Pseudo-sugars. VI. Synthesis of Six Isomers of 5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol (Pseudo-hexopyranose) and Their Derivatives[1]

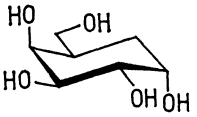
Seiichiro Ogawa,* Masayasu Ara, Takashi Kondoh, Michio Saitoh, Reiko Masuda, Tatsushi Toyokuni, and Tetsuo Suami

Department of Applied Chemistry, Faculty of Engineering, Keio University, Hiyoshi, Yokohama 223

(Received October 15, 1979)

Six isomers of 5-hydroxymethyl-1,2,3,4-cyclohexanetetrol, including naturally occurring (1,2/3,4,5)-isomer, and their several derivatives were synthesized from the *exo*-2-substituted *endo*-3-acetoxy-*endo*-5-acetoxymethyl-7-oxabicyclo[2.2.1]heptane compounds.

The isolation of an antibacterial substance, (+)-(1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (pseudo-α-D-galactopyranose) (**1**)[2] in fermentation broth of *actinomyces Streptomyces* sp. MA-4145[3] prompted us to investigate a structure-activity relationship of stereoisomers of (hydroxymethyl)cyclohexanetetrol (pseudo-hexopyranose) and its related substances. In the present paper, we wish to report a synthesis of two isomeric pseudo-hexopyranoses (**1**, racemate, and **14**) and their derivatives by acetolysis of *exo*-2-substituted *endo*-3-acetoxy-*endo*-5-acetoxymethyl-7-oxabicyclo[2.2.1]heptane compounds (**2**—**5**). In addition, nucleophilic substitution reaction of bromo(hydroxymethyl)cyclohexanetriols (**8** and **16**) thus obtained from **4** led to the other four isomers (**20**, **24**, **28**, and **32**) and their amino deoxy derivatives.



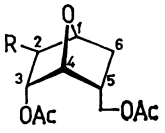
(+)-(1,2/3,4,5)-5-Hydroxymethyl-1,2,3,4-cyclohexanetetrol (**1**)

Treatment of *exo*-2, *endo*-3-diacetoxy-*endo*-5-acetoxymethyl-7-oxabicyclo[2.2.1]heptane (**2**)[4] with a mixture of acetic acid and acetic anhydride containing sulfuric acid in a sealed tube at 80 °C overnight resulted in cleavage of the anhydro ring giving rise to a mixture of products, from which on fractional crystallization penta-*O*-acetyl-5-hydroxymethyl-1,2,3,4-cyclohexanetetrols (**6**, 19%) and (**13**, 18%) were isolated. As expected, **6** and **13** were shown to be identical with authentic samples with (1,2/3,4,5)-[5] and (1,3,5/2,4)-configurations,[4] respectively. Compounds **6** and **13** were converted into the corresponding pentols (**1**, racemate) and (**14**) by treatment with methanolic sodium methoxide.

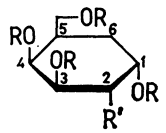
A similar procedure was used for the acetolysis of **3**,[6] **4**,[7] and **5**.[7] Compound **3** gave 2-*O*-methyl-(1,2/3,4,5)- (**7**) and 2-*O*-methyl-(1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol tetraacetates (**15**) in 28 and 12% yields, respectively. In the ^{1}H NMR spectra of **7** and **15**, signals due to the protons on the carbon atoms attached to methoxyl groups appeared as a one-proton doublet of doublets with 3 and 11-Hz splittings at δ 4.30 and a one-proton triplet with 11-Hz splitting at δ 3.90, respectively, confirming the assigned structures. Similarly, the structures of tetra-*O*-acetyl-2-bromo-5-hydroxymethyl-1,3,4-cyclohexanetriols (**8**, 31%) and (**16**, 13%) obtained by acetolysis of **4** were assigned to possess (1,2/3,4,5)- and (1,3,5/2,4)-configurations, respectively, by the ^{1}H NMR signal due to the proton on the carbon atom attached to the bromo group.

On the other hand, acetolysis of **5** gave a sole crystalline tetra-*O*-acetyl(hydroxymethyl)cyclohexanetriol (**17**) in 58% yield. In order to establish the structure, **8** and **16** were subjected to hydrogenolysis with Raney nickel T-4[8] in the presence of Amberlite IR-45 (OH^-) to give the corresponding debromo compounds (**9**, 62%) and (**17**, 36%),[9] respectively. Compounds **9** and **17** were therefore assigned to tetraacetates of (1/3,4,5)- and (1,3,5/4)-5-hydroxymethyl-1,3,4-cyclohexanetriols, respectively. In the case of **5**, the anhydro ring was opened preferentially at C-1 by an acetate ion.

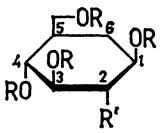
To prepare the other isomers of pseudo-hexopyranose and their derivatives, nucleophilic substitution reaction of **8** and **16** with an acetate or azide ion was studied. Treatment of **8** with an excess of sodium acetate in 90% aqueous 2-methoxyethanol at boiling temperature for 2 days gave, after acetylation, **6** (10%) and the hitherto unknown isomer (**19**, 31%). Since formation



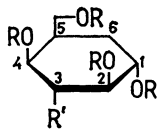
	R
2	OAc
3	OMe
4	Br
5	H



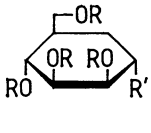
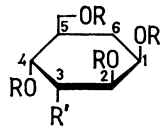
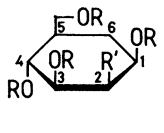
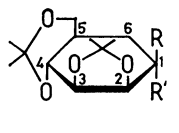
	R	R′
6	Ac	OAc
7	Ac	OMe
8	Ac	Br
9	Ac	H
10	H	H
11	Ac	N_3
12	Ac	NHAc



	R	R′
13	Ac	OAc
14	H	OH
15	Ac	OMe
16	Ac	Br
17	Ac	H
18	H	H



	R	R′
19	Ac	OAc
20	H	OH
21	Ac	N_3
22	Ac	NHAc

	R	R′
23	Ac	OAc
24	H	OH
25	Ac	N_3
26	Ac	NHAc

	R	R′
27	Ac	OAc
28	H	OH
29	Ac	N_3
30	Ac	NHAc

	R	R′
31	Ac	OBz
32	H	OH
33	Ac	OAc
34	Ac	N_3
35	Ac	NHAc

	R	R′
36	H	OH
37	–O–	
38	OH	H

of **6** suggested that the reaction involved the intermediary 2,3-cyclic acetoxonium ion *via* an anchimeric assistance of the C-3 acetoxyl group, **19** was tentatively assigned to have (1,3/2,4,5)-configuration, resulting from the back side attack of an acetate ion at C-3.

The similar treatment of **16** with an acetate ion gave new isomers (**23**, 29%) and (**27**, 27%). When **16** was treated with sodium benzoate in dimethyl sulfoxide at 120 °C for 2 days, direct S_N2 reaction occurred to give 2-*O*-benzoyl-(1,2,3,5/4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol tetraacetate (**31**) in 49% yield. The assigned structure was supported by appearance of a one-proton triplet (J=2.5 Hz, H-2) at δ 5.78 together with a one-proton triplet (J=10 Hz, H-4) at δ 5.40 and a one-proton doublet of doublets (J=2.5 and 10 Hz, H-3) at δ 5.04 in the ^{1}H-NMR spectrum.

O-Deacylation of **19**, **23**, **27**, and **31** in the usual way gave the corresponding pentols (**20**), (**24**), (**28**), and (**32**), respectively. Compound **32** was further characterized as the pentaacetate (**33**), which was found not to be identical with either **23** or **27**.

In order to determine the structures of **23** and **27**, the following sequence of the reactions was carried out. Treatment of **24** with 2,2-dimethoxypropane in *N*,*N*-dimethylformamide in the presence of *p*-toluenesulfonic acid gave a sole crystalline di-*O*-isopropylidene derivative (**36**) in 71% yield. Oxidation with ruthenium tetraoxide in a mixture of chloroform–water in the presence of sodium metaperiodate gave a ketone (**37**) in 61% yield, the structure of which was supported by ^{1}H NMR spectroscopy. Hydrogenation with platinum oxide in ethyl acetate gave a syrupy di-*O*-isopropylidene derivative (**38**) of pentol different from **36**. Compound **38** was then converted into a pentol identical with **32** in all respects. Three isomers with (1,3,5/2,4)-, (1,4/2,3,5)-, and (1,2,5/3,4)-configurations were considered to be formed from **16** by the anchimeric reaction involving the cyclic acetoxonium ions between C-1 and C-2, and/or C-2 and C-3. Therefore, these results showed that **23** was C-1 epimer of **32**, possessing (1,4/2,3,5)-configuration, and then **27** was tentatively assigned to the (1,2,5/3,4)-isomer.

Treatment of **8** with an excess of sodium azide in aqueous 2-methoxyethanol at boiling temperature for 2 days, followed by acetylation, gave two azides (**11**, 15%) and (**21**, *ca.* 80%). By analogy to the reaction with an acetate ion, two compounds were presumed to be tetra-*O*-acetyl-(1,2/3,4,5)-2-azido-5-hydroxymethyl-1,3,4- and tetra-*O*-acetyl-(1,3/2,4,5)-3-azido-5-hydroxymethyl-1,2,4-cyclohexanetriols. The ^{1}H NMR spectrum of **11** was fully interpreted by first-order method, being consistent with the former structure. In the spectrum of **21**, appearance of a one-proton triplet (J=10 Hz) due to the proton on a carbon atom attaching to the azido group showed that **21** had the latter structure, all the substituent except for the acetoxymethyl group locating in equatorial positions in the favored conformation. Hydrogenation of **11** and **21** with Raney nickel T-4 in methanol containing acetic anhydride gave the corresponding tetra-*O*-acetyl-(acetamido)(hydroxymethyl)cyclohexanetriols (**12**) and (**22**), respectively.

The similar azidolysis of **16** followed by acetylation gave, after fractionation by a silica gel column, two syrupy azides (**25**, 48%) and (**29**, 54%).[10] On hydrogenation and acetylation in the usual way, **25** and **29** were converted into the corresponding amino alcohol pentaacetates (**26**) and (**30**). Their structures were deduced by analogy to those of **23** and **27** obtained by the similar reaction with an acetate ion, and finally confirmed by ^{1}H NMR spectroscopy. Judging from the patterns of the signals due to C-7 methylene protons, the structures of **25** and **29** might be able to correlate with those of **23** and **27**, respectively. Further evidence was obtained by the spectrum of **26**, which showed after deuteration a one-proton narrow quartet (J= 3.5 Hz, H-4) at δ 4.18. Therefore, **26** and **30** were assigned to possess (1,4*N*/2,3,6)- and (1,2,5/3*N*,4)-configurations, respectively, as shown in the Scheme.

When dimethyl sulfoxide was used as the reaction solvent in the azidolysis of **16**, direct S_N2 reaction occurred to give an azide (**34**) with the inversion of the configuration at C-2. In the ^{1}H NMR spectrum, a narrow triplet (J=2.5 Hz, H-2) at δ 4.20 clearly supported the axial-equatorial-axial conformation for H-1, H-2, and H-3. Hydrogenation of **34** followed by acetylation gave tetra-*O*-acetyl-(1,2,3,5/4)-2-acetamido-5-hydroxymethyl-1,3,4-cyclohexanetriol (**35**).

Compounds **12** and **35** are considered to be carbocyclic analogs of 2-amino-2-deoxy-α-DL-galactopyranose and β-DL-mannopyranose. Biochemical and biological studies of pseudo-hexopyranoses and their amino deoxy derivatives obtained in this work are on the way.

Experimental

Unless otherwise stated, melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Solutions were evaporated under reduced pressure at 40—50 °C. IR spectra were recorded on a Hitachi

225 spectrometer in potassium bromide pellets. ^{1}H NMR spectra were taken on a Varian EM-360A (60 MHz) in deuteriochloroform with reference to tetramethylsilane as an internal standard and the peak positions are given in terms of δ-values. Values given for coupling constants are of first-order. TLC was performed on precoated silica gel 60 F-254 plaques (Merck, Darmstadt; 0.25 mm thickness). The silica gel used for a column chromatography was Wakogel C-300 (Wako Pure Chemical Industries, Ltd.).

Acetolysis of exo-*2*, endo-*3-Diacetoxy*-endo-*5-acetoxymethyl-7-oxabicyclo[2.2.1]heptane (**2**).*[4] A mixture of **2** (4 g), acetic acid (12 ml), acetic anhydride (7 ml), and concentrated sulfuric acid (0.7 ml) was sealed in a glass tube and heated at 80—85 °C for 20 h in an oil bath. The brown reaction mixture was poured into ice–water (200 ml), and the solution was neutralized with sodium hydrogencarbonate and extracted with ethyl acetate (3×30 ml). The extracts were washed with water thoroughly, dried over anhydrous sodium sulfate, filtered through a short column of alumina and concentrated. The syrupy residue was crystallized from a small amount of ethanol to give penta-*O*-acetyl-(1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**6**, 1.2 g, 19%) as crystals: mp 137—138 °C, 144.5—145 °C (hot-stage) [lit,[5] 147—148 °C (hot-stage)]. The ^{1}H NMR spectrum ($CDCl_3$) was superimposable on that of an authentic sample reported.[5] (Found: C, 52.57; H, 6.22%).

The mother liquor from **6** was concentrated to a small volume and kept in a refrigerator for a week to give penta-*O*-acetyl-(1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**13**, 1.15 g, 18%) as practically pure crystals: mp 109.5—111 °C. Recrystallization from ethanol gave a pure sample: mp 111.5—112.5 °C (lit,[4] 111—112 °C), which was identified with an authentic sample by comparison with IR and ^{1}H NMR spectra.

Compound **6** (1 g) was treated with 1 M methanolic sodium methoxide (1.1 ml) in methanol (50 ml) at reflux temperature for 0.5 h. After cooling, the solution was neutralized with Amberlite IR-120 (H^+) and concentrated to give a crystalline residue, which was crystallized from ethanol to give racemic (1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**1**, 0.44 g, 96%) as crystals: mp 167—168 °C [lit,[5] 173—174 °C (hot-stage)] (Found: C, 47.04; H, 7.92%).

Compound **13** was *O*-deacetylated as described above to give (1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**14**) as a homogeneous syrup, identical with an authentic sample[4] in all respects.

Acetolysis of 3-endo-*Acetoxy-5*-endo-*acetoxymethyl-2*-exo-*methoxy-7-oxabicyclo[2.2.1]heptane (**3**).*[6] A mixture of **3** (3 g), acetic acid (9 ml), acetic anhydride (4 ml), and concentrated sulfuric acid (0.4 ml) was heated in a glass sealed tube at 90—95 °C overnight. The mixture was poured into ice–water (150 ml) and the solution was extracted with chloroform (3×30 ml). The extracts were washed thoroughly with aqueous sodium hydrogencarbonate and water, successively, dried, and filtered through a short column of alumina. Evaporation of the solvent gave a crystalline mixture of products (2.45 g, 59%), which was fractionally crystallized from ethanol to give first 1,3,4,7-tetra-*O*-acetyl-2-*O*-methyl-(1,2/3,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**7**, 0.49 g, 12%) as plates: mp 144.5—145 °C. ^{1}H NMR ($CDCl_3$) δ=2.04 (6H, s) and 2.10 (6H, s) (OAc), 3.36 (3H, s, OMe), 3.48 (1H, dd, J=3 and 10 Hz, H-2), 3.8—4.0 (2H, m, C<u>H</u>$_2$OAc), 5.06 (1H, dd, J=3 and 10 Hz, H-3), 5.50 (2H, m, H-1 and H-4).

From the mother liquor of **7**, 1,3,4,7-tetra-*O*-acetyl-2-*O*-methyl-(1,3,5/2,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**15**, 1.15 g, 28%) was obtained as prisms: mp 80—81.5 °C. ^{1}H NMR ($CDCl_3$) δ=2.05 (6H, s), 2.07 (3H, s) and 2.10 (3H, s), 3.30 (1H, t, J=10 Hz, H-2), 3.44 (3H, s, OMe), 3.9—4.2 (2H, m, C<u>H</u>$_2$OAc), 4.6—5.1 (3H, m, H-1, H-3, and H-4).

Found for **7**: C, 53.47; H, 6.67%; and for **15**: C, 53.27; H, 6.72%. Calcd for $C_{16}H_{24}O_9$: C, 53.33; H, 6.71%.

Acetolysis of endo-*3-Acetoxy*-endo-*5-acetoxymethyl*-exo-*2-bromo-7-oxabicyclo[2.2.1]heptane (**4**).* A mixture of **4** (4 g), acetic acid (12 ml), acetic anhydride (8 ml), and concentrated sulfuric acid (0.5 ml) was heated in a sealed tube at 90—95 °C overnight. The brown mixture was poured into ice–water (200 ml) and the resulting crystals were collected by filtration and washed with water. The product was dissolved in hot ethanol, treated with active carbon, and crystallized to give a mixture of crystals (3.7 g, 64%). Fractional crystallization from ethanol first gave tetra-*O*-acetyl-(1,2/3,4,5)-2-bromo-5-hydroxymethyl-1,3,4-cyclohexanetriol (**8**, 1.6 g, 31%) as prisms or plates: mp 161.5—162.5 °C. ^{1}H NMR ($CDCl_3$) δ=2.03 (3H, s), 2.06 (3H, s), 2.12 (3H, s), and 2.17 (3H, s) (OAc), 3.85—4.0 (2H, m, C<u>H</u>$_2$OAc), 4.30 (1H, dd, J=3 and 11 Hz, H-2), 5.27 (1H, dd, J=3 and 11 Hz, H-3), 5.38 (1H, t, J=3 Hz, H-4), 5.52 (1H, q, J=3 Hz, H-1).

From the mother liquor of **8**, tetra-*O*-acetyl-(1,3,5/2,4)-2-bromo-5-hydroxymethyl-1,3,4-cyclohexanetriol (**16**, 0.7 g, 13%) was obtained as thin plates: mp 145—146 °C. ^{1}H NMR ($CDCl_3$) δ=2.03 (6H, s), 2.07 (3H, s), and 2.10 (3H, s) (OAc), 3.9—4.1 (2H, m, C<u>H</u>$_2$OAc), 3.90 (1H, t, J=11 Hz, H-2), 4.88 (1H, t, J=11 Hz, H-3), 4.92 (1H, m, H-1), 5.23 (1H, t, J=11 Hz, H-4).

Found for **8**: C, 44.25; H, 5.11; Br, 19.20%; and for **14**: C, 44.06; H, 5.08; Br, 19.50%. Calcd for $C_{15}H_{21}O_8Br$: C, 44.02; H, 5.17; Br, 19.53%.

Acetolysis of 2-endo-*Acetoxy-6*-endo-*acetoxymethyl-7-oxabicyclo-[2.2.1]heptane (**5**).*[6] a) A mixture of **5** (4 g), acetic acid (12 ml), acetic anhydride (8 ml), and concentrated sulfuric acid (0.5 ml) was heated in a sealed tube at 90—95 °C overnight. The reaction mixture was poured into ice–water (100 ml) and the resulting precipitates were collected by filtration. The aqueous filtrate was extracted with chloroform and the extracts were worked up in the usual manner to give an additional crop of crystals. Recrystallization of the combined crude crystals from ethanol gave tetra-*O*-acetyl-(1,3,5/2)-3-hydroxymethyl-1,2,5-cyclohexanetriol (**17**, 3.42 g, 58.4%) as needles: mp 104—105 °C. ^{1}H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.01 (3H, s), and 2.04 (6H, s) (OAc).

Found: C, 54.39; H, 6.55%. Calcd for $C_{15}H_{22}O_8$: C, 54.53; H, 6.73%.

b) A solution of **16** (0.88 g) in ethyl acetate (10 ml) was hydrogenated (Parr shaker apparatus) in the presence of Raney nickel T-4[8] (3 ml) and Amberlite IR-45 (OH^-) in the initial hydrogen pressure of 3.4 kg cm^{-2} at ambient temperature overnight. The catalyst and resin were filtered off and the filtrate was concentrated. The residue was recrystallized from ethanol to give **17** (0.24 g, 36%) as needles, which was identical with the compound obtained from **5** in all respects.

*(1,3,5/2,4)-3-hydroxymethyl-1,2,5-cyclohexanetriol (**18**).* To a solution of **17** (4 g) in methanol (200 ml) was added 1 M methanolic sodium methoxide (12 ml) and the mixture was refluxed for 1.5 h. The mixture was processed in the usual manner to give a product, which was crystallized from ethanol to give **18** (1.9 g, 96%) as needles: mp 125—127 °C.

Found: C, 51.68; H, 8.60%. Calcd for $C_7H_{14}O_5$: C, 51.84; H, 8.70%.

*Tetra-O-acetyl-(1,2,3/5)-3-hydroxymethyl-1,2,5-cyclohexanetriol (**9**).* A solution of **8** (3 g) in ethyl acetate (20 ml) was hydrogenated similarly as described in the preparation of **17**. The crude product was recrystallized from ethanol to give **9** (1.5 g, 62%) as needles: mp 98—99 °C. ^{1}H NMR ($CDCl_3$) δ=1.99 (3H, s), 2.05 (3H, s), 2.09 (3H, s), and 2.11 (3H, s) (OAc), 3.8—4.1 (2H, m, C$\underline{H}_2$OAc), 5.01 (1H, dd, J=2.5 and 9 Hz, H-1), 5.24 (1H, t, J=2.5 Hz, H-5), 5.46 (1H, t, J=2.5 Hz, H-2).

Found: C, 54.52; H, 6.70%. Calcd for $C_{15}H_{22}O_8$: C, 54.53; H, 6.73%.

*(1,2,3/5)-3-Hydroxymethyl-1,2,5-cyclohexanetriol (**10**).* Compound **9** (0.3 g) was *O*-deacetylated in methanol (20 ml) containing 1 M methanolic sodium methoxide (0.5 ml) similarly as described in the preparation of **1**. The crude product was purified by a silica gel column with methanol to give a homogeneous syrup (0.15 g, 98%).

Found: C, 52.12; H, 8.42%. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70%.

*Reaction of **8** with Sodium Acetate.* A mixture of **8** (2.9 g), anhydrous sodium acetate (3 g), and 90% aqueous 2-methoxyethanol (70 ml) was refluxed for three days and concentrated under reduced pressure. The solid residue was dried by coevaporation with toluene and then treated with acetic anhydride (10 ml) and pyridine (15 ml) at ambient temperature overnight. An insoluble material was removed by filtration and the filtrate was concentrated. The syrup was dissolved in chloroform and filtered through a short column of alumina. Removal of the solvent and crystallization from ethanol gave **6** (0.26 g, 10%) as prisms: mp 136—137 °C, identical with the compound obtained from **2**. The mother liquor of **6** was kept in a refrigerator for a week to give penta-*O*-acetyl-(1,3/2,4,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**19**, 0.8 g, 31%) as plates: mp 106—107 °C. ^{1}H NMR ($CDCl_3$) δ=2.00 (12H, s) and 2.12 (3H, s) (OAc), 4.18 (2H, d, J=6 Hz, C$\underline{H}_2$OAc).

Found: C, 52.81; H, 6.22%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23%.

O-Deacetylation of **19** (0.5 g) with methanolic sodium methoxide in the usual manner to give a crystalline pentol (**20**, 0.17 g, 75%), which was recrystallized from ethanol to give an analytical sample: mp 154.5—156 °C.

Found: C, 46.95; H, 7.75%. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92%.

*Reaction of **16** with Sodium Acetate.* A mixture of **16** (2 g), anhydrous sodium acetate (2.9 g), and 90% aqueous 2-methoxyethanol was refluxed for 43 h and concentrated under reduced pressure. The reaction mixture was processed similarly as described in the reaction of **6**. A crystalline mixture of products (1.5 g) was fractionally crystallized from ethanol. The first crop of crystals (0.6 g) was recrystallized twice to give penta-*O*-acetyl-(1,4/2,3,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**23**, 0.27 g, 14%) as prisms: mp 99.5—100 °C. ^{1}H NMR ($CDCl_3$) δ=1.99 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.12 (3H, s), and 2.13 (3H, s) (OAc), 3.98—4.15 (2H, m, C$\underline{H}_2$OAc), 4.98 (1H, q, J=3 Hz, H-1), 5.0—5.5 (3H, m, H-2, H-3, and H-4).

The second crop of crystals (0.9 g) was fractionally crystallized from ethanol to give practically pure **23** (0.3 g, total yield 29%) and penta-*O*-acetyl-(1,2,5/3,4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**27**, 0.51 g, 27%) as prisms: mp 106—107 °C. ^{1}H NMR ($CDCl_3$) δ=2.01 (6H, s), 2.06 (3H, s), 2.10 (3H, s), and 2.13 (3H, s) (OAc), 4.05 (2H, d, J=5 Hz, C$\underline{H}_2$OAc), 4.9—5.35 (4H, m, H-1, H-2, H-3, and H-4).

Found for **23**: C, 52.71; H, 6.21%, and for **27**: C, 52.32; H, 6.11%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23%.

O-Deacetylation of **23** (0.25 g) in the usual manner gave the pentol (**24**, 0.10 g, 84%) as a homogenous syrup.

O-Deacetylation of **27** (0.25 g) in the usual manner gave a crystalline pentol (**28**, 0.075 g, 65%), which was recrystallized from ethanol to give prisms: mp 143.5—144.5 °C.

Found for **24**: C, 47.34; H, 7.74%, and for **28**: C, 46.96; H, 7.74%. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92%.

*1,3,4,7-Tetra-O-acetyl-2-O-benzoyl-(1,2,3,5/4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**31**).* A stirred mixture of **16** (1.24 g), sodium benzoate (1.2 g), 18-crown-6 (0.4 g) in dimethyl sulfoxide (30 ml) was heated at 115—120 °C for 2 d. After cooling, the reaction mixture was diluted with ethyl acetate (100 ml) and the solution was washed well with water. The organic layer was dried and filtered through a short column of alumina. The filtrate was concentrated and the residue was crystallized from ethanol to give **31** (0.67 g, 49%) as prisms: mp 134—135 °C. ^{1}H NMR ($CDCl_3$) δ=1.94 (3H, s), 1.96 (3H, s), 2.03 (3H, s), and 2.10 (3H, s) (OAc), 4.06 (2H, broad s, C$\underline{H}_2$OAc), 5.05 (1H, dd, J=2.5 and 10 Hz, H-3), 5.40 (1H, t, J=10 Hz, H-4), 5.79 (1H, t, J=2.5 Hz, H-2), 7.45 (3H, m) and 8.05 (2H, m) (phenyl).

Found: C, 58.79; H, 5.91%. Calcd for $C_{22}H_{26}O_{10}$: C, 58.66; H, 5.82%.

O-Deacylation of **31** (0.23 g) in the usual manner gave a crystalline pentol (**32**), which was recrystallized from ethanol–water to give needles: mp 198—199 °C.

Found: C, 47.16; H, 7.76%. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92%.

Acetylation of **32** (0.05 g) with acetic anhydride and pyridine in the usual manner gave, after crystallization from ethanol, a pentaacetate (**33**, 0.1 g, 90%) as prisms: mp 123—125 °C. ^{1}H NMR ($CDCl_3$) δ=1.98 (3H, s), 2.02 (3H, s), 2.06 (3H, s), and 2.20 (3H, s) (OAc), 4.01 (2H, broad d, J=4 Hz, C$\underline{H}_2$OAc), 4.91 (1H, dd, J=2.5 and 10 Hz, H-3), 5.23 (1H, t, J=10 Hz, H-4), 5.56 (1H, t, J=2.5 Hz, H-2).

Found: C, 52.69; H, 6.33%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23%.

*2,3:4,7-Di-O-isopropylidene-(1,4/2,3,5)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**36**).* The crude **24** obtained from **23** (0.8 g) in the usual manner was heated with 2,2-dimethoxypropane (4 ml) in *N,N*-dimethylformamide (10 ml) in the presence of *p*-toluenesulfonic acid (15 mg) at 60 °C for 1 h. After cooling, the mixture was treated with Amberlite IRA-400 (OH^-) and concentrated. The residue was crystallized from ethanol to give **36** (0.36 g, 71%) as crystals: mp 147.5—148.5 °C. ^{1}H NMR ($CDCl_3$) δ=1.35 (3H, s), 1.41 (3H, s), 1.50 (3H, s), and 1.52 (3H, s) (isopropylidene), 3.61 (1H, d) and 3.80 (1H, broad d) (J=5 Hz, H-7 and H-7′), 4.10 (3H, broad s, H-2, H-3, and, H-4).

Found: C, 60.50; H, 8.60%. Calcd for $C_{13}H_{22}O_5$: C, 60.43; H, 8.60%.

The acetate was prepared in the conventional way. The crude product was recrystallized from ethanol to give prisms: mp 140.5—141 °C. ^{1}H NMR ($CDCl_3$) δ=1.37 (3H, s), 1.45 (3H, s), 1.49 (3H, s), and 1.51 (3H, s) (isopropylidene), 3.69 (2H, AB-quartet, H-7 and H-7′), 3.9—4.2 (2H, m, H-2 and H-3), 5.25 (1H, broad q, J=3 Hz, H-1).

Found: C, 59.72; H, 7.70%. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05%.

The tosylate was prepared by treatment with *p*-toluenesulfonyl chloride in pyridine. The crude product was crystallized from 2-propanol to give crystals: mp 137—138 °C.

Found: C, 58.46; H, 6.77; S, 7.52%. Calcd for $C_{20}H_{28}O_7S$: C, 58.22; H, 6.86; S, 7.77%.

2,3:4,7-Di-O-isopropylidene-(2,3,5/4)-2,3,4-trihydroxy-5-(hy-

droxymethyl)cyclohexanone (37). Compound **36** (0.5 g) was dissolved in ethanol-free chloroform (10 ml), and a catalytic amount of ruthenium dioxide and aqueous sodium hydrogencarbonate were added. A 5% aqueous sodium metaperiodate (10 ml) was added to the mixture during 20 min under ice cooling with vigorous agitation. After 2.5 h, an excess of periodate and ruthenium tetraoxide were destroyed with 2-propanol, and black precipitates were removed by filtration. The organic layer was separated, washed with water thoroughly, and dried. Removal of the solvent gave a crystalline residue which was recrystallized from ethanol to give **37** (0.3 g, 61%) as crystals: mp 124 °C (after sintering at 119 °C). ^{1}H NMR ($CDCl_3$) δ=1.40 (3H, s), 1.48 (3H, s), and 1.50 (6H, s) (isopropylidene), 1.8—2.6 (3H, m, H-5, H-6, and H-6'), 3.3—4.0 (3H, m, H-4, H-7, and H-7'), 4.4—4.6 (2H, m, H-2 and H-3).

Found: C, 61.01; H, 7.77%. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.

Compound **37** (0.13 g) was hydrogenated in ethyl acetate (5 ml) in the presence of platinum oxide in the usual manner to give a homogeneous syrup of 2,3:4,7-di-*O*-isopropylidene-(1,2,3,5/4)-5-hydroxymethyl-1,2,3,4-cyclohexanetetrol (**38**, 0.12 g), which was not identical with **36** in all respects. Crude **38** was directly treated with 80% aqueous acetic acid (5 ml) at 80 °C for 1 h. The reaction mixture was concentrated and the residue was recrystallized from ethanol–water to give **32** (83 mg, 92%): mp 196—197 °C, identical with the compound obtained from **31**.

Reaction of 8 with Sodium Azide. A mixture of **8** (5.7 g), sodium azide (6 g), and 90% aqueous 2-methoxyethanol (120 ml) was refluxed for 44 h and concentrated under reduced pressure. The residue was dried by coevaporation with toluene several times and then treated with acetic anhydride (20 ml) and pyridine (30 ml) at ambient temperature overnight. An insoluble material was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate (50 ml) and filtered through a short column of alumina (20 g). The filtrate was concentrated and the syrupy residue was crystallized from ethanol to give tetra-*O*-acetyl-(1,2/3,4,5)-2-azido-5-hydroxymethyl-1,3,4-cyclohexanetriol (**11**, 0.79 g, 15%) as prisms: mp 145—147 °C. ^{1}H NMR ($CDCl_3$) δ=2.03 (3H, s), 2.07 (3H, s), and 2.13 (6H, s) (OAc), 3.6—4.0 (2H, m, C<u>H</u>$_2$OAc), 3.75 (1H, dd, J=3 and 11 Hz, H-2), 5.17 (1H, dd, J=3 and 11 Hz, H-3), 5.40 (1H, q, J=3 Hz, H-1), 5.53 (1H, t, J=3 Hz, H-4).

Found: C, 48.67; H, 5.72; N, 11.11%. Calcd for $C_{15}H_{21}N_3O_8$: C, 48.52; H, 5.70; N, 11.32%.

The mother liquor of **11** was concentrated to give a syrup which consisted mainly of tetra-*O*-acetyl-(1,3/2,4,5)-3-azido-5-hydroxymethyl-1,2,4-cyclohexanetriol (**21**, 5.1 g). ^{1}H NMR ($CDCl_3$) δ=2.02 (3H, s), 2.09 (3H, s), 2.11 (3H, s), and 2.13 (3H, s) (OAc), 3.79 (1H, t, J=10 Hz, H-3), 4.8—5.2 (3H, m, H-1, H-2, and H-4). Purification of **21** was not attempted because its mobility on TLC was similar to that of **11** in various solvent systems.

Tetra-O-acetyl-(1,2/3,4,5)-2-acetamido-5-hydroxymethyl-1,3,4-cyclohexanetriol (12). A solution of **11** (0.6 g) in ethanol (35 ml), acetic anhydride (0.8 ml), and Raney nickel T-4 (one-spoonful) was hydrogenated with 3.4 kg cm^{-2} starting pressure of hydrogen gas at ambient temperature overnight in a Parr hydrogenation apparatus. The catalyst was removed by filtration and the filtrate was concentrated. Recrystallization of the crude product from ethanol gave **12** (0.48 g, 82%) as needles: mp 184—185.5 °C. ^{1}H NMR ($CDCl_3$) δ=1.83 (3H, s, NAc), 1.95 (3H, s), 2.02 (3H, s), and 2.13 (3H, s) (OAc), 3.85—4.0 (2H, m, C<u>H</u>$_2$OAc), 4.52 (1H, ddd, J=3, 9, and 11 Hz, H-2), 5.12 (1H, dd, J=3 and 11 Hz, H-3), 5.25 (1H, t, J=3 Hz, H-4), 5.53 (1H, q, J=3 Hz, H-1), 5.70 (1H, d, J=9 Hz, N<u>H</u>).

Found: C, 52.54; H, 6.41; N, 3.70%. Calcd for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.51; N, 3.62%.

Tetra-O-acetyl-(1,3/2,4,5)-3-acetamido-5-hydroxymethyl-1,2,4-cyclohexanetriol (22). The crude **21** (5 g) was hydrogenated similarly as described in the preparation of **12**. The crude product was recrystallized from ethanol–ether to give **22** (2.7 g, 51% yield based on **8** used) as needles: mp 159—160 °C. ^{1}H NMR ($CDCl_3$) δ=1.91 (3H, s, NAc), 2.03 (6H, s), 2.07 (3H, s), and 2.13 (3H, s) (OAc), 4.2—4.3 (2H, m, C<u>H</u>$_2$OAc), 5.71 (1H, d, J=9 Hz, N<u>H</u>).

Found: C, 52.64; H, 6.45; N, 3.76%. Calcd for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.51; N, 3.62%.

Reaction of 16 with Sodium Azide. A mixture of **16** (3 g), sodium azide (3.4 g), and 90% aqueous 2-methoxyethanol (70 ml) was refluxed for 40 h. The reaction mixture was processed and acetylated similarly as described in the reaction of **8**. The syrupy mixture (3.2 g) of azides obtained was chromatographed on a silica-gel column (70 g) with butanone–toluene (1:6, v/v) as an eluent to give tetra-*O*-acetyl-(1,4/2,3,6)-4-azido-6-hydroxymethyl-1,2,3-cyclohexanetriol (**25**, 1.3 g, 48%) as a homogeneous syrup, which crystallized on standing in a refrigerator for two months: mp 84—84.5 °C, and tetra-*O*-acetyl-(1,2,5/3,4)-3-azido-5-hydroxymethyl-1,2,4-cyclohexanetriol (**29**, 1.5 g, 54%) as a homogeneous syrup, which also crystallized on standing in a refrigerator for two months: mp 66—67 °C. ^{1}H NMR ($CDCl_3$) data for **25**: δ=1.99 (3H, s), 2.02 (3H, s), 2.05 (3H, s), and 2.12 (3H, s) (OAc), 3.8—4.1 (3H, m, H-4 and C<u>H</u>$_2$OAc), 5.0—5.3 (3H, m, H-1, H-2, and H-3), and for **29**: 2.00 (3H, s), 2.07 (3H, s), 2.12 (3H, s), and 2.14 (3H, s) (OAc), 4.0—4.1 (3H, m, H-3 and C<u>H</u>$_2$OAc), 4.9—5.3 (3H, m, H-1, H-2, and H-4).

Found for **25**: C, 48.31; H, 5.62; N, 11.11%, and for **29**: C, 48.51; H, 5.67; N, 11.17%. Calcd for $C_{15}H_{21}N_3O_8$: C, 48.52; H, 5.70; N, 11.32%.

Tetra-O-acetyl-(1,4/2,3,6)-4-acetamido-6-hydroxymethyl-1,2,3-cyclohexanetriol (26). The crude syrupy **25** (0.35 g) was hydrogenated similarly as described in the preparation of **12**. The crude crystalline product was recrystallized from ethanol–ether to give **26** (0.16 g, 44%) as prisms: mp 181—182 °C. The overall yield from **16** was 24%. ^{1}H NMR ($CDCl_3$) δ=1.99 (6H, s), 2.03 (3H, s), 2.06 (3H, s), and 2.10 (3H, s) (NAc and four OAc), 4.05 (2H, broad d, C<u>H</u>$_2$OAc), 4.18 (1H, m, H-4, the signal changes to a quartet with 3.5 Hz splitting on deuteration), 5.1—5.3 (3H, m, H-1, H-2, and H-3), 6.70 (1H, J=8 Hz, N<u>H</u>).

Found: C, 52.99; H, 6.57; N, 3.64%. Calcd for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.51; N, 3.62%.

A mixture of **25** and **29** obtained from **16** (2.7 g) was without separation directly hydrogenated followed by acetylation to give **26** (0.12 g, 24%): mp 179—180 °C, cleanly crystallized out of the mixture of products.

Tetra-O-acetyl-(1,2,5/3,4)-3-acetamido-5-hydroxymethyl-1,2,4-cyclohexanetriol (30). The crude syrupy **29** (0.47 g) was hydrogenated and acetylated similarly as described in the preparation of **12**. The syrupy product (0.41 g, 84%) was purified by a silica gel column with chloroform–ethyl acetate (5:1, v/v) as an eluent to give **30** as a homogeneous syrup. ^{1}H NMR ($CDCl_3$) δ=1.96 (3H, s) and 2.05 (12H, s) (NAc and four OAc), 4.41 (2H, d, J=6 Hz, C<u>H</u>$_2$OAc), 4.62 (1H, broad td, J=4 Hz, H-3), 5.0—5.25 (3H, m, H-1, H-2, and H-4), 6.60 (1H, d, J=9 Hz, N<u>H</u>).

Found: C, 52.47; H, 6.38; N, 3.53%. Calcd for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.51; N, 3.62%.

Tetra-O-acetyl-(1,2,3,5/4)-2-acetamido-5-hydroxymethyl-1,3,4-

*cyclohexanetriol (**35**).* A stirred mixture of **16** (2 g), sodium azide (2 g), and dimethyl sulfoxide (35 ml) was heated at 110 °C for 10 h. The reaction mixture was diluted with water (100 ml) and the solution was extracted with ethyl acetate (3×50 ml). The extracts were washed with water, dried, and filtered through a short column of alumina (10 g). The filtrate was concentrated to give tetra-*O*-acetyl-(1,2,3,5/4)-2-azido-5-hydroxymethyl-1,3,4-cyclohexanetriol (**34**, 1 g, 51%) as a chromatographically homogeneous syrup: ^{1}H NMR ($CDCl_3$) δ=2.07 (3H, s), 2.09 (3H, s), 2.11 (3H, s), and 2.13 (3H, s) (OAc), 3.93 (2H, broad s, C$\underline{H}_2$OAc), 4.20 (1H, t, J=2.5 Hz, H-2), 4.75—5.2 (3H, m, H-1, H-3, and H-4).

The crude syrup was directly hydrogenated and acetylated similarly as described in the preparation of **12**. The crude product was recrystallized from chloroform–ether to give **35** (0.6 g, 31% yield based on **16** used) as needles: mp 177—179 °C. ^{1}H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.00 (3H, s), and 2.05 (9H, s) (NAc and four OAc), 4.02 (2H, AB quartet, C$\underline{H}_2$OAc), 4.8—5.2 (3H, m, H-1, H-3, and H-4), 6.10 (1H, J=8 Hz, N$\underline{H}$).

Found: C, 52.47; H, 6.45; N, 3.55%. Calcd for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.51; N, 3.62%.

The present work was partially supported by a Grand-in-Aid for Scientific Research No. 355376 from the Ministry of Education, Science and Culture. The authors wish to express their thanks to Mr. Saburo Nakada for elemental analyses.

References

1) Presented in part at the 37th National Meeting of the Chemical Society of Japan, Yokohama, April 1978, Abstr. No. 3R04. For paper V of this series, see S. Ogawa, T. Toyokuni, M. Omata, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, **53**, 455 (1980). All the compounds described in this paper are racemic. Unless otherwise stated, all the formulas depict one enantiomer of the respective racemates.

2) The nomenclature is based on the IUPAC-IUB Tentative Cyclitol Nomenclature Rule [*J. Biol. Chem.*, **22**, 5809 (1968)]. Alternatively, according to the proposal of G. E. McCasland [G. E. McCasland and S. Furuta, *J. Org. Chem.*, **31**, 1516 (1966)], 5-hydroxymethyl-1,2,3,4-cyclohexanetetrols are named as pseudo-hexopyranoses.

3) T. W. Miller, B. H. Arison, and G. Albers-Schönberg, *Biotechnol. Bioeng.*, **15**, 1075 (1973).

4) T. Suami, S. Ogawa, K. Nakamoto, and I. Kasahara, *Carbohydr. Res.*, **58**, 240 (1977).

5) G. E. McCasland, S. Furuta, and L. J. Durham, *J. Org. Chem.*, **33**, 2841 (1968).

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

7) S. Ogawa, I. Kasahara, and T. Suami, *Bull. Chem. Soc. Jpn.*, **52**, 118 (1979).

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

9) Formation of anhydro compounds during hydrogenolysis of **16** in the presence of the basic resin decreased the yield of **17**.

10) These azides crystallized spontaneously on standing in a refrigerator for two months. Analytical samples were obtained by recrystallization from ethanol.