Pseudo-sugars. 3. Alternative Synthesis of Penta-*N,O*-acetyl-DL-validamine and Its Analogs[1]

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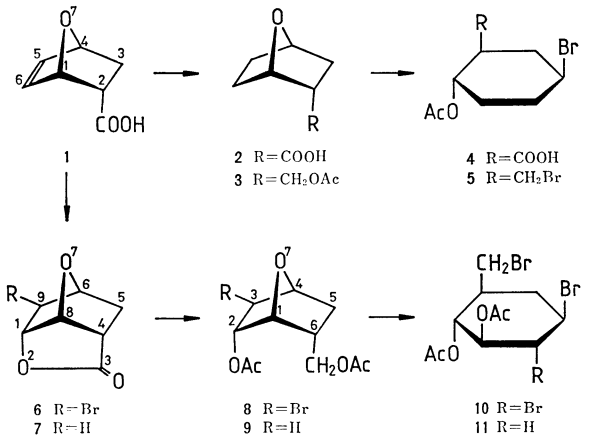
DL-Validamine and its amino deoxy and deoxy analogs were synthesized as the acetyl derivatives from *endo*-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid, the Diels-Alder adduct of acrylic acid and furan.

In a previous paper[2] a report was given on the first synthesis of penta-*N,O*-acetyl-DL-validamine starting from the Diels-Alder adduct of furan with acrylic acid, *endo*-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**1**).[3] Acetolysis of tri-*O*-acetyl-2,3-dihydroxy-6-hydroxymethyl-7-oxabicyclo[2.2.1]heptane gave a poor yield of the desired intermediate, penta-*O*-acetyl-(1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (pseudo-β-D-glucopyranose),[4] since anhydro ring formation occurs simultaneously to give a dioxatricyclo compound.[5] Thus, bromination of the substituted 2-hydroxymethyl-7-oxabicyclo[2.2.1]heptane with hydrogen bromide in acetic acid has been studied in order not only to open the 1,4-anhydro ring, but also to introduce a bromine substituent into the cyclohexane ring, which can be replaced by an amino function. In the present paper, we report on the alternative synthesis of acetyl derivatives of DL-validamine and its several analogs starting from the substituted bromohydroxymethylcyclohexanes derived from **1**.

Hydrogenation of **1** with palladium black gave *endo*-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (**2**)[3] in high yield. This was reduced by lithium aluminum hydride (LAH) in tetrahydrofuran (THF) followed by acetylation with acetic anhydride in pyridine to give *endo*-2-acetoxymethyl-7-oxabicyclo[2.2.1]heptane (**3**) as a syrup in 80% yield.

Reaction of **2** with 15% hydrogen bromide in acetic acid in a sealed tube overnight at 85—90 °C resulted in cleavage of the 1,4-anhydro ring to give rise to a mixture of acetoxybromocyclohexanecarboxylic acids, from which crystalline (1,5/2)-2-acetoxy-5-bromocyclohexanecarboxylic acid (**4**) was isolated in 59% yield. In its ^{1}H NMR spectrum, a triplet of doublets at δ 5.00 having 4.5, 10, and 10 Hz-splittings could be ascribed to H-2, in line with the 1,2-trans configuration between the acetoxyl and carboxyl groups. Under similar reaction conditions, **3** afforded crystalline dibromo compound (**5**) in an isolated yield of 35%. In this case, the primary acetoxyl group was replaced by a bromide ion in addition to opening the anhydro ring. The ^{1}H NMR spectrum of **5** contained a pattern of the signals due to methine protons very similar to that of **4**. The structure of **5** was tentatively assigned to (1/2,4)-4-bromo-2-(bromomethyl)cyclohexyl acetate.



1
2 R=COOH
3 R=CH₂OAc
4 R=COOH
5 R=CH₂Br
6 R=Br
7 R=H
8 R=Br
9 R=H
10 R=Br
11 R=H

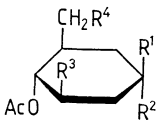
Scheme 1.

On the other hand, bromolactonization of **1** proceeded smoothly to give the bromolactone (**6**) in 91% yield. Reduction of **6** with LAH in THF followed by acetylation gave *endo*-2-acetoxy-*endo*-6-acetoxymethyl-*exo*-3-bromo-7-oxabicyclo[2.2.1]heptane (**8**) in 84% yield. Hydrogenolysis of **8** with Raney nickel in the presence of Amberlite IRA-45 (OH^-) gave the corresponding debromo compound (**9**) in 94% yield, which was also obtained analogously from the lactone (**7**) derived by hydrogenolysis of **6**.

The same treatment of **8** with hydrogen bromide in acetic acid gave selectively a single crystalline tribromide (**10**) almost quantitatively. Similarly, dibromide (**11**) was obtained from **9** in 75% yield. The structures of **10** and **11** were deduced on the basis of analytical data and ^{1}H NMR spectroscopy. Thus, the ^{1}H NMR spectrum of **10** revealed two one-proton relatively wide triplets coupled with each other at δ 4.92 and 5.22, respectively, indicating the presence of two acetoxyl groups in vicinal trans positions. These were accounted for by opening of the anhydro ring at C-4 by a bromide ion, the structure being tentatively assigned to di-*O*-acetyl-(1,3/2,4,6)-3,4-dibromo-6-bromomethyl-1,2-cyclohexanediol. In the ^{1}H NMR spectrum, **11** showed a triplet of doublets at δ 4.76 having 3.5, 8.5, and 8.5 Hz-splittings and a doublet of doublets at δ 4.96 having 8.5 and 10 Hz-splittings attributed to H-1 and H-2, respectively. Thus, **11** was assigned to di-*O*-acetyl-(1,3,5/2)-5-bromo-3-bromomethyl-1,2-cyclohexanediol.

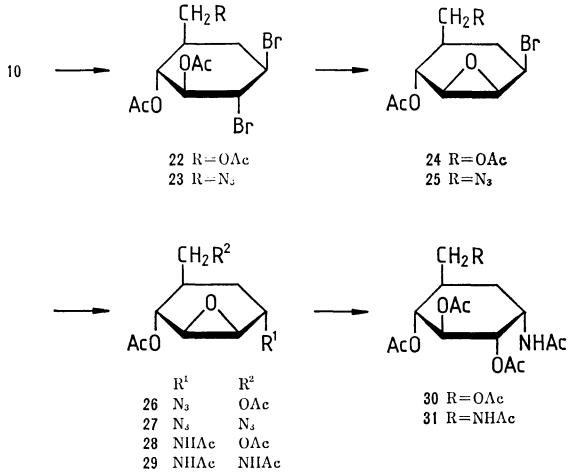
Accordingly, the 1,4-anhydro ring was cleaved by a bromide ion regioselectively in **8** or **9** at the carbon atom adjacent to the methylene group, while, in the case of **2** and **3**, the selectivity appears to decrease, somewhat presumably, owing to the stereoelectric effects.

Dideoxyvalidamine and Its Analog. Reduction of **4** with LAH in THF followed by acetylation gave the corresponding di-*O*-acetyl-bromohydroxymethylcyclohexanol (**12**) as a syrup in 46% yield, which,



	R^1	R^2	R^3	R^4
12	Br	H	H	OAc
13	H	N_3	H	OAc
14	H	NHAc	H	OAc
15	H	N_3	H	N_3
16	H	NHAc	H	NHAc
17	Br	H	OAc	OAc
18	H	N_3	OAc	OAc
19	H	NHAc	OAc	OAc
20	H	N_3	OAc	N_3
21	H	NHAc	OAc	NHAc

Scheme 2.



Scheme 3.

without purification, was treated with sodium azide in boiling 90% aqueous 2-methoxyethanol for 2 days to give the crude azido compound (**13**). Its ^{1}H NMR spectrum showed a relatively narrow multiplet due to the proton attached to the carbon atom bearing the azido group, suggesting that the bromine group was replaced by an azide ion with inversion of the configuration. Compound **13** was hydrogenated with Raney nickel followed by acetylation to give crystalline tri-*N,O*-acetyl-(1,4/2)-4-amino-2-hydroxymethyl-1-cyclohexanol (dideoxyvalidamine) (**14**) in 25% yield.

The similar treatment of **5** with sodium azide gave a syrupy diazido compound (**15**), which was hydrogenated and successively acetylated to give tri-*N,O*-acetyl-(1,4/2)-4-amino-2-aminomethyl-1-cyclohexanol (**16**) in 30% overall yield.

Deoxyvalidamine and Its Analog. Compound **11** was treated with 2 molar equiv. of sodium acetate in 90% aqueous 2-methoxyethanol at 90 °C overnight and then the product was acetylated to give tri-*O*-acetyl-(1,3,5/2)-5-bromo-3-hydroxymethyl-1,2-cyclohexanediol (**17**) in 78% yield. The ^{1}H NMR spectrum was compatible with the proposed structure, in which only C-7 bromine atom of **11** was replaced by an acetoxyl group. Thus, in **17**, C-7 methylene signal shifted downfield as compared with that of **11**. Reaction of **17** with an azide ion gave a syrupy azido compound (**18**) with inversion of the configuration at C-5, which was directly hydrogenated followed by acetylation to give a crystalline tetra-*N,O*-acetyl-(1,3/2,5)-5-amino-3-hydroxymethyl-1,2-cyclohexanediol (deoxyvalidamine) (**19**) in 40% yield. The structure was fully supported by the ^{1}H NMR spectrum (see Experimental).

Analogously, **11** was converted to the diazido compound (**20**) which was hydrogenated and then acetylated to give tetra-*N,O*-acetyl-(1,3/2,5)-5-amino-3-aminomethyl-1,2-cyclohexanediol (**21**) in 58% overall yield. Its ^{1}H NMR spectrum showed a pattern of ring proton signals very similar to that of **19**.

Validamine and Its Analog. Treatment of **10** with sodium acetate (2 molar equiv.) in 90% aqueous 2-methoxyethanol at 90 °C for 2 days led to the selective displacement at C-7 with an acetate ion affording tri-*O*-acetyl-(1,3/2,4,6)-3,4-dibromo-6-hydroxymethyl-1,2-cyclohexanediol (**22**) as the major product in 50% yield.[6] Similarly, on treatment with sodium azide (2 molar equiv.), **10** gave the corresponding 7-azido compound (**23**) in 91% yield. Reaction of **22** with excess methanolic sodium methoxide in chloroform followed by acetylation gave di-*O*-acetyl-1,2-anhydro-(1,2,4,6/3)-6-bromo-4-hydroxymethyl-1,2,3-cyclohexanetriol (**24**) in a quantitative yield. The ^{1}H NMR spectrum revealed a doublet due to H-3 having 9 Hz-splitting at δ 4.88, which confirmed the assigned structure of **24**, excluding the 2,3-anhydro structure resulting from an oxirane ring migration under basic conditions. Under the same conditions, **23** gave the corresponding epoxide (**25**) in 78% yield.

The reaction of **24** with 1.5 molar equiv. sodium azide in *N,N*-dimethylformamide at 90 °C was monitored by TLC.[7] After **24** had been consumed in 2.5 h, one major component was formed together with four minor components. Separation of the mixture by column chromatography gave the epoxy azide (**26**) in 30% yield as a homogeneous syrup. In its ^{1}H NMR spectrum, the signal due to proton on a carbon atom attached to the azido group appeared as a doublet of doublets having 3 and 9.5 Hz-splittings at δ 4.19. Lack of a coupling between H-1 and H-6 suggests that the azido group is located in the trans position to the adjacent anhydro ring. Hydrogenation of **26** with Raney nickel in methanol containing acetic anhydride gave the epoxy amide (**28**) which, without purification, was successively treated with boiling 80% aqueous acetic acid followed by acetylation to give a crystalline penta-*N,O*-acetyl-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (validamine) (**30**) in 30% yield. The compound was identical with an authentic sample[8] except for an optical activity. The anhydro ring in **28** seems to be cleaved at C-1 preferentially by an anchimeric assistance of the neighboring acetamido group, giving rise to the triol with the desired configuration.

By an analogous sequence of reactions (**27**→**29**→**31**), the 7-amino-7-deoxy analog (**31**) of validamine was prepared in an overall yield of 21%. The structure was supported by comparison of its ^{1}H NMR spectrum with that of **30**.

Experimental

Unless otherwise noted, melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. Solutions were evaporated under reduced pressure at 40—50 °C. ^{1}H NMR spectra were measured at 60 MHz on a Varian A-60D spectrometer in deuteriochloroform ($CDCl_3$) or dimethyl-d_6 sulfoxide (DMSO-d_6) with reference to tetramethylsilane as an internal standard, the peak positions being given in δ-values. Values given for chemical shifts and coupling constants are of first-order. TLC was performed on silica gel (Wakogel B-10, Wako Pure Chemical Industries, Ltd.) using a mixture of butanone and toluene as an eluent. Column chromatography was carried out on Wakogel C-200.

endo-2-Acetoxymethyl-7-oxabicyclo[2.2.1]heptane (3). To a solution of the acid (**2**)[3] (6.0 g) prepared by catalytic reduction of *endo*-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**1**)[2b] in tetrahydrofuran (THF) (100 ml) was added a slurry of lithium aluminum hydride (LAH) (2.1 g) in THF (20 ml), and the mixture was stirred at an ambient temperature for 4 h. A mixture of THF (4.2 ml) and water (4.2 ml) was added to the reaction mixture and it was left to stand overnight. A white solid was removed by filtration and washed with hot THF (20 ml). The filtrate and washings were combined and evaporated to give a colorless syrup (5.4 g), whose TLC showed a single spot in butanone–toluene (1 : 1, v/v). A 2.3 g-portion of this syrup was treated with acetic anhydride (10 ml) in pyridine (20 ml) overnight at an ambient temperature. The reaction mixture was evaporated to dryness and the residue was dissolved in ethyl acetate and washed with 0.5 M hydrochloric acid, aqueous saturated sodium hydrogencarbonate solution, and water, successively. The solution was dried over anhydrous sodium sulfate and then evaporated to give **3** (2.7 g, 89%) as a homogeneous syrup.

Found: C, 63.60; H, 8.20% Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%.

Treatment of the alcohol with *p*-nitrobenzoyl chloride in pyridine at 70 °C for 30 min gave a crystalline *p*-nitrobenzoate. An analytical sample was obtained by recrystallization of the crude product from ethanol, mp 104—105 °C.

Found: C, 60.79; H, 5.61; N, 5.12%. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05%.

(1,5/2)-2-Acetoxy-5-bromocyclohexanecarboxylic Acid (4). A mixture of **2**[3] (0.2 g) and 15% hydrogen bromide in acetic acid (2 ml) was heated at 80—85 °C in a sealed tube for 17 h, the reaction mixture being then poured into ice-water (40 ml). The resulting gum was collected by decantation and dissolved in chloroform. The solution was washed with water, dried, and evaporated to give a partially crystalline product. Recrystallization from ethanol–hexane gave **4** (0.23 g, 59%): mp 156—158 °C; ^{1}H NMR ($CDCl_3$) δ 1.23—2.90 (7H, m, H-1 and the six methylene protons), 2.02 (3H, s, OAc), 3.97 (1H, tt, $J_{4ax,5}=J_{5,6eq}=11$ Hz, $J_{4eq,5}=J_{5,6eq}=4.5$ Hz, H-5), 5.00 (1H, td, $J_{1,2}=J_{2,3ax}=10$ Hz, $J_{2,3eq}=4.5$ Hz, H-2), 9.35 (1H, s, COOH).

Found: C, 40.51; H, 4.77; Br, 30.45%. Calcd for $C_9H_{13}O_4Br$: C, 40.78; H, 4.94; Br, 30.14%.

(1/2,4)-4-Bromo-2-(bromomethyl)cyclohexyl Acetate (5). Compound **3** (1.6 g) was treated with hydrogen bromide in acetic acid in the same way as for **4**. The reaction mixture was poured into ice-water and extracted with chloroform, and the extracts were processed in the usual manner. The crude product was crystallized from ethanol to give **5** (1.03 g, 35%): mp 110.5—112 °C; ^{1}H NMR ($CDCl_3$) δ 1.23—2.90 (7H, m, H-2 and the six ring methylene protons), 2.05 (3H, s, OAc), 3.32—3.45 (2H, m, CH_2Br), 3.99 (1H, tt, $J_{3ax,4}=J_{4,5ax}=11$ Hz, $J_{3eq,4}=J_{4,5eq}=4.5$ Hz, H-4), 4.77 (1H, td, $J_{1,2}=J_{1,6ax}=10$ Hz, $J_{1,6eq}=4.5$ Hz, H-1).

Found: C, 34.37; H, 4.48; Br, 51.11%. Calcd for $C_9H_{14}O_2Br_2$: C, 34.42; H, 4.49; Br, 50.89%.

exo-*9-Bromo-2,7-dioxabicyclo[4.2.1.0^{4,8}]nonan-3-one (6).* Compound **1**[3] (10 g) was dissolved in water (300 ml) containing sodium hydrogencarbonate (7.2 g). Bromine (4 ml) was added dropwise to this solution under vigorous agitation. After completion of the addition, the mixture was stirred for 1 h, and precipitates were collected by filtration and washed with water thoroughly. Recrystallization of the crude product from ethyl acetate gave **6** (14.2 g, 91%) as prisms: mp 155—156 °C; ^{1}H NMR (DMSO-d_6) δ 2.00—2.29 (2H, m, C-5 methylene), 2.69 (1H, m, H-4), 4.37 (1H, s, H-9), 4.75 (1H, m, H-6), 4.95 (1H, d, $J_{1,8}=5$ Hz, H-1), 5.53 (1H, t, $J_{4,8}=5$ Hz, H-8).

Found: C, 38.11; H, 3.26; Br, 36.34%. Calcd for $C_7H_7O_2Br$: C, 38.39; H, 3.22; Br, 36.48%.

2,7-Dioxabicyclo[4.2.1.0^{4,8}]nonan-3-one (7). A solution of **6** (1.1 g) in ethyl acetate (20 ml) was hydrogenated in the presence of Raney nickel T-4[9] and Amberlite IR-45 (OH^-) (7.5 ml) in the initial hydrogen pressure of 3.4 kg·cm^{-2} at an ambient temperature overnight. The catalyst and resin were removed by filtration and the filtrate was evaporated. The residue was crystallized from ethyl acetate–hexane to give **7** (0.46 g, 65%) as needles: mp 85.5—87 °C; ^{1}H NMR ($CDCl_3$) δ 1.42—2.46 (4H, m, C-5 and C-9 methylene), 2.71 (1H, broad five-line peak, $J_{4,5endo}=4.5$ Hz, $J_{4,5exo}=8.5$ Hz, H-4), 4.65—4.92 (2H, m, H-1 and H-6), 5.31 (1H, t, $J_{1,8}=J_{4,8}=5$ Hz, H-8).

Found: C, 60.20; H, 5.82%. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75%.

endo-*2-Acetoxy*-endo-*6-acetoxymethyl*-exo-*3-bromo-7-oxabicyclo-[2.2.1]heptane (8).* To an ice-cooled solution of **6** (10 g) in THF (250 ml) was added dropwise a slurry of LAH (2 g) in THF (30 ml) with vigorous agitation. The reaction mixture was stirred at an ambient temperature for 3 h and worked up in the usual manner to give a syrup, which was directly acetylated by the conventional method. The product was crystallized from ethyl acetate–hexane to give **8** (11.7 g, 83.5%) as colorless needles: mp 61—62 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (1H, dd, $J_{5gem}=12.5$ Hz, $J_{5endo,6}=5.5$ Hz, H-5*endo*), 1.63—2.79 (2H, m, H-5*exo* and H-6), 2.02 (3H, s) and 2.06 (3H, s) (OAc), 3.85 (1H, d, $J_{2,3}=3$ Hz, H-3), 4.19 (1H, dd) and 4.32 (1H, dd) ($J_{6,7}=J_{6,7'}=3$ Hz, $J_{7gem}=7$ Hz, CH_2OAc), 4.61 (1H, d, $J_{4,5exo}=6$ Hz, H-4), 4.65 (1H, t, $J_{1,2}=5$ Hz, H-1), 5.36 (1H, broad dd, H-2).

Found: C, 42.88; H, 4.82; Br, 26.14%. Calcd for $C_{11}H_{15}O_5Br$: C, 43.12; H, 4.92; Br, 26.02%.

endo-*2-Acetoxy*-endo-*6-acetoxymethyl-7-oxabicyclo[2.2.1]heptane (9).* a) A solution of **8** (10 g) in ethyl acetate (20 ml) was hydrogenated with Raney nickel and Amberlite IR-45 (OH^-) in the same way as for **7**. The product was crystallized from ethyl acetate–hexane to give **9** (7 g, 94%) as needles: mp 48—49 °C; ^{1}H NMR ($CDCl_3$) δ 1.12—1.51 (2H, m, H-3*endo* and H-5*endo*), 2.02 (6H, s, two OAc), 1.67—2.66 (3H, m, H-3*exo*, H-5*exo*, and H-6), 4.21—4.67 (4H, m, H-1, H-4, and CH_2OAc), 5.04 (1H, m, H-2).

Found: C, 57.67; H, 6.91%. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.06%.

b) Compound **9** was also prepared, in 52% yield, by reduction of **7** with LAH in THF as in the preparation

of **8**.

The di-*p*-nitrobenzoate was prepared by the usual method. An analytical sample crystallized from ethanol melted at 206 °C.

Found: C, 57.11; H, 4.27; N, 6.19%. Calcd for $C_{21}H_{18}N_2O_9$: C, 57.02; H, 4.10; N, 6.33%.

*Di-O-acetyl-(1,3/2,4,6)-3,4-dibromo-6-bromomethyl-1,2-cyclohexanediol (**10**).* Compound **8** (1.6 g) was treated with hydrogen bromide in acetic acid in the same way as for **4**. Recrystallization of a crude crystalline product (2.2 g) gave **10** (1.75 g, 74%) as prisms: mp 153—154 °C; ^{1}H NMR ($CDCl_3$) δ 1.79—2.85 (3H, m, C-5 methylene and H-6), 2.04 (3H, s) and 2.08 (3H, s) (OAc), 3.22 (1H, dd, $J_{6,7}$= 3.5 Hz, J_{7gem}=10 Hz, H-7), 3.45 (1H, dd, $J_{6,7'}$=1.5 Hz, H-7′), 4.02 (1H, m, H-4), 4.10 (1H, t, $J_{2,3}=J_{3,4}$=9 Hz, H-3), 4.92 (1H, t, $J_{1,2}=J_{1,6}$=9 Hz, H-1), 5.22 (1H, t, H-2).

Found: C, 29.22; H, 3.33; Br, 52.96%. Calcd for $C_{11}H_{15}O_4Br_3$: C, 29.30; H, 3.35; Br, 53.16%.

*Di-O-acetyl-(1,3,5/2)-5-bromo-3-bromomethyl-1,2-cyclohexanediol (**11**).* Compound **9** (1 g) was treated with hydrogen bromide in acetic acid in the same way as for **4**. The crude product was recrystallized from ethanol to give **11** (1.2 g, 75%): mp 136—137 °C; ^{1}H NMR ($CDCl_3$) δ 1.63—2.86 (5H, m, H-3, and C-4 and C-6 methylene), 2.01 (3H, s) and 2.05 (3H, s) (OAc), 3.26—3.40 (2H, m, $C\underline{H}_2$Br), 4.00 (1H, nine-line peak, H-5), 4.76 (1H, td, $J_{1,2}=J_{1,6ax}$=8.5 Hz, $J_{1,6eq}$=3.5 Hz, H-1), 4.96 (1H, dd, $J_{2,3}$=10 Hz, H-2).

Found: C, 35.50; H, 4.27; Br, 43.07%. Calcd for $C_{11}H_{16}O_4Br_2$: C, 35.51; H, 4.33; Br, 42.95%.

*Tri-N,O-acetyl-(1,4/2)-4-amino-2-hydroxymethyl-1-cyclohexanol (**14**).* To a solution of **4** (0.53 g) in THF (10 ml) was added a suspension of LAH (0.09 g) in THF (6 ml) at 0 °C, and the reaction mixture was stirred at an ambient temperature for 1.5 h, and then worked up in the usual manner. The syrupy product was acetylated and purified by chromatography on silica gel with chloroform to give di-*O*-acetyl-(1/2,4)-4-bromo-2-hydroxymethyl-1-cyclohexanol (**12**) (0.27 g, 46%) as a homogeneous syrup; ^{1}H NMR ($CDCl_3$) δ 1.19—2.57 (7H, m, H-2, and C-3, C-4, and C-5 methylene), 2.03 (3H, s) and 2.06 (3H, s) (OAc), 4.00 (1H, tt, $J_{3ax,4}=J_{4,5ax}$=13 Hz, $J_{3eq,4}=J_{4,5eq}$=4.5 Hz, H-4), 4.01 (2H, d, $C\underline{H}_2$OAc), 4.65 (1H, td, $J_{1,2}=J_{1,6eq}$= 4 Hz, H-1).

A mixture of crude **12** (0.21 g), sodium azide (0.2 g), and 90% aqueous 2-methoxyethanol (10 ml) was heated at reflux for 45 h, and then evaporated to dryness. The residue was directly acetylated in the usual manner and the product was purified by chromatography on alumina with chloroform to give di-*O*-acetyl-(1,4/2)-4-azido-2-hydroxymethyl-1-cyclohexanol (**13**) as a homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ 1.45—2.41 (7H, m, H-2, and C-3, C-5, and C-6 methylene), 2.04 (6H, s, two OAc), 3.76—3.99 (1H, m, H-4), 3.96—4.11 (2H, m, $C\underline{H}_2$OAc), 4.65 (1H, td, $J_{1,2}=J_{1,6ax}$=10 Hz, $J_{1,6eq}$=4.5 Hz, H-1).

A solution of crude **13** (0.16 g) in ethanol (6 ml) was hydrogenated with Raney nickel at an ambient temperature overnight. The product was acetylated in the usual manner. Recrystallization of the crude product from ethanol–ether gave **14** (0.043 g, 25%) as needles: mp 111—112.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.19—2.21 (7H, m, H-2, and C-3, C-5, and C-6 methylene), 1.99 (3H, s, NAc), 2.05 (6H, s, two OAc), 3.88—4.26 (3H, m, H-4 and $C\underline{H}_2$NHAc), 4.73 (1H, td, $J_{1,2}=J_{1,6ax}$=8.5 Hz, $J_{1,6eq}$=4.5 Hz, H-1), 5.73 (1H, d, J=6 Hz, N$\underline{H}$).

Found: C, 57.23; H, 7.58; N, 5.29%. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16%.

*Tri-N,O-acetyl-(1,4/2)-4-amino-2-aminomethyl-1-cyclohexanol (**16**).* A mixture of **5** (0.47 g), sodium azide (0.59 g), and 90% aqueous 2-methoxyethanol (15 ml) was heated at 110 °C for 17 h, and then evaporated to dryness. The residue was acetylated in the usual manner and the product was purified by chromatography on alumina to give (1,4/2)-4-azido-2-(azidomethyl)cyclohexyl acetate (**15**) as a homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ 1.21—2.41 (7H, m, H-2, and C-3, C-5, and C-6 methylene), 2.06 (3H, s, OAc), 3.32 (2H, d, J=4.5 Hz, $C\underline{H}_2N_3$), 3.78—3.96 (1H, m, H-4), 4.95 (1H, td, $J_{1,2}=J_{1,6ax}$=9.5 Hz, $J_{1,6eq}$=5 Hz, H-1).

Crude **15** was hydrogenated in ethanol with Raney nickel as in the case of crude **13**. The product was acetylated in the usual manner. Recrystallization of the crude product from ethanol gave **16** (0.12 g, 30% based on **5** used) as needles: mp 189—190 °C; ^{1}H NMR ($CDCl_3$) δ 1.10—2.38 (7H, m, H-1, and C-3, C-5, and C-6 methylene), 1.97 (6H, s, two NAc), 2.06 (3H, s, OAc), 2.83—3.72 (2H, m, $C\underline{H}_2$-NHAc).

Found: C, 57.53; H, 8.12; N, 10.12%. Calcd for $C_{13}H_{22}N_2O_4$: C, 57.76; H, 8.20; N, 10.36%.

*Tetra-N,O-acetyl-(1,3/2,5)-5-amino-3-hydroxymethyl-1,2-cyclohexanediol (**19**).* A mixture of **11** (1.86 g), anhydrous sodium acetate (1.23 g), and 90% aqueous 2-methoxyethanol (35 ml) was heated at 90 °C with stirring overnight. The reaction mixture was evaporated and the residue was extracted with hot chloroform (50 ml). The extracts were passed through a short alumina column and then evaporated to give tri-*O*-acetyl-(1,3,5/2)-5-bromo-3-hydroxymethyl-1,2-cyclohexanediol (**17**) (1.37 g, 78%) as a homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ 1.62—2.87 (5H, m, H-3, and C-6 methylene), 2.01 (3H, s), 2.03 (3H, s), and 2.06 (3H, s) (OAc), 3.75—4.27 (3H, m, H-5 and $C\underline{H}_2$OAc), 4.76 (1H, td, $J_{1,2}=J_{1,6ax}$=9.5 Hz, $J_{1,6eq}$=5 Hz, H-1), 4.96 (1H, t, $J_{2,3}$=9.5 Hz, H-2).

A mixture of crude **17** (1.05 g), sodium azide (0.6 g), and 90% aqueous 2-methoxyethanol (30 ml) was refluxed for 20 h. The reaction mixture was evaporated and acetylated in the usual manner. The product was purified by chromatography on alumina to give tri-*O*-acetyl-(1,3/2,5)-5-azido-3-hydroxymethyl-1,2-cyclohexanediol (**18**) (1.05 g) as a homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ 1.52—2.57 (5H, m, H-3, and C-4 and C-6 methylene), 1.99 (3H, s) and 2.03 (6H, s) (OAc), 3.72—4.28 (3H, m, H-5 and $C\underline{H}_2$OAc), 4.72—5.25 (2H, m, H-1 and H-2).

Compound **18** (1.0 g) was hydrogenated in ethanol (20 ml) containing acetic anhydride (0.5 ml) with Raney nickel in the same way as for **7**. The product was crystallized from ether to give **19** (0.37 g, 40% based on **17** used) as needles: mp 193—194 °C; ^{1}H NMR ($CDCl_3$) δ 1.49—2.48 (5H, m, H-3, and C-4 and C-6 methylene), 1.99 (6H, s), 2.02 (3H, s), and 2.03 (3H, s) (OAc), 3.88 (1H, dd, J_{7gem}=11.5 Hz, $J_{3,7}$=4.5 Hz, H-7), 4.15 (1H, dd, $J_{3,7'}$=4 Hz, H-7′), 4.28 (1H, m, H-5), 4.88 (1H, t, $J_{1,2}=J_{2,3}$=9 Hz, H-2), 4.97 (1H, td, $J_{1,6ax}$=9 Hz, $J_{1,6eq}$=3 Hz, H-1), 6.38 (1H, d, $J_{5,NH}$=7 Hz, N$\underline{H}$).

Found: C, 55.00; H, 7.01; N, 4.27%. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25%.

*Tetra-N,O-acetyl-(1,3/2,5)-5-amino-3-aminomethyl-1,2-cyclohexanediol (**21**).* A mixture of **11** (0.74 g), sodium azide (0.78 g), and 90% aqueous *N,N*-dimethylformamide (20 ml) was heated at 125 °C for 20 h. The reaction mixture was processed by the usual method and the syrupy product was purified by alumina column to give di-*O*-acetyl-(1,3/2,5)-5-azido-3-azidomethyl-1,2-cyclohexanediol (**20**) (0.61 g, 97%) as a homogeneous syrup. The compound was di-

rectly hydrogenated as in the case of **18** and the product was crystallized from ethanol to give **21** (0.39 g, 59%) as needles: mp 236—237 °C (capil); ^{1}H NMR (DMSO-d_6) δ 1.36—2.46 (5H, m, H-3, and C-4 and C-6 methylene), 1.88 (3H, s) and 1.92 (3H, s) (NAc), 2.02 (3H, s) and 2.08 (3H, s) (OAc), 3.2—3.56 (2H, m, CH_2NHAc), 4.08—4.39 (1H, m, H-5), 4.85 (1H, t, $J_{1,2}=J_{2,3}=9.5$ Hz, H-2), 5.22 (1H, td, $J_{1,6ax}=9.5$ Hz, $J_{1,6eq}=5$ Hz, H-1), 7.93 (1H, t, $J_{7,NH}=J_{7',NH}=5.5$ Hz, CH_2NHAc), 8.27 (1H, d, $J_{5,NH}=6.5$ Hz, CHNHAc).

Found: C, 54.63; H, 7.28; N, 8.54%. Calcd for $C_{15}H_{24}N_2O_6$: C, 54.87; H, 7.37; N, 8.53%.

Tri-O-*acetyl-(1,3/2,4,6)-3,4-dibromo-6-hydroxymethyl-1,2-cyclohexanediol* (**22**). A mixture of **10** (9.0 g), anhydrous sodium acetate (4.9 g), and 90% aqueous 2-methoxyethanol (100 ml) was heated at 90 °C for two days. The reaction mixture was worked up by the usual method and the product was directly acetylated. TLC indicated the formation of one major and three minor components. Crystallization of the mixture from ethanol gave the main product, **22** (4.3 g, 50%) as prisms: mp 128—129 °C; ^{1}H NMR ($CDCl_3$) δ 1.77—2.71 (3H, m, H-6 and C-5 methylene), 2.01 (3H, s) and 2.06 (6H, s) (OAc), 3.74—4.26 (4H, m, H-3, H-4, and CH_2OAc), 4.91 (1H, dd, $J_{1,2}=9$ Hz, $J_{1,6}=10$ Hz, H-1), 5.20 (1H, t, $J_{2,3}=10$ Hz, H-2).

Found: C, 36.42; H, 4.17; Br, 37.65%. Calcd far $C_{13}H_{18}O_6Br_2$: C, 36.30; H, 4.22; Br, 37.16%.

Di-O-*acetyl-(1,3/2,4,6)-6-azidomethyl-3,4-dibromo-1,2-cyclohexanediol* (**23**). A mixture of **10** (4.5 g), sodium azide (1.95 g), and 90% aqueous 2-methoxyethanol (60 ml) was heated at 95 °C for 90 min. The reaction mixture was worked up by the usual method. The product was recrystallized from ethanol to give **23** (3.8 g, 91%) as needles: mp 114—115 °C; ^{1}H NMR ($CDCl_3$) δ 1.71—2.73 (3H, m, H-6 and C-5 methylene), 2.04 (3H, s) and 2.07 (3H, s) (OAc), 3.18 (1H, dd, $J_{7gem}=11$ Hz, $J_{6,7}=3.5$ Hz, H-7), 3.44 (1H, dd, $J_{6,7'}=2$ Hz, H-7'), 3.94—4.18 (2H, m, H-3 and H-4), 4.86 (1H, t, $J_{1,2}=J_{1,6}=10$ Hz, H-1), 5.19 (1H, t, $J_{2,3}=10$ Hz, H-2).

Found: C, 32.08; H, 3.68; N, 10.26; Br, 38.78%. Calcd for $C_{11}H_{15}N_3O_4Br_2$: C, 31.99; H, 3.66; N, 10.17; Br, 38.69%.

Di-O-*acetyl-1,2-anhydro-(1,2,4,6/3)-6-bromo-4-hydroxymethyl-1,2,3-cyclohexanetriol* (**24**). To a solution of **22** (2.15 g) in methanol (20 ml) was added 1 M-methanolic sodium methoxide (10 ml, 2 molar equiv.) and the mixture was stirred at an ambient temperature for 3 h. The solution was neutralized with 1 M-hydrochloric acid and then evaporated to dryness. The residue was treated with acetic anhydride (5 ml) and pyridine (10 ml) overnight. The product was purified by alumina column to give a syrup which crystallized spontaneously to give **24** (1.5 g, 98%) as prisms: mp 58—59.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.54—2.19 (3H, m, H-4 and C-5 methylene), 2.05 (3H, s) and 2.11 (3H, s) (OAc), 3.26 (1H, d, $J_{1,2}=3.5$ Hz, H-2), 3.52 (1H, broad d, $J_{1,6}=2$ Hz, H-1), 3.90—4.02 (2H, m, CH_2OAc), 4.37 (1H, eight-line peak, $J_{5ax,6}=J_{5eq,6}=6$ Hz, H-6), 4.88 (1H, d, $J_{3,4}=9$ Hz, H-3).

Found: C, 42.92; H, 4.90; Br, 26.12%. Calcd for $C_{11}H_{15}O_5Br$: C, 43.02; H, 4.92; Br, 26.02%.

O-*Acetyl-1,2-anhydro-(1,2,4,6/3)-4-azidomethyl-6-bromo-1,2,3-cyclohexanetriol* (**25**). To a solution of **23** (3.3 g) in methanol (30 ml) was added 1 M-methanolic sodium methoxide (16 ml, 2 molar equiv.) and the mixture was left to stand at an ambient temperature for 5 h. The reaction mixture was processed as in the preparation of **24**. The product was chromatographed on silica gel (85 g) with butanone-toluene (1 : 12, v/v) as an eluent to give **25** (1.82 g, 78%) as a homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ 1.56—2.19 (3H, m, H-4 and C-5 methylene), 2.13 (3H, s, OAc), 3.20—3.35 (3H, m, H-2 and CH_2N_3), 3.51 (1H, broad q, $J_{1,2}=4$ Hz, $J_{1,6}=2$ Hz, H-1), 4.36 (1H, eight-line peak, $J_{5ax,6}=11$ Hz, $J_{5eq,6}=6$ Hz, H-6), 4.84 (1H, broad d, $J_{3,4}=9$ Hz, H-3).

Found: C, 37.19; H, 4.14; N, 14.41; Br, 27.27%. Calcd for $C_9H_{12}N_3O_3Br$: C, 37.26; H, 4.17; N, 14.48; Br, 27.54%.

Di-O-*acetyl-1,2-anhydro-(1,2,4/3,6)-6-azido-4-hydroxymethyl-1,2,3-cyclohexanetriol* (**26**). A mixture of **24** (0.92 g), sodium azide (0.59 g), and *N,N*-dimethylformamide (15 ml) was heated at 90 °C for 2.5 h. TLC indicated the formation of one major component, together with **24** and three minor components. The reaction mixture was processed by the usual method and the product was purified in the same way as for **25** to give the main product, **26** (0.25 g, 31%) as a homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ 1.51—2.55 (3H, m, H-4 and C-5 methylene), 2.05 (3H, s) and 2.12 (3H, s) (OAc), 3.10 (1H, d, $J_{1,2}=3$ Hz, H-2), 3.23 (1H, t, $J_{1,6}=3$ Hz, H-1), 3.94—4.01 (2H, m, CH_2OAc), 4.19 (1H, broad q, $J_{5ax,6}=J_{5eq,6}=3$ Hz, H-6), 4.87 (1H, d, $J_{3,4}=9.5$ Hz, H-3).

Found: C, 48.83; H, 5.56; N, 15.37%. Calcd for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61%.

Penta-N,O-*acetyl-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (validamine)* (**30**). A solution of **26** (0.47 g) in methanol (14 ml) containing acetic anhydride (0.5 ml) was hydrogenated in the presence of Raney nickel as in the preparation of **7** to give a crude syrup of tri-*N,O*-acetyl-1,2-anhydro-(1,2,4/3,6)-6-amino-4-hydroxymethyl-1,2,3-cyclohexanetriol (**28**). The compound was treated with refluxing 80% aqueous acetic acid (10 ml) for 13 h and the reaction mixture was evaporated to dryness. The residue was acetylated in the usual manner and the product was crystallized from ethanol to give **30** (0.2 g, 30%) as prisms: mp 197—198 °C. The compound was identified with an authentic active sample[8] by comparison of ^{1}H NMR ($CDCl_3$) and IR spectra.

Penta-N,O-*acetyl-(1,3,4/2,6)-4-amino-6-aminomethyl-1,2,3-cyclohexanetriol* (**31**). A mixture of (0.87 g), sodium azide (0.59 g), and *N,N*-dimethylformamide (15 ml) was heated at 90 °C for 2 h. TLC indicated the formation of one major and five minor components. The products were fractionated by silica gel column (50 g) with butanone-toluene (1 : 12, v/v) as an eluent. The major fraction gave *O*-acetyl-1,2-anhydro-(1,2,4/3,6)-6-azido-4-azidomethyl-1,2,3-cyclohexanetriol (**27**) (0.37 g, 50%) as a homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ 1.48—2.30 (3H, m, H-6 and C-5 methylene), 2.14 (3H, s, OAc), 3.09 (1H, d, $J_{1,2}=3.5$ Hz, H-2), 3.17—3.55 (3H, m, H-1 and CH_2N_3), 4.19 (1H, q, $J_{1,6}=J_{5ax,6}=J_{5eq,6}=2.5$ Hz, H-6), 4.83 (1H, d, $J_{3,4}=9.5$ Hz, H-3). Compound **27** decomposed on being left to stand at an ambient temperature, no satisfactory analytical data being obtained. Thus, crude **27** was directly used in the next step.

A solution of **27** (0.34 g) in methanol containing acetic anhydride (0.5 ml) was hydrogenated with Raney nickel in the same way as for **7**, and the reduction product was treated with aqueous acetic acid as in the preparation of **30**. The acetylated product was crystallized from ethanol-ether to give **31** (0.11 g, 21%) as needles: mp 246—248 °C; ^{1}H NMR ($CDCl_3$) δ 1.41—2.38 (3H, m, H-6 and C-5 methylene), 2.01 (6H, s, two NAc), 2.03 (3H, s) 2.17 (3H, s), and 2.19 (3H, s) (OAc), 2.66—3.11 (1H, m) and 3.41—3.88 (1H, m) (CH_2NHAc), 4.35—4.76 (1H, m, H-4), 4.78 (1H, t, $J_{1,2}=J_{1,6}=9.5$ Hz, H-1), 4.91 (1H, dd, $J_{2,3}=$

9.5 Hz, $J_{3,4}=4$ Hz, H-3), 5.30 (1H, t, H-2), 6.00—6.28 (2H, broad d, two NH).

Found: C, 52.52; H, 6.65; N, 7.18%. Calcd for $C_{17}H_{28}N_2O_8$: C, 52.84; H, 6.78; N, 7.25%.

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References

1) Presented at the 26th International Congress of Pure and Applied Chemistry, Tokyo, September 8, 1977 (abstracts of papers of the meeting, p. 1099). All the compounds described in this paper are racemic. All the formulas depict one enantiomer of the respective racemates.

2) The preceding papers of this series: a) T. Suami, S. Ogawa, T. Ishibashi, and I. Kasahara, *Bull. Chem. Soc. Jpn.*, **49**, 1388 (1976); b) T. Suami, S. Ogawa, K. Nakamoto, and I. Kasahara, *Carbohydr. Res.*, **58**, 240 (1977).

3) M. P. Kunstman, D. S. Tarbell, and R. L. Autry, *J. Am. Chem. Soc.*, **84**, 4115 (1962). The facile synthesis of **1** by Diels-Alder reaction of acrylic acid with furan had been reported.[2b]

4) The nomenclature used in this paper is based on the IUPAC-IUB Tentative Cyclitol Nomenclature Rule [*J. Biol. Chem.*, **22**, 5809 (1968)]. Alternatively, according to McCasland's proposal, 5-hydroxymethyl-1,2,3,4-cyclohexanetetrols are designated pseudo-aldohexopyranoses, and their configurations are unambiguously determined by use of prefix of the corresponding true sugars (including anomers) [G. E. McCasland, S. Furuta, and L. J. Durham, *J. Org. Chem.*, **31**, 1516 (1966)].

5) In addition to penta-*O*-acetyl-pseudo-β-DL-glucopyranose, 9-*endo*-acetoxy-2,7-dioxatricyclo[4.2.1.$0^{4,8}$]nonane was isolated in 8% yield: crystals, mp 75—76 °C (lit,[3] 80—81 °C).

6) The mother liquor from crystallization of **22** was condensed and the mixture was fractionated by silica gel column to give mainly crystalline tetra-*O*-acetyl-(1,4,6/2,3)-6-bromo-4-hydroxymethyl-1,2,3-cyclohexanetriol and syrupy tetra-*O*-acetyl-(3,6/4,5)-3,4,5-trihydroxy-6-hydroxymethylcyclohex-1-ene, structures of which were tentatively assigned.

7) One of the by-products was found to be tri-*O*-acetyl-(1,2,4/3,6)-2,4-diazido-6-hydroxymethyl-1,3-cyclohexanediol, which was isolated by fractionation of the acetylated products.

8) An authentic sample was prepared by conventional acetylation of validamine hydrochloride kindly supplied by Dr. Satoshi Horii.

9) S. Nishimura, *Bull. Chem. Soc. Jpn.*, **32**, 61 (1959).