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Pseudo-Sugars. XIV. Synthesis of Sweet-Tasting Pseudo-β-DL-fructopyranose

Tetsuo Suami,* Seiichiro Ogawa, Makoto Takata, Kuninobu Yasuda,
Kiyoshi Takei, and Atsuo Suga
Department of Applied Chemistry, Faculty of Science and Technology, Keio University,
Hiyoshi, Yokohama 223

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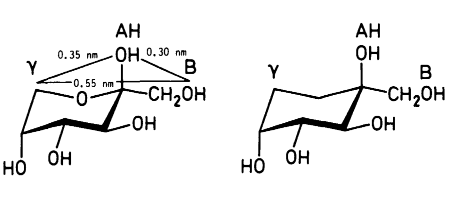
Pseudo-β-DL-fructopyranose was synthesized from DL-1,2-di-*O*-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol by a six steps reaction: Dehydrobromination, epoxidation, acetolysis, reduction, and deacetylation, in overall yield of 4.8%. Pseudo-β-DL-fructopyranose was found to be nearly as sweet as D-fructose which is the most sweet sugar known in naturally occurring carbohydrates.

In the preceding paper,[1] it was described that pseudo-β-DL-glucopyranose was equally as sweet as D-glucose. Therefore, a ring-oxygen in a pyranoid sugar plays no important role in an appearance of sweetness and a replacement of the ring-oxygen by a methylene group gives no detrimental effect on an intensity of its sweetness. This is not surprising, since a conformational feature of sweetness eliciting units, an AH (proton donor), a B (proton acceptor)[2–5] and a third hydrophobic component (γ),[6] of the pyranoid sugar with a distance of 0.30 (AH–B), 0.35 (AH–γ) and 0.55 nm (B–γ) is almost the same as those of the pseudo-hexopyranose.

While D-fructose is the most sweet sugar known in naturally occurring carbohydrates and its intense sweetness (1.8 times more sweet than sucrose) is attributable only to a β-D-fructopyranose form.[2,7,8] And it is anticipated that pseudo-β-D-fructopyranose must be fairly sweet. This expectation prompted us to synthesize pseudo-β-DL-fructopyranose (**1**) for an evaluation of its sweetness. A starting material used in the present synthesis is known DL-1,2-di-*O*-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol[9] (**3**).

Results and Discussion

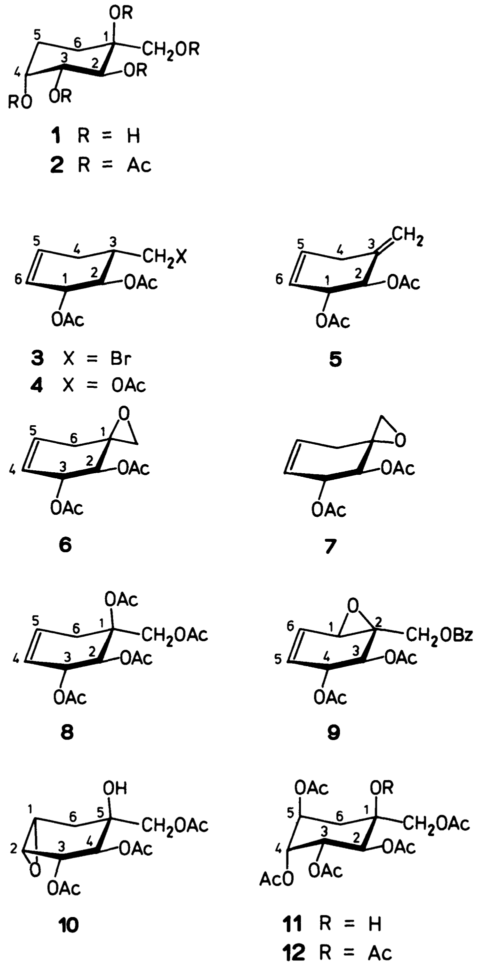
Dehydrobromination of **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene afforded the aimed diene diacetate (**5**) as a major product in 56% yield, and the triacetate (**4**) as a minor by-product in 12% yield. The structure of **5** was elucidated by the ^{1}H NMR spectrum that exhibited the two broad singlets due to the methylene protons of the cyclic and exocyclic double bond at δ 3.00 (2H) and 5.05 (3H), respectively. Compound **4** is considered to be formed by a substitution of the bromo group in **3** with an acetate ion generated in situ by a partial deacetylation of **3**.



β-D-Fructopyranose Pseudo-β-D-fructopyranose

Scheme 1.

Preferential epoxidation of the exocyclic double bond in **5** with *m*-chloroperbenzoic acid (*m*CPBA) in the presence of phosphate buffered solution (pH 8) gave the epoxide (**6**) in 52% yield (based on **5** consumed) and a complex mixture which consisted



Formulas depict only one of the respective enantiomers.

Scheme 2.

mainly of another epoxide (**7**).[10] The structure of **6** was deduced from the following successive reactions.

Nucleophilic opening of the oxirane ring of **6** with an acetate ion, followed by acetylation with acetic anhydride and 4-dimethylaminopyridine (DMAP) gave the crystalline tetraacetate (**8**) as a sole product in 81% yield. The structure of **8** was elucidated by the fact that **8** was also obtained from known DL-3,4-di-*O*-acetyl-1,2-anhydro-(1,2,3/4)-2-*C*-benzoyloxymethyl-5-cyclohexene-1,2,3,4-tetrol[11] (**9**) by LiAlH$_4$ reduction, hydrolysis and subsequent acetylation.

Deacetylation of **8** in methanolic sodium methoxide and successive epoxidation with *m*CPBA in acetic acid for 6 d, followed by acetylation afforded the epoxide triacetate (**10**) in 59% yield, as well as the pentaacetate (**11**) in 12% yield. The structure of **10** was established by the ^{1}H NMR spectrum that showed a doublet of doublets at δ 3.50 (J=4.2 and 2.3 Hz), a doublet of doublets at δ 5.58 (J=9 and 2.3 Hz), and another doublet at δ 5.18 (J=9 Hz). These signals were attributable to H-2, H-3, and H-4, respectively. The structure of **11** was also assigned by the ^{1}H NMR spectrum that revealed four sharp singlets due to the five acetoxyl groups at δ 1.98 (3H), 2.07 (3H), 2.09 (6H), and 2.11 (3H). Furthermore, an exhaustive acetylation of **11** with acetic anhydride in the presence of DMAP gave the crystalline hexaacetate (**12**), which showed four sharp singlets ascribed to the six acetoxyl groups at δ 1.96 (3H), 2.04 (9H), 2.06 (3H), and 2.10 (3H) in its ^{1}H NMR spectrum.

Epoxidation of the double bond of the deacetylated **8** with *m*CPBA in acetic acid seemed to proceed stereoselectively with a cis-directing effect of the vicinal hydroxyl group on C-3[12] and **10** was obtained as a primary product, and a part of **10** was converted to **11** by hydrolysis during the prolonged reaction period of 6 d.

Reduction of **10** with LiAlH$_4$ in THF, followed by acetylation afforded the pentaacetate (**2**), mp 147—148 °C in 34% yield. The ^{1}H NMR spectrum of **2** revealed a doublet of doublets at δ 5.17 (J=10.5 and 3.3 Hz) which was due to an axial proton on C-3 coupled with an equatorial proton on C-4. The reaction seemed to proceed regioselectively through a reductive opening of the oxirane ring which was conducted by an existence of an axial tertiary hydroxyl group on C-5.[13]

Deacetylation of **2** in methanolic sodium methoxide gave pseudo-β-DL-fructopyranose **1** as a syrup in a quantitative yield. An evaluation of an intensity of its sweetness was carried out with six college personnel by a comparison with D-fructose, and **1** was found to be nearly as sweet as D-fructose.

Experimental

General. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were taken on a Varian EM-390 (90 MHz) in chloroform-*d* with a reference to tetramethylsilane as an internal standard. TLC was performed on a plate coated with silica gel 60 F-254 (Merck, Darmstadt). The silica gel used for a column chromatography was Wakogel C-300 (Wako Co., Osaka). Organic solutions were dried over anhydrous sodium sulfate and concentrated below 45 °C under reduced pressure.

DL-(1,3/2)-1,2-Diacetoxy-3-acetoxymethyl-5-cyclohexene (4) and DL-*trans*-1,2-diacetoxy-3-methylene-5-cyclohexene (5). A mixture of DL-(1,3/2)-1,2-diacetoxy-3-bromomethyl-5-cyclohexene[9] (3) (22.3 g, 77 mmol), DBU (25 ml, 160 mmol) and toluene (250 ml) was stirred at 120 °C for 2.5 h. The cooled mixture was washed successively with 1 M hydrochloric acid(1 M=1 mol dm^{-3}), aqueous sodium hydrogencarbonate and water, dried, and concentrated, giving 15.8 g of a crude mixture of products. Chromatography on a silica-gel column (390 g) with ethyl acetate–toluene (1:20, v/v) as an eluant gave 9.1 g (56%) of **5** as a syrup: TLC, R_f=0.44 (ethyl acetate–toluene, 1:8); ^{1}H NMR (CDCl$_3$, 90 MHz) δ=2.04 (3H, s) and 2.10 (3H, s) (2 OAc), 2.87—3.03 (2H, m, H-4 and 4′), 5.00—5.10 (3H, m, H-1, 7, and 7′), 5.44 (1H, narrow m, H-2), 5.60 (1H, dq, $J_{5,6}$=10,5 Hz, $J_{1,5}$=$J_{4,5}$=$J_{4',5}$=2 Hz, H-5), 5.89 (1H, dt, $J_{1,6}$=$J_{4,6}$=3.4 Hz, H-6).

Found: C, 62.85; H, 6.71%. Calcd for $C_{11}H_{14}O_4$: C, 62.61; H, 6.67.

Another fraction gave 2.6 g (12%) of **4** as a syrup: TLC, R_f=0.20 (ethyl acetate–toluene, 1:8). ^{1}H NMR (CDCl$_3$, 90 MHz) δ=2.00 (6H, s) and 2.03 (3H, s) (3 OAc), 3.92 (1H, dd, $J_{3,7}$=5 Hz, J_{7gem}=11.3 Hz, H-7), 4.20 (1H, dd, $J_{3,7'}$=3.5 Hz, H-7′), 5.13 (1H, dd, $J_{1,2}$=7.5 Hz, $J_{2,3}$=11.5 Hz, H-2).

Found: C, 58.08; H, 6.72%. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71%.

DL-2,3-Di-*O*-acetyl-1,7-anhydro-(1,2/3)-1-*C*-hydroxymethyl-4-cyclohexene-1,2,3-triol (6). A mixture of **5** (2.1 g, 10 mmol), *m*CPBA (1.73 g, 10 mmol), 1,2-dichloroethane (60 ml), and 0.1 M phosphate buffer solution (pH 8) (30 ml) was stirred vigorously at 0—5 °C for 20 h. The mixture was washed with 10% aqueous sodium thiosulfate (10 ml), and the organic layer was dried and concentrated, giving 2.3 g of a syrup. Chromatography on silica-gel column (200 g) with 2-butanone–toluene (1:2, v/v) gave 0.75 g (52% yield based on **5** consumed) of **6** and 0.27 g of a mixture which consisted mainly of the isomeric epoxide (**7**), together with 0.92 g of **2** (recovered yield 44%). ^{1}H NMR (CDCl$_3$, 90 MHz) for **6**, δ=2.05 (3H, s) and 2.08 (3H, s) (2 OAc), 2.40 (2H, br s, H-6 and 6′), 2.70 (1H, d) and 2.08 (1H, d) ($J_{4,5}$=4.5 Hz, H-4 and 5), 5.06 (1H, d, $J_{2,3}$=6 Hz, H-2), 5.40—5.60 (1H, br d, H-3), 5.72 (1H, br dq, $J_{4,5}$=10.5 Hz, H-5), 5.95 (1H, dt, $J_{3,4}$=$J_{4,6}$=3.4 Hz, H-4), and for **7**, δ=2.56 (2H, d, J=6 Hz, H-6 and 6′), 2.82 (2H, br s, H-7 and 7′), 5.62 (1H, br d) and 5.91 (1H, br d) (J=12 Hz, H-4 and 5).

Found for **6**: C, 58.14; H, 6.26%. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24%.

DL-1,2,3-Tri-*O*-acetyl-(1,2/3)-1-*C*-acetoxymethyl-4-cyclohexene-1,2,3-triol (8). A mixture of **6** (0.44 g, 1.9 mmol), anhydrous sodium acetate (0.47 g, 5.7 mmol), and 90% aqueous 2-methoxyethanol (10 ml) was stirred at 75 °C for 2 h. The mixture was concentrated and the residue was treated with acetic anhydride (5 ml) and pyridine (5 ml) in the presence of DMAP (40 mg) at 75 °C for 14 h. The product was purified by a silica-gel column with 2-butanone–toluene (1:10, v/v) as an eluant, giving crystals which were recrystallized from a small amount of water to yield 0.52 g (81%) of **8** as prisms; mp 76—77 °C. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.00 (6H, s), 2.04 (3H, s), and 2.06 (3H, s) (4 OAc), 2.56 (1H, br dd, $J_{5,6}$=2.3 Hz, J_{6gem}=18.5 Hz, H-6), 3.19 (1H, dd, $J_{5,6'}$=3.5 Hz, H-6′), 4.52 (2H, s, $C\underline{H}_2OAc$), 5.36 (1H, d, $J_{2,3}$=7.5 Hz, H-2), 5.50—5.77 (3H, m, H-3, 4, and 5).

Found: C, 54.91; H, 6.03%. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.03%.

Preparation of 8 from DL-3,4-Di-*O*-acetyl-1,2-anhydro-(1,2,3/4)-2-*C*-benzoyloxymethyl-5-cyclohexene-1,2,3,4-tetrol[11] (9). A mixture of **9** (0.10 g), $LiAlH_4$ (33 mg, 3 molar equiv), and THF (3 ml) was stirred at room temperature for 2 h. Excess reagent was decomposed by addition of ethyl acetate, the precipitates were filtered and the filtrate was concentrated. The residue was acetylated with acetic anhydride and pyridine at 60 °C for 28 h, and the product was purified by a silica-gel column, giving 23 mg (24%) of **8** as a syrup, the ^{1}H NMR spectrum of which was superposable on that of the compound obtained before.

DL-3,4-Di-*O*-acetyl-1,2-anhydro-(1,2,3/4,5)-5-*C*-acetoxymethyl-1,2,3,4,5-cyclohexanepentol (10) and DL-2,3,4,5-Tetra-*O*-acetyl-(1,2,5/3,4)-1-*C*-acetoxymethyl-1,2,3,4,5-cyclohexanepentol (11). To a solution of **8** (0.28 g, 0.85 mmol) in methanol (2 ml) was added 1 M methanolic sodium methoxide (0.15 ml), and the mixture was stirred at room temperature for 20 min. After neutrallization with Amberlite IR-120 (H^+) resin, the solution was concentrated. The residue was dissolved in acetic acid (2 ml) and treated with *m*CPBA (0.29 g, 1.7 mmol) at room temperature for 6 d. The mixture was processed in the usual way and the products were acetylated with acetic anhydride and pyridine. Fractionation of the crude products on a silica-gel column with ethyl acetate–hexane (2:3, v/v) as an eluant gave first 0.15 g (59%) of **10** as a syrup: ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.05 (3H, s), 2.07 (3H, s), and 2.10 (3H, s) (3 OAc), 2.65 (1H, br s, OH), 3.33 (1H, td, $J_{1,2}$=4.2 Hz, $J_{1,6}$=4 Hz, $J_{1,6'}$=ca. 1 Hz, H-1), 3.50 (1H, dd, $J_{2,3}$=2.3 Hz, H-2), 3.74 (1H, d) and 4.03 (1H, d) (J_{7gem}=11 Hz, $C\underline{H}_2OAc$), 5.18 (1H, d, $J_{3,4}$=9 Hz, H-4), 5.58 (1H, dd, H-3).

Found: C, 51.65; H, 5.84%. Calcd for $C_{13}H_{18}O_8$: C, 51.65; H, 6.00%.

The second fraction gave 0.04 g (12%) of **11** as a syrup: ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.98 (3H, s), 2.07 (3H, s), 2.09 (6H, s), and 2.11 (3H, s) (5 OAc), 3.87 (1H, d) and 4.07 (1H, d) (J_{7gem}=11.3 Hz, $C\underline{H}_2OAc$), 5.02 (1H, q, $J_{4,5}$=$J_{5,6}$=$J_{5,6'}$=*ca.* 4 Hz, H-5), 5.36 (1H, dd, $J_{3,4}$=3 Hz, H-4), 5.51 (1H, dd, $J_{2,3}$=9.8 Hz. H-3).

Compound **11** (22 mg, 0.05 mmol) was acetylated in the presence of DMPA, and the product was purified by a silica-gel column with 2-butanone–toluene (1:4, v/v) as an eluant to give the hexaacetate (**12**) (25 mg, 100%) as prisms; mp 135.5—136 °C. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.96 (3H, s), 2.04 (9H, s), 2.06 (3H, s), and 2.10 (3H, s) (6 OAc), 4.40 (2H, s, $C\underline{H}_2OAc$), 5.09 (1H, q, $J_{4,5}$=$J_{5,6}$=$J_{5,6'}$=3 Hz, H-5), 5.29—5.59 (3H, m, H-2, 3, and 4).

Found: C, 50.88; H, 5.72%. Calcd for $C_{19}H_{26}O_{12}$: C, 51.12; H, 5.87%.

DL-1,2,3,4-Tetra-*O*-acetyl-(1,2/3,4)-1-*C*-acetoxymethyl-1,2,3,4-cyclohexanetetrol (2). To a solution of **10** (81 mg) in THF (10 ml) was added $LiAlH_4$ (52 mg, 5 molar equiv) and the mixture was refluxed for 0.5 h. After water had been added, an insoluble material was removed by filtration. The filtrate was concentrated and the residue was acetylated in the presence of DMAP. The product was purified by a silica-gel column with 2-butanone–toluene (1:10, v/v) as an eluant, giving 35 mg (34%) of **2** as prisms; mp 147—148 °C. ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.96 (3H, s), 2.05 (6H, s), and 2.13 (6H, s) (5 OAc), 4.48 (2H, s, $C\underline{H}_2OAc$), 5.17 (1H, dd, $J_{2,3}$=10.5 Hz, $J_{3,4}$=3.3 Hz, H-3), 5.45 (1H, d, H-2), 5.30—5.52 (2H, m, H-4 and 5).

Found: C, 52.58; H, 6.23%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.81; H, 6.21%.

DL-(1,2/3,4)-1-*C*-Hydroxymethyl-1,2,3,4-cyclohexanetetrol (Pseudo-β-DL-fructopyranose) (1). A mixture of **2** (56 mg) and methanol (0.5 ml) containing 1 M methanolic sodium methoxide (15 μl) was stirred at room temperature for 2.5 h. The mixture was then passed through a short column of Amberlite IR-120 (H^+) resin and concentrated, giving 26 mg (100%) of **1** as a syrup.

Found: C, 47.43; H, 7.78%. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.92%.

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