Synthesis of Valiolamine and Its N-Substituted Derivatives AO-128, Validoxylamine G, and Validamycin G via Branched-Chain Inosose Derivatives[1]

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Novel synthetic routes to valiolamine (**1a**) and N-substituted valiolamine derivatives via branched-chain inosose derivatives are described. (1*S*)-(1(OH),2,4/1,3)-2,3,4-Tri-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-5-oxo-1,2,3,4-cyclohexanetetrol (**3**), a branched-chain inosose derivative prepared from D-glucose,[2] has been converted into **1a** via the ketoxime **7** followed by hydrogenation. N-Substituted valiolamine derivatives having strong α-D-glucosidase inhibitory activity have been synthesized by the direct reductive amination of the branched-chain inosose derivative **3** with an appropriate amino compound to construct the N-substituent moiety, followed by removal of the *O*-benzyl protecting group. The stereoselective preparation of two representative derivatives, *N*-[2-hydroxy-1-(hydroxymethyl)ethyl]valiolamine (**2a**, AO-128)[3] and *N*-[(1*R*,2*R*)-2-hydroxycyclohexyl]valiolamine (**2b**)[3] is described. Application of branched-chain inosose derivatives **3** and **23** to the total synthesis of natural N-substituted valiolamine derivatives validoxylamine G (**5a**) and validamycin G (**6a**) is also described.

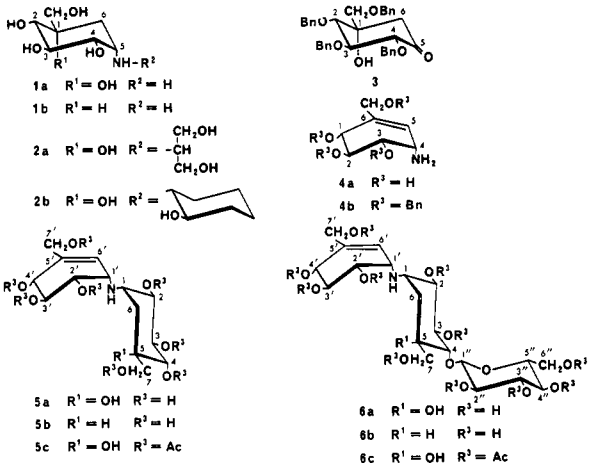
Introduction

In the course of the development program of *N*-[2-hydroxy-1-(hydroxymethyl)ethyl]valiolamine (**2a**, AO-128)[3] for the treatment of diabetes, the ^{14}C-labeled compound of AO-128 was required for adsorption, metabolism, and excretion studies. In this case, high specific activity of the ^{14}C-labeled compound was essential because of the high potency of AO-128, i.e., low administration doses. However, incorporation of labeled compound into valienamine and valiolamine by a feeding experiment with ^{14}C-labeled D-glucose using *Streptomyces hygroscopicus* subsp. *limoneus* was insufficient. These considerations prompted a search for a new approach to the synthesis of N-substituted valiolamine derivatives starting from D-glucose. In this report, we first describe the practical synthesis of valiolamine (**1a**) and AO-128 (**2a**) via (1*S*)-(1(OH),2,4/1,3)-2,3,4-tri-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-5-oxo-1,2,3,4-cyclohexanetetrol (**3**), a branched-chain inosose derivative which can be stereospecifically synthesized from D-glucose.[2]

As previously reported,[3] when the synthons to construct the N-substituents are available as the corresponding aldehydes, ketones, epoxides, or halides, **1a** is the key compound for the synthesis of N-substituted valiolamine derivatives. On the other hand, the branched-chain inosose derivative **3** is a useful synthon for preparing the branched-chain cyclitol moiety of N-substituted valiolamine derivatives, especially when the synthons to construct the N-substituents are conveniently available as amines.

As an example, *N*-[(1*R*,2*R*)-2-hydroxycyclohexyl]valiolamine (**2b**),[3] an N-substituted valiolamine derivative having strong α-D-glucosidase inhibitory activity, was first prepared as a mixture of two diastereomers, **2b** and its biologically much less active (1*S*,2*S*) isomer, by reaction of **1a** with cyclohexene oxide, followed by chromatographic separation of the diastereomeric pair. Thus, **2b** has been synthesized stereospecifically by reductive N-alkylation of (1*R*,2*R*)-2-aminocyclohexanol with the branched-chain inosose derivative **3**.

Chart I



This synthetic approach to N-substituted valiolamine derivatives using branched-chain inosose derivatives has also been applied to the total synthesis of naturally occurring validoxylamine G (**5a**) and validamycin G (**6a**).[4] These two compounds are validamycin congeners having valiolamine (**1a**) as a constituent, unlike validoxylamine A (**5b**) and validamycin A (**6b**) which have validamine (**1b**) as a constituent. Validoxylamine G (**5a**) and validamycin G (**6a**) have been synthesized by reductive N-alkylation of tetra-*O*-benzylvalienamine (**4b**) with the corresponding branched-chain inosose derivatives **3** and **23**, all of which can be synthesized from D-glucose. Details of the results are reported herein.

Results and Discussion

Synthesis of Valiolamine. The branched-chain inosose derivative **3** was first converted to the ketoxime **7** with hydroxylamine in methanol. Next, hydrogenation of **7** by catalytic reduction with Raney nickel under pressure (3.5 kg/cm^2) at room temperature and removal of the *O*-benzyl protecting groups with palladium black and formic acid

(1) Part of this work was presented in Sept 1989 at the 198th National Meeting of the American Chemical Society. See: *Abstracts of Papers*. 198th National Meeting of the American Chemical Society: Washington, DC, 1989; Abstr. CARB 19.

(2) (a) Fukase, H.; Horii, S. *J. Org. Chem.*, the preceding paper in this issue. (b) Horii, S.; Fukase, H. *Eur. Pat. Appl.* EP 260,121, 1988 (*Chem. Abstr.* **1988**, *109*, 129587).

(3) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; N. Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. AO-128 is the preclinical study code number of **2a**.

(4) Kameda, Y.; Asano, N.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. *J. Antibiotics* **1986**, *39*, 1491.

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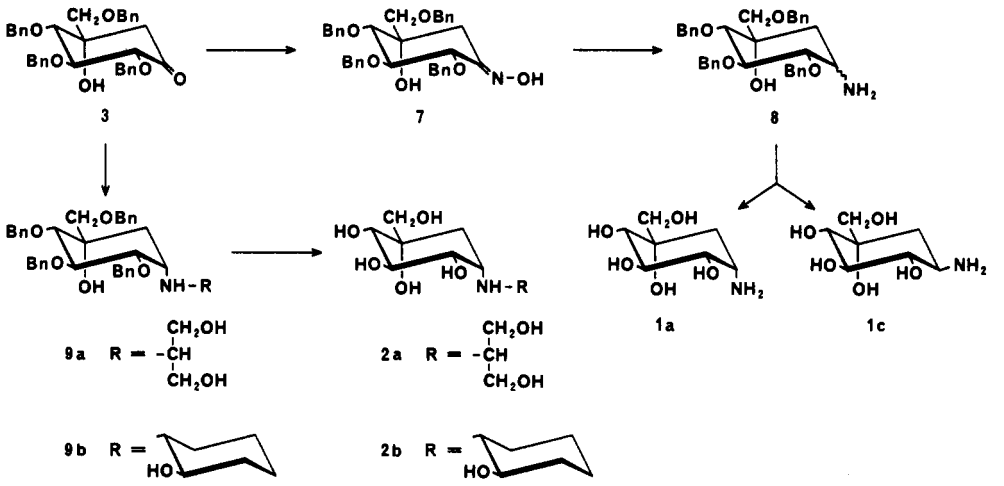
Scheme I



gave the branched-chain aminocyclitol as a mixture of the two epimers, which were separated into **1a** and **1c** in the approximate ratio of 16:1 by ion-exchange resin chromatography. The chief reaction product **1a** was identical to naturally occurring valiolamine, and the *R* configuration at the chiral center bearing amino group of the byproduct **1c** was confirmed by ^{1}H NMR spectral data [δ 2.95 ($J_{5,6eq}$ 4.0 Hz, $J_{4,5}$ 9.4 Hz, $J_{5,6ax}$ 12.6 Hz)].

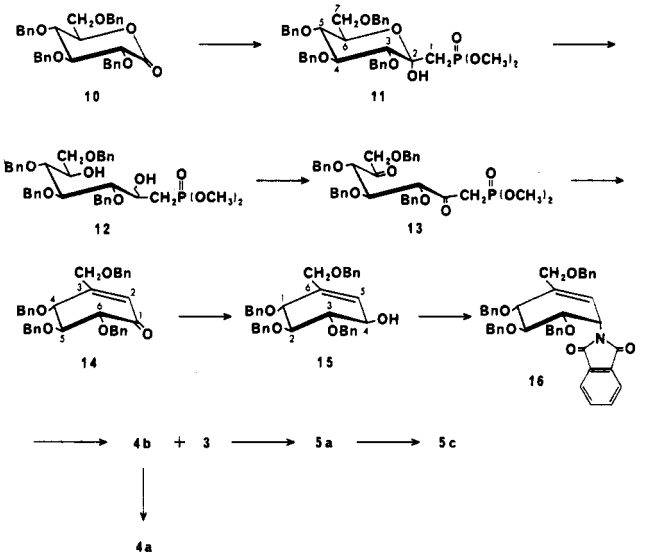
Synthesis of *N*-[2-Hydroxy-1-(hydroxymethyl)-ethyl]valiolamine (AO-128). *N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]valiolamine (AO-128, **2a**) was synthesized with high stereoselectivity by direct reductive amination of the branched-chain inosose **3** with 2-amino-1,3-propanediol and then removal of the *O*-benzyl protecting group. The epimer of **2a** was not found in the reaction mixture. This result can be explained on the basis that attack by the reducing agent occurs on the less-hindered side of the intermediate Schiff base.

The ^{14}C-labeled version of AO-128 (**2a**) has also been successfully synthesized from [U-^{14}C]-D-glucose by this method, and this labeled compound will contribute to the further clarification of the effectiveness and safety of AO-128.

Synthesis of *N*-[(1*R*,2*R*)-2-Hydroxycyclohexyl]valiolamine. To further demonstrate the versatility of this synthetic method, we have prepared *N*-[(1*R*,2*R*)-2-hydroxycyclohexyl]valiolamine (**2b**). As expected, reductive amination of the branched-chain inosose derivative **3** with (1*R*,2*R*)-2-aminocyclohexanol followed by removal of the protecting groups gave stereospecifically **2b**, $[\alpha]^{24}_D$ −41.5° (*c* 1, H_2O), −21.7° (*c* 1, 0.1N HCl).

Synthesis of Tetra-*O*-benzylvalienamine from D-Glucose.[5] Tetra-*O*-benzylvalienamine (**4b**) has been synthesized via the branched unsaturated inosose derivative **14**,[6] which was synthesized by an intramolecular Horner–Emmons reaction[7] starting from tetra-*O*-benzyl-D-glucono-1,5-lactone (**10**) which is readily available from D-glucose.

Scheme II



As the first step, **10** was treated with 2 equiv of lithium dimethyl methylphosphonate to yield the (dimethoxyphosphoryl)heptulopyranose derivative **11**. Direct oxidation of the C-6 hydroxyl group of the heptulopyranose derivative **11** proved difficult because the hydroxyl group is blocked by pyranose ring formation. Therefore, before oxidation, the pyranose ring of the heptulose derivative **11** was reductively opened with sodium borohydride ($NaBH_4$) to give the heptitol derivative **12**. The newly formed C-2 and released C-6 hydroxyl groups of **12** were oxidized with a reagent combination of DMSO, trifluoroacetic anhydride (TFAA), and Et_3N. The intramolecular cyclization reaction of the resulting 2,6-heptodiulose derivative **13** was accomplished with potassium carbonate in the presence of 18-crown-6 to give the branched unsaturated inosose derivative **14**.

Next, the oxo group of **14** was converted to the axial amino group to give valienamine (**4a**) in the following manner. The α,β-unsaturated keto group of **14** was reduced stereoselectively to an allylic equatorial secondary hydroxyl group with $NaBH_4$/cerous chloride[8] in ethanol, cooling with a dry ice–acetone bath.

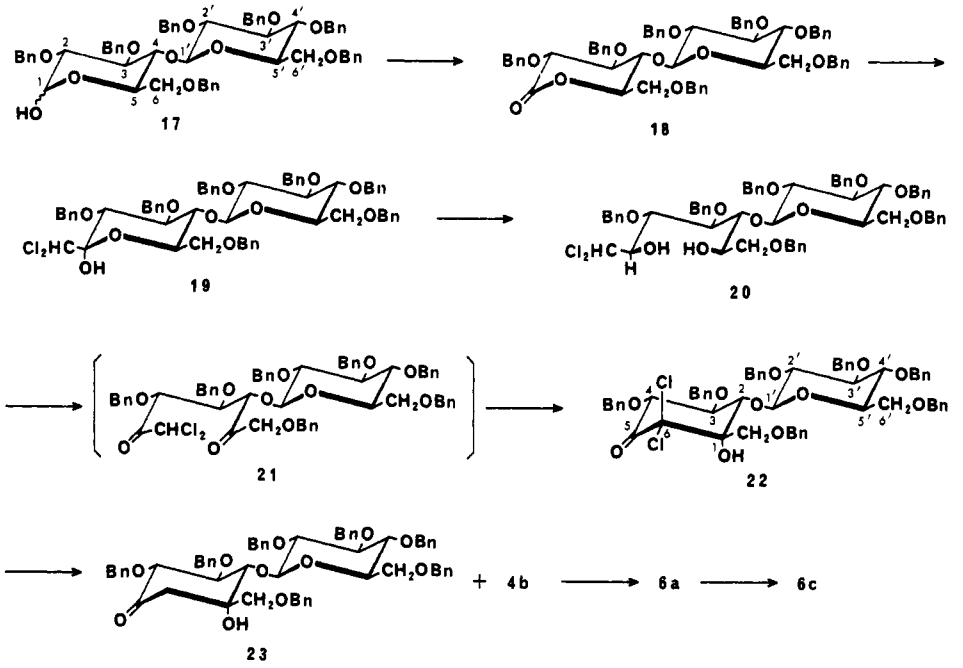
(5) The primary experimental work of this part was disclosed in the following patent applications: Horii, S.; Fukase, H. (Takeda Chem. Ind. Ltd.) *Jpn. Pat. Appl.* JP 63-119438, 1988 (Filed: May 14, 1986; *Eur. Pat. Appl.* EP 240,175; *Chem. Abstr.* **1988**, *109*, 55166h).

(6) Synthesis of the branched unsaturated inosose derivative **14** by an intramolecular Horner–Emmons reaction starting from an appropriately protected D-glucose diethyl dithioacetal was published before the disclosure of our patent:[5] Paulsen, H.; von Deyn, W. *Liebigs Ann. Chem.* **1987**, 125 (Received for publication: July 18, 1986).

(7) (a) Lim, M.-I.; Marquez, V. E. *Tetrahedron Lett.* **1983**, *24*, 5559. (b) Altenbach, H.-J.; Holzapfel, W.; Smerat, G.; Finkler, S. H. *Tetrahedron Lett.* **1985**, *26*, 6329.

(8) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J. L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (c) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269. (d) Elliot, J.; Warren, S. *Tetrahedron Lett.* **1986**, *27*, 645.

Scheme III

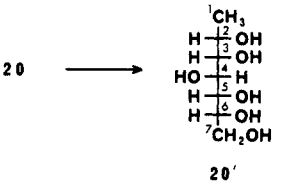


The resulting branched unsaturated inositol derivative **15** was converted to the phthalimido derivative **16**, employing a Mitsunobu reaction which proceeded with complete inversion of the configuration; namely, the free hydroxyl group at the allylic position was replaced with a phthalimido group using the DEAD/triphenylphosphine (Ph_3P) system.[9] Removal of the phthaloyl group of the phthalimido derivative **16** with hydrazine and subsequent removal of the *O*-benzyl protecting groups with sodium in liquid ammonia gave the unsaturated pseudoamino sugar which was identical to naturally occurring valienamine (**4a**). In contrast, reduction of the oxime of the unsaturated inosose derivative **14** with $LiAlH_4$ gave a complicated reaction mixture, and reduction of the oxime with $NaBH_4$ in the presence of molybdenum trioxide[10] gave the epimer at the asymmetric center bearing amino group of valienamine in a very low yield (5%), but the formation of valienamine was not detected in the reaction mixtures obtained by this method.

Synthesis of Validoxylamine G. Tetra-*O*-benzylvalienamine (**4b**) and the branched-chain inosose derivative **3** were coupled to yield octa-*O*-benzylvalidoxylamine G by a reductive N-alkylation reaction with sodium cyanoborohydride ($NaBH_3CN$). Next, deprotection of the benzyl ethers was accomplished with sodium in liquid ammonia to give validoxylamine G (**5a**), but only in 10% yield. Identification of the synthetic validoxylamine G was accomplished by comparison of the octa-*O*-acetate **5c** with the octa-*O*-acetate of the naturally occurring material. On the other hand, reductive N-alkylation of the tetra-*O*-benzylvaliolamine with the branched-chain unsaturated inosose derivative **14** gave a complicated reaction mixture, and the desired octa-*O*-benzylvalidoxylamine G was not found in the reaction mixture.

Synthesis of (1*S*)-(1(OH),2,4/1,3)-3,4-Di-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-2-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-5-oxo-1,2,3,4-cyclohexanetetrol from D-Cellobiose. Hepta-*O*-benzyl-D-cellobiose (**17**)[11] was oxidized to hepta-*O*-benzyl-4-*O*-(β-D-glucopyranosyl)-D-glucono-1,5-lactone (**18**) with a reagent combination of DMSO and acetic anhydride. The D-glucono-1,5-lactone derivative **18** was lengthened by one carbon with dichloromethyl carbanion, which was generated from dichloromethane and LDA, to yield the 1-*C*-(dichloromethyl) derivative **19**. The 1-*C*-(dichloromethyl)-α-D-glucopyranose moiety of the disaccharide **19** was converted to a branched inosose moiety to give the β-D-glucopyranosyl-(branched dichloroinosose) derivative **22**. First, the pyranose ring of the 1-*C*-(dichloromethyl)-D-glucopyranose moiety of **19** was opened by reduction with $NaBH_4$ to give the 4-*O*-(β-D-glucopyranosyl)-1-deoxy-1,1-dichloroheptitol derivative **20**. This reduction reaction proceeded stereoselectively, and the resulting heptitol derivative was exclusively the D-*glycero*-D-*gulo*-heptitol derivative **20**.

The configuration of the newly formed carbinol chiral center of the dichloroheptitol moiety was determined to be *R* by converting the dichloroheptitol moiety to 1-deoxy-D-*glycero*-D-*gulo*-heptitol (**20′**),[2a,12] by dechlorination with Bu_3SnH/AIBN, removal of the benzyl protecting groups by catalytic transfer hydrogenation with palladium black and formic acid, and then acid hydrolysis of the resulting glycoside.



The two free hydroxyl groups of the dichloroheptitol moiety of **20** were oxidized to oxo groups with a reagent combination of DMSO, TFAA, and Et_3N to give the diketo derivative **21**. An attempt to purify the resulting unstable compound by silica gel chromatography with toluene/ethyl acetate (19:1) was not successful but afforded directly the

(9) Hayashida, M.; Sakairi, N.; Kuzuhara, H. *Carbohydr. Res.* **1986**, *154*, 115.
(10) Ipaktschi, J. *Chem. Ber.* **1984**, *117*, 856.
(11) Koto, S.; Morishima, N.; Irisawa, T.; Hashimoto, Y.; Yamazaki, M.; Zen, S. *Nippon Kagaku Kaishi* (*J. Chem. Soc. Jpn.*) **1982**, 1651.
(12) Zissis, E.; Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1951**, *73*, 4714.

desired hepta-*O*-benzyl derivative of 2-*O*-(β-D-glucopyranosyl)-1-*C*-(hydroxymethyl)-6,6-dichloro-5-oxo-1,2,3,4-cyclohexanetetrol (**22**) via an intramolecular aldol condensation of the diketo derivative **21** on contact with the silica gel.

The branched dichloroinosose derivative **22** was subjected to a reductive dehalogenation reaction with Bu_3SnH/AIBN to give the β-D-glucopyranosyl-(branched inosose) derivative **23**. The axial position of the tertiary hydroxyl group of **23** was ascertained by the long-range spin–spin couplings (J 2.0 Hz)[13] between the tertiary hydroxyl proton and the axial proton on the methylene carbon of the cyclohexyl moiety, which were in accord with the corresponding signals of the branched-chain inosose derivative **3**.[2]

Synthesis of Validamycin G. In a manner similar to that used in the synthesis of validoxylamine G (**5a**), the β-D-glucopyranosyl-(branched-chain inosose) derivative **23** and tetra-*O*-benzylvalienamine (**4b**) were coupled by a reductive *N*-alkylation reaction with $NaBH_3CN$, followed by removal of the *O*-benzyl protecting groups with sodium in liquid ammonia, to give validamycin G (**6a**), but only in 6% yield. The purified product exhibited spectral and physical properties in accord with those reported for the natural product. The identity was further confirmed by comparison of the undeca-*O*-acetate **6c** of the synthetic validamycin G with that of the naturally occurring one. The low yields of **5a** and **6a** are attributable to carbon–nitrogen bond cleavage of the allylic amine moiety under the condition of debenzylation with sodium in liquid ammonia. This is thought to be the case since valiolamine (**1a**) and β-D-glucopyranosylvaliolamine were produced concomitantly as degradation products by the debenzylation of *O*-benzylvalidoxylamine G and *O*-benzylvalidamycin G, respectively.

The product formed by reductive N-alkylation of tetra-*O*-benzylvalienamine (**4b**) with the corresponding inosose derivatives **3** and **23** was almost completely a single stereoisomer, and the configuration of the formed carbon–nitrogen bond is identical to that of natural validoxylamine G (**5a**) and validamycin G (**6a**).

Experimental Section

Melting points are uncorrected. Thin-layer chromatography (TLC) was performed on precoated Kieselgel F_{254} plates (Merck) with *n*-PrOH/AcOH/H_2O (4:1:1), unless otherwise specified. Chromatography columns of silica gel were prepared with Kieselgel (70–230 mesh). Column chromatography was monitored by refractive index, if necessary. Ratios for mixtures of solvents are expressed by volume (v/v), unless otherwise indicated. Organic solutions were dried over anhydrous sodium sulfate before evaporation, if necessary. Solutions were evaporated under reduced pressure using a rotary evaporator.

(1*S*)-(1(OH),2,4/1,3)-2,3,4-Tri-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-5-(hydroxyimino)-1,2,3,4-cyclohexanetetrol (7). To a solution of the inosose derivative **3** (5.0 g, 9 mmol) in MeOH (100 mL) were added hydroxylamine hydrochloride (10.0 g) and AcONa (5.0 g). The mixture was stirred for 4 h at room temperature and then concentrated. The residue was partitioned between EtOAc (200 mL) and H_2O (100 mL) with stirring. The organic layer was washed with 2 N HCl and saturated aqueous $NaHCO_3$ and then evaporated. The residue was chromatographed on a column of silica gel (400 mL) with toluene/EtOAc (4:1). The eluate was concentrated to give the hydroxyimino derivative **7** (4.85 g, 94%) as a colorless syrup: $[\alpha]^{22}_D$ +61.7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (1 H, dd, *J* 1.5, 15.2 Hz, 6-Hax), 2.63 (1 H, d, *J* 1.5 Hz, 1-OH), 3.25 and 3.55 (each 1 H, ABq, *J* 8.7 Hz, $-CH_2O-$), 3.30 (1 H, d, *J* 15.2 Hz, 6-Heq), 3.81 (1 H, d, *J* 8.4 Hz, 2-H), 3.98 (1 H, t*, *J* 8.2, 8.4 Hz, 3-H), 4.11 (1 H, d, *J* 8.2 Hz, 4-H), 7.81 (1 H, br s, =NOH) (*apparent splitting pattern). Anal. Calcd for $C_{35}H_{37}NO_6$: C, 74.05; H, 6.57; N, 2.47. Found: C, 73.77; H, 6.62; N, 2.72.

(1*S*)-(1(OH),2,4,5/1,3)-5-Amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (Valiolamine, 1a) and (1*S*)-(1-(OH),2,4/1,3,5)-5-Amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (1c). To a solution of the hydroxyimino derivative **7** (4.5 g, 7.9 mmol) in MeOH was added Raney Ni (1.0 g). The mixture was hydrogenated for 5 h at room temperature at a pressure of 3.5–4 kg/cm^2. The mixture was filtered, and the catalyst was washed with MeOH. The filtrate and the washings were combined and concentrated to give *O*-benzylaminocyclitol as a syrup. The syrup was chromatographed on a column of silica gel (200 mL) with $CHCl_3$/MeOH (20:1) to give 2,3,4-tri-*O*-benzyl-5-amino-1-*C*-[(benzyloxy)methyl]-1,2,3,4-cyclohexanetetrol (**8**, 3.8 g, a mixture of tetra-*O*-benzylvaliolamine and a very small amount of its C-5 epimer) as a colorless syrup. For the NMR spectroscopic characterization of the major product, aliquots were purified by repeated chromatography on silica gel ($CHCl_3$/MeOH (20:1)) to give pure tetra-*O*-benzylvaliolamine as a colorless syrup.

Tetra-*O*-benzylvaliolamine: ^1H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.76 (1 H, dd, *J* 2.6, 14.5 Hz, 6-Hax), 1.80 (1 H, dd, *J* 2.5, 14.5 Hz, 6-Heq), 3.22 and 3.54 (each 1 H, ABq, *J* 8.6 Hz, $-CH_2O-$), 3.54 (1 H, dd, *J* 4.2, 9.6 Hz, 4-H), 3.61 (1 H, d, *J* 9.6 Hz, 2-H), 3.61 (1 H, q*, *J* 2.5, 2.6, 4.2 Hz, 5-H), 4.18 (1 H, t, *J* 9.6 Hz, 3-H); 4.40 (2 H, s), 4.60 (1 H, d, *J* 11.1 Hz), 4.66 (1 H, d, *J* 11.7 Hz), 4.72 (1 H, d, *J* 11.7 Hz), 4.86 (1 H, d, *J* 10.7 Hz), 4.92 (1 H, d, *J* 11.1 Hz) and 4.93 (1 H, d, *J* 10.7 Hz) ($PhCH_2-$ × 4); 7.26–7.33 (20 H, m, C_6H_5- × 4) (*apparent splitting pattern). Anal. Calcd for $C_{35}H_{39}NO_5$: C, 75.92; H, 7.10; N, 2.53. Found: C, 75.83; H, 7.29; N, 2.55.

To a solution of **8** (3.8 g, 5.8 mmol) in 90% formic acid/MeOH (1:19, 200 mL) was added Pd-black (1.0 g). The mixture was stirred for 20 h at room temperature under N_2. After filtering off the catalyst and washing with MeOH/H_2O (1:1), the filtrate and the washings were combined and concentrated. The residue was chromatographed on a column of Amberlite CG-50 (NH_4^+, 200 mL). The column was washed with H_2O and then eluted with 0.1 N ammonium hydroxide to separate the earlier eluted fraction containing the C-5 epimer of valiolamine (the minor product) and the later eluted fraction containing valiolamine (the major component). Each fraction was subjected to additional chromatographic purification on a column of Dowex 1 × 2 (OH^-, 150 mL) with elution of H_2O to give valiolamine (**1a**, 1.1 g, 64%) and its C-5 epimer (**1c**, 72 mg, 4%).

1a: $[\alpha]^{25}_D$ +19.6° (*c* 1, H_2O); ^1H NMR (D_2O, 300 MHz) δ 1.68 (1 H, dd, *J* 3.8, 15.5 Hz, 6-Hax), 1.88 (1 H, dd, *J* 2.9, 15.5 Hz, 6-Heq), 3.33 (1 H, q*, *J* 2.9, 3.8, 4.2 Hz, 5-H), 3.41 (1 H, d, *J* 9.5 Hz, 2-H), 3.44 and 3.52 (each 1 H, ABq, *J* 11.3 Hz, $-CH_2O-$), 3.57 (1 H, dd, *J* 4.2, 9.9 Hz, 4-H), 3.83 (1 H, t*, *J* 9.5, 9.9 Hz, 3-H) (*apparent splitting pattern); TLC R_f 0.30. Anal. Calcd for $C_7H_{15}NO_5 \cdot H_2O$: C, 39.81; H, 8.11; N, 6.63. Found: C, 39.89; H, 8.18; N, 6.56.

1c: $[\alpha]^{24}_D$ −23.2° (*c* 0.5, H_2O); ^1H NMR (D_2O, 300 MHz) δ 1.45 (1 H, t*, *J* 12.6, 14.1 Hz, 6-Hax), 1.91 (1 H, dd, *J* 4.0, 14.1 Hz, 6-Heq), 2.95 (1 H, ddd, *J* 4.0, 9.4, 12.6 Hz, 5-H), 3.14 (1 H, t, *J* 9.4 Hz, 4-H), 3.44 (1 H, d, *J* 9.4 Hz, 2-H), 3.49 and 3.58 (each 1 H, ABq, *J* 11.5 Hz, $-CH_2O-$), 3.57 (1 H, t, *J* 9.4 Hz, 3-H) (*apparent splitting pattern); TLC R_f 0.32. Anal. Calcd for $C_7H_{15}NO_5 \cdot H_2O$: C, 39.81; H, 8.11; N, 6.63. Found: C, 40.05; H, 7.84; N, 6.71.

(1*S*)-(1(OH),2,4,5/1,3)-2,3,4-Tri-*O*-benzyl-5-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-1-*C*-[(benzyloxy)methyl]-1,2,3,4-cyclohexanetetrol (9a). To a solution of the inosose derivative **3** (4.0 g, 7.2 mmol) and 2-amino-1,3-propanediol (2.0 g, 22 mmol) in MeOH (20 mL) was added $NaBH_3CN$ (1.0 g, 16 mmol) with stirring. Stirring was continued for 16 h at room temperature. The reaction mixture was concentrated, and the residue was partitioned between EtOAc (150 mL) and H_2O (100 mL). The organic layer was separated, washed with 1% (w/v) aqueous phosphoric acid solution and saturated aqueous $NaHCO_3$, and then concentrated. The residue was chromatographed on a column of silica gel (100 mL) with EtOAc to give **9a** (3.4 g, 75%) as a colorless syrup: $[\alpha]^{22}_D$ +30.0° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.63 (1 H, dd, *J* 2.7, 15.1 Hz, 6-Hax), 1.91 (1 H, dd, *J* 3.0, 15.1 Hz, 6-Heq), 2.73–2.80 (1 H, m, $-CH(CH_2OH)_2$),

(13) Meinwald, J.; Lewis, A. *J. Am. Chem. Soc.* **1961**, *83*, 2769.

3.20 and 3.54 (each 1 H, ABq, J 8.6 Hz, 7-H), 3.39 (1 H, q*, J 2.7, 3.0, 4.2 Hz, 5-H), 4.12 (1 H, t, J 9.6 Hz, 3-H) (*apparent splitting pattern). Anal. Calcd for $C_{38}H_{45}NO_7$: C, 72.70; H, 7.23; N, 2.23. Found: C, 72.43; H, 7.27; N, 2.31.

(1*S*)-(1(OH),2,4,5/1,3)-5-[[2-Hydroxy-1-(hydroxymethyl)-ethyl]amino]-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (AO-128, 2a). To a solution of the tetra-*O*-benzyl derivative **9a** (3.0 g, 4.8 mmol) in 90% formic acid/MeOH (1:19, 60 mL) was added Pd-black (0.5 g). The mixture was stirred under N_2 overnight at room temperature. The solid was removed by filtration and washed with MeOH/H_2O (1:1). The filtrate and the washings were combined and concentrated. The residue was chromatographed on a column of Dowex 50W × 8 (H^+, 250 mL). The column was washed with H_2O and then eluted with 0.5 N ammonium hydroxide. The eluate was concentrated, and the residue was chromatographed on a column of Amberlite CG-50 (NH_4^+, 400 mL) with H_2O. The eluate was concentrated, and EtOH (50 mL) was added to the residue. The mixture was boiled for about 15 min and then was allowed to stand overnight in a refrigerator to give AO-128 (**2a**, 1.2 g, 94%) as colorless crystals: mp 162–163 °C; $[\alpha]^{25}_D$ +26.2° (c 1, H_2O); ^1H NMR (D_2O, 400 MHz) δ 1.50 (1 H, dd, J 2.9, 15.3 Hz, 6-Hax), 2.05 (1 H, dd, J 3.3, 15.3 Hz, 6-Heq), 2.86 (1 H, m, $-CH(CH_2OH)_2$), 3.38 (1 H, dt*, J 2.9, 3.3, 4.2 Hz, 5-H), 3.41 (1 H, d, J 9.5 Hz, 2-H), 3.49 and 3.52 (each 1 H, ABq, J 11.4 Hz, 7-H), 3.59 (dd, J 6.6, 11.5 Hz) and 3.66 (dd, J 4.9, 11.5 Hz) (each 1 H, $-CH_2O-$), 3.69 (1 H, dd, J 4.2, 9.8 Hz, 4-H), 3.64 (dd, J 3.8, 11.7 Hz) and 3.71 (dd, J 5.1, 11.7 Hz) (each 1 H, $-CH_2O-$), 3.83 (1 H, t*, J 9.5, 9.8 Hz, 3-H) (*apparent splitting pattern); ^{13}C NMR (D_2O, 25.2 MHz) δ 30.3 (t), 55.2 (d), 57.4 (d), 59.4 (t), 62.9 (t), 65.9 (t), 72.8 (d), 73.8 (d), 74.7 (d), 76.8 (s); TLC R_f 0.29. Anal. Calcd for $C_{10}H_{21}NO_7$: C, 44.94; H, 7.92; N, 5.24. Found: C, 44.86; H, 7.88; N, 5.11.

(1*S*)-(1(OH),2,4,5/1,3)-2,3,4-Tri-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-5-[[(1*R*,2*R*)-2-hydroxycyclohexyl]amino]-1,2,3,4-cyclohexanetetrol (9b). To a solution of **3** (1.0 g, 1.8 mmol) and (1*R*,2*R*)-2-aminocyclohexanol (0.5 g, 4.3 mmol) in AcOH/MeOH (1:19, 20 mL) was added $NaBH_3CN$ (250 mg, 4 mmol) with stirring. Stirring was continued for 10 h at room temperature. The reaction mixture was concentrated, and the residue was partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was separated, washed with H_2O, and then concentrated. The residue was chromatographed on a column of silica gel (150 mL) with toluene/EtOAc (1:1) to give **9b** (895 mg, 76%) as a colorless syrup: $[\alpha]^{24}_D$ +39.1° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.1–1.35 (4 H, m), 1.55–1.75 (2 H, m) and 1.95–2.2 (2 H, m) ($-CH_2-$ × 4); 1.61 (1 H, dd, J 2.9, 15.1 Hz, 6-Hax), 2.02 (1 H, dd, J 2.7, 15.1 Hz, 6-Heq), 2.29 (1 H, ddd, J 3.7, 9.1, 11.1 Hz, –CHN–), 3.20 and 3.55 (each 1 H, ABq, J 8.6 Hz, $-CH_2O-$), 3.20–3.30 (1 H, m, –CH(OH)–), 3.39 (1 H, q*, J 2.7, 2.9, 4.3 Hz, 5-H), 3.62 (1 H, dd, J 4.3, 9.7 Hz, 4-H), 3.66 (1 H, d, J 9.7 Hz, 2-H), 4.11 (1 H, t, J 9.7 Hz, 3-H) (*apparent splitting pattern). Anal. Calcd for $C_{41}H_{49}NO_6$: C, 75.55; H, 7.58; N, 2.15. Found: C, 75.94; H, 7.76; N, 2.06.

(1*S*)-(1(OH),2,4,5/1,3)-[[(1*R*,2*R*)-2-Hydroxycyclohexyl]-amino]-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (2b). To a solution of **9b** (800 mg, 1.2 mmol) in 90% formic acid/MeOH (1:19, 20 mL) was added Pd-black (100 mg). The mixture was stirred under N_2 overnight at room temperature. The solid was removed by filtration and washed with MeOH/H_2O (1:1). The filtrate and the washings were combined and concentrated. The residue was chromatographed on a column of Dowex 50W × 8 (H^+, 150 mL). The column was washed with H_2O and then eluted with 0.5 N ammonium hydroxide. The eluate was concentrated, and the residue was chromatographed on a column of Amberlite CG-50 (NH_4^+, 150 mL) with H_2O. The eluate was concentrated and lyophilized to give *N*-[(1*R*,2*R*)-2-hydroxycyclohexyl]valiolamine (**2b**, 295 mg, 90%) as a white solid: $[\alpha]^{24}_D$ –41.5° (c 1, H_2O), –21.7° (c 1, 0.1 N HCl); ^1H NMR (D_2O, 300 MHz) δ 1.10–1.40 (4 H, m), 1.62–1.74 (2 H, m), 1.88–1.96 (1 H, m) and 1.98–2.05 (1 H, m) ($-CH_2-$ × 4); 1.56 (1 H, dd, J 2.7, 15.0 Hz, 6-Hax), 2.04 (1 H, dd, J 3.5, 15.0 Hz, 6-Heq), 2.44 (1 H, dt*, J 4.3, 9.8, 10.3 Hz, –CHN–), 3.35 (1 H, q*, J 2.7, 3.5, 4.2 Hz, 5-H), 3.35–3.41 (1 H, m, –CH(OH)–), 3.41 (1 H, d, J 9.2 Hz, 2-H), 3.45 and 3.53 (each 1 H, ABq, J 11.3 Hz, $-CH_2O-$), 3.67 (1 H, dd, J 4.2, 9.8 Hz, 4-H), 3.79 (1 H, t*, J 9.2, 9.8 Hz, 3-H) (*apparent splitting pattern). Anal. Calcd for $C_{13}H_{25}NO_6 \cdot {}^1/_4H_2O$: C, 52.77; H, 8.69; N, 4.73. Found: C, 52.68; H, 8.79; N, 4.65.

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-1-(dimethoxyphosphoryl)-α-D-*gluco*-2-heptulopyranose (11). A solution of n-butyllithium in n-hexane (1.6 M solution, 46.5 mL, 74 mmol) was added to a solution of dimethyl methylphosphonate (9.2 g, 74 mmol) in THF (135 mL) under argon at –70 to –78 °C with stirring, and then stirring was continued for 30 min. To the solution was added a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**10**; 20.0 g, 37 mmol) in THF (100 mL) at –70 to –78 °C. Stirring was continued for an additional 1 h at the same temperature. The mixture was removed from the cooling bath and allowed to warm to 0 °C with stirring. Ice-cold 10% (w/v) NH_4Cl solution (300 mL) was added to the reaction mixture, and the resulting oily substance was extracted with EtOAc. The EtOAc solution was washed with 2 N HCl and saturated aqueous $NaHCO_3$ and then concentrated. Et_2O/petroleum ether (1:3; 400 mL) was added to the residue, and the mixture was refrigerated to give (dimethoxyphosphoryl)heptulopyranose derivative **11** (23.3 g, 95%) as white crystals: mp 112–113 °C; $[\alpha]^{23}_D$ –15.6° (c 1, $CHCl_3$); IR (KBr) 3450 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66 (1 H, dd, J 15.3, 18.4 Hz) and 2.28 (1 H, dd, J 15.3, 17.6 Hz) (1-H), 3.25 (1 H, d, J 9.3 Hz, 3-H), 3.59 (1 H, dd, J 2.0, 10.7 Hz) and 3.72 (1 H, dd, J 3.6, 10.7 Hz) (7-H), 3.61 (3 H, d, J 11.1 Hz, $-OCH_3$), 3.66 (3 H, d, J 11.2 Hz, $-OCH_3$), 3.67 (1 H, t, J 9.3 Hz, 5-H), 4.07 (1 H, ddd, J 2.0, 3.6, 9.5 Hz, 6-H), 4.11 (1 H, t, J 9.3 Hz, 4-H), 5.74 (1 H, br s, –OH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 32.70 (dt, J_{CP} 135.1 Hz, 1-C), 51.75 (dq, J_{CP} 6.4 Hz, $-OCH_3$), 53.28 (dq, J_{CP} 5.6 Hz, $-OCH_3$), 68.94 (t, 7-C), 71.13 (d, 6-C); 73.32 (t), 74.80 (t), 75.14 (t) and 75.57 (t) ($PhCH_2-$ × 4); 78.46 (d, 5-C), 82.75 (dd, J_{CP} 13.3 Hz, 3-C), 83.46 (dd, J_{CP} 4.3 Hz, 4-C), 96.71 (d, J_{CP} 7.7 Hz, 2-C); 127.55–138.63, 137.91 (s), 137.98 (s), 138.35 (s) and 138.63 (S) (C_6H_5- × 4). Anal. Calcd for $C_{37}H_{43}O_9P$: C, 67.06; H, 6.54; P, 4.67. Found: C, 67.09; H, 6.39; P, 4.82.

A Mixture of 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-1-(dimethoxyphosphoryl)-D-*glycero*-D-*gulo*-heptitol and 1,3,4,5-Tetra-*O*-benzyl-7-deoxy-7-(dimethoxyphosphoryl)-D-*glycero*-L-*gulo*-heptitol (12). To a stirred solution of **11** (20 g, 30 mmol) in THF (200 mL) was added $NaBH_4$ (1.5 g, 40 mmol), and stirring was continued for 18 h at room temperature. Insoluble material was removed by filtration and washed with THF. The filtrate and the washings were combined and concentrated. The residue was partitioned between EtOAc (600 mL) and H_2O (300 mL). The organic layer was washed with H_2O and then concentrated. The residue was chromatographed on a column of silica gel (600 mL) with toluene/acetone (2:1) to give the (dimethoxyphosphoryl)-heptitol derivative **12** (a mixture of two epimers; 18.8 g, 94%) as a colorless syrup: ^1H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 1.64 (ddd, J 3.5, 15.5, 19.0 Hz), 1.92 (dt, J 9.8, 15.9, 15.9 Hz), 2.04 (dt*, J 9.6, 15.5, 16.0 Hz) and 2.17 (ddd, J 2.6, 15.9, 19.4 Hz) (total 2H, $-CH_2P-$); 3.65 (d, J 10.9 Hz), 3.65 (d, J 10.9 Hz), 3.68 (d, J 11.0 Hz) and 3.69 (d, J 10.9 Hz) (total 6H, $-OCH_3$ × 2) (*apparent splitting pattern). Anal. Calcd for $C_{37}H_{45}O_9P$: C, 66.86; H, 6.82; P, 4.66. Found: C, 66.91; H, 6.93; P, 4.81.

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-1-(dimethylphosphoryl)-D-*xylo*-2,6-heptodiulose (13). A solution of TFAA (22.1 mL) in CH_2Cl_2 (170 mL) was added dropwise to a stirred solution of DMSO (16.7 mL) in CH_2Cl_2 (170 mL) at –65 to –75 °C, and stirring was continued for 30 min. To the stirred solution was added dropwise a solution of the (dimethoxyphosphoryl)heptitol derivative **12** (26.0 g, 39 mmol) in CH_2Cl_2 (100 mL) at –65 to –75 °C, and then stirring was continued for 1 h. Et_3N (43.7 mL) in CH_2Cl_2 (100 mL) was added dropwise to the reaction mixture at –65 to –75 °C with stirring. The mixture was removed from the cooling bath and allowed to warm to 0 °C with stirring. To the mixture was added 2 N HCl (470 mL) with ice cooling and stirring. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, and then concentrated. The residue was chromatographed on a column of silica gel (1.1 L) with toluene/EtOAc (1:1) to give the heptodiulose derivative **13** (22.4 g, 94%) as a colorless syrup: $[\alpha]^{23}_D$ –28.5° (c 1, $CHCl_3$); IR ($CHCl_3$) 1733, 1704 cm^{-1} (CO); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 52.82 (dq, J_{CP} 6.1 Hz, $-OCH_3$), 53.18 (dq, J_{CP} 6.1 Hz, $-OCH_3$), 64.75 (t, 7-C), 66.54 (t) and 66.22 (t) (1-C); 73.44 (t), 75.00 (t), 75.00 (t) and 75.78 (t) ($PhCH_2-$ × 4); 78.68 (d) and 78.96 (d), 82.99 (d) and 83.03 (d), 83.67 (d) and 83.81 (d) (3, 4, 5-C); 127.62–128.51, 137.45 (s), 137.69 (s), 137.78 (s) and 137.88 (s) (C_6H_5- × 4); 168.94 (s) and 169.04

(s) (CO), 194.94 and 195.02 (CO). Anal. Calcd for $C_{37}H_{41}O_9P$: C, 67.26; H, 6.25; P, 4.69. Found: C, 67.70; H, 6.32; P, 4.69.

4L-(4,6/5)-4,5,6-Tris(benzyloxy)-3-[(benzyloxy)methyl]-2-cyclohexenone (14). To a solution of the heptodiulose derivative **13** (18.0 g, 27 mmol) in toluene (500 mL) were added 18-crown-6 (270 mg, 1 mmol) and potassium carbonate (5.4 g, 39 mmol). The mixture was stirred for 8 h at room temperature, and insoluble material was then removed by filtration and washed with toluene. The filtrate and the washings were combined, washed with 2 N HCl and saturated aqueous $NaHCO_3$, and concentrated. The residue was chromatographed on a column of silica gel (1 L). The column was washed with toluene and then eluted with toluene/EtOAc (20:1) to give the branched unsaturated inosose derivative **14** (10.8 g, 76%) as a colorless syrup: $[\alpha]^{23}_D$ −12.2° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1694 cm^{-1} (CO); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.01 (1 H, dd, *J* 7.5, 10.6 Hz, 5-H), 4.08 (1 H, d, *J* 10.6 Hz, 6-H), 4.08 (1 H, dd, *J* 3.0, 16.1 Hz) and 4.27 (1 H, br d, *J* 16.1 Hz) (−CH_2O−), 4.38 (1 H, br d, *J* 7.5 Hz, 4-H), 6.22 (1 H, dd, *J* 1.1, 3.0 Hz, 2-H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 68.82 (t, −CH_2O−); 72.96 (t), 74.19 (t), 75.38 (t) and 75.46 (t) ($PhCH_2$− × 4); 79.00 (d), 83.82 (d) and 84.71 (d) (4, 5, 6-C), 123.75 (d, 2-C); 127.57–128.36, 137.39 (s), 137.63 (s), 137.81 (s) and 138.06 (s) (C_6H_5− × 4); 158.95 (s, 3-C), 196.40 (s, 1-C). Anal. Calcd for $C_{35}H_{34}O_5$: C, 78.63; H, 6.41. Found: C, 78.83; H, 6.27.

1L-(1,3/2,4)-2,3,4-Tri-*O*-benzyl-5-[(benzyloxy)methyl]-5-cyclohexene-1,2,3,4-tetrol (15). $NaBH_4$ (2.2 g, 58 mmol) was added to a stirred solution of cerous chloride (7.5 g, 20 mmol) in EtOH (150 mL) at −70 to −78 °C, and stirring was continued for 1 h. To the stirred mixture was added a solution of the branched unsaturated inosose derivative **14** (10.0 g, 18.7 mmol) in EtOH/THF (1:1, 100 mL) at −70 to −78 °C. After being stirred for 1 h at the same temperature, the reaction mixture was partitioned between EtOAc (500 mL) and 2 N HCl (250 mL) with stirring at ice-bath temperature. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, and then concentrated. Et_2O/petroleum ether (1:10, 220 mL) was added to the syrupy residue, and the mixture was refrigerated to give the branched unsaturated inositol derivative **15** as colorless crystals (7.5 g, 75%): mp 74–75 °C; $[\alpha]^{21}_D$ −66.9° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.85–2.05 (1 H, m, −OH), 3.56 (1 H, dd, *J* 7.4, 9.8 Hz, 3-H), 3.85 (1 H, dd, *J* 7.1, 9.8 Hz, 2-H), 3.90 (1 H, br d, *J* 12.2 Hz) and 4.24 (1 H, br d, *J* 12.2 Hz) (−CH_2O−), 4.27–4.34 (2 H, m, 1-H, 4-H), 5.72 (1 H, br s, 5-H). Anal. Calcd for $C_{35}H_{36}O_5$: C, 78.33; H, 6.76. Found: C, 78.24; H, 6.64.

(1*R*)-(1,3,4/2)-1,2,3-Tri-*O*-benzyl-6-[(benzyloxy)methyl]-4-phthalimido-5-cyclohexene-1,2,3-triol (16). To a stirred solution of the branched unsaturated inositol derivative **15** (9.0 g, 16.8 mmol), phthalimide (5.0 g, 34 mmol), and Ph_3P (12.0 g, 46 mmol) in THF (200 mL) was added DEAD (8.0 g, 46 mmol) at −10 to −15 °C, and stirring was continued for 1 h at the same temperature and then for 18 h at ice-bath temperature. The mixture was concentrated, and the residue was chromatographed on a column of silica gel (500 mL) with toluene/EtOAc (20:1) to give tetra-*O*-benzyl-*N*-phthaloylvalienamine (**16**, 5.2 g, 52%) as a colorless syrup: $[\alpha]^{24}_D$ −84.6° (*c* 1, $CHCl_3$); IR (KBr) 1770, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.90 (1 H, dd, *J* 6.6, 10.0 Hz, 2-H), 4.06 and 4.22 (each 1 H, ABq, *J* 12.7 Hz, −CH_2O−), 4.26 (1 H, br d, *J* 6.6 Hz, 1-H), 4.46 (1 H, dd, *J* 4.5, 10.0 Hz, 3-H), 5.29 (1 H, t*, *J* 4.5, 5.5 Hz, 4-H), 5.73 (1 H, dd, *J* 1.5, 5.5 Hz, 5-H), 7.71 (2 H, dd, *J* 3.1, 5.5 Hz) and 7.82 (2 H, dd, *J* 3.1, 5.5 Hz) (phthaloyl-H) (*apparent splitting pattern). Anal. Calcd for $C_{43}H_{39}NO_6$: C, 77.57; H, 5.90; N, 2.10. Found: C, 77.40; H, 6.06; N, 2.11.

(1*R*)-(1,3,4/2)-1,2,3-Tri-*O*-benzyl-4-amino-6-[(benzyloxy)methyl]-5-cyclohexene-1,2,3-triol (Tetra-*O*-benzylvalienamine, 4b). To a stirred solution of the *N*-phthaloyl derivative **16** (5.0 g, 30 mmol) in MeOH/THF (2:1, 60 mL) was added hydrazine monohydrate (2.5 mL, 51 mmol), and stirring was continued for 3 h at room temperature. The reaction mixture was concentrated, and the residue was partitioned between EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with H_2O and concentrated. The residue was chromatographed on a column of silica gel (150 mL) with EtOAc to give tetra-*O*-benzylvalienamine (**4b**, 3.6 g, 74%) as a colorless syrup: $[\alpha]^{24}_D$ +6.3° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 3.55–3.60 (1 H, m, 4-H), 3.57 (1 H, dd, *J* 4.4, 11.2 Hz, 3-H), 3.90 (1 H, d, *J* 11.9 Hz) and 4.25 (1 H, br d, *J* 11.9 Hz) (−CH_2O−), 3.93 (1 H, ddd, *J* 2.4, 6.6, 11.2 Hz, 2-H), 4.16 (1 H, br d, *J* 6.6 Hz, 1-H); 4.43 (1 H, d, *J* 11.7 Hz), 4.49 (1 H, d, *J* 11.7 Hz), 4.65 (1 H, d, *J* 11.7 Hz), 4.67 (1 H, d, *J* 11.1 Hz), 4.74 (1 H, d, *J* 11.0 Hz), 4.74 (1 H, d, *J* 11.7 Hz), 4.81 (1 H, d, *J* 11.1 Hz) and 4.91 (1 H, d, *J* 11.0 Hz) ($PhCH_2$− × 4); 5.87 (1 H, br d, *J* 4.0 Hz, 5-H), 7.24–7.36 (20 H, m, C_6H_5− × 4). Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; N, 2.61. Found: C, 78.55; H, 6.99; N, 2.45.

(1*R*)-(1,3,4/2)-4-Amino-6-(hydroxymethyl)-5-cyclohexene-1,2,3-triol (Valienamine, 4a). To a solution of tetra-*O*-benzylvalienamine (**4b**, 1.0 g) in THF (10 mL) was added liquid ammonia (30 mL). To the mixture was added sodium (2.0 g) by portions at −65 to −70 °C with stirring. Stirring was continued for 2 h at the same temperature, and then NH_4Cl (5.0 g) was added by portions. The reaction mixture was removed from the cooling bath, and liquid ammonia was evaporated at room temperature. Water (100 mL) was added to the residue. The insoluble material was removed by filtration. The filtrate was chromatographed on a column of Dowex 50W × 8 (H^+, 300 mL). The column was washed with H_2O and eluted with 0.5 N ammonium hydroxide. The eluate was concentrated, and the residue was chromatographed on a column of Dowex 1 × 2 (OH^-, 200 mL) with H_2O. The eluate was concentrated, and the syrupy residue was crystallized from EtOH to give valienamine (**4a**, 225 mg, 62%) as colorless crystals: $[\alpha]^{24}_D$ +67.4° (*c* 1, 0.1 N HCl); ^1H NMR (D_2O, 400 MHz) δ 3.53 (1 H, m, 4-H), 3.68 (1 H, dd, $J_{3,4}$ 3.8 Hz, $J_{2,3}$ 10.3 Hz, 3-H), 3.70 (1 H, dd, $J_{1,2}$ 5.6 Hz, $J_{2,3}$ 10.3 Hz, 2-H), 4.11 (1 H, m, 1-H), 4.12 (1 H, dd, $J_{5,7a}$ 1.2 Hz, $J_{7a,7b}$ 14.0 Hz) and 4.24 (1 H, dq*, $J_{1,7b}$ 1.0 Hz, $J_{4,7b}$ 1.2 Hz, $J_{5,7b}$ 1.5 Hz, $J_{7a,7b}$ 14.0 Hz) (7-H), 5.83 (1 H, dq*, $J_{5,7a}$ 1.2 Hz, $J_{5,7b}$ 1.5 Hz, $J_{1,5}$ 1.7 Hz, $J_{4,5}$ 5.1 Hz, 5-H) (*apparent splitting pattern); ^{13}C NMR (D_2O + DCl, 25.2 MHz) δ 50.2 (d), 61.9 (d), 67.4 (d), 71.7 (d), 72.5 (d), 116.3 (d), 146.5 (s); TLC R_f 0.42. Anal. Calcd for $C_7H_{13}NO_4 \cdot H_2O$: C, 43.51; H, 7.83; N, 7.25. Found: C, 43.54; H, 7.81; N, 7.33.

***N*-[(1*S*,2*S*)-(2,4/3)-2,3,4-Trihydroxy-5-(hydroxymethyl)-5-cyclohexenyl]valiolamine (5a, Validoxylamine G).** To a solution of tetra-*O*-benzylvalienamine (**4b**, 2.5 g, 4.7 mmol) and the inosose derivative **3** (2.5 g, 4.5 mmol) in MeOH/THF (3:1, 15 mL) was added $NaBH_3CN$ (500 mg, 8 mmol). The mixture was stirred overnight at room temperature and then for 4 h at 60 °C. The reaction mixture was concentrated and then partitioned between $CHCl_3$ (150 mL) and H_2O (150 mL). The organic layer was washed with H_2O and then concentrated. Petroleum ether (200 mL) was added to the residue. The resulting amorphous solid was dried and then dissolved in liquid ammonia. To the solution was added by portions sodium (4.0 g) at −60 to −70 °C. The mixture was stirred for 4 h at −60 to −70 °C and then quenched with NH_4Cl (10 g). After evaporation of the liquid ammonia at room temperature, H_2O (150 mL) was added to dissolve the residue, and the insoluble material was removed by extracting with EtOAc. The aqueous solution was subjected to column chromatography on Dowex 50W × 8 (H^+, 300 mL, washed with H_2O and then eluted with 0.5 N ammonium hydroxide), Amberlite CG-50 (NH_4^+, 180 mL, eluted with H_2O), and then Dowex 1 × 2 (OH^-, 180 mL, eluted with H_2O) to give validoxylamine G (**5a**, 180 mg, 10%) as a white solid: $[\alpha]^{25}_D$ +118.6° (*c* 1, H_2O); ^1H NMR (D_2O, 90 MHz) δ 1.50 (1 H, dd, *J* 3, 15.5 Hz, 6-Hax), 2.12 (1 H, dd, *J* 3, 15.5 Hz, 6-Heq), 3.35–4.2 (12 H, m), 6.06 (1 H, d, *J* 4.5 Hz, 6′-H); ^{13}C NMR (D_2O, 25.2 MHz) δ 31.4 (t), 54.4 (d), 56.7 (d), 64.3 (t), 67.8 (t), 72.4 (d), 74.3 (d), 74.4 (d), 75.5 (d), 75.6 (d), 76.7 (d), 78.4 (s), 125.3 (d), 142.2 (s); TLC R_f 0.23. Anal. Calcd for $C_{14}H_{25}NO_{10} \cdot H_2O$: C, 45.52; H, 7.36; N, 3.79. Found: C, 45.39; H, 7.58; N, 3.88.

Octa-*O*-acetylvalidoxylamine G (5c). Acetylation of **5a** (100 mg, 0.26 mmol) with Ac_2O/pyridine (2:1, 15 mL) gave octa-*O*-acetylvalidoxylamine G (**5c**, 108 mg, 59%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.69 (1 H, dd, *J* 2.9, 15.4 Hz, 6-Hax), 1.94 (1 H, dd, *J* 3.1, 15.4 Hz, 6-Heq); 2.02, 2.05, 2.07, 2.07, 2.07, 2.07, 2.08, and 2.14 (each 3 H, s, acetyl × 8); 3.55 (1 H, dt*, *J* 2.9, 3.1, 4.6 Hz, 1-H), 3.60 (1 H, br t, *J* 5.1 Hz, 1′-H), 3.65 and 4.04 (each 1 H, ABq, *J* 11.4 Hz, 7-H), 4.38 and 4.60 (each 1 H, br ABq, *J* 13.4 Hz, 7′-H), 4.98 (1 H, dd, *J* 5.1, 10.6 Hz, 2′-H), 5.02 (1 H, dd, *J* 4.6, 10.3 Hz, 2-H), 5.07 (1 H, d, *J* 10.3 Hz, 4-H), 5.40 (1 H, br d, *J* 6.8 Hz, 4′-H), 5.43 (1 H, dd, *J* 6.8, 10.6 Hz, 3′-H), 5.61 (1 H, t, *J* 10.3 Hz, 3-H), 6.00 (1 H, br d, *J* 5.1 Hz, 6′-H), 6.59 (1 H, br s, −NH−) (*apparent splitting pattern).

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-D-glucono-1,5-lactone (18). To a solution of 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-D-glucopyranose[11] (17, 5.0 g, 5.1 mmol) in DMSO (20 mL) was added Ac_2O (10 mL). The solution was stirred for 20 h at room temperature. The reaction mixture was diluted with H_2O (500 mL) and stirred for 3 h at room temperature to deposit the glucono-1,5-lactone derivative 18 as crystals. Recrystallization from Et_2O/petroleum ether (1:10, 30 mL) gave colorless crystals (4.7 g, 94%): mp 114–115 °C; $[\alpha]^{23}_D$ +71.2° (*c* 1, $CHCl_3$); IR (KBr) 1748 cm^{-1} (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.64 (1 H, dd, *J* 3.0, 11.2 Hz) and 3.70 (1 H, dd, *J* 3.9, 11.2 Hz) (6-H), 4.09 (1 H, d, *J* 4.9 Hz, 2-H), 4.12 (1 H, dd, *J* 3.3, 4.9 Hz, 3-H), 4.21 (1 H, dd, *J* 3.3, 8.1 Hz, 4-H), 4.45 (1 H, d, *J* 7.9 Hz, 1'-H), 4.64 (1 H, ddd, *J* 3.0, 3.9, 8.1 Hz, 5-H). Anal. Calcd for $C_{61}H_{62}O_{11}$: C, 75.44; H, 6.45. Found: C, 75.37; H, 6.44.

2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1-*C*-(dichloromethyl)-α-D-glucopyranose (19). A solution of LDA[2a] (20 mmol) in THF (15 mL) was added dropwise to a stirred solution of the 4-*O*-(β-D-glucopyranosyl)-D-glucono-1,5-lactone derivative 18 (4.67 g, 4.8 mmol) in CH_2Cl_2 (20 mL) under argon at −70 to −75 °C, and stirring was continued for 1 h at −70 to −75 °C. The reaction mixture was partitioned between ice-cold CH_2Cl_2 (150 mL) and H_2O (100 mL). The organic layer was washed with 2 N HCl and saturated aqueous $NaHCO_3$. The solvent was evaporated, and the residue was chromatographed on a column of silica gel (250 mL) with toluene/EtOAc (20:1). The eluate was concentrated, and then petroleum ether was added to the residue. The mixture was allowed to stand in a refrigerator to give the 1-*C*-dichloromethyl derivative 19 (4.78 g, 94%) as colorless crystals: mp 124–127.5 °C; $[\alpha]^{23}_D$ +25.5° (*c* 1, $CHCl_3$); IR (KBr) 3432 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.32 (1 H, s, –OH), 3.66 (1 H, dd, *J* 1.0, 11.5 Hz) and 3.96 (1 H, dd, *J* 3.5, 11.5 Hz) (6-H), 3.90 (1 H, ddd, *J* 1.0, 3.5, 9.8 Hz, 5-H), 3.94 (1 H, d, *J* 8.5 Hz, 2-H), 3.96 (1 H, t, *J* 8.5 Hz, 3-H), 4.13 (1 H, dd, *J* 8.5, 9.8 Hz, 4-H), 4.61 (1 H, d, *J* 8.1 Hz, 1'-H), 5.77 (1 H, s, –$CHCl_2$). Anal. Calcd for $C_{62}H_{64}Cl_2O_{11}$: C, 70.51; H, 6.11; Cl, 6.71. Found: C, 70.88; H, 6.21; Cl, 6.58.

(1*R*)-2,3,6-Tri-*O*-benzyl-1-*C*-(dichloromethyl)-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-D-glucitol (20). To a solution of the 1-*C*-(dichloromethyl)glucopyranose derivative 19 (4.5 g, 4.3 mmol) in diethylene glycol dimethyl ether (25 mL) was added $NaBH_4$ (500 mg, 13 mmol). After the reaction mixture was stirred overnight at room temperature, H_2O (250 mL) was added. The resulting oily substance was extracted with EtOAc (150 mL × 2). The extract was washed with 2 N HCl and saturated aqueous $NaHCO_3$ and then concentrated. The residue was chromatographed on a column of silica gel (250 mL). The column was washed with toluene and then eluted with toluene/EtOAc (15:1) to give the 1-*C*-(dichloromethyl)glucitol derivative 20 (3.9 g, 87%) as a colorless syrup: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.73 (1 H, d, *J* 7.1 Hz, 5-OH), 3.57 (1 H, dd, *J* 3.4, 9.8 Hz) and 3.73 (1 H, dd, *J* 4.4, 9.8 Hz) (6-H), 4.02–4.09 (1 H, m, 5-H),4.08 (1 H, d, *J* 9.5 Hz, 1-OH), 4.10 (1 H, dd, *J* 6.5, 8.0 Hz, 2-H), 4.15 (1 H, dd, *J* 1.7, 6.5 Hz, 3-H), 4.17 (1 H, ddd, *J* 2.2, 8.0, 9.5 Hz, 1-H), 4.32 (1 H, dd, *J* 1.7, 7.8 Hz, 4-H), 4.47 (1 H, d, *J* 7.8 Hz, 1'-H), 6.23 (1 H, d, *J* 2.2 Hz, –$CHCl_2$). Anal. Calcd for $C_{62}H_{66}Cl_2O_{11}$: C, 70.38; H, 6.29; Cl, 6.70. Found: C, 70.15; H, 6.49; Cl, 6.38.

1-Deoxy-D-*glycero*-D-*gulo*-heptitol (20′). To a solution of the 1-*C*-(dichloromethyl)glucitol derivative 20 (200 mg, 0.19 mmol) in toluene (20 mL) were added Bu_3SnH (100 mg, 0.3 mmol) and AIBN (20 mg, 0.1 mmol). The solution was stirred for 1 h at 90 °C. The reaction mixture was allowed to cool to room temperature and subjected to chromatography on silica gel (150 mL). The column was washed with toluene and then eluted with toluene/EtOAc (1:1). The eluate was concentrated, and the residue was dissolved in MeOH/formic acid (19:1, 20 mL). The solution was stirred for 5 h with Pd-black (200 mg) under N_2 at room temperature. The catalyst was removed by filtration and washed with MeOH. The filtrate and the washings were combined and concentrated. To a solution of the residue in H_2O (25 mL) was added Dowex 50W × 8 (H^+, 10 mL). The mixture was refluxed for 20 h with stirring. The ion-exchange resin was removed by filtration and washed with H_2O. The filtrate and the washings were combined and then concentrated. The residue was chromatographed on a column of activated charcoal (100 mL) with H_2O. The eluate was concentrated and then lyophilized to give the 1-deoxyheptitol 20′ as a white solid (31.2 mg, 84%): $[\alpha]^{23}_D$ +6.4° (*c* 1, H_2O) is in fair agreement with that reported ($[\alpha]^{20}_D$ +6.8° (*c* 1, H_2O)).[12] The ^1H NMR (D_2O, 300 MHz) spectrum was superimposable on the spectrum of 1-deoxy-D-*glycero*-D-*gulo*-heptitol derived from 2,3,4,6-tetra-*O*-benzyl-1-*C*-[bis(methylthio)methyl]-D-glucitol.[2a] Anal. Calcd for $C_7H_{16}O_6$: C, 42.85; H, 8.22. Found: C, 42.59; H, 8.38.

(1*S*)-(1(OH),2,4/1,3)-3,4-Di-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-2-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-6,6-dichloro-5-oxo-1,2,3,4-cyclohexanetetrol (22). A solution of TFAA (2.8 mL) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of DMSO (1.9 mL) in CH_2Cl_2 (15 mL) at −60 and −65 °C, and stirring was continued for an additional 15 min at that temperature. To the stirred mixture was added a solution of the diol derivative 20 (3.5 g, 3.3 mmol). Stirring was continued for 1 h, keeping the temperature below −65 °C, followed by dropwise addition of a solution of Et_3N (4.5 mL) in CH_2Cl_2 (10 mL). The reaction temperature was maintained below −65 °C until the addition of Et_3N was completed. The reaction mixture was stirred for 15 min and then removed from the cooling bath. Stirring was continued while the reaction mixture was allowed to warm to 0 °C, and then 2 N HCl (50 mL) was added. The reaction mixture was stirred for 10 min, and then the CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The CH_2Cl_2 layers were combined, washed with saturated aqueous $NaHCO_3$, and then concentrated. The residue was chromatographed on a column of silica gel (150 mL) with toluene/EtOAc (19:1) to give the 6,6-dichloroinosose derivative 22 (2.3 g, 66%) as a colorless syrup: $[\alpha]^{23}_D$ +12.3° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3526 (OH), 1761 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.00 (1 H, s, –OH), 3.83 and 3.90 (each 1 H, ABq, *J* 10.0 Hz, –CH_2O–), 3.95 (1 H, t, *J* 9.3 Hz, 3-H), 4.68 (1 H, d, *J* 7.8 Hz, 1'-H), 4.81 (1 H, d, *J* 9.3 Hz) and 4.83 (1 H, d, *J* 9.3 Hz) (2-H, 4-H). Anal. Calcd for $C_{62}H_{62}Cl_2O_{11}$: C, 70.65; H, 5.93; Cl, 6.73. Found: C, 70.84; H, 6.15; Cl, 6.52.

(1*S*)-(1(OH),2,4/1,3)-3,4-Di-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-2-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-5-oxo-1,2,3,4-cyclohexanetetrol (23). To a solution of the 6,6-dichloroinosose derivative 22 (2.3 g, 2.2 mmol) in toluene (50 mL) were added Bu_3SnH (1.3 g, 4.5 mmol) and AIBN (100 mg, 0.6 mmol). The solution was stirred for 1 h in a bath at about 100 °C. The reaction mixture was allowed to cool to room temperature and chromatographed on a column of silica gel (250 mL). The column was washed with toluene and then eluted with toluene/EtOAc (15:1) to give the dechlorinated compound 23 (1.8 g, 84%) as a colorless syrup: $[\alpha]^{23}_D$ +35.4° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3450 (OH), 1735 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (1 H, d, *J* 14.4 Hz, 6-Heq), 2.38 (1 H, d, *J* 2.0 Hz, –OH), 2.71 (1 H, br dd, *J* 2.0, 14.4 Hz, 6-Hax), 3.08 and 3.68 (each 1 H, ABq, *J* 8.9 Hz, –CH_2O–), 3.91 (1 H, t, *J* 9.3 Hz, 3-H), 3.92 (1 H, br d, *J* 9.3 Hz, 4-H), 4.32 (1 H, d, *J* 9.3 Hz, 2-H), 4.46 (1 H, d, *J* 7.8 Hz, 1'-H). Anal. Calcd for $C_{62}H_{64}O_{11}$: C, 75.59; H, 6.55. Found: C, 75.71; H, 6.49.

***N*-[(1*S*,2*S*)-2,3,4-Trihydroxy-5-(hydroxymethyl)-5-cyclohexenyl]-4-*O*-(β-D-glucopyranosyl)valiolamine (6a, Validamycin G).** A solution of the β-D-glucopyranosyl-(branched inosose) derivative 23 (1.7 g, 1.7 mmol) and tetra-*O*-benzylvalienamine (4b, 1.0 g, 1.87 mmol) in MeOH/THF (3:1, 15 mL) was stirred for 30 min at room temperature. $NaBH_3CN$ (500 mg, 8 mmol) was added to the solution, followed by stirring overnight at near 60 °C. The reaction mixture was concentrated, and then the residue was partitioned between $CHCl_3$ (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O and then concentrated. Petroleum ether (200 mL) was added to the residue, and the resulting amorphous solid (about 2 g) was dried and dissolved in liquid ammonia (50 mL). Sodium (3.0 g) was added to the solution by portions at −60 to −70 °C. After the solution was stirred for 1 h at −60 to −70 °C, EtOH (5 mL) was added to the reaction mixture. An additional amount of sodium (1.0 g) was added to the reaction mixture at −60 to −70 °C. The stirring was continued for 30 min, and then the reaction mixture was quenched with NH_4Cl (10 g). Workup as described for the preparation of 5a gave validamycin G (6a, 58 mg, 6%) as a white solid: $[\alpha]^{25}_D$ +52.8° (*c* 1, H_2O); ^1H NMR (D_2O, 90 MHz) δ 1.53 (1 H, dd, *J* 3, 15.5 Hz, 6-Hax), 2.12 (1 H, dd, *J* 3, 15.5 Hz, 6-Heq),

3.3-4.2 (18 H, m), 4.47 (1 H, d, J 7 Hz, 1''-H), 6.04 (1 H, d, J 4.5 Hz, 6'-H); ^{13}C NMR (D_2O, 25.2 MHz) δ 31.8 (t), 54.5 (d), 56.4 (d), 63.2 (t), 64.3 (t), 67.1 (t), 72.1 (d), 72.5 (d), 72.9 (d), 74.3 (d), 75.4 (d), 75.8 (d), 76.2 (d), 78.5 (d), 78.7 (d), 79.0 (s), 86.0 (d), 105.8 (d), 125.0 (d), 142.0 (s); TLC R_f 0.18. Anal. Calcd for $C_{20}H_{35}NO_{14}\cdot H_2O$: C, 45.19; H, 7.01; N, 2.63. Found: C, 45.23; H, 7.22; N, 2.54.

Undeca-*O*-acetylvalidamycin G (6c). Acetylation of **6a** (25 mg, 0.047 mmol) with Ac_2O/pyridine (2:1, 15 mL) gave the undeca-*O*-acetate of validamycin G (**6c**, 20 mg, 54.5%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (1 H, dd, J 2.7, 15.3 Hz, 6-Hax), 1.90 (1 H, dd, J 3.1, 15.3 Hz, 6-Heq); 1.99, 2.00, 2.03, 2.04, 2.05, 2.06, 2.06, 2.07, 2.08, 2.10, and 2.14 (each 3 H, s, acetyl × 11); 3.43 (1 H, dt*, J 2.7, 3.1, 4.4 Hz, 1-H), 3.60 (1 H, m, 1'-H), 3.63 (1 H, ddd, J 2.3, 4.1, 9.1 Hz, 5''-H), 3.66 (1 H, d, J 9.9 Hz, 4-H), 3.92 and 4.13 (each 1 H, ABq, J 11.1 Hz, 7-H), 4.04 (1 H, dd, J 2.3, 12.5 Hz) and 4.40 (1 H, dd, J 4.1, 12.5 Hz) (6''-H), 4.37 and 4.60 (each 1 H, br ABq, J 13.3 Hz, 7'-H), 4.50 (1 H, d, J 9.1 Hz, 1''-H), 4.93 (1 H, dd, J 4.4, 9.9 Hz, 2-H), 4.97 (1 H, t, J 9.1 Hz, 2''-H), 4.99 (1 H, dd, J 5.1, 10.2 Hz, 2'-H), 5.09 (1 H, t, J 9.1 Hz, 4''-H), 5.16 (1 H, t, J 9.1 Hz, 3''-H), 5.38 (1 H, br d, J 6.6 Hz, 4'-H), 5.42 (1 H, dd, J 6.6, 10.2 Hz, 3'-H), 5.52 (1 H, t, J 9.9 Hz, 3-H), 5.97 (1 H, br d, J 5.1 Hz, 6'-H), 5.87 (1 H, br s, -NH-) (*apparent splitting pattern).

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Registry No. **1a**, 83465-22-9; **1c**, 141042-85-5; **2a**, 83480-29-9; **2b**, 101540-73-2; **3**, 114250-39-4; **4a**, 38231-86-6; **4b**, 114779-32-7; **5a**, 106054-18-6; **5c**, 106357-01-1; **6a**, 106054-17-5; **6c**, 106357-02-2; **7**, 140926-93-8; **8**, 140926-94-9; *epi*-**8**, 141115-25-5; **9a**, 115250-39-0; **9b**, 140926-95-0; **10**, 13096-62-3; **11**, 140926-87-0; **12** (isomer 1), 115250-30-1; **12** (isomer 2), 115305-00-5; **13**, 115250-32-3; **14**, 110391-10-1; **15**, 99695-34-8; **16**, 140926-88-1; **17**, 83921-62-4; **18**, 88970-25-6; **19**, 140926-89-2; **20**, 140926-90-5; **20'**, 5328-46-1; **22**, 140926-91-6; **23**, 140926-92-7; 2-amino-1,3-propanediol, 534-03-2; dimethyl methanephosphonate, 756-79-6.

Supplementary Material Available: Complete ^{1}H NMR data of compounds **7**, **9a,b**, **11**, **12**, **14-16**, **18-20**, **22** and **23** (7 pages). Ordering information is given on any current masthead page.

Syntheses and NMR Behavior of Calix[4]quinone and Calix[4]hydroquinone

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Calix[4]quinone (**7**) and calix[4]hydroquinone (**6**) have been synthesized using three different synthetic pathways. The first pathway to **7** from calix[4]arene (**1**) consists of six steps: acetylation, Fries rearrangement, Baeyer-Villiger oxidation after acetylation, hydrolysis, and oxidation. The second pathway to **7** from **1** consists of four steps: acetylation, Fries rearrangement, reaction of the product obtained by Fries rearrangement with sodium azide, and oxidation. The third pathway to **7** from **1** is most convenient and consists of three steps: diazo coupling reaction, reduction, and oxidation. The NMR behavior of **6** and **7** is described.

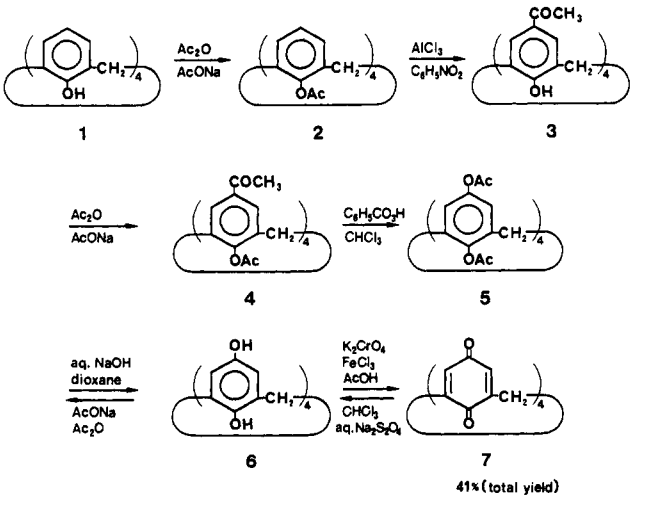
Calixarenes, which are accessible from base-catalyzed condensation of para-substituted phenols with formaldehyde, are now well-known compounds.[1] These compounds have lately attracted considerable attention because their potential as enzyme mimics has been suggested.[2]

Since the first paper of Gutsche on calixarenes[3] was issued, we have been studying the syntheses of various calixarenes and their characteristics.[4] On the other hand, we have been searching for a new redox system. If calix[4]hydroquinone (**6**) and calix[4]quinone (**7**), which are calixarene-type compounds comprised of cyclic arrays of *p*-hydroquinone residues and *p*-quinone residues attached by methylene groups, respectively, are synthesized from readily available *p-tert*-butylcalix[4]arene, they not only form new redox systems but also become new compounds which are able to form charge-transfer complexes.[5] Thus, we finally found a convenient synthesis of **6** and **7**. In this paper we report their synthetic methods using three different pathways and their NMR behavior.

Results and Discussion

Syntheses of 6 and 7. The synthesis of **7** has been attempted by Gutsche's group, that is, they have obtained a material which seems to have a calix[4]quinone structure, but attempts to purify it have not been successful.[6]

Scheme I



(1) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.
(2) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161.
(3) Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.

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