Pseudo-Sugars. XV. A Facile Synthesis of Pseudo-β-DL-fructopyranose

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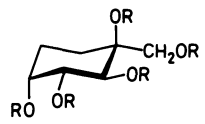
Synopsis. Pseudo-β-DL-fructopyranose, DL-(1,2/3,4)-1-*C*-hydroxymethyl-1,2,3,4-cyclohexanetetrol, has been synthesized from DL-1,2-di-*O*-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol by the seven-steps sequence in 21% overall yield.

In recent years, biochemical properties of pseudo-sugars have stimulated considerable synthetic effort toward their stereoisomers. In continuation to the preceding paper,[1] since we required large quantities of pseudo-β-DL-fructopyranose (**1**) in order not only to carry out biological test in detail, but also to use as an intermediate for derivatization, the improved stereospecific route to **1** has been worked out. The present synthesis should be applied for preparation of an optically active **1**,[2] which would give an interesting knowledge on a sweet tasting property of sugars in terms of the molecular chirality.

O-Deacetylation of DL-1,2-di-*O*-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol (**3**)[3] with hydrochloric acid in ethanol gave the dihydroxy compound (**4**) in 83% yield. Epoxidation of **4** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane, followed by acetylation, gave 80% yield of single epoxide (**5**) preferentially. The stereospecificity may be attributed to the *cis*-directing effect of the adjacent C-1 hydroxyl group.[4] Dehydrobromination of **5** with silver fluoride in pyridine at room temperature afforded the *exo*-methylene compound (**6**) in a quantitative yield. Reductive cleavage of the epoxide ring of **6** was carried out with lithium aluminum hydride (LAH) in tetrahydrofuran (THF), followed by acetylation with acetic anhydride in pyridine, gave the triacetate (**7**) in 52% yield. Epoxidation of the *exo*-methylene group of **7** with MCPBA gave 90% yield of a single spiro epoxide (**8**). Treatment of **8** with sodium acetate in refluxing aqueous 2-methoxyethanol, followed by acetylation in the presence of 4-dimethylaminopyridine, afforded the pentaacetyl derivative (**2**) of **1** in 66% yield.[5] This compound was identical with an authentic sample[1] in all respects. These results also supported the assigned structures of **5** and **8**. Compound **2** could readily be converted into the free pseudo-sugar **1** quantitatively.[1] Therefore, the overall yield of **1** from **3** was 21%.



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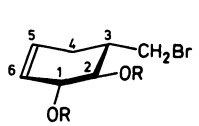

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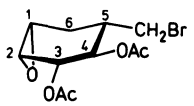
4 R = H



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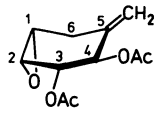

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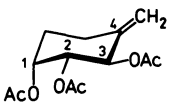

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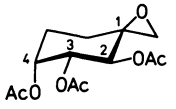

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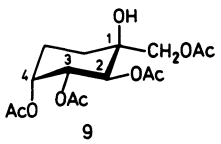

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Experimental

General. The same method was used as described in the preceding paper.[1]

DL-(1,3/2)-3-Bromomethyl-5-cyclohexene-1,2-diol (4). A mixture of DL-1,2-di-*O*-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol (**3**)[3] (10.0 g, 34 mmol) and ethanol (150 ml), and concd hydrochloric acid (50 ml) was stirred at room temperature for 13 h. The reaction mixture was treated with sodium hydrogencarbonate and then concentrated. The residue was extracted with ethanol several times and the extracts were concentrated to give a solid, which was purified by a silica-gel column (200 g) with ethyl acetate–hexane (1:3) as an eluant, giving 5.88 g (83%) of **4** as crystals: mp 80—80.5 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.74—2.35 (2H, m, H-3, 4), 3.36—3.85 (3H, m, H-2, 7, and 7'), 3.94—4.29 (1H, m, H-1), 5.37—5.87 (2H, m, H-5, 6).

Found: C, 40.43; H, 5.26; Br, 38.38%. Calcd for $C_7H_{11}BrO_2$: C, 40.60; H, 5.35; Br, 38.59%.

DL-3,4-Di-*O*-acetyl-1,2-anhydro-(1,2,3,5/4)-5-bromomethyl-1,2,3,4-cyclohexanetetrol (5). A mixture of **4** (0.10 g, 0.48 mmol) and MCPBA (0.16 g, 0.90 mmol) in dichloromethane (2 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated and the residue was treated with acetic anhydride (1 ml) and pyridine (2 ml) at room temperature overnight. The mixture was concentrated and the residue was taken up in ethyl acetate and the solution was washed with saturated sodium hydrogencarbonate and water thoroughly. Evaporation of the solvent gave a solid, which was purified by a silica-gel column to give 0.12 g (80%) of **5** as crystals: mp 110—110.5 °C. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.05 (3H, s) and 2.10 (3H, s) (OAc), 1.58—2.54 (3H, m, H-5, 6, and 6'), 3.07—3.45 (4H, m, H-1, 2, 7, and 7'), 5.04 (1H, dd, *J*=8.1 and 9.2 Hz, H-4), 5.26 (1H, dd, *J*=8.1 and 2 Hz, H-3).

Found: C, 42.91; H, 4.92; Br, 25.76%. Calcd for $C_{11}H_{15}BrO_5$: C, 43.02; H, 4.92; Br, 26.02%.

DL-3,4-Di-*O*-acetyl-1,2-anhydro-(1,2,3/4)-5-methylene-1,2,3,4-cyclohexanetetrol (6). A suspension of **5** (0.20 g, 0.65 mmol), silver fluoride (0.20 g, 2 molar equiv), in pyridine (5 ml) was stirred at room temperature for 1 h. An insoluble material was removed by filtration and the filtrate was concentrated. The residue was purified by a silica-gel column (8 g) with ethyl acetate, giving 0.15 g (100%) of **6** as a syrup: ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.10 (3H, s) and 2.13 (3H, s) (OAc), 2.75—2.90 (2H, m, H-6 and 6'), 3.30—3.49 (2H, m, H-1 and 2), 4.87—5.03 (2H,

m, H-7 and 7'), 5.13 (1H, dd, J=8.3 and 2 Hz, H-3), 5.43 (1H, br d, J=8.3 Hz, H-4).

Found: C, 58.17; H, 6.36%. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24%.

DL-1,2,3-Tri-*O*-acetyl-(1,2/3)-4-methylene-1,2,3-cyclohexanetriol (7). To a solution of **6** (0.50 g, 2.2 mmol) in THF (24 ml) was added $LiAlH_4$ (0.42 g, 11 mmol) gradually, and the mixture was stirred at room temperature for 3 h. Then the mixture was filtered through a celite bed and the filtrate was concentrated and the residue was acetylated in the usual way. The product was purified by a silica-gel column (20 g) with ethyl acetate–hexane (1:5) as an eluant, giving 0.31 g (52%) of **7** as crystals: mp 60—61 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.01 (3H, s) and 2.13 (6H, s) (OAc), 1.45—2.56 (4H, m, H-5, 5', 6, and 6'), 4.85—5.08 (3H, m, H-1, 7, and 7'), 5.34—5.66 (2H, m, H-2 and 3).

Found: C, 57.60; H, 6.66%. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71%.

DL-2,3,4-Tri-*O*-acetyl-1,7-anhydro-(1,2/3,4)-1-*C*-hydroxymethyl-1,2,3,4-cyclohexanetetrol (8). A mixture of **7** (95 mg, 0.35 mmol), MCPBA (217 mg, 2.5 molar equiv), and dichloromethane (3 ml) was stirred at room temperature for 4 h. Excess peroxy acid was destroyed by sodium thiosulfate and the mixture was concentrated. The residue was processed as described in the preparation of **5** and the product was purified by a silica-gel column to give 90 mg (90%) of **8** as a syrup: ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.00 (3H, s), 2.06 (3H, s), and 2.10 (3H, s) (OAc), 2.68 (2H, s, H-7 and 7'), 1.35—2.93 (4H, m, H-5, 5', 6, and 6'), 4.89—5.53 (3H, m, H-2, 3, and 4).

Found: C, 54.51; H, 6.37%. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34%.

DL-2,3,4-Tri-*O*-acetyl-(1,2/3,4)-1-*C*-acetoxymethyl-1,2,3,4-cyclohexanetetrol (9). A mixture of **8** (0.47 g, 1.7 mmol), anhydrous sodium acetate (0.68 g, 8.3 mmol), and 90% aqueous 2-methoxyethanol (10 ml) was stirred at 80 °C for 6 h. The mixture was concentrated and the residue was acetylated in the usual way. The product was purified on a silica-gel column (40 g) with ethyl acetate–hexane (5:9) to give 0.45 g (78%) of **9** as crystals: mp 108—109 °C. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.96 (3H, s), 2.08 (6H, s), and 2.10 (3H, s) (4 OAc), 3.90 and 4.00 (1H, d, J=11.4 Hz, $C\underline{H}_2OAc$), 5.25—5.50 (3H, m, H-2, 3, and 4).

Found: C, 52.17; H, 6.35%. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40%.

DL-1,2,3,4-Tetra-*O*-acetyl-(1,2/3,4)-1-*C*-acetoxymethyl-1,2,3,4-cyclohexanetetrol (2). A mixture of **8** (67 mg, 0.23 mmol), anhydrous sodium acetate (95 mg, 1.1 mmol), and 90% aqueous 2-methoxyethanol (2 ml) was heated at 80 °C for 6 h. The product was acetylated with acetic anhydride (1.5 ml) and pyridine (1.5 ml) in the presence of 4-dimethylaminopyridine (30 mg) at 60 °C for 14 h, and then at 90 °C for 4 h. The mixture was processed in the usual way and the product was purified by a silica-gel column with ethyl acetate–hexane (3:8) as an eluant, giving 60 mg (66%) of **2** as crystals: mp 147.5—148 °C. This compound was identical with an authentic sample[1] in all respects.

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References

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2) The optically active **3** has been synthesized: S. Ogawa and T. Takagaki, *J. Org. Chem.*, **50**, 2356 (1985).

3) S. Ogawa, T. Toyokuni, T. Kondoh, Y. Hattori, S. Iwasaki, M. Suetsugu, and T. Suami, *Bull. Chem. Soc. Jpn.*, **54**, 2739 (1981).

4) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, **1957**, 1958. H. O. House, "Modern Synthetic Reactions" 2nd ed., Benjamin, California (1972), p. 304.

5) When the product was treated with acetic anhydride and pyridine in the absence of 4-dimethylaminopyridine, the tetraacetate (**9**) was obtained mainly in 78% yield.