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Pseudo-sugars. VIII. Synthesis of DL-1-Epivalidamine and Related Compounds[1,2]

Seiichiro OGAWA, Masayuki OYA, Tatsushi TOYOKUNI, Noritaka CHIDA, and Tetsuo SUAMI*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223

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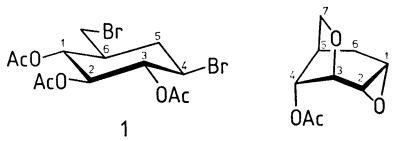
DL-1-Epivalidamine has been synthesized starting from the dianhydro compound derived from DL-1,2,3-tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol. DL-7-Amino-7-deoxy-1-epivalidamine, which is considered to be a homolog of 2-deoxystreptamine, has also been prepared.

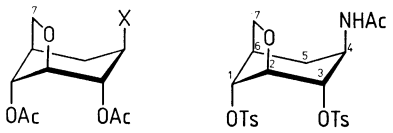
In connection with the previous paper of this series,[3] the 1-epimer of validamine and its derivatives have been synthesized regioselectively from the dianhydro derivative of (hydroxymethyl)cyclohexanetetrol.

It was described that the nucleophilic substitution reaction of DL-1,2,3-tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**1**)[3] with an azide ion proceeded specifically through an S_N2 mechanism to give the diazido compound with an inversion of the configuration at C-4.[3] On the other hand, attempted introduction of an azido function at C-4 with retention of the configuration have been made *via* an intermediate cyclic 3,4-acetoxonium ion or a 3,4-epoxide,[4] but all failed probably due to a steric hindrance of a bulky substituent at C-6 and/or a ready anchimeric assistance of the C-2 acetoxyl group at C-3. Therefore, in order to control the course of a nucleophilic attack at the oxirane ring, the 2,7-anhydro ring was introduced to protect the C-2 hydroxyl group and to restrict a conformational flexibility. Thus, treatment of **1** with an excess of methanolic sodium methoxide at reflux for 2 h gave selectively the dianhydro compound **2** in 65% yield. The structure of **2** was confirmed on the basis of analytical data and ^{1}H NMR spectroscopy. In the ^{1}H NMR spectrum, the signal due to the C-7 endo proton appeared as a doublet (J_{gem}=9 Hz) at δ 3.75, which would correspond to the dihedral angle $\Phi_{5,7endo}$ (90°) ($J_{5,7endo}$= *ca.* 0 Hz) derived from a Dreiding model.

A nucleophilic substitution reaction of **2** with a methoxide ion or azide ion occurred regiospecifically at C-1 to give, after successive acetylation, the methyl ether **3** (87%) or the azide **4** (81%). An attack of an anion at C-2 seemed to be hindered by the ring oxygen atom. The structures were established by the ^{1}H NMR spectra. In the spectrum of **3**, the signal for the C-7 endo proton was remarkably deshielded (*ca.* 0.25 ppm) by a close proximity of the endo methoxyl group. Compound **4** was hydrogenated in ethanol in the presence of Raney nickel followed by acetylation to give the amine acetate **5** in 40% yield, which was alternatively prepared in 74% yield by ammonolysis of **2** in methanol followed by acetylation. *O*-Deacetylation of **5** with methanolic sodium methoxide followed by the conventional tosylation gave the ditosylate **6** in 45% overall yield. Opening of the anhydro ring of **3** was effected by heating in acetic acid–acetic anhydride (1:1) in a sealed tube at 85 °C for 20 h to give DL-2,3,4-tri-*O*-acetyl-1-*O*-methyl-(1,3,5/2,4)-5-acetoxymethyl-1,2,3,4-cyclohexanetetrol (**7**) in 39% yield.



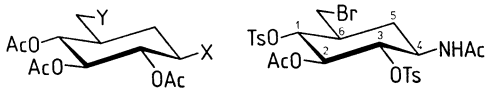
1 **2**



6

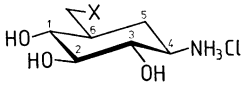
	X
3	OMe
4	N_3
5	NHAc

Scheme 1.



12

	X	Y
7	OMe	OAc
8	NHAc	Br
9	NHAc	OAc
10	NHAc	N_3
11	NHAc	NHAc

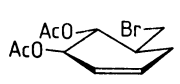


	X
13	OH
14	NH_3Cl

Scheme 2.

The anhydro ring of **5** was cleaved readily by the influence of 30% hydrobromic acid in acetic acid in a sealed tube at 75 °C for 23 h to give DL-1,2,3-tri-*O*-acetyl-(1,3/2,4,6)-4-acetamido-6-bromomethyl-1,2,3-cyclohexanetriol (**8**, 67%). Similarly, the corresponding bromo ditosylate **12** was obtained from **6** in 45% yield. The ^{1}H NMR spectrum of **12** was in fully accord with the assigned structure, establishing the ring structure of **4**.

The C-7 bromine atom of **8** was easily displaced by an acetate ion or an azide ion in the usual way to produce a peracetyl 1-epivalidamine (**9**, 61%) or the azido compound (**10**, 90%). Compound **10** was reduced with Raney nickel and successively acetylated to give the diamine diacetate **11** in 92% yield. Acid hydrolysis of **9** and **11** with 6 M hydrochloric acid



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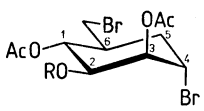
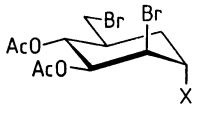
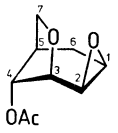


R	
16	H
17	Ac



X	
18	Br
19	OAc
20	OH



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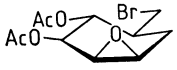
Scheme 3.



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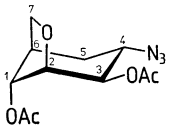

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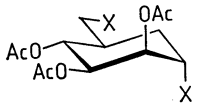

X	
24	N_3
25	NHAc

Scheme 4.

(1 M=1 mol dm^{-3}) at reflux for 2 h gave the hydrochloride **13** and the dihydrochloride **14** in quantitatively yields, respectively.

Compound **13** was pseudo-β-DL-glucopyranosylamine, and **14** was considered to be a homolog of 2-deoxystreptamine, a common constituent of clinically important aminocyclitol containing antibiotics.[5] Therefore, biological activities of antibiotics being replaced the 2-deoxystreptamine moiety with this homolog may be of considerable interest.

Interest in a reactivity of the stereoisomer **21** of **2** stimulated us to prepare it from (bromomethyl)cyclohexenediol diacetate **15**.[1] Treatment of **15** with bromine in aqueous acetic acid at room temperature afforded, after chromatography on silica gel, three dibromides **16** (34%), **19** (1.4%), and **20** (16%), and one tribromide **18** (0.7%). The ^{1}H NMR spectrum of triacetate **17** derived from **16** was interpreted by a first-order method, confirming the assigned structure. Mechanistically, an intermediate α-bromonium ion was opened by the adjacent trans acetoxyl group followed by acetyl group migration to give **16**, whereas, a β-bromonium ion was attacked from the rear side by nucleophiles present.[6] A similar treatment of **16** with an excess of methanolic sodium methoxide gave **21** in 84% yield. The ^{1}H NMR spectrum of **21** showed the signal for the C-7 endo proton as a doublet (J_{gem}=9.3 Hz) at δ 3.87 somewhat higher-field as compared with that of the *exo*-epoxide **2**.

In contrast with the case of **2**, a nucleophilic substitution reaction of **21** with an azide ion was shown to be very slow and give a complex mixture of products after a prolonged reaction time. The C-4 endo acetoxyl group seemed to interfere the attack of a nucleophile at C-1 or C-2. Therefore, the epoxide **22** was prepared by treatment of **15** with *m*-chloroperoxybenzoic acid in 1,2-dichloroethane in 23% yield.[7] Reaction of **22** with sodium azide and ammonium chloride in aqueous *N*,*N*-dimethylformamide gave selectively the diazide **24** in 65% yield. When the similar reaction was carried out in the absence of ammonium chloride, the monoazide **23** was obtained in 25% yield, together with **24** (48%). The epoxide ring seemed to be first opened by an azide ion and then the C-3 hydroxyl group, formed by an acetyl group migration under the basic conditions, competed with an azide ion to attack the C-6 bromomethyl group. Compound **24** was similarly converted into the diamine diacetate **25** in 41% yield. The ^{1}H NMR spectra of **24** and **25** supported their assigned structures.

Experimental[8]

DL-*4*-O-*Acetyl-1,2*:*3,7*-dianhydro-*(1,2,4/3,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol* (syn-*9-Acetoxy*-trans-*3,8-dioxatricyclo*[*4.2.1.0*^{2,4}]*nonane) (2).* A mixture of DL-tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**1**)[3] (10 g) in methanol (140 ml) containing sodium (2.33 g) was refluxed for 2 h. After having been cooled, the reaction mixture was treated with 1 M hydrochloric acid for neutralization and then evaporated to dryness. The residue was treated with acetic anhydride (20 ml) and pyridine (30 ml) at room temperature overnight. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and the solution was passed through a short column of alumina. The filtrate was evaporated and the residue was recrystallized from ligroin to give 2.8 g (65%) of **2** as needles: mp 64.5—65.5 °C. ^{1}H NMR ($CDCl_3$) δ=2.03 (3H, s, OAc), 3.03—3.20 (2H, br s, H-1 and H-2), 3.75 (1H, d, J_{gem}=9 Hz, H-7endo), 4.10 (1H, ddd, $J_{5,7exo}$=7.5 Hz, $J_{6exo,7exo}$=2 Hz, H-7exo), 4.78—4.83 (2H, m, H-3 and H-4).

Found: C, 58.68; H, 6.57%. Calcd for $C_9H_{12}O_4$: C, 58.38; H, 6.57%.

DL-*2,4-Di*-O-*acetyl-3,7-anhydro-1*-O-*methyl-(1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (3).* A mixture of **2** (0.20 g) and 5 M methanolic sodium methoxide (8 ml) was refluxed for 1 h. The reaction mixture was processed similarly as described for the preparation of **2** and the product was acetylated in the usual way to give, after crystallization from ethanol, 0.24 g (87%) of **3** as plates: mp 75—76.5 °C. ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s) and 2.08 (3H, s) (OAc), 3.35 (3H, s, OMe), 3.81 (1H, ddd, $J_{5,7exo}$=4.5 Hz, $J_{6exo,7exo}$=1.5 Hz, J_{gem}=7.5 Hz, H-7exo), 4.00 (1H, d, H-7endo), 4.26 (1H, t, $J_{2,3}$=$J_{3,4}$=4.5 Hz, H-3), 4.85 (2H, t, $J_{1,2}$=$J_{4,5}$=4.5 Hz, H-2 and H-4).

Found: C, 55.76; H, 6.92%. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.04%.

DL-*1,3-Di*-O-*acetyl-2,7-anhydro-(1,3/2,4,6)-4-azido-6-hydroxymethyl-1,2,3-cyclohexanetriol (4).* A mixture of **2** (0.30 g), sodium azide (0.37 g), and 90% aqueous 2-methoxy-

ethanol (6 ml) was heated at 110 °C for 1 h. The reaction mixture was evaporated to dryness and the residue was treated with acetic anhydride and pyridine at 60 °C for 2 h. The product was crystallized from ethanol–ether to give 0.36 g (81%) of **4** as prisms: mp 62.5—63.5 °C. ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s) and 2.08 (3H, s) (OAc), 3.67—4.07 (2H, m, H-7 and H-7′), 4.25 (1H, dd, $J_{1,2}$=3 Hz, $J_{2,3}$=5 Hz, H-2), 4.76—5.03 (2H, m, H-1 and H-3).

Found: C, 49.14; H, 5.73; N, 15.59%. Calcd for $C_{11}H_{16}N_3O_5$: C, 48.88; H, 5.98; N, 15.55%.

DL-*1,3-Di*-O-*acetyl-2,7-anhydro-(1,3/2,4,6)*-4-*acetamido*-6-*hydroxymethyl-1,2,3-cyclohexanetetrol* (**5**). *a)*: A solution of **4** (0.20 g) in ethanol (10 ml) was hydrogenated in the presence of Raney nickel T-4[9] (one spatula) at room temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was treated with acetic anhydride and pyridine in the usual way. The product was crystallized from ethanol–ether to give 85 mg (40%) of **5** as needles: mp 108.5—109.5 °C. ^{1}H NMR ($CDCl_3$) δ=1.95 (3H, s), 2.00 (3H, s), and 2.14 (3H, s) (NAc and OAc), 3.88 (2H, br s, H-7 and H-7′), 4.00—4.27 (1H, m, H-4), 4.14 (1H, dd, $J_{1,2}$=6 Hz, $J_{2,3}$=3 Hz, H-2), 4.74 (1H, t, $J_{3,4}$=3 Hz, H-3), 4.90 (1H, t, $J_{1,6}$=6 Hz, H-1), 6.19 (1H, br d, J=9 Hz, NH).

Found: C, 54.98; H, 6.67; N, 5.16%. Calcd for $C_{13}H_{19}NO_6$: C, 54.72; H, 6.73; N, 4.91%.

b): A mixture of **2** (2.8 g) and methanolic ammonia (150 ml, saturated at 5 °C) was heated in a sealed tube at 105 °C for 30 h. After having been cooled, the reaction mixture was concentrated and the residue was treated with acetic anhydride and pyridine in the usual way. The product was recrystallized from ethanol–ether to give 3.2 g (74%) of **5**, identical with the compound obtained from **4**.

DL-*2,7-Anhydro-1,3-di*-O-p-*tolylsulfonyl*-*(1,3/2,4,6)*-*4*-*acetamido*-*6*-*hydroxymethyl*-*1,2,3*-*cyclohexanetriol* (**6**). Compound **5** (0.26 g) was dissolved in 1 M methanolic sodium methoxide (5 ml) and the mixture was allowed to stand at room temperature overnight. The reaction mixture was neutralized with Amberlite IR-120 (H^+) and concentrated to an oil, which was treated with *p*-toluenesulfonyl chloride (1.1 g) in pyridine (7 ml) at room temperature for 2 d. The reaction mixture was poured into ice-water and extracted with chloroform (10 ml×3). The extracts were washed with aqueous sodium hydrogencarbonate and water, and dried. Evaporation of the solvent gave an oil (0.38 g), which was crystallized from ethanol to give 0.21 g (45%) of **6** as prisms: mp 156—157 °C. ^{1}H NMR ($CDCl_3$) δ=1.77 (3H, s, NAc), 2.40 (6H, s, tosyl methyl), 3.68—4.10 (4H, m, H-2 ,H-4, H-7, and H-7′), 4.41 (1H, dd, $J_{2,3}$=4.5 Hz, $J_{3,4}$=3 Hz, H-3), 4.72 (1H, t, $J_{1,2}$=$J_{1,6}$=4.5 Hz, H-1), 5.83 (1H, br d, J=7.5 Hz, NH), 7.23 (2H, d) and 7.67 (2H, d) and 7.26 (2H, d), and 7.76 (2H, d) (J=9 Hz, phenyl).

Found: C, 53.93; H, 5.32; N, 2.62; S. 12.31%. Calcd for $C_{23}H_{27}NO_8S_2$: C, 54.21; H, 5.35; N, 2.75; S, 12.58%.

DL-*2,3,4-Tri*-O-*acetyl*-*1*-O-*methyl*-*(1,3,5/2,4)*-*5*-*acetoxymethyl*-*1,2,3,4-cyclohexanetetrol* (**7**). A mixture of **3** (0.2 g), acetic acid (2 ml), and acetic anhydride (2 ml) was heated in a sealed tube at 85 °C for 20 h. After having been cooled , the mixture was poured into ice water (20 ml) and then neutralized with sodium hydrogencarbonate and extracted with ethyl acetate (20 ml). The extract was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated to dryness. The product was crystallized from ethanol–ether to give 0.11 g (39%) of **7** as needles: mp 74.5—75.5 °C. ^{1}H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.00 (3H, s), and 2.03 (6H, s) (OAc), 3.33 (3H, s, OCH_3), 3.16—3.57 (1H, m, H-1), 3.90—4.17 (2H, m, H-7 and H-7′), 4.73—5.37 (3H, m, H-2, H-3, and H-4).

Found C, 53.56; H, 6.66%. Calcd for $C_{16}H_{24}O_9$: C, 53.32; H, 6.73%.

DL-*1,2,3-Tri*-O-*acetyl*-*(1,3/2,4,6)*-*4*-*acetamido*-*6*-*bromomethyl*-*1,2,3-cyclohexanetriol* (**8**). A mixture of **5** (2.0 g) and 30% hydrogen bromide–acetic acid (4 ml) was heated in a sealed tube at 75 °C for 23 h. After having been cooled, the mixture was poured into ice-water and the solution was processed similarly as described for preparation of **7**. The product was crystallized from ethanol to give 1.9 g (67%) of **8** as prisms: mp 184—184.5 °C. ^{1}H NMR ($CDCl_3$) δ=1.92 (3H, s), 1.98 (3H, s), and 2.03 (6H, s) (NAc and OAc), 3.34 (2H, br d, $J_{6,7}$=$J_{6,7'}$=3 Hz, H-7 and H-7′). 3.83—4.37 (1H, m, H-4), 4.83 (1H, t) and 5.11 (1H, t) ($J_{1,2}$=$J_{2,3}$=9 Hz, H-2 and H-3), 4.91 (1H, t, $J_{1,6}$=9 Hz, H-1), 5.82 (1H, br d, J=7.5 Hz, NH).

Found: C, 44.06; H, 5.29; N, 3.55; Br, 19.31%. Calcd for $C_{15}H_{22}O_7BrN$: C, 44.12; H, 5.44; N, 3.43; Br, 19.57%

DL-*2*-O-*Acetyl-1,3-di*-O-p-*tolylsulfonyl*-*(1,3/2,4,6)*-*4*-*acetamido*-*6*-*bromomethyl*-*1,2,3-cyclohexanetriol* (**12**). A mixture of **6** (0.15 g) and 15% hydrogen bromide in acetic acid (2 ml) was heated in a sealed tube at 85 °C for 22 h. The reaction mixture was poured into ice-water (30 ml) and, after, neutralization with sodium hydrogencarbonate, extracted with chloroform (45 ml). The extract was processed similarly as described for preparation of **7**. The product was crystallized from acetone to give 0.17 g (45%) of **12** as prisms: mp 207—209 °C. ^{1}H NMR (DMSO-d_6) δ=1.49 (3H, s) and 1.73 (3H, s) (NAc and OAc), 2.88—3.62 (2H, m, H-7 and H-7′), 3.80—4.30 (1H, m, H-4), 4.56 (1H, dd) and 4.67 (1H, dd) ($J_{1,2}$=$J_{2,3}$=10.5 Hz, $J_{1,6}$=$J_{3,4}$=7.5 Hz, H-1 and H-3), 5.19 (1H, t, H-2), 7.33 (2H, d) and 7.59 (2H, d), and 7.38 (2H, d) and 7.68 (2H, d) (J=9 Hz, phenyl).

Found: C, 47.28; H, 4.77; N, 2.08%. Calcd for $C_{25}H_{30}O_9BrNS_2$: C, 47.46; H, 4.79; N, 2.21%.

DL-*1,2,3-Tri*-O-*acetyl*-*(1,3/2,4,6)*-*4*-*acetamido*-*6*-*acetoxymethyl*-*1,2,3-cyclohexanetriol* (**9**). A mixture of **8** (0.2 g), anhydrous sodium acetate (0.24 g), and 90% aqueous 2-methoxyethanol (5 ml) was heated at 85 °C for 23 h. The reaction mixture was evaporated and the residue was acetylated in the usual way. The product was recrystallized from ethanol–ether to give 0.12 g (61%) of **9** as prisms: mp 109—110 °C. ^{1}H NMR δ=1.89 (3H, s), 1.96 (3H, s), 1.98 (3H, s), and 2.00 (6H, s) (NAc and OAc), 3.82—4.27 (3H, m, H-4, H-7, and H-7′), 4.78 (1H, t) and 5.08 (1H, t) ($J_{1,2}$=$J_{2,3}$=$J_{3,4}$=9 Hz, H-2 and H-3), 4.96 (1H, t, $J_{1,6}$=9 Hz, H-1), 5.73 (1H, br d, J=7.5 Hz, NH).

Found: C, 52.61; H, 6.38; N, 3.59%. Calcd for $C_{17}H_{25}NO_9$: C, 52.70; H, 6.52; N, 3.62%.

DL-*1,2,3-Tri*-O-*acetyl*-*(1,3/2,4,6)*-*4*-*acetamido*-*6*-*azidomethyl*-*1,2,3-cyclohexanetriol* (**10**). A mixture of **8** (0.20 g), sodium azide (0.1 g), and 90% aqueous 2-methoxyethanol (4 ml) was heated at 85 °C for 3 h. The reaction mixture was evaporated and the residue was acetylated in the usual way. The product was recrystallized from ethanol to give 0.16 g (90%) of **10** as prisms: mp 152.5—154 °C. ^{1}H NMR ($CDCl_3$) δ=1.91 (3H, s), 1.97 (3H, s), 2.02 (3H, s), and 2.03 (3H, s) (NAc and OAc), 3.18 (1H, dd, $J_{6,7}$=4.5 Hz, J_{gem}=12 Hz, H-7), 3.36 (1H, dd, $J_{6,7'}$=4.5 Hz, H-7′), 3.87—4.27 (1H, m, H-4), 4.79 (1H, t) and 5.08 (1H, t) ($J_{1,2}$=$J_{2,3}$=$J_{3,4}$=9 Hz, H-2 and H-3), 4.84 (1H, t, $J_{1,6}$=9 Hz, H-1), 5.85 (1H, br d, J=7.5 Hz, NH).

Found: C, 48.78; H, 5.97; N, 14.84%. Calcd for $C_{15}H_{22}N_4O_7$: C, 48.63; H, 6.00; N, 15.13%.

DL-*1,2,3-Tri*-O-*acetyl*-*(1,3/2,4,6)*-*4*-*acetamido*-*6*-*acetamido*-

*methyl-1,2,3-cyclohexanetriol (**11**).* A mixture of **10** (0.10 g) in ethanol (10 ml) was hydrogenated in the presence of Raney nickel T-4 (one spatula) in a Parr shaker apparatus at room temperature overnight. The mixture was processed as described for the preparation of **5**. The product was crystallized from ethanol to give 0.10 g (92%) of **11**: mp 56—57.5 °C. ^{1}H NMR ($CDCl_3$) δ=1.87 (3H, s), 1.97 (6H, s), 2.00 (3H, s), and 2.05 (3H, s) (NAc and OAc), 2.83 (1H, dd, $J_{6,7}$=5 Hz, J_{gem}=7.5 Hz, H-7), 3.55 (1H, dd, $J_{6,7'}$= 3 Hz, H-7'), 3.90—4.28 (1H, m, H-4), 4.71 (1H, dd) and 4.74 (1H, dd) ($J_{1,2}$=$J_{2,3}$=9 Hz, $J_{1,6}$=10 Hz, $J_{3,4}$=10.5 Hz, H-1 and H-3), 5.09 (1H, t, H-2), 5.75 (1H, br d, J=5 Hz, 4-NH), 6.01 (1H, m, 7-NH).

Found: C, 52.98; H, 6.73; N, 6.91%. Calcd for $C_{17}H_{26}N_2O_8$: C, 52.82; H, 6.79; N, 7.25%.

DL-*(1,3/2,4,6)-4-Amino-6-hydroxymethyl-1,2,3-cyclohexanetriol Hydrochloride (**13**).* A mixture of **9** (0.20 g) and 6 M hydrochloric acid (10 ml) was refluxed for 90 min, and then evaporated to dryness. The residue was crystallized from ethanol–water to give 0.11 g (100%) of **13** as prisms: mp 195—196 °C. TLC (cellulose): R_f 0.37, 1-butanol–ethanol–water–17% aqueous ammonia (4:5:2:4).[10]

Found: C, 39.59; H, 7.63; N, 6.31; Cl, 16.80%. Calcd for $C_7H_{16}NO_4Cl$: C, 39.34; H, 7.56; N, 6.56; Cl, 16.59%.

DL-*(1,3/2,4,6)-4-Amino-6-aminomethyl-1,2,3-cyclohexanetriol Dihydrochloride (**14**).* A mixture of **11** (0.61 g) and 6 M hydrochloric acid (25 ml) was refluxed for 2 h, and then evaporated to dryness. The residue was crystallized from ethanol–water to give 0.39 g (100%) of **14** as prisms: mp 194 °C, decomposed at 200—228 °C. TLC (cellulose): R_f 0.22, 1-butanol–ethanol–water–17% aqueous ammonia (4:5:2:4).[10]

Found: C, 33.54; H, 7.04; N, 11.00; Cl, 28.59%. Calcd for $C_7H_{18}N_2O_3Cl_2$: C, 33.74; H, 7.30; N, 11.25; Cl, 28.45%.

Bromination of DL-*1,2-Di-O-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol (**15**).*[11] Compound **15**[1] (2.0 g) was dissolved in acetic acid (30 ml) and then water (15 ml) was added. To the stirred solution was added bromine water (40 ml) containing 0.67 ml of bromine dropwise during 20 min at room temperature. After the reaction mixture was allowed to stand in a refrigerator overnight, the precipitates were collected by filtration and washed thoroughly with water to give a crystalline mixture (1.65 g) of products, which contained one major (R_f 0.20) together with two minor components [R_f 0.33 and 0.75 in 2-butanone–toluene (1:6)]. Recrystallization of the mixture from ethanol gave DL-1,3-di-*O*-acetyl-(1,4/2,3,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**16**, 0.92 g, 34%) as needles: mp 176—178 °C. ^{1}H NMR ($CDCl_3$) δ=2.11 (6H, s, OAc), 3.36 (2H, d, J=4.5 Hz, H-7 and H-7'), 4.12 (1H, br dd, $J_{1,2}$=9.5 Hz, $J_{2,3}$=3 Hz, H-2, on deuteration), 4.20—4.35 (1H, m, H-4), 4.90 (1H, t, $J_{1,6}$=9.5 Hz, H-1), 5.12 (1H, br t, $J_{3,4}$= 3 Hz, H-3).

Found: C, 34.14; H, 4.17; Br, 40.96%. Calcd for $C_{11}H_{16}O_5Br_2$: C, 34.05; H, 4.16; Br, 41.18%.

Compound **16** (0.82 g) was acetylated with acetic anhydride in pyridine in the usual way and the product was recrystallized from ethanol to give 0.41 g (45%) of the triacetate **17** as prisms: mp 96.5—97 °C. ^{1}H NMR ($CDCl_3$, 60 MHz) δ=2.00 (3H, s), 2.09 (3H, s), and 2.17 (3H, s) (OAc), 3.34 (2H, d, J=4.5 Hz, H-7 and H-7'), 4.33 (1H, q, $J_{3,4}$=$J_{4,5ax}$=$J_{4,5eq}$=3 Hz, H-4), 5.29 (1H, t, $J_{1,2}$=$J_{1,6}$= 9.5 Hz, H-1), 5.63 (1H, dd, $J_{2,3}$=3 Hz, H-2).

Found: C, 36.40; H, 4.22; Br, 37.35%. Calcd for $C_{13}H_{18}O_6Br_2$: C, 36.30; H, 4.42; Br, 37.16%.

The mother liquor of the crystalline mixture was neutralized with sodium hydrogencarbonate and extracted with ethyl acetate (150 ml). The extracts were concentrated and the residual oil was chromatographed on a silica gel column (50 g) with 2-butanone–toluene (1:15) as an eluent. The first fraction gave DL-1,2-di-*O*-acetyl-(1,4/2,3,6)-3,4-dibromo-6-bromomethyl-1,2-cyclohexanediol (**18**, 22 mg, 0.7%) as prisms: mp 94—95 °C. ^{1}H NMR ($CDCl_3$) δ=1.99 (6H, s, OAc), 3.19—3.35 (2H, m, H-7 and H-7'), 5.12—5.34 (2H, m, H-1 and H-2).

Found: C, 29.55; H, 3.51; Br, 52.95%. Calcd for $C_9H_{10}O_4Br_3$: C, 29.30; H, 3.35; Br, 53.16%.

The second fraction gave (R_f 0.54) gave DL-1,3,4-tri-*O*-acetyl-(1,4/2,3,5)-2-bromo-5-bromomethyl-1,3,4-cyclohexanetriol (**19**, 40 mg, 1.4%) as an oil. ^{1}H NMR ($CDCl_3$) δ= 2.00 (6H, s) and 2.04 (3H, s) (OAc), 3.10—3.42 (2H, m, H-7 and H-7'), 4.29 (1H, dd, $J_{1,2}$=3 Hz, $J_{2,3}$=3.5 Hz, H-2), 4.90 (1H, dd, $J_{3,4}$=9 Hz, H-3), 5.02—5.32 (2H, m, H-1 and H-4).

Found: C, 36.64; H, 4.20; Br, 37.17%. Calcd for $C_{13}H_{18}O_6Br_2$: C, 36.30; H, 4.23; Br, 37.15%.

The third fraction (R_f 0.33) gave DL-3,4-di-*O*-acetyl-(1,4/2,3,5)-2-bromo-5-bromomethyl-1,3,4-cyclohexanetriol (**20**, 0.44 g, 16%) as prisms: mp 109—110 °C. ^{1}H NMR ($CDCl_3$) δ=2.00 (6H, s, OAc), 3.12—3.46 (2H, m, H-7 and H-7'), 4.06—4.25 (1H, m, H-1), 4.25—4.40 (1H, m, H-2), 4.95—5.30 (2H, m, H-3 and H-4).

Found: C, 34.27; H, 4.29; Br, 40.97%. Calcd for $C_{11}H_{16}O_5Br_2$: C, 34.05; H, 4.16; Br, 41.18%.

The fourth fraction gave an additional amount of **16** (37 mg, total yield, 35.5%).

DL-*4-O-Acetyl-1,2:3,7-dianhydro-(1,2,3,5/4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**21**).* A mixture of **16** (0.40 g) and 1 M methanolic sodium methoxide (6.4 ml) was heated at 60 °C for 3.5 h. TLC [2-butanone–toluene (1:2)] indicated that **16** (R_f 0.44) disappeared immediately with a formation of an intermediate compound (R_f 0.08) which was then converted into a single compound (R_f 0.31). The reaction mixture was neutralized with 1 M hydrochloric acid and concentrated. The residue was treated with acetic anhydride and pyridine at room temperature overnight. The product was purified by chromatography on silica gel with 2 butanone–toluene (1:5) as an eluent to give 0.16 g (84%) of **21** as an oil. TLC: R_f 0.38 [2-butanone–toluene (1:4)]. ^{1}H NMR ($CDCl_3$) δ=2.14 (3H, s, OAc), 2.47—2.82 (1H, m, H-5), 3.87 (1H, d, J_{gem}=9.3 Hz, H-7endo), 4.08 (1H, dd, $J_{5,7exo}$=4.7 Hz, H-7exo), 4.22—4.47 (1H, m, H-1 or H-2), 4.47—4.69 (2H, m, H-3 and H-1 or H-2), 5.13 (1H, t, $J_{3,4}$=$J_{4,5}$=4.8 Hz, H-4).

Found: C, 58.40; H, 6.50%. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57%.

DL-*3,4-Di-O-acetyl-1,2-anhydro-(1,2,3,5/4)-5-bromomethyl-1,2,3,4-cyclohexanetetrol (**22**).* A mixture of **15** (1.5 g), *m*-chloroperoxybenzoic acid (1.52 g, *ca.* purity 70%), and dry 1,2-dichloroethane (40 ml) was refluxed for 3 h. The reaction mixture was washed with successively with 10% aqueous sodium sulfite (40 ml×3), saturated aqueous sodium hydrogencarbonate (40 ml×3), and water (40 ml×2), and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil, which was crystallized from ethanol. Recrystallization from ethanol–ether gave 0.44 g (23%) of **22**: mp 112.5—114 °C. ^{1}H NMR ($CDCl_3$) δ=2.02 (3H, s) and 2.05 (3H, s) (OAc), 3.08—3.45 (4H, H-1, H-2, H-7, and H-7'), 5.01 (1H, dd, $J_{3,4}$=8.5 Hz, $J_{4,5}$=9.5 Hz, H-4), 5.19 (1H, dd, $J_{2,3}$=1.5 Hz, H-3).

Found: C, 43.10; H, 4.85; Br, 25.76%. Calcd for $C_{11}H_{15}O_5Br$: C, 43.01; H, 4.92; Br, 26.02%.

*Reaction of **22** with Sodium Azide.* *a) In the Presence of Ammonium Chloride*: A mixture of **22** (63 mg), sodium

azide (67 mg, 5 molar equiv.), ammonium chloride (110 mg, 10 molar equiv.), and 90% aqueous *N,N*-dimethylformamide (DMF) (5 ml) was stirred at 80—85 °C for 3 h. The mixture was concentrated and the residue was treated with acetic anhydride (5 ml) and pyridine (5 ml) at room temperature overnight. Evaporation of the excess reagent gave a crude product which was purified by chromatography on silica gel (3 g) with 2-butanone–toluene (1:10) as an eluent to give 48 mg (67%) of DL-1,2,3-tri-*O*-acetyl-(1,4/2,3,6)-4-azido-6-azidomethyl-1,2,3-cyclohexanetriol (**24**) as an oil. TLC: R_f 0.52 [2-butanone–toluene (1:5)]. ^{1}H NMR ($CDCl_3$) δ=1.98 (3H, s), 2.04 (3H, s), and 2.11 (3H, s) (OAc), 3.24 (1H, dd, $J_{6,7}$=6 Hz, J_{gem}=12 Hz, H-7), 3.41 (1H, dd, $J_{6,7'}$=4 Hz, H-7'), 3.87 (1H, br q, J=*ca.* 4 Hz, H-4), 5.01—5.32 (3H, m, H-1, H-2, and H-3).

Found: C, 44.34; H, 5.36; N, 23.48%. Calcd for $C_{13}H_{18}N_6O_6$: C, 44.07; H, 5.12; N, 23.72%.

b) In the Absence of Ammonium Chloride: A mixture of **22** (0.10 g), sodium azide (0.11 g, 5 molar equiv.), and 90% aqueous DMF (5 ml) was stirred at 80—85 °C for 3 h. The mixture was concentrated and the residue was treated with acetic anhydride and pyridine in the usual way. TLC indicated the formation of two major products [R_f 0.52 and 0.45, 2-butanone–toluene (1:5)]. Evaporation of the excess reagent and the products were fractionated by a silica-gel column (5 g) with 2-butanone–toluene (1:10) as an eluent. The first fraction (R_f 0.52) gave 55 mg (48%) of **24** as an oil. The second fraction (R_f 0.45) gave DL-1,3-di-*O*-acetyl-2,7-anhydro-(1,4/2,3,6)-4-azido-6-hydroxymethyl-1,2,3-cyclohexanetriol (**23**, 22 mg, 25%) as an oil. ^{1}H NMR ($CDCl_3$) δ=2.12 (3H, s) and 2.15 (3H, s) (OAc), 2.65 (1H, quintet, J=3.3 Hz, H-6), 3.65—4.12 (3H, m, H-4 and CH_2O), 4.19 (1H, br d, J=*ca.* 6 Hz, H-2), 4.90—5.19 (2H, m, H-1 and H-3).

Found: C, 48.89; H, 5.54; N, 15.92%. Calcd for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61%.

*DL-1,2,3-Tri-O-acetyl-(1,4/2,3,6)-4-acetamido-6-acetamidomethyl-1,2,3-cyclohexanetriol (**25**).* A solution of **24** (0.54 g) in ethanol (10 ml) containing acetic anhydride (0.9 ml) was hydrogenated in the presence of Raney nickel T-4 for 28 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was taken up in chloroform (50 ml) and passed through a short column of alumina. The filtrate was concentrated and the residue was crystallized from ethanol to give 0.24 g (41%) of **25** as prisms: mp 197—199 °C. ^{1}H NMR ($CDCl_3$, 60 MHz) δ=2.00 (9H, s), 2.07 (3H, s), and 2.11 (3H, s) (NAc and OAc), 3.30—4.30 (2H, br m, H-7 and H-7'), 4.90—5.45 (4H, m, H-1, H-2, H-3, and H-4), 6.30 (1H, br t, J=6 Hz, C_7–NHAc), 6.70 (1H, br d, J=7 Hz, C_4–NHAc).

Found: C, 52.98; H, 6.78; N, 7.12%. Calcd for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25%.

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References

1) The preceding paper of this series: S. Ogawa, T. Toyokuni, T. Kondoh, Y. Hattori, S. Iwasaki, M. Suetsugu, and T. Suami, *Bull. Chem. Soc. Jpn.*, **54**, 2739 (1981).

2) The nomenclature and numbering of cyclitols used in this paper follow IUPAC and IUB tentative rules for cyclitol nomenclature [*J. Biol. Chem.*, **243**, 5809 (1968)]. All compounds described in this paper are racemic and the formulas depict only one of the respective enantiomers.

3) S. Ogawa, K. Nakamoto, M. Takahara, Y. Tanno, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, **52**, 1174 (1979).

4) Unpublished results.

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6) The structures of **18**, **19**, and **20** were tentatively assigned on the basis of analytical data and ^{1}H NMR spectra.

7) The isomeric epoxide expected to be formed as a major product seemed to be decomposed by an anchimeric reaction of the adjacent acetoxyl group under these conditions.

8) Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Unless otherwise noted, ^{1}H NMR spectra were taken on a Varian EM-390 (90 MHz) spectrometer with reference to tetramethylsilane as an internal standard. The 60 MHz spectra were similarly taken on a Varian EM-360 spectrometer. The peak positions are given in terms of δ-values and values given for coupling constants are of first-order. TLC was performed on precoated silica gel 60 F-254 plates (Merck, Darmstadt; 0.25 mm thickness). The silica gel used for a column chromatography was Wakogel C-300 (Wako Pure Chemical Industries, Ltd.). Organic solutions were concentrated below 50 °C under reduced pressure.

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

10) TLC was performed on precoated cellulose F-254 plates (Merck, Darmstadt; 0.10 mm thickness).

11) This experiment was carried out by assistance of Mr. Kenji Kato, to whom our thanks are due.