Synthesis of Some Anhydro Derivatives of DL-1-*C*-Hydroxymethyl-1,2,3,4,5,6-cyclohexanehexol[1)]

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Synopsis. Three stereoisomers of DL-1-*C*-(hydroxymethyl) conduritol epoxides have been synthesized in order to investigate their inhibitory activity against certain glycosyl hydrolases.

Several conduritol 5-cyclohexene-1,2,3,4-tetrol derivatives, bromides,[2)] epoxides[3)] etc., have been shown to be glycosidase inactivators. In this note, we describe synthesis of the title four conduritol epoxides (**1**—**4**) with branched hydroxymethyl group, in order to study structure–activity relationship of this kind of enzyme inhibitors.

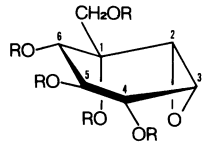
Oxidation of DL-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol triacetate[4)] (**5**) with osmium(VII) tetraoxide in aqueous acetone, followed by acetylation afforded, after separation by chromatography on silica gel, 60% of DL-(1,2,4/3)-1-*C*-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol pentaacetate[5)] (**6**) and 15% of the 1-epimer[5)] (**7**), together with a small proportion (<1% yield) of new DL-(1,2,4/3,5)-6-methylenecyclohexane-1,2,3,4,5-pentol pentaacetate (**8**). The structure of **8** was established on the basis of ^{1}H NMR spectrum which revealed all $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ with a spacing of 9.5—10 Hz, indicating that the acetoxyl groups at C-2,3,4,5 were all in equatorial orientation.

Direct epoxidation of **6** with 3-chloroperbenzoic acid was shown to give a poor yield (15%) of the epoxide **1a**, the ^{1}H NMR spectrum of which contained signals of the epoxide protons as a doublet of doublets (J=1.6 and 3.5 Hz) and a doublet (J=3.5 Hz) at δ=3.60 and 3.81, indicating that the epoxy group existed in the *cis* position[6)] to the 4-OAc group.

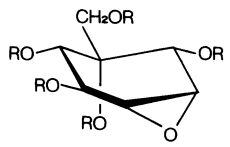
Reaction of **6** with *N*-bromosuccinimide in aqueous 1,4-dioxane at room temperature afforded two crystalline bromohydrins **9** (41%) and **10** (30%). The ^{1}H NMR spectrum of **9** contained a wide triplet (J=10.8 Hz) at δ=4.37, indicative of the presence of the equatorial bromo group at C-3 with two trans acetoxyl groups at C-2,4. In the spectrum of **10**, a narrow doublet (J=3.3 Hz, δ=4.33) was attributable to the signal due to CHBr, showing the existence of the bromo group at C-2 in axial position. Mechanistically, the intermediate bromonium ion formed at C-5,6 was cleaved by assistance of the trans-acetoxyl groups at C-1 and 4, followed by the acetyl group migration under acidic conditions, to yield the bromohydrins having tertially hydroxyl groups.

Treatment of **9** with excess of potassium carbonate in methanol at room temperature and successive acetylation produced a mixture of products, from which only two epoxides **1a** (24%) and **2a** (5.2%) were isolated by chromatography on silica gel. The free pentol **1b** convertible from **1a** seemed to be stable under basic conditions, but in the case of **2a**, the pentol **2b** was likely to be converted into other isomers through epoxy group migration by attack of the adjacent trans hydroxyl and/or the hydroxymethyl groups. On the other hand, similar reaction of **10** with potassium carbonate proceeded cleanly to give, after acetylation, 82% yield of a single epoxide **3a**, the structure of which was confirmed by the ^{1}H NMR spectrum that contained a doublet (J=5 Hz, δ=3.57) due to the epoxide proton. In this case, the tertiary 1-OH function seemed to attack directly the 2-carbon atom bearing the bromo atom and epoxy group migration was not possible.

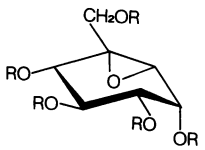
Likewise, the bromohydrin **11** was selectively obtained from **7** in 81% yield. The structure of **11** was confirmed by the ^{1}H NMR spectrum that contained a doublet of doublets (J=3.7 and 9.5 Hz, δ=4.17) due to CHBr. Similarly, epoxidation of **11** produced a mixture of several products, from which only **4a** was



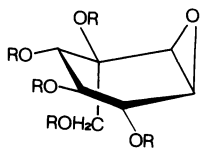
1a,b



2a,b



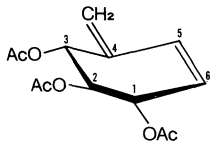
3a,b



4a,b

a: R = Ac

b: R = H



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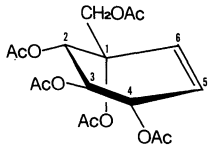

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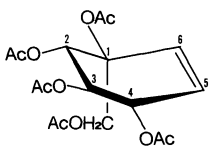

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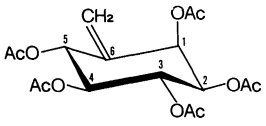

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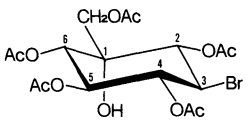

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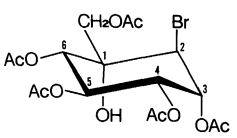

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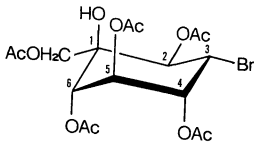

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obtained pure in 26% yield.

The pentaacetates **1a**, **3a**, and **4a** were converted into the free epoxides **1b**, **3b**, and **4b**.

Experimental

General Methods. Melting points were determined with a MEL-TEMP capillary melting-point apparatus and are uncorrected. The ^{1}H NMR spectra were measured with a JEOL JNM-EX 90 (90 MHz) spectrometer for solution of $CDCl_3$ (TMS). Spectrum at 270 MHz were measured with a JEOL JNM-GX 270 FT instrument. TLC was performed on Wakogel B-10 (Wako Co., Osaka) with detection by charring with sulfuric acid. The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka).

DL-(1,2,4/3)-1-*C*-Acetoxymethyl-1,2,3,4-tetra-*O*-acetyl-5-cyclohexene-1,2,3,4-tetrol (6) and DL-(1,3/2,4)-1-*C*-Acetoxymethyl-1,2,3,4-tetra-*O*-acetyl-5-cyclohexene-1,2,3,4-tetrol (7), and DL-(1,2,4/3,5)-1,2,3,4,5-Penta-*O*-acetyl-6-methylene-1,2,3,4,5-cyclohexanepentol (8). DL-(1,3/2)-1,2,3-tri-*O*-acetyl-4-methylene-5-cyclohexene-1,2,3-triol (**5**)[4] (5.0 g, 19 mmol) was dissolved in a mixture of acetone (75 ml) and water (175 ml). To the mixture was added 97% 4-methylmorpholine *N*-oxide (2.9 g, 21 mmol) and 0.05 M osmium tetraoxide (1 M=1 mol dm^{-3}) in 2-methyl-2-propanol (7.5 ml, 0.37 mmol), and it was stirred at room temperature for 26 h. Sodium hydrogensulfite (4.1 g, 40 mmol) was added to quench the exess oxidant, then the mixture was concentrated, and the residue was acetylated with acetic anhydride (280 ml) in pyridine (80 ml). TLC (1:5, 2-butanone–toluene) then revealed three products (R_f 0.49, 0.45 and 0.42). The mixture was concentrated, and solution of the residue in ethyl acetate was washed with water, dried, and concentrated. Chromatography of the residue on a silica gel with 2-butanone–toluene (1:30) gave first, **8** (72 mg, 1.0%) as prisms: mp 98.5—99.5 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.01, 2.02, 2.03, 2.12 and 2.15 (5 s, each 3H, 5 OAc), 4.91 (dd, 1H, $J_{2,3}$=10 Hz, $J_{1,2}$=3.5 Hz, H-2), 5.04 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.5 Hz, H-4), 5.28 and 5.42 (2 d, each 1H, J=2.2 Hz, H-7, H-7′), 5.58 (dd, 1H, H-3), 5.75 (m, 1H, H-5), 5.82 (d, 1H, H-1). Found: C, 52.50; H, 5.51%. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74%.

Eluted second was **6** (4.3 g, 60%), isolated as a syrup. This compound was identical with an authentic sample[5] in all respects.

Eluted third was **7** (1.1 g, 15%), isolated as prisms: mp 97.5—98.5 °C (recrystallized from ethanol) (lit,[5] mp 94.0—96.0 °C). This compound was identical with an authentic sample[5] in all respects.

DL-(1,2,3,4,6/5)-1-*C*-Acetoxymethyl-1,4,5,6-tetra-*O*-acetyl-2,3-anhydro-1,2,3,4,5,6-cyclohexanehexol (1a). To a solution of **6** (0.10 g, 0.26 mmol) in 1,2-dichloroethane (3 ml) was added 70% 3-chloroperbenzoic acid (0.57 g, ca. 2.3 mmol), and the mixture was stirred at 50 °C for 14 days. The mixture was treated with 20% aqueous sodium thiosulfate and extracted with chloroform, and the extract was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel with 2-butanone–toluene (1:10) to give recovered **6** (31 mg, 31%) and **1a** (16 mg, 15%) as prisms: mp 137—139 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.00, 2.07, 2.12, 2.13, and 2.18 (5 s, each 3H, 5 OAc), 3.60 (dd, 1H, $J_{2,3}$=3.5 Hz, $J_{3,4}$=1.6 Hz, H-3), 3.81 (d, 1H, H-2), 4.21 and 4.74 (2 d, each 1H, J=11 Hz, H-7, H-7′). Found: C, 50.89; H, 5.48%. Calcd for $C_{17}H_{22}O_{11}$: C, 50.75; H, 5.51%.

DL-(1,2,4,6/3,5)-1-*C*-Acetoxymethyl-2,4,5,6-tetra-*O*-acetyl-3-bromo-1,2,4,5,6-cyclohexanepentol (9) and DL-(1,3,4,6/2,5)-1-*C*-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-2-bromo-1,3,4,5,6-cyclohexanepentol (10). To a solution of **6** (0.67 g, 1.7 mmol) in 10 ml of 1,4-dioxane–water (1:1) mixture was added *N*-bromosuccinimide (1.5 g, 8.7 mmol), and the mixture was stirred at room temperature for 3 days. TLC (1:3, 2-butanone–toluene) then revealed two major products (R_f 0.36 and 0.26). The mixture was concentrated, and the residue was dissolved in ethyl acetate, and the solution was washed with water, dried, and concentrated. Chromatography of the crude product on a sillica gel with 2-butanone–toluene (1:9) gave first, **9** (0.35 g, 41%) as prisms: mp 217—218 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 270 MHz) δ=1.99, 2.07, 2.08, 2.10, and 2.18 (5 s, each 3H, 5 OAc), 2.62 (s, 1H, OH), 3.85 and 3.90 (2 d, each 1H,

J=11.5 Hz, H-7, H-7′), 4.37 (t, 1H, $J_{2,3}$=$J_{3,4}$=10.8 Hz, H-3), 5.32 (d, 1H, $J_{5,6}$=9.7 Hz, H-6), 5.37 (dd, 1H, $J_{4,5}$=9.7 Hz, H-4), 5.41 (d, 1H, H-2), 5.44 (t, 1H, H-5). Found: C, 41.93; H, 4.81%. Calcd for $C_{17}H_{23}BrO_{11}$: C, 42.25; H, 4.80%.

Eluted second was **10** (0.25 g, 30%), isolated as prisms: mp 144.0—145.5 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 270 MHz) δ=2.02, 2.03, 2.11, 2.12, and 2.15 (5 s, each 3H, 5 OAc), 3.10 (s, 1H, OH), 4.25 and 4.30 (2 d, each 1H, J=12.5 Hz, H-7, H-7′), 4.33 (d, 1H, $J_{2,3}$=3.3 Hz, H-2), 5.66 (t, 1H, $J_{3,4}$=3.3 Hz, H-3), 5.66 (d, 1H, $J_{5,6}$=6.2 Hz, H-6). Found: C, 42.31; H, 4.65%. Calcd for $C_{17}H_{23}BrO_{11}$: C, 42.25; H, 4.80%.

DL-(1,2,3,4,6/5)-1-*C*-Acetoxymethyl-1,4,5,6-tetra-*O*-acetyl-2,3-anhydro-1,2,3,4,5,6-cyclohexanehexol (1a) and DL-(1,2,3,4,6/5)-1-*C*-Acetoxymethyl-1,2,5,6-tetra-*O*-acetyl-3,4-anhydro-1,2,3,4,5,6-cyclohexanehexol (2a). To a solution of **9** (0.53 g, 1.1 mmol) in methanol (20 ml) was added anhydrous potassium carbonate (0.31 g, 2.2 mmol), and the solution was stirred at room temperature for 7 h, then neutralized with 1 M hydrochloric acid. The mixture was concentrated, and the residue was acetylated in the usual way. TLC (1:4, acetone–hexane) then revealed two major products (R_f 0.35 and 0.32). The mixture was concentrated and the residue was dissolved in ethyl acetate, and the solution was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel with acetone–hexane (1:8) to give first, **2a** (23 mg, 5.2%) as prisms: mp 176.5—178 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.04, 2.09, 2.11, 2.15, and 2.17 (5 s, each 3H, 5 OAc), 3.27 (d, 1H, $J_{3,4}$=3.8 Hz, H-4), 3.42 (dd, 1H, $J_{2,3}$=3.0 Hz, H-3), 4.52 and 4.79 (2 d, each 1H, J=12 Hz, H-7, H-7′), 5.63 (d, 1H, H-2). Found: C, 50.18; H, 5.42%. Calcd for $C_{17}H_{22}O_{11}$: C, 50.75; H, 5.51%.

Eluted second was **1a** (0.11 g, 24%), isolated as prisms. This compound was identical with the sample obtained by direct epoxidation of **6** in all respects.

DL-(1,2,3,4,6/5)-1-*C*-Acetoxymethyl-3,4,5,6-tetra-*O*-acetyl-1,2-anhydro-1,2,3,4,5,6-cyclohexanehexol (3a). Compound **10** (0.48 g, 0.99 mmol) was treated with anhydrous potassium carbonate, followed by acetylation as described in the preparation of **1a** and **2a**, to give a single epoxide **3a** (0.33 g, 82%) as prisms: mp 121.5—122.5 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.01, 2.02, 2.08, 2.12, and 2.16 (5 s, each 3H, 5 OAc), 3.57 (d, 1H, $J_{2,3}$=5.0 Hz, H-2), 3.82 and 4.37 (2 d, each 1H, J=12.3 Hz, H-7, H-7′), 4.96 (dd, 1H, $J_{4,5}$=10 Hz, $J_{3,4}$=5.0 Hz, H-4), 5.37 (dd, 1H, $J_{5,6}$=8.2 Hz, H-5), 5.47 (t, 1H, H-3), 5.57 (d, 1H, H-6). Found: C, 50.39; H, 5.42%. Calcd for $C_{17}H_{22}O_{11}$: C, 50.75; H, 5.51%.

DL-(1,2,5/3,4,6)-1-*C*-Acetoxymethyl-2,4,5,6-tetra-*O*-acetyl-3-bromo-1,2,4,5,6-cyclohexanepentol (11). Compound **7** (0.84 g, 2.2 mmol) was treated with *N*-bromosuccinimide as described in the preparation of **9** and **10** to give a single product **11** (0.85 g, 81%) as prisms: mp 180.5—182.5 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 270 MHz) δ=2.08, 2.10, 2.11, 2.14, and 2.20 (5 s, each 3H, 5 OAc), 2.82 (s, 1H, OH), 4.19 and 4.28 (2 d, each 1H, J=12.3 Hz, H-7, H-7′), 4.71 (dd, 1H, $J_{2,3}$=9.5 Hz, $J_{3,4}$=3.7 Hz, H-3), 5.07 (t, 1H, $J_{4,5}$=$J_{5,6}$=3.7 Hz, H-5), 5.19 (d, 1H, H-6), 5.34 (t, 1H, H-4), 5.59 (d, 1H, H-2). Found: C, 42.30; H, 4.70%. Calcd for $C_{17}H_{23}BrO_{11}$: C, 42.25; H, 4.80%.

DL-(1,2,3,5/4,6)-1-*C*-Acetoxymethyl-1,4,5,6-tetra-*O*-acetyl-2,3-anhydro-1,2,3,4,5,6-cyclohexanehexol (4a). Compound **11** (0.32 g, 0.66 mmol) was treated with anhydrous potassium carbonate as described in the preparation of **1a**, **2a** and **3a** to give a single epoxide **4a** (69 mg, 26%) as prisms: mp 98.5—99.5 °C (recrystallized from ethanol). ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.00, 2.05, 2.09, and 2.18 (4s, 3H, 6H, 3H, 3H, 5 OAc), 3.25 and 4.14 (2 d, each 1H, $J_{2,3}$=3.8 Hz, H-2, H-3), 4.51 and 4.98 (2 d, each 1H, J=11.4 Hz, H-7, H-7′). Found: C, 50.73; H, 5.32%. Calcd for $C_{17}H_{22}O_{11}$: C, 50.75; H, 5.51%.

DL-(1,2,3,4,6/5)-2,3-Anhydro-1-*C*-hydroxymethyl-1,2,3,4,5,6-cyclohexanehexol (1b). To a solution of **1a** (0.10 g, 0.25 mmol) in methanol (3.6 ml) was added methanolic 1 M sodium methoxide (0.4 ml). The solution was stirred at room temperature for 2 h, then neutralized with Amberlite IR-120B (H^+) resin, and concentrated to give **1b** (46 mg, 96%) as a syrup. Found: C, 42.64; H, 6.00%. Calcd for $C_7H_{12}O_6 \cdot 0.25H_2O$: C, 42.75; H, 6.41%.

DL-(1,2,3,4,6/5)-1,2-anhydro-1-*C*-hydroxymethyl-1,2,3,4,5,6-cyclohexanehexol (3a). Treatment of **3a** (0.20 g, 0.25 mmol) as described in the preparation of **1b** gave **3b** (89 mg, 93%) as prisms: mp 180.5—182.5 °C (recrystallized from methanol). Found: C, 43.11; H, 6.02%. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29%.

DL-(1,2,3,5/4,6)-2,3-Anhydro-1-*C*-hydroxymethyl-1,2,3,4,5,6-cyclohexanehexol (4b). Treatment of **4a** (83 mg, 0.21 mmol) as described in the preparation of **1b** and **3b** gave **4b** (38 mg, 95%) as a syrup. Found: C, 40.43; H, 6.89%. Calcd for $C_7H_{12}O_6 \cdot H_2O$: C, 40.00; H, 6.71%.

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References

1) Pseudo-Sugars. Part XXVI. For Part XXV, see S. Ogawa and T. Tonegawa, *Carbohydr. Res.*, in press.

2) R. Datema, P. A. Romero, G. Legler, and R. T. Schwarz, *Proc. Natl. Acad. Sci. U.S.A.*, **79**, 6787 (1982).

3) G. Legler and M. Herrchen, *FEBS Lett.*, **135**, 139 (1981).

4) S. Ogawa, T. Toyokuni, M. Omata, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, **53**, 455 (1980).

5) S. Ogawa and Y. Shibata, *Carbohydr. Res.*, **156**, 273 (1986).

6) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 1481 (1968); T. Suami, S. Ogawa, S. Oki, and K. Ohashi, *Bull. Chem. Soc. Jpn.*, **45**, 2597 (1972).