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# SYNTHESIS OF SWEET TASTING PSEUDO-β-FRUCTOPYRANOSE

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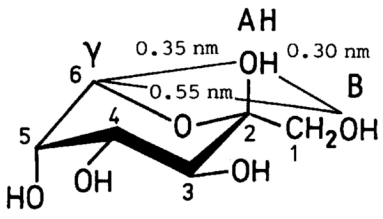
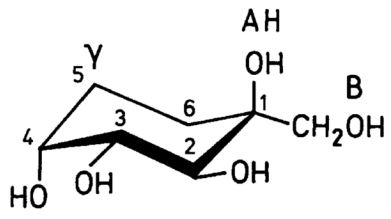
Pseudo-β-DL-fructopyranose has been synthesized from DL-1,2-di-*O*-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol by two reaction routes. The pseudosugar was found to be sweet and this fact provides a strong support for Shallenberger's sweetness-structure hypothesis.

D-Fructose is the most sweet sugar known in naturally occurring carbohydrates and its intense sweetness arises only from a β-D-fructopyranose form.[1-3] The sweetness eliciting units, an AH (proton donor) and a B (proton acceptor) component in β-D-fructopyranose are assigned as an anomeric OH-2 and a $CH_2OH$-1 group, respectively.[1,4-6] When Lemieux's principles of a rotational isomer population arising from a rotation around a C-$CH_2OH$ bond of a hexopyranoid structure[7] are applied to the case of β-D-fructopyranose, it is comprehensible that an intramolecular hydrogen bonding between $CH_2OH$-1 and OH-2 groups with a fixed distance of 0.30 nm would promote its sweetness. The C-6 atom is added to the AH, B system as a third hydrophobic component (γ),[8] completing a triangular saporous unit. It has been described that an axial OH-5 group links a ring-oxygen of β-D-fructopyranose, allowing the OH-2 group free to be the AH component and it exerts a maximum effect on a sweetness intensity. Pseudofructopyranose has no ring-oxygen and regardless of a configuration of the OH-4 group, the OH-1 is always ready to be the AH. Furthermore, a pseudosugar is nonreducing and a good model compound to study a sweetness-structure relationship, since a true sugar implicates an anomeric and a pyranose-furanose equilibrium in an aq. solution, causing complexities in an investigation of a sensory effect of a particular reducing sugar structure. On the other hand, a




β-D-Fructopyranose

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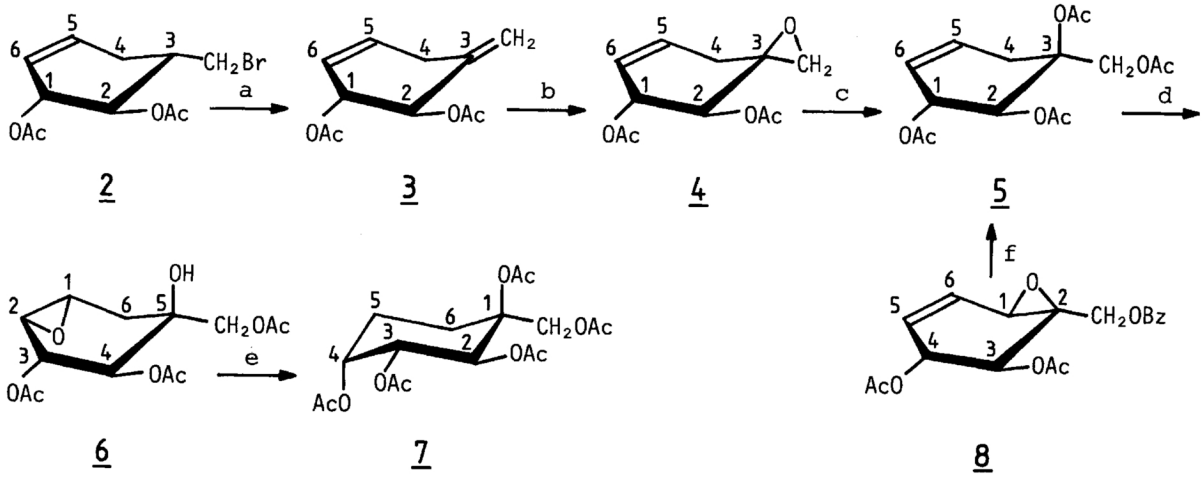
Pseudo-β-DL-fructopyranose†

†The formulas depict only one of the respective enantiomers.

pseudosugar has a stable preferred conformation in a solution, in which an exact conformation of each OH group is known. Since a replacement of a ring-oxygen in a pyranoid sugar by a $CH_2$ group gives no detrimental effect on its sweetness,[9] pseudo-β-D-fructopyranose may have same sweetness as D-fructose. A relative sweetness of L-glucose is almost same as that of D-enantiomer,[10] but this may not be true of the enantiomeric fructopyranoses because the tripartite groups are not the same. Inspection of models indicates that one enantiomer is possibly sweeter than the other.[11] Nevertheless at the first step a synthesis of pseudo-β-DL-fructopyranose (1) has been carried out by the following two different routes, starting from DL-1,2-di-*O*-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol[12] (2).

a) Dehydrobromination of 2 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the diene (3) in 66% yield as a syrup.[13] Preferential epoxidation of the exocyclic C=C bond of 3 with *m*-chloroperoxybenzoic acid (*m*CPBA) afforded a mixture of the spiro epoxide (4) and its stereoisomer, which were separated by a column chromatography in 52 and 20% yield, respectively.[14] Nucleophilic opening of the oxirane ring of 4 with sodium acetate in aq. 2-methoxyethanol, followed by acetylation with acetic anhydride and 4-dimethylaminopyridine (DMAP) in pyridine gave the tetraacetate (5), mp 76-77 °C in 83% yield.[15] The structure of 5 has been demonstrated by the fact that 5 was obtained by reductive cleavage of known DL-3,4-di-*O*-acetyl-1,2-anhydro-(1,2,3/4)-2*C*-(benzoyloxymethyl)-5-cyclohexene-1,2,3,4-tetrol[16,17] (8) with $LiAlH_4$ and subsequent acetylation.

Hydrolysis of 5 in methanolic $CH_3ONa$ and successive epoxidation of the C=C bond with *m*CPBA in acetic acid, followed by conventional acetylation gave the epoxide (6), mp 82-83 °C in 59% yield.[18] Reduction of 6 with $LiAlH_4$ in THF and subsequent acetylation with acetic anhydride and DMAP in pyridine afforded DL-1,2,3,4,7-penta-*O*-acetyl-(1,2/3,4)-1*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (7), mp 147-148 °C in 34% yield (5.8% yield from 2).[19]

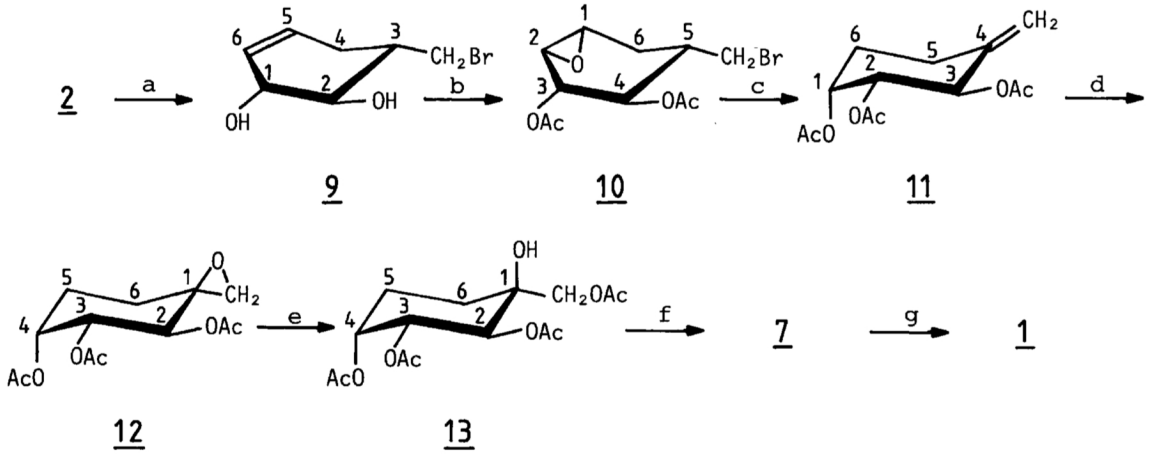



(a) DBU; (b) *m*CPBA; (c) $CH_3CO_2Na$; $(CH_3CO)_2O$, DMAP, pyridine; (d) $CH_3ONa$; *m*CPBA; $(CH_3CO)_2O$, pyridine; (e) $LiAlH_4$; $(CH_3CO)_2O$, DMAP, pyridine; (f) $LiAlH_4$; $(CH_3CO)_2O$, pyridine.

Scheme 1†.

b) By an alternative route (Scheme 2), 7 was obtained in a better yield. Hydrolysis of 2 in ethanol-HCl gave DL-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol (9), mp 80-81 °C in 83% yield.[20] Stereoselective epoxidation of 9 with *m*CPBA[21] in $CH_2Cl_2$, followed by acetylation afforded the compound (10), mp 110-111 °C in 80% yield.[22] Dehydrobromination of 10 with AgF in pyridine and subsequent reduction with $LiAlH_4$ in THF, followed by acetylation gave the compound (11), mp 60-61 °C in 52% yield.[23] Stereopreferential epoxidation of the exocyclic C=C bond of 11 with *m*CPBA in $CH_2Cl_2$ gave the spiro epoxide (12) in 90% yield as a syrup.[24] Nucleophilic opening of the oxirane ring of 12 by sodium acetate in aq. 2-methoxyethanol and successive acetylation gave DL-2,3,4,7-tetra-*O*-acetyl-(1,2/3,4)-1*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (13), mp 108-109 °C in 78% yield.[25] Acetylation of 13 with acetic anhydride and DMAP in pyridine gave 7, mp 147-148 °C in 66% yield (16% yield from 2).

Deacetylation of 7 or 13 in methanolic $CH_3ONa$ and successive deionization with Amberlite IR-120B ($H^+$ type) and IRA-400 ($HO^-$ type) gave 1 in a quantitative yield as an amorphous product.[26] Compound 1 was found to be nearly as sweet as D-fructose by an evaluation with six college personnel.




(a) HCl; (b) *m*CPBA; $(CH_3CO)_2O$, pyridine; (c) AgF; $LiAlH_4$; $(CH_3CO)_2O$, pyridine; (d) *m*CPBA; (e) $CH_3CO_2Na$; $(CH_3CO)_2O$, pyridine; (f) $(CH_3CO)_2O$, DMAP, pyridine; (g) $CH_3ONa$.

Scheme 2†.

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13) Compound 3, $R_f$ 0.33 on TLC [Silica Gel 60 F-254 (Merck)] in 1:8 (v/v) ethyl acetate-hexane. Found: C, 62.61; H, 6.67%. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%.
14) Compound 4, syrup, $R_f$ 0.33 on TLC in 1:20 (v/v) 2-butanone-toluene. Found: C, 58.10; H, 6.26%. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24%. The isomer, syrup, $R_f$ 0.37 on TLC in the same solvent. Found: C, 58.64; H, 6.34%.
15) Compound 5, $R_f$ 0.42 on TLC in 1:4 (v/v) 2-butanone-toluene. Found: C, 54.78; H, 6.24%. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14%.
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18) Compound 6, $R_f$ 0.24 on TLC in 1:4 (v/v) 2-butanone-toluene. Found: C, 51.57; H, 6.06%. Calcd for $C_{13}H_{18}O_8$: C, 51.66; H, 6.00%.
19) Compound 7 was obtained by recrystallization from ethanol; $R_f$ 0.61 on TLC in 1:2 (v/v) 2-butanone-toluene; $^1$H NMR ($CDCl_3$, 90 MHz) δ 1.96 (3H, s, OAc), 2.05 (6H, s, 2 × OAc), 2.13 (6H, s, 2 × OAc), 4.48 (2H, s, H-7), 5.17 (1H, dd, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 5.43 (1H, d, $J_{2,3}$ = 10.5 Hz, H-2), Found: C, 52.83; H, 6.15%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23%.
20) Compound 9. 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%.
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22) Compound 10. 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%.
23) Compound 11, $R_f$ 0.40 on TLC in 1:5 (v/v) ethyl acetate-hexane. Found: C, 57.60; H, 6.66%. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71%.
24) Compound 12, $R_f$ 0.14 on TLC in 1:3 (v/v) ethyl acetate-hexane. Found: C, 54.51; H, 6.37%. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34%.
25) Compound 13, $R_f$ 0.27 on TLC in 1:1 (v/v) ethyl acetate-hexane. Found: C, 52.17; H, 6.35%. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40%.
26) Compound 1. Found: C, 47.43; H, 7.78%. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.92%.

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