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Pseudo-sugars. X. Synthesis of Several Branched-chain Unsaturated Cyclitols and Their Derivatives[1]

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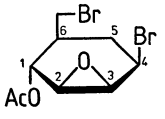
Some racemic (hydroxymethyl)cyclohexenepolyols and their derivatives of biological interest have been synthesized from DL-1,2,3-tri-*O*-acetyl-(1/2,3)-4-methylene-5-cyclohexene-1,2,3-triol derived from the corresponding dibromide by treatment with sodium acetate in hexamethylphosphoric triamide.

In connection with the previous paper,[2] several (hydroxymethyl)cyclohexenepolyols and its derivatives have been synthesized as peracetates from readily available DL-1-*O*-acetyl-2,3-anhydro-(1/2,3,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**1**).[3]

Compound **1** was treated with aqueous acetone containing 1% concd sulfuric acid at reflux, followed by acetylation with acetic anhydride in pyridine, to produce DL-1,2,3-tri-*O*-acetyl-(1,2/3,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**2**) in 87% yield. Opening of the epoxide ring proceeds selectively *via* an anchimeric assistance of the C-1 acetoxyl group at C-2. As the corresponding (1,3/2,4,6)-isomer,[3] **2** was expected to be a versatile synthetic intermediate for various kinds of branched-chain cyclitol derivatives.[4,5]

Treatment of **2** with 4 molar equiv. of sodium acetate in *N*,*N*-dimethylformamide (DMF) at 80 °C for 8 h resulted in a preferential replacement of the primary bromo group with an acetate ion to give the tetraacetate **3** in 75% yield, along with the elimination product, DL-1,2,3-tri-*O*-acetyl-(1/2,3)-4-methylene-5-cyclohexene-1,2,3-triol (**4**, 14%). When the similar reaction was carried out at an elevated temperature (110 °C) for 32 h, the elimination of hydrobromic acid between C-4 and C-5 further occurred to give DL-1,2,3-tri-*O*-acetyl-(1,4/2,3)-4-acetoxymethyl-5-cyclohexene-1,2,3-triol (**5**) in 48% yield, along with **4** (22%). On the other hand, hexamethylphosphoric triamide (HMPA) was used as the solvent instead of DMF, **4** was obtained predominantly in 69% yield, after having been heated at 120 °C for 2 h. Whereas, a reaction of **3** with zinc dust in acetic acid at 65 °C for 35 h gave DL-1,2-di-*O*-acetyl-(1,2/3)-3-acetoxymethyl-5-cyclohexene-1,2-diol (**6**) in 51% yield. The



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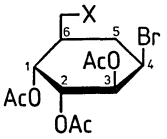
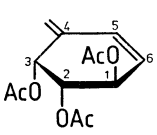


2 X = Br
3 X = OAc



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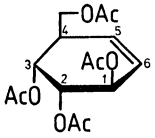

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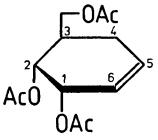

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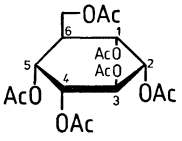

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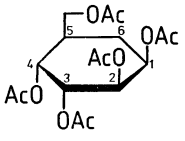
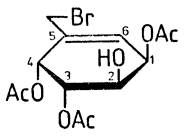
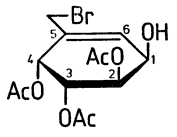


8

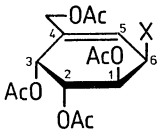
	X	Y	Z
9	H	Br	Br
10	Br	H	Br
11	N_3	H	N_3
12	NHAc	H	NHAc
13	OAc	H	Br
14	OAc	H	OAc
15	OAc	H	N_3
16	OAc	H	NHAc
17	H	OAc	Br
18	H	OAc	OAc
19	H	OAc	N_3



20a



20b



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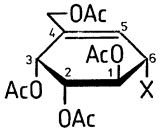


b

21 X = Br
22 X = N_3

Scheme 1.

structures of **5** and **6** were deduced on the basis of analytical data and ^{1}H NMR spectra, and finally established by converting them into branched-chain cyclitols. Thus, the conventional osmium tetraoxide-oxidation of **5** and **6**, followed by acetylation, afforded mainly the peracetyl (hydroxymethyl)cyclohexanepentol **7** and tetrol **8**[6] in 33 and 70% yields, respectively. The ^{1}H NMR spectrum of **7** showed the signals due to six acetoxyl methyl groups as four singlets with 2:1:2:1 relative intensity, indicative of the presence of the plane of the symmetry in the molecule, being consistent with the assigned structure. The postulated structure of **8** was supported by the ^{1}H NMR spectral

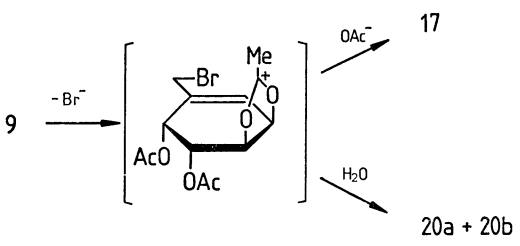
signal-pattern similar to that of **3** in the region of the ring protons attached to the carbon atoms bearing the acetoxyl groups, and finally confirmed by identification with the compound derived by the alternative synthetic route.[7]

The structure of **4** was confirmed by the appearance of the signal for the exocyclic methylene protons at δ=5.22 as a two-proton doublet (J=6 Hz) and that for the olefinic proton at δ=6.19 as a doublet (J=10 Hz) in the ^{1}H NMR spectrum. In contrast to the corresponding (1,3/2)-isomer,[8] **4** is unstable and readily polymerizes during purification. But it can be preserved as an ethyl acetate solution for several days.

Bromination of **4** with bromine in acetic acid–acetic anhydride (1:3) at room temperature gave a mixture of the 1,4-addition products, which were fractionated by a silica-gel column to give the dibromides **9** (30%) and **10** (3%), along with the monobromide **13** (5%). The ^{1}H NMR spectrum of **9** revealed the olefinic proton as a narrow doublet (J=3 Hz) at δ=6.12, in support of a pseudoequatorial orientation of the C-6 bromo group.[9] Compounds **9** and **10** are interconvertible each other in the presence of a bromide ion, and the more thermodynamically stable isomer **9** predominates in the reaction mixture. Compound **13** seems to be formed from **9** by an attack of an acetate ion at C-6 from the pseudoaxial direction.

The structure of **9** was further confirmed by the reaction with silver acetate (4 molar equiv.) in acetic acid, which proceeded through a neighboring group participation reaction of the C-1 acetoxyl group at C-6 giving rise to an intermediate 1,6-cyclic acetoxonium ion.[4] When the reaction was carried out in aqueous acetic acid, the acetoxonium ion was attacked by water to give a mixture of DL-1,3,4- (**20a**) and 2,3,4-tri-*O*-acetyl-(1,2/3,4)-5-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (**20b**) in 72% yield. While, under anhydrous conditions (in acetic acid–acetic anhydride), the acetoxonium ion was likely to undergo a back side attack by an acetate ion at the allylic position giving the pentaacetate **18** with the inversion of the configuration at C-6. On the other hand, a molar equiv. of silver acetate was used in the above reaction, the secondary bromo group was only displaced to give the bromo tetraacetate **17** in 48% yield. The mixture of **20a** and **20b** was converted into the pentaacetate **14** by further treatment with sodium acetate in aqueous DMF, followed by acetylation.

Nucleophilic substitution reactions of the bromides thus obtained were then studied. Treatment of **9** with an azide ion in DMF at room temperature gave smoothly a single diazido compound **11** in 67% yield



Scheme 2.

via an S_N2 reaction with inversion of the configuration at C-6. In the ^{1}H NMR spectrum of **11**, the signal for the olefinic proton appeared as a doublet (J=4.5 Hz) at δ=5.86, in support of the assigned structure. Reduction of **11** with hydrogen sulfide, followed by acetylation, gave bis(acetamide) **12** in 78% yield. Similar azidolysis of **17** and **20a,b** gave the corresponding azides **19** and **15** (after acetylation) in 59 and 69% yields, respectively. Compound **15** could easily be converted into the acetamide **16** in 52% yield.

Finally, in order to introduce a desired nucleophile into the C-6 position, attempts to displace first the primary bromo group of **9** by an acetate ion were made. Treatment of **9** with a molar equiv. of sodium acetate in DMF at room temperature gave a mixture of the unstable 6-bromo compounds **21a** and **21b** in 67% yield. Compounds **21a** and **21b** are interconvertible each other in the presence of a bromide ion, and are isolated as an equilibrium mixture. Without further purification, the mixture was directly treated with sodium azide in DMF at room temperature yielded a mixture of the azides **22a** and **22b** in 74% yield. The ^{1}H NMR spectrum of the mixture showed the methylene signal as a singlet at δ=4.44, in support of the presence of the acetoxyl group at the branched-chain carbon atom. Therefore, **21a,b** would be useful as a synthon for preparation of some isomeric validoxylamine A[10] and α-glucosidase inhibitors.[11]

Experimental

General. 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 Varian EM-390 (90 MHz) in chloroform-*d* with reference to tetramethylsilane as an internal standard. The peak positions were given in terms of δ-values and values given for coupling constants were of first-order. TLC was performed on a 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.).

DL-*1,2,3-Tri*-O-*acetyl-(1,2/3,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (2).* A solution of DL-1-*O*-acetyl-2,3-anhydro-(1/2,3,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**1**)[3] (3.0 g) in acetone (27 ml) containing 10% sulfuric acid (3 ml) was refluxed for 3 h. The reaction mixture was neutralized with sodium hydrogencarbonate and then evaporated to dryness. The residue was treated with acetic anhydride (6 ml) and pyridine (6 ml) at room temperature overnight. The reaction mixture was poured into ice water and the precipitates were collected by filtration. Recrystallization of the crude product from ethanol gave 3.4 g (87%) of **2** as plates: mp 126.5—127.5 °C; ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s), 2.11 (3H, s), and 2.19 (3H, s) (OAc), 3.18—3.54 (2H, m, C$\underline{H}_2$Br), 4.40 (1H, ddd, J=3, 5.5, and 12 Hz, H-4), 4.98 (1H, dd, J=3 and 10.5 Hz, H-1), 5.25 (1H, dd, J=3 and 4 Hz, H-3), and 5.34 (1H, dd, J=3 and 4 Hz, H-4).

Found: C, 36.08; H, 4.01; Br, 36.84%. Calcd for $C_{13}H_{18}Br_2O_6$: C, 36.30: H, 4.22; Br, 37.16%.

DL-*1,2,3-Tri*-O-*acetyl-(1,2/3,4,6)-6-acetoxymethyl-4-bromo-1,2,3-cyclohexanetriol (3).* A mixture of **2** (0.30 g), sodium acetate (0.25 g), and *N,N*-dimethylformamide (DMF)

(5 ml) was stirred at 80 °C for 8 h. The reaction mixture was concentrated and coevaporated with 1-butanol and toluene. The residue was extracted with chloroform and the extracts were filtered through a short column of alumina. The filtrate was concentrated and the residue was fractionated on a silica-gel column (12 g) with ethyl acetate–hexane (1 : 2) as an eluent. The first fraction (R_f 0.14) gave an oil, which was recrystallized from ethanol to give 0.21 g (75%) of **3** as prisms: mp 104.5—105 °C; ^{1}H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.06 (3H, s), 2.11 (3H, s), and 2.18 (3H, s), (OAc), 3.97 (2H, d, J=4 Hz, C$\underline{H}_2$OAc), 4.37 (1H, ddd, J=3, 6, and 11 Hz, H-6), 4.95 (1H, dd, J=3 and 11 Hz, H-3), 5.20 (1H, dd, J=3 and 4 Hz, H-1), and 5.25 (1H, dd, J=3 and 4 Hz, H-2).

Found: C, 44.00; H, 5.01; Br, 19.06%. Calcd for $C_{15}H_{21}BrO_8$: C, 44.03; H, 5.17; Br, 19.53%.

The second fraction (R_f 0.29) gave 24 mg (14%) of DL-1,2,3-tri-*O*-acetyl-(1/2,3)-4-methylene-5-cyclohexene-1,2,3-triol (**4**) as an oil: ^{1}H NMR ($CDCl_3$) δ=2.04 (3H, s) and 2.08 (6H, s) (OAc), 5.09 (1H, dd, J=3 and 7.5 Hz, H-2), 5.22 (2H, d, J=6 Hz, C=C$\underline{H}_2$), 5.58—5.80 (3H, m, H-1, H-3, and H-6), and 6.19 (1H, d, J=10 Hz, H-5).

This compound was very unstable and a satisfactory analytical data were not obtained. Therefore, practically pure sample was directly used in the succeeding reactions.

*Reaction of **2** with Sodium Acetate.* *a) In DMF*: A mixture of **2** (4.0 g), sodium acetate (3.3 g, 4 molar equiv.), and DMF (35 ml) was stirred at 110 °C for 32 h. TLC indicated the formation of two products [R_f 0.47 and 0.25, ethyl acetate–hexane (1 : 5)]. The reaction mixture was concentrated and the residue was chromatographed on a silica-gel column (120 g) with ethyl acetate–hexane (1 : 2) as an eluent. The first fraction gave 0.48 g (22%) of **4** as an oil, which was identical with the compound obtained before. The second fraction gave 1.45 g (47.5%) of DL-1,2,3-tri-*O*-acetyl-(1,4/2,3)-4-acetoxymethyl-5-cyclohexene-1,2,3-triol (**5**) as an oil: ^{1}H NMR ($CDCl_3$) δ=2.05 (6H, s) and 2.06 (6H, s) (OAc), 2.75 (1H, br q, J=*ca.* 5 Hz, H-4), 4.09 (2H, d, J=5 Hz, C$\underline{H}_2$OAc), 5.05—5.36 (3H, m, H-1, H-2, and H-3), and 5.71 (2H, s, H-5 and H-6).

Found: C, 54.68; H, 6.02%. Calcd for $C_{15}H_{20}O_8$: C, 54.88; H, 6.14%.

b) In Hexamethylphosphoric Triamide (HMPA): A mixture of **2** (0.30 g), sodium acetate (0.23 g, 4 molar equiv), and HMPA (5 ml) was stirred at 120 °C for 2 h. TLC indicated the formation of one main component [R_f 0.55, ethyl acetate–hexane (1 : 4)], along with four minor components. The reaction mixture was diluted with ethyl acetate (20 ml) and washed thoroughly with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil, which was rapidly chromatographed on a silica-gel column (6 g) with ethyl acetate–hexane (1 : 4) as an eluent. The main fraction gave 0.12 g (69%) of **4** as an oil, which could be preserved as an ethyl acetate solution in a refrigerator.

*DL-1,2-Di-O-acetyl-(1,2/3)-3-acetoxymethyl-5-cyclohexene-1,2-diol (**6**).* A mixture of **3** (0.40 g) and zinc dust (1.95 g) in acetic acid (10 ml) was stirred at 65 °C for 35 h. The reaction mixture was filtered and the insoluble material was washed thoroughly with acetic acid. The filtrate and washings were combined and concentrated to give crystals, which were recrystallized from ethanol to give 0.14 g (51%) of **6** as prisms: mp 57.5—59 °C; ^{1}H NMR ($CDCl_3$) δ=1.99 (3H, s), 2.01 (3H, s), and 2.05 (3H, s) (OAc), 3.85—4.25 (2H, m, C$\underline{H}_2$OAc), 4.93 (1H, dd, J=3.5 and 11 Hz, H-2), 5.42 (1H, br t, J=3.5 Hz, H-1), 5.61 (1H, br dd, J=3.5 and 10 Hz, H-6), and 5.92 (1H, ddd, J=2.5, 4, and 10 Hz, H-5).

Found: C, 57.51; H, 6.64%. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71%.

*Osmium Tetraoxide-oxidation of **5**.* To a solution of **5** (0.34 g) in *t*-butyl alcohol (8 ml) containing 30% hydrogen peroxide (2 ml) was added *t*-butyl alcohol (2.5 ml) containing osmium tetraoxide (0.01 g), and the mixture was stirred at room temperature for 1 d. The reaction mixture was diluted with water and the excess hydrogen peroxide was destroyed by addition of sodium sulfite. The mixture was concentrated to dryness and the residue was treated with acetic anhydride and pyridine in the usual way. The product was purified by passage through a short column of alumina with chloroform. The filtrate was concentrated to give crystals, which were recrystallized from ethanol to give 0.15 g (33%) of 1,2,3,4,5-penta-*O*-acetyl-(1,2,4,5/3,6)-6-acetoxymethyl-1,2,3,4,5-cyclohexanepentol (**7**) as prisms: mp 170.5—171.5 °C; ^{1}H NMR ($CDCl_3$) δ=2.01 (6H, s), 2.02 (3H, s), 2.06 (6H, s), and 2.11 (3H, s) (OAc), 2.65 (1H, m, H-6), 4.11 (2H, d, J=3 Hz, C$\underline{H}_2$OAc), and 5.10—5.30 (5H, m, H-1, H-2, H-3, H-4, and H-5).

Found: C, 50.81; H, 5.88%. Calcd for $C_{19}H_{26}O_{12}$: C, 51.12; H, 5.87%.

*Osmium Tetraoxide-oxidation of **6**.* Compound **6** (0.62 g) was treated with osmium tetraoxide in *t*-butyl alcohol similarly as described in the preparation of **7**. The product was acetylated and then purified by a short column of alumina with chloroform. Recrystallization of the crude product from ethanol gave 0.62 g (70%) of DL-1,2,3,4-tetra-*O*-acetyl-(1,2,5/3,4)-5-acetoxymethyl-1,2,3,4-cyclohexanetetrol (**8**) as prisms: mp 105—106.5 °C; ^{1}H NMR ($CDCl_3$) δ=1.97 (6H, s), 2.01 (3H, s), 2.07 (3H, s), and 2.09 (3H, s) (OAc), 4.03 (2H, d, J=5 Hz, C$\underline{H}_2$OAc), 5.03 (1H, dd, J=3.5 and 10 Hz, H-4), and 5.03—5.36 (3H, m, H-1, H-2, and H-3); (Found: C, 52.87; H, 6.24%). It was identical with the compound (mp 106—107 °C) derived by the alternative route.[7]

The mother liquor of **8** was concentrated and the residue was chromatographed on a silica-gel column (15 g) with ethyl acetate–hexane (1 : 2) as an eluent. The first fraction (R_f 0.55) gave 12 mg (1.8%) of 2,6-diacetoxy-4-methylene-2,5-cyclohexadiene-1-one as an oil: ^{1}H NMR ($CDCl_3$) δ=2.04 (3H, s) and 2.23 (3H, s) (OAc), 4.94 (2H, s, C=C$\underline{H}_2$), and 7.08 (2H, s, H-3 and H-5). The second fraction (R_f 0.43) gave 19 mg (2.1%) of DL-(hydroxymethyl)-cyclohexanetetrol pentaacetate as an oil: ^{1}H NMR ($CDCl_3$) δ=1.93 (3H, s), 1.97 (3H, s), 2.00 (3H, s), 2.04 (3H, s), and 2.08 (3H, s) (OAc), 3.90 (1H, dd, J=3.5 and 11 Hz) and 4.09 (1H, dd, J=5 and 11 Hz) (C$\underline{H}_2$OAc). These compounds were not further characterized because of minute quantities.

*Reaction of **4** with Bromine in Acetic Acid and Acetic Anhydride.* An 1 : 3 mixture of acetic acid and acetic anhydride was heated at reflux for 2 h before use as a solvent. To a stirred solution of crude **4** (0.35 g) in the mixture of solvent (7 ml) was added dropwise 5% bromine-acetic acid (1.35 ml) at room temperature, and then the stirring was continued for 1.5 h. TLC indicated the formation of one major component (R_f 0.53), along with two mionr components (R_f 0.51 and 0.36) [irrigated two times in ethyl acetate–hexane (1 : 4)]. The reaction mixture was diluted with ethyl acetate, washed thoroughly with saturated sodium hydrogencarbonate, and dried. Evaporation of the solvent gave an oil, which was fractionated on a silica-gel column (30 g) with ethyl acetate–hexane (1 : 4) as an eluent.

The first fraction gave crystals, which were recrystallized

from ethanol to give 0.17 g (30%) of DL-1,2,3-tri-*O*-acetyl-(1/2,3,6)-6-bromo-4-bromomethyl-4-cyclohexene-1,2,3-triol (**9**) as prisms: mp 108.5—109 °C; ^{1}H NMR ($CDCl_3$) δ= 1.99 (3H, s), 2.08 (3H, s), and 2.13 (3H, s) (OAc), 3.87 (2H, s, C$\underline{H}_2$Br), 4.54 (1H, br dd, J=3 and 7.5 Hz, H-6), 5.02 (1H, dd, J=4 and 10.5 Hz, H-2), 5.63 (1H, dd, J= 7.5 and 10.5 Hz, H-1), 5.80 (1H, d, J=4 Hz, H-3), and 6.12 (1H, d, J=3 Hz, H-5).

Found: C, 36.18; H, 3.77; Br, 37.15%. Calcd for $C_{13}H_{16}Br_2O_6$: C, 36.48; H, 3.77; Br, 37.33%.

The second fraction gave 16 mg (3%) of DL-1,2,3-tri-*O*-acetyl-(1,6/2,3)-6-bromo-4-bromomethyl-4-cyclohexene-1,2,3-triol (**10**) as an oil: ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s), 2.08 (3H, s), and 2.12 (3H, s) (OAc), 3.84 (2H, s, C$\underline{H}_2$Br), 4.90—5.16 (2H, m, H-2 and H-6), 5.27—5.62 (1H, m, H-1), 5.86 (1H, d, J=4 Hz, H-3), and 6.15 (1H, d, J=4 Hz, H-5). Compound **10** was not stable enough to give satisfactory analytical data. The third fraction gave crystals, which were recrystallized from ethanol to give 26 mg (5%) of DL-1,2,3,4-tetra-*O*-acetyl-(1,2/3,4)-5-bromomethyl-5-cyclohexene-1,2,3-triol (**13**) as prisms: 120.5—121 °C; ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s), 2.02 (3H, s), 2.06 (3H, s), and 2.08 (3H, s) (OAc), 3.84 (2H, s, C$\underline{H}_2$Br), 5.20—5.50 (2H, m, H-2 and H-3), 5.63 (1H, br dd, J=2.5 and 5 Hz, H-1), 5.87 (1H, d, J=3 Hz, H-4), and 5.94 (1H, d, J=5 Hz, H-6).

Found: C, 43.98; H, 4.62; Br, 19.29%. Calcd for $C_{15}H_{19}BrO_8$: C, 44.25; H, 4.70; Br, 19.62%.

DL-*1,2,3,4-Tetra-O-acetyl-(1,2/3,4)-5-acetoxymethyl-5-cyclohexene-1,2,3,4-tetrol* (**14**). A mixture of **9** (0.30 g), silver acetate (0.13 g, 4 molar equiv.), and 90% aqueous acetic acid (10 ml) was stirred at room temperature for 20 h in the dark. The reaction mixture was filtered and the filtrate was concentrated to an oil, which was chromatographed on a silica-gel column (15 g) with 2-butanone-toluene (1 : 3) as an eluent. The main fraction gave 0.18 g (72%) of a mixture of 1,3,4- (**20a**) and 2,3,4-tri-*O*-acetyl-(1,2/3,4)-5-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (**20b**) as an oil: ^{1}H NMR ($CDCl_3$) for **20a** δ=2.05 (3H, s), 2.06 (3H, s), 2.10 (3H, s), and 2.12 (3H, s) (OAc), 2.27—2.53 (1H, m, O$\underline{H}$), 3.81 (2H, s, C$\underline{H}_2$Br), 4.12 (1H, dd, J=4 and 9 Hz, H-2), 5.16—5.50 (2H, m, H-1 and H-3), 5.82 (1H, d, J=4 Hz, H-4), and 5.97 (1H, d, J=4 Hz, H-6). The signal due to the C-1 proton of **20b** appeared as a narrow multiplet at δ=4.43—4.54, of which intensity was estimated at *ca.* one third of that of **20a**.

Found: C, 42.39; H, 4.66; Br, 22.20%. Calcd for $C_{13}H_{17}BrO_7$: C, 42.76; H, 4.69; Br, 21.88%.

A 0.12 g portion of the mixture was treated with sodium acetate (30 mg) in 90% aqueous DMF (3 ml) for 8 h. The reaction mixture was diluted with ethyl acetate, washed with water, and dried. The residue was acetylated in the usual way and the product was purified by a short column of alumina with chloroform. The product was recrystallized from ethanol to give 63 mg (49%) of **14** as prisms: mp 118.5—119 °C; ^{1}H NMR ($CDCl_3$) δ=1.98 (3H, s), 2.00 (3H, s), and 2.06 (9H, s) (OAc), 4.45 (2H, br s, C$\underline{H}_2$-OAc), 5.36 (2H, m, H-2 and H-3), 5.55—5.80 (2H, m, H-1 and H-4), and 5.87 (1H, br d, J=5.5 Hz, H-6).

Found: C, 53.08; H, 5.80%. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74%.

DL-*1,2,3,4-Tetra-O-acetyl-(1,3,4/2)-5-acetoxymethyl-5-cyclohexene-1,2,3,4-tetrol* (**18**). A mixture of silver acetate (0.31 g, 4 molar equiv.) in acetic acid (6 ml) and acetic anhydride (6 ml) was refluxed for 2 h, and then **9** (0.20 g) was added to it, and the mixture was refluxed for 8 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on a silica-gel column with ethyl acetate-hexane (1 : 1) as an eluent. The product was recrystallized from ethanol to give 79 mg (26%) of **18** as prisms: mp 93—94 °C; ^{1}H NMR ($CDCl_3$) δ=1.95 (3H, s), 2.00 (3H, s), 2.04 (6H, s), and 2.07 (3H, s) (OAc), 4.43 (2H, s, C$\underline{H}_2$OAc), 5.07 (1H, ddd, J=3.5, 8.5, and 12 Hz, H-2), 5.45 (1H, br d, J=8.5 Hz, H-1), 5.62 (1H, d, J=3.5 Hz, H-4), and 5.74 (1H, br s, H-6).

Found: C, 52.91; H, 5.72%. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74%.

DL-*1,2,3,4-Tetra-O-acetyl-(1,3,4/2)-5-bromomethyl-5-cyclohexene-1,2,3,4-tetrol* (**17**). A mixture of silver acetate (0.12 g, a molar equiv.), acetic acid (8 ml), and acetic anhydride (8 ml) was refluxed for 2 h, and then **9** (0.30 g) was added to it, and the mixture was refluxed for 2 h. The reaction mixture was processed as described in the preparation of **18**. The product was chromatographed on a silica-gel column with ethyl acetate-hexane (1 : 2) to give 0.14 g (48%) of **17** as an oil: ^{1}H NMR ($CDCl_3$) δ=1.97 (3H, s), 2.00 (3H, s), 2.04 (3H, s), and 2.10 (3H, s) (OAc), 3.83 (2H, s, C$\underline{H}_2$Br), 5.03 (1H, m, H-3), 5.42 (1H, d, J=7.5 Hz, H-2), 5.33—5.53 (1H, m, H-1), 5.79 (1H, d, J=3.5 Hz, H-4), and 5.83 (1H, br d, J=1.5 Hz, H-6).

Found: C, 44.42; H, 4.68; Br, 19.35%. Calcd for $C_{15}H_{19}BrO_8$: C, 44.25; H, 4.70; Br, 19.62%.

DL-*1,2,3-Tri-O-acetyl-(1,6/2,3)-6-azido-4-azidomethyl-4-cyclohexene-1,2,3-triol* (**11**). A mixture of **9** (0.30 g), sodium azide (0.18 g, 3 molar equiv.), and DMF (10 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate, washed with water, and dried. Evaporation of the solvent gave an oil, which was purified by a silica-gel column (7 g) with ethyl acetate-hexane (1 : 2) to give crystals. Recrystallization from ethanol gave 0.17 g (67%) of **11** as needles: mp 80—81 °C; ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s), 2.07 (3H, s), and 2.12 (3H, s) (OAc), 2.75 (2H, s, C$\underline{H}_2N_3$), 4.30—4.55 (1H, br s, H-6), 5.33 (2H, br s, H-1 and H-2), 5.61 (1H, br s, H-3), and 5.86 (1H, br d, J=4.5 Hz, H-5).

Found: C, 44.15; H, 4.60; N, 23.55%. Calcd for $C_{13}H_{16}N_6O_6$: C, 44.32; H, 4.58; N, 23.85%.

DL-*1,2,3-Tri-O-acetyl-(1,6/2,3)-6-acetamido-4-acetamidomethyl-4-cyclohexene-1,2,3-triol* (**12**). Compound **11** (0.11 g) was dissolved in a mixture of pyridine (4 ml) and water (4 ml), and hydrogen sulfide was bubbled into it at room temperature for 1 h. Excess hydrogen sulfide was removed by a nitrogen stream and then the reaction mixture was concentrated. The residual product was acetylated in the usual way and the product was chromatographed on a silica-gel column (5 g). The column was eluted in turn with toluene and with ethanol-toluene (1 : 3). The product was recrystallized from acetone to give 95 mg (78%) of **12** as prisms: mp 224—225 °C; ^{1}H NMR (DMSO-d_6) δ=1.77 (6H, s), 1.88 (3H, s), 1.90 (3H, s), and 2.00 (3H, s) (NAc and OAc), 3.59 (2H, br d, J=5.5 Hz, C$\underline{H}_2$-NHAc), 4.68 (1H, br dt, J=4.5, 4.5, and 9 Hz, H-6), 4.95 (1H, dd, J=4.5 and 10.5 Hz, H-1), 5.22 (1H, dd, J=4 and 10.5 Hz, H-2), 5.36 (1H, d, J=4 Hz, H-3), 5.51 (1H, br d, J=4.5 Hz, H-5), and 7.80—8.00 (2H, m, N$\underline{H}$Ac).

Found: C, 52.51; H, 6.21; N, 7.19%. Calcd for $C_{17}H_{24}N_2O_8$: C, 53.12; H, 6.29; N, 7.29%.

DL-*1,2,3,4-Tetra-O-acetyl-(1,2/3,4)-5-azidomethyl-5-cyclohexene-1,2,3,4-tetrol* (**15**). A mixture of **20a** and **20b** (0.18 g) was treated with sodium azide (65 mg, 2 molar equiv.) in DMF (5 ml) at room temperature for 2.5 h. The reaction mixture was processed as described in the preparation of **11**. The product, after the conventional acetylation, was purified by

crystallization from ethanol to give 0.13 g (69%) of **15** as prisms: mp 109.5—110 °C; ^{1}H NMR ($CDCl_3$) δ=1.98 (3H, s), 2.00 (3H, s), 2.04 (3H, s), and 2.06 (3H, s) (OAc), 3.74 (2H, s, C$\underline{H}_2N_3$), 5.33 (2H, m, H-2 and H-3), 5.50—5.73 (2H, m, H-1 and H-4), and 5.86 (1H, br d, J=4.5 Hz, H-6).

Found: C, 48.99; H, 5.17; N, 11.56%. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38%.

DL-*1,2,3,4-Tetra*-O-*acetyl-(1,3,4/2)-5-azidomethyl-5-cyclohexene-1,2,3,4-tetrol (**19**).* Compound **17** (0.14 g) was treated with sodium azide (44 mg, 2 molar equiv.) in DMF (5 ml) at room temperature for 18 h. The reaction mixture was processed as described in the preparation of **11** to give 73 mg (59%) of **19** as an oil: ^{1}H NMR ($CDCl_3$) δ=1.98 (3H, s), 2.03 (3H, s), 2.09 (3H, s), and 2.14 (3H, s) (OAc), 3.79 (2H, s, C$\underline{H}_2N_3$), 5.11 (1H, m, H-3), 5.50 (1H, d, J=7 Hz, H-2), 5.35—5.60 (1H, m, H-1), 5.64 (1H, d, J=3.5 Hz, H-4), and 5.88 (1H, br s, H-6).

Found: C, 48.60; H, 5.26; N, 11.12%. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38%.

DL-*1,2,3,4-Tetra*-O-*acetyl-(1,2/3,4)-5-acetamidomethyl-5-cyclohexene-1,2,3,4-tetrol (**16**).* Compound **15** (61 mg) was reduced with hydrogen sulfide as described in the preparation of **12**. The product was acetylated in the usual way. Recrystallization of the crude crystals from ethanol gave 33 mg (52%) of **16** as prisms: mp 181—182 °C; ^{1}H NMR ($CDCl_3$) δ=1.99 (3H, s), 2.01 (6H, s), 2.06 (3H, s), and 2.09 (3H, s) (NAc and OAc), 3.85 (2H, d, J=6 Hz, C$\underline{H}_2$NHAc, changing to a singlet on deuteration), 5.37 (2H, m, H-2 and H-3), 5.51—5.81 (4H, m, H-1, H-4, H-6, and N$\underline{H}$).

Found: C, 53.12; H, 6.06; N, 3.46%. Calcd for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.64%.

DL-*1,2,3-Tri*-O-*acetyl-(1,6/2,3)-* ***(22a)*** *and -(1/2,3,6)-4-acetoxymethyl-6-azido-4-cyclohexene-1,2,3-triol (**22b**).* A mixture of **9** (0.20 g), sodium acetate (38 mg, a molar equiv.), and DMF (5 ml) was stirred at room temperature for 38 h. TLC indicated the disappearance of **9** (R_f 0.48) and the formation of one major component [R_f 0.33, ethyl acetate-hexane (1 : 2)]. The reaction mixture was diluted with ethyl acetate and washed with water and dried. Evaporation of the solvent gave an oil, which was chromatographed on a silica-gel column with ethyl acetate-hexane (1 : 2) to give 0.13 g (67%) of a mixture of the 6-bromo compounds (**21a** and **21b**) as an unstable oil. Without further purification, these compounds were used in the next step.

A 0.13 g portion of the mixture was treated with sodium azide (41 mg, 2 molar equiv.) in DMF (5 ml) at room temperature for 19 h. The reaction mixture was processed as described above and the product was purified by use of a silica-gel column with ethyl acetate-hexane (1 : 2) to give 85 mg (74%) of a mixture of the azides (**22a** and **22b**) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ=1.98, 1.99, 2.01, 2.02, 2.03, and 2.07 (12H, six s, OAc), 3.90—4.50 (1H, m, H-6), 4.44 (2H, s, C$\underline{H}_2$OAc), 4.98 (0.5H, dd, J=3.5 and 11 Hz, H-2 of **22a**), 5.27—5.48 (1.5 H, m, H-1 and H-2), 5.56—5.71 (1H, m, H-3), and 5.73—5.90 (1H, m, H-5).

Found: C, 48.75; H, 5.27; N, 11.36%. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38%.

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