 g) in acetic anhydride (60 mL) was stirred for 30 min at 120–130°. After the mixture had cooled to room temperature, acetone was added. The resulting crystals were filtered off and washed with acetone. The filtrate and washings were combined and evaporated, and the residue was partitioned between ethyl ether and water. The organic layer was separated, washed with a mixture of saturated aqueous sodium hydrogencarbonate and 5% aqueous sodium thiosulfate (5:1), and evaporated. The residue was applied to a column of silica gel (400 mL) that was eluted with 4:1 toluene–ethyl acetate, and the eluate was evaporated. The residue was dissolved with heating in a small amount of ethyl ether. Petroleum ether was added and the solution was ice-cooled to give the iodomethyl derivative **11** (16.9 g) as crystals, m.p. 85–86°, $[\alpha]_D^{24} +49.5^\circ$ (*c* 1, methanol); 1H -n.m.r. ($CDCl_3$): δ 1.92 (s, 3 H), 1.97 (s, 3 H), 2.00 (s, 3 H), 3.01 (dd, 1 H, *J* 6, 10 Hz), 3.21 (dd, 1 H, *J* 3, 10 Hz), 4.15–4.4 (m, 1 H), 4.7–5.4 (m, 3 H), 5.09 (s, 2 H), and 7.37 (s, 5 H).

Anal. Calc. for $C_{21}H_{26}INO_8$: C, 46.08; H, 4.79; N, 2.56. Found: C, 46.57; H, 4.77; N, 2.51.

1L(1R)-(1,3,4/2)-Tri-O-acetyl-4-[(benzyloxycarbonyl)amino]-6-methylene-1,2,3-cyclohexanetriol (12a). — A solution of the iodomethyl derivative **11** (15 g) and silver fluoride (15 g) in pyridine (90 mL) was stirred for 3.5 h at 20–25°. The mixture was added to ethyl ether (1.5 L), and the mixture was stirred. The resulting precipitate was filtered off and washed with ethyl ether. The combined filtrate and washings were washed with a mixture of saturated aqueous sodium hydrogencarbonate and 5% aqueous sodium thiosulfate (5:1), and evaporated. The residue was applied to a column of silica gel (550 mL) that was eluted with 3:1 toluene–ethyl acetate. The eluate was evaporated to give a colorless syrup, which was dried under diminished pressure to give the 6-exomethylene derivative **12a** (11.6 g), $[\alpha]_D^{24}$

+23.0° (c 1, methanol); ν_{\max}^{KBr} 1744, 1717, 1538 cm^{-1} ; ^1H -n.m.r. (CDCl_3): δ 1.91 (s, 3 H), 2.00 (s, 3 H), 2.09 (s, 3 H), 2.47 (d, 2 H, J 4 Hz), 4.25–4.55 (m, 1 H), 4.7–5.5 (m, 6 H), 5.08 (s, 2 H), and 7.37 (s, 5 H).

Anal. Calc. for $\text{C}_{21}\text{H}_{25}\text{NO}_8$: C, 60.13; H, 6.01; N, 3.34. Found: C, 60.31; H, 6.13; N, 3.09.

1L(IR)-(1,3,4/2)-[(Benzyloxycarbonyl)amino]-6-methylene-1,2,3-cyclohexanetriol (12b). — To a solution of the tri-*O*-acetyl derivative **12a** (6.0 g) in ethanol (50 mL) was added 5M ammonium hydroxide (50 mL). The mixture was stirred for 4 h and kept for 4 days at room temperature. The mixture was evaporated, and 50% aqueous methanol (50 mL) was added to the residue. The mixture was refrigerated overnight to give the deacetylated exomethylene derivative **12b** (3.5 g) as crystals, m.p. 119–120°, $[\alpha]_{\text{D}}^{23} +36.5^\circ$ (c 1, methanol); ν_{\max}^{KBr} 1693 (C=O), 1515 cm^{-1} (–NHCO–); ^1H -n.m.r. ($\text{Me}_2\text{SO}-d_6 + \text{D}_2\text{O}$): δ 2.23 (dd, 1 H, J 4.5, 14 Hz), 2.54 (dd, 1 H, J 6, 14 Hz), 3.1–4.05 (m, 4 H), 4.91 (broad s, 1 H, vinyl-*H*), 5.13 (s, 3 H, vinyl-*H* and PhCH_2 -), and 7.48 (s, 5 H, C_6H_5 -).

Anal. Calc. for $\text{C}_{15}\text{H}_{19}\text{NO}_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.14; H, 6.34; N, 4.47.

1-(Bromomethyl)-6,7,8-trihydroxy-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (14a). — A solution of bromine (1.8 g) in methanol (20 mL) was added to a solution of the exomethylene derivative **12b** (2.9 g) in methanol (40 mL) dropwise at 0–5°, and the solution was stirred for 1 h at the same temperature. The mixture was evaporated, and the residue was partitioned between ethyl acetate and water. The water layer was separated, washed with ethyl acetate, and evaporated. The residue was chromatographed on a column of MCI Gel CHP20P resin (250 mL). The column was washed with water and eluted with a gradient of water–50% aqueous methanol. The eluate was concentrated to ~20 mL, and the concentrate was refrigerated overnight to give the bromomethyl cyclic carbamate **14a** (2.4 g) as crystals, m.p. 251–252° (dec.); $[\alpha]_{\text{D}}^{23} +6.4^\circ$ (c 1, dimethyl sulfoxide); ν_{\max}^{KBr} 1691 cm^{-1} (C=O); ^1H -n.m.r. ($\text{Me}_2\text{SO}-d_6$): δ 1.78 (dd, 1 H, J 2.5, 15 Hz, 9-*CH*), 1.97 (dd, 1 H, J 4, 15 Hz, 9-*CH*), 3.1–3.55 (m, 4 H), 3.67 (s, 2 H, – CH_2Br), 4.83–5.03 (m, 2 H, –OH \times 2), 5.17 (d, 1 H, J 6 Hz, –OH), and 7.41 (d, 1 H, J 4.5 Hz, –CONH-); ^{13}C -n.m.r. ($\text{Me}_2\text{SO}-d_6$): δ (from Me_4Si): 27.6(t), 38.1(t), 50.0(d), 74.1(d), 74.6(d), 75.1(d), 80.9(s), and 152.3(s).

Anal. Calc. for $\text{C}_8\text{H}_{12}\text{BrNO}_5$: C, 34.06; H, 4.29; Br, 28.33; N, 4.97. Found: C, 34.04; H, 4.15; Br, 28.32; N, 5.00.

6,7,8-Triacetoxy-1-(bromomethyl)-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (14b). — A solution of bromine (1.7 g) in methanol (20 mL) was added to a solution of the exomethylene derivative **12a** (4.2 g) in methanol (30 mL) at 5–10°, and the solution was stirred for 1.5 h at the same temperature. The mixture was evaporated, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 5% aqueous sodium thiosulfate and evaporated. A 1:1 mixture of ethyl ether–petroleum ether was added to the residue, and the mixture was refrigerated overnight to give the cyclic carbamate **14b** (3.3 g) as crystals, m.p. 122–123°

(decomp.), $[\alpha]_D^{24} +45.2^\circ$ (c 1, methanol); ν_{\max}^{KBr} 1759, 1747, 1712 cm^{-1} ; ^1H -n.m.r. ($\text{Me}_2\text{SO}-d_6$, at 400 MHz, with Me_4Si as internal standard): δ 1.97, 2.02, 2.06 (s, each 3 H, acetyl \times 3), 2.16 (dd, 1 H, J 4.4, 14.4 Hz, 9-CH), 2.37 (broad d, J 14.4 Hz, 9-CH), 3.49 and 3.70 (ABq, each 1 H, J 11.0 Hz, $-\text{CH}_2\text{Br}$), 3.73 (m, 1 H, 5-CH), 4.95 (dd, 1 H, J 3.1, 9.7 Hz, 6-CH), 5.15 (t, 1 H, J 9.7 Hz, 7-CH), 5.36 (d, 1 H, J 9.7 Hz, 8-CH), and 8.03 (d, 1 H, J 4.9 Hz, $-\text{CONH}-$); ^{13}C -n.m.r. ($\text{Me}_2\text{SO}-d_6$): δ (from Me_4Si): 20.4(q), 20.4(q), 20.8(q), 26.8(t), 35.7(t), 46.7(d), 70.4(d), 73.2(d), 74.1(d), 79.7(s), 151.0(s), 169.4(s), 169.5(s), and 169.7(s).

Anal. Calc. for $\text{C}_{14}\text{H}_{18}\text{BrNO}_8$: C, 41.19; H, 4.44; Br, 19.58; N, 3.43. Found: C, 41.17; H, 4.35; Br, 19.56; N, 3.33.

6,7,8-Triacetoxy-1-(acetoxymethyl)-3-oxo-2-oxa-4-azabicyclo[3.3.1]nonane (14c). — Silver acetate (500 mg) was added to a solution of the 1-(bromomethyl) derivative **14b** (500 mg) in *N,N*-dimethylformamide (10 mL), and the mixture was stirred for 10 h at 120–130°. The mixture was evaporated, and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was separated, washed with 2M hydrochloric acid and saturated aqueous sodium hydrogencarbonate, and evaporated. Addition of ethyl ether to the residue gave the 1-(acetoxymethyl) derivative **14c** (340 mg) as crystals. The m.p., $[\alpha]_D$, and i.r. and ^1H -n.m.r. spectra of **14c** were identical with those of **7b**.

Anal. Calc. for $\text{C}_{16}\text{H}_{21}\text{NO}_{10}$: C, 49.61; H, 5.46; N, 3.62. Found: C, 49.68; H, 5.39; N, 3.63.

1L(1S)-(1(1OH),2,4,5/1,3)-5-Amino-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (valiolamine; 1a). — (a) *From 7a.* Barium hydroxide (200 g) was added to a solution of the cyclic carbamate **7a** (50 g) in water (1.5 L). The mixture was heated for 3 h at 70–80° with stirring. The mixture was cooled to room temperature, and carbon dioxide gas was bubbled through the mixture. The resultant precipitate was filtered off and washed with water. The filtrate and washings were combined and applied to a column of Amberlite CG-50 resin (NH_4^+ , 1.6 L). The column was washed with water (1 L) and eluted with 0.2M ammonium hydroxide. The eluate was concentrated to ~200 mL and chromatographed on a column of Dowex 1 \times 2 resin (OH^- , 1.6 L) with water as the developing solvent. The eluate was concentrated and lyophilized to give **1a** (42.7 g) as a white solid, $[\alpha]_D^{25} +19.6^\circ$ (c 1, water); m/z 194 ($\text{M} + 1$) $^+$; ^1H -n.m.r. (D_2O): δ 1.80 (dd, 1 H, J 3.8, 15.5 Hz), 2.07 (dd, 1 H, J 3, 15.5 Hz), 3.4–3.6 (1 H), 3.55 (d, 1 H, J 10 Hz), 3.63 (2 H), 3.72 (dd, 1 H, J 4.2, 10 Hz), and 3.99 (t, 1 H, J 10 Hz); ^1H -n.m.r. (D_2O , at 400 MHz, with sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) as internal standard): δ 1.70 (dd, 1 H, J 3.9, 15.1 Hz, 6-CH_{ax}), 1.89 (dd, 1 H, J 2.9, 15.1 Hz, 6-CH_{eq}), 3.34 [q (apparent splitting pattern), 1 H, J 2.9, 3.9, 4.2 Hz, 5-CH], 3.43 (d, 1 H, J 9.5 Hz, 2-CH), 3.46 and 3.53 (ABq, each 1 H, J 11.2 Hz, $-\text{CH}_2\text{O}-$), 3.58 (dd, 1 H, J 4.2, 9.8 Hz, 4-CH), and 3.85 [t (apparent splitting pattern), J 9.5, 9.8 Hz, 3-CH]; ^{13}C -n.m.r. (D_2O): δ (from Me_4Si , reference 1,4-dioxane at 67.4): 33.5(t), 51.0(d), 66.3(t), 71.9(d), 74.5(d), 74.5(d), and 76.8(s).

Anal. Calc. for $\text{C}_7\text{H}_{15}\text{NO}_5 \cdot \text{H}_2\text{O}$: C, 39.80; H, 8.11; N, 6.63. Found: C, 39.94; H, 8.03; N, 6.67.

(b) *From 14a.* Barium hydroxide (1.0 g) was added to a suspension of the bromomethyl cyclic carbamate **14a** (200 mg). The suspension was stirred for 5 h at 60–70°. After cooling to room temperature, carbon dioxide gas was bubbled into the mixture. The resulting precipitate was filtered off, and washed with water. The combined filtrate and washings were applied to a column of Amberlite CG-50 resin (NH_4^+ , 150 mL) that was washed with water and then eluted with 0.1M ammonium hydroxide. The eluate was evaporated, and the residue was applied to a column of Dowex 1 \times 2 resin (OH^- , 200 mL) that was eluted with water, and the eluate was concentrated and then lyophilized to give **1a** (104 mg) as a white solid.

(c) *From 14b.* Barium hydroxide (2.5 g) was added to a suspension of the *O*-acetyl cyclic carbamate **14b** (500 mg) in water (50 mL), and the mixture was stirred for 3 h at 90–100°. The mixture was treated as described in method *b* to give **1a** (240 mg) as a white solid.

p-Toluenesulfonic acid salt of valioline. — A solution of **1a** (200 mg) and *p*-toluenesulfonic acid (210 mg) in water (5 mL) was evaporated. Ethanol (30 mL) was added to the residue and the solution refrigerated overnight to give the *p*-toluenesulfonic acid salt of **1a** (284 mg) as colorless needles, m.p. 193–195° (dec.), $[\alpha]_D^{24} + 8.2^\circ$ (c 1, water); ^1H -n.m.r. (D_2O): δ 2.06 (dd, 1 H, *J* 4, 16 Hz), 2.33 (dd, 1 H, *J* 2.5, 16 Hz), 2.60 (s, 3 H), 3.6–3.73 (m, 1 H), 3.67 (s, 2 H), 3.75–4.1 (m, 3 H), 7.58 (d, 2 H, *J* 8.5 Hz), and 7.94 (d, 2 H, *J* 8.5 Hz).

Anal. Calc. for $\text{C}_{14}\text{H}_{23}\text{NO}_8\text{S}$: C, 46.02; H, 6.34; N, 3.83; S, 8.77. Found: C, 46.09; H, 6.24; N, 3.80; S, 8.52.

1L-(1,3,4/2)-4-Amino-6-C-(hydroxymethyl)-5-cyclohexene-1,2,3-triol 3,4-carbamate (15). — *N*-(Benzyloxycarbonyl)valienamine (**4a**, 20 g) was dissolved in M sodium hydroxide (200 mL) and stirred for 2 h at room temperature. The mixture was adjusted to pH 5.5 with 2M hydrochloric acid, washed with ethyl ether, and evaporated. The residue was applied to a column (400 mL) of activated carbon that was washed with water and eluted with 50% aqueous methanol. The eluate was concentrated, lyophilized, and the residue crystallized from ethanol to give the 3,4-carbamate **15** (12 g); $\nu_{\text{max}}^{\text{KBr}}$ 1740 cm^{-1} (C=O); ^1H -n.m.r. (D_2O): δ 4.07 (t, 1 H, *J* 7.5 Hz), 4.25–4.6 (m, 3 H), 4.65–5.1 (m, 2 H), and 5.90–6.05 (m, 1 H).

Anal. Calc. for $\text{C}_8\text{H}_{11}\text{NO}_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.71; H, 5.48; N, 7.05.

1,7-O-Isopropylidene-1L-(1,3,4/2)-4-amino-6-C-(hydroxymethyl)-5-cyclohexene-1,2,3-triol 3,4-carbamate (16). — A solution of the carbamate **15** (10 g), 2,2-dimethoxypropane (20 mL), and *p*-toluenesulfonic acid (250 mg) in *N,N*-dimethylformamide (150 mL) was stirred for 2 h at 100°. After cooling to room temperature, Dowex 1 \times 2 resin (OH^- , ~50 mL) was added to the mixture. The mixture was stirred for 30 min. The resin was filtered off and washed with ethanol, and the combined filtrate and washings were evaporated. After azeotropic removal of the remaining *N,N*-dimethylformamide with toluene, the residue was dissolved in water and applied to a column of MCI CHP20P resin (400 mL). The column was washed with water and eluted with a gradient of water-methanol. The eluate was

concentrated and then lyophilized to give **16** (11.3 g), as a white solid; $\nu_{\text{max}}^{\text{KBr}}$ 1735 cm^{-1} (C=O); $^1\text{H-n.m.r.}$ (D_2O): δ 1.54 (s, 3 H), 1.77 (s, 3 H), 4.07 (t, 1 H, J 9 Hz), 4.35–5.1 (m, 5 H), and 5.77–5.90 (m, 1 H).

Anal. Calc. for $\text{C}_{11}\text{H}_{15}\text{NO}_5 \cdot 0.5 \text{H}_2\text{O}$: C, 52.80; H, 6.44; N, 5.60. Found: C, 52.85; H, 5.99; N, 5.55.

2-O-(Benzyloxycarbonyl)-1,7-O-isopropylidene-1L-(1,3,4/2)-4-amino-6-C-(hydroxymethyl)-5-cyclohexene-1,2,3-triol 3,4-carbamate (17). — Benzyl chloroformate (5.1 mL) and then triethylamine (3.1 mL) were added to a solution of **16** (4.8 g) in *N,N*-dimethylformamide (50 mL) previously cooled to -40 to -45° . The mixture was stirred for 2 h at -20° to -10° . The mixture was partitioned between cold, 2M hydrochloric acid (500 mL) and ethyl acetate (500 mL). The organic layer was separated, washed with water, and evaporated. The residue was applied to a column of silica gel (250 mL). The column was eluted with 1:1 toluene–ethyl acetate, and the eluate was concentrated. A 1:10 mixture (300 mL) of ether and petroleum ether was added to the concentrate and the solution was refrigerated to give the 2-*O*-benzyloxycarbonate **17** (4.3 g) as crystals; $\nu_{\text{max}}^{\text{KBr}}$ 1810, 1740 cm^{-1} (C=O); $^1\text{H-n.m.r.}$ (CDCl_3): δ 1.38 (s, 3 H), 1.47 (s, 3 H), 3.80 (t, 1 H, J 9 Hz), 4.0–4.5 (m, 3 H), 4.53 (d, 1 H, J 9 Hz), 4.6–4.9 (m, 1 H), 5.30 (s, 2 H), 5.73–5.87 (m, 1 H), and 7.25–7.55 (m, 5 H).

Anal. Calc. for $\text{C}_{19}\text{H}_{21}\text{NO}_7$: C, 60.79; H, 5.64; N, 3.37. Found: C, 60.68; H, 5.48; N, 3.51.

(1R)-(1-(CH₂OH),2,4,5/1,3)-5-Amino-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (epivaliolamine, 1b). — (a) *From 12a.* A solution of osmium tetroxide (2.4 g) in ethyl ether (20 mL) was added to a solution of **12a** (3.8 g) and pyridine (3 mL) in ethyl ether (50 mL) with cooling in an ice–water bath. The solution was stirred for 4 h and kept overnight at room temperature. The mixture was cooled for 2 h in an ice–water bath. The resulting precipitate was collected by filtration, washed with cold ethyl ether, and dried under diminished pressure. The precipitate (2.8 g) was dissolved in ethanol (50 mL) and water (100 mL), and then sodium sulfite (14 g) were added to the solution, which was then stirred for 20 h at room temperature. The resulting black precipitate was filtered off and washed with ethanol. The filtrate and washings were combined and evaporated, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with water and evaporated to give (1R)-(1(CH₂OH),2,4,5/1,3)-2,3,4-tri-*O*-acetyl-5-[(benzyloxycarbonyl)amino]-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (2.0 g) as an oil. Palladium black (500 mg) was added to a solution of the oil in 1:1:0.2 methanol–water–acetic acid (70 mL), and mixture was stirred in a stream of hydrogen for 2.5 h at room temperature. The catalyst was filtered off and washed with 50% aqueous methanol. The filtrate and washings were combined and evaporated. A solution of the residue in M sodium hydroxide (100 mL) was stirred for 3 h at room temperature, adjusted to pH 5 with 2M hydrochloric acid, and passed through a column of Amberlite CG-50 resin (NH_4^+ , 250 mL). The

column was washed with water and then eluted with 0.2M ammonium hydroxide. The eluate was concentrated and then lyophilized to give **1b** as a white solid (400 mg); $[\alpha]_D^{23} +17.5^\circ$ (c 1, water); m/z 194 ($M + 1$)⁺; ¹H-n.m.r. (D₂O, at 400 MHz, with DSS as the internal standard): δ 1.73 (dd, 1 H, J 4.1, 14.5 Hz, 6-CH_{ax}), 1.93 (dd, 1 H, J 6.6, 14.5 Hz, 6-CH_{eq}), 3.40 (dt, 1 H, J 4.1, 4.1, 6.6 Hz, 5-CH), 3.56 and 3.66 (ABq, each 1 H, J 11.6 Hz, -CH₂O-), 3.58 (d, 1 H, J 7.2 Hz, 2-CH), 3.76 (dd, 1 H, J 4.1, 7.2 Hz, 4-CH), and 3.99 (t, 1 H, J 7.2 Hz, 3-CH); ¹³C-n.m.r. (D₂O): δ (from Me₄Si, reference 1,4-dioxane at 67.4): 36.3(t), 47.2(d), 65.9(t), 72.4(d), 73.9(d), 75.7(d), and 76.2(s).

Anal. Calc. for C₇H₁₅NO₅ · H₂O: C, 39.80; H, 8.11; N, 6.63. Found: C, 40.25; H, 7.97; N, 6.40.

(b) *From 17.* A solution of bromine (1.8 g) in acetonitrile (20 mL) was added dropwise to a solution of **17** (3.7 g) in acetonitrile (60 mL) with cooling in an ice-water bath, and then the mixture was stirred for 5.5 h at the same temperature. The resulting precipitate was collected by filtration, and washed with a small amount of acetonitrile and ethyl acetate. Sodium borohydride (500 mg) was added to a solution of the precipitate (1.2 g) in 50% aqueous ethanol (20 mL) with cooling in an ice-bath. The mixture was stirred for 4 h at room temperature and concentrated. The concentrate was passed through a column of activated carbon (180 mL). The column was washed with water and eluted with 50% aqueous methanol. The eluate was concentrated, and barium hydroxide (2.0 g) was added to the concentrate (~20 mL). The mixture was boiled under reflux for 2 h, cooled to room temperature, whereupon carbon dioxide gas was bubbled through the mixture. The precipitate was filtered off and washed with water, and the filtrate and washings were combined and adsorbed onto a column of Amberlite CG-50 resin (NH₄⁺, 200 mL). The column was washed with water and eluted with 0.2M ammonium hydroxide. The eluate was concentrated and then lyophilized to give **1b** (120 mg) as a white solid.

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