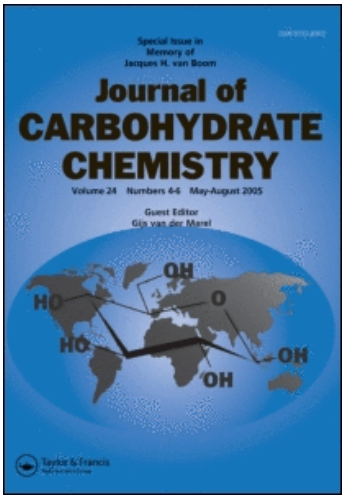

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Synthesis and Sweetness of Pseddo-β-D and L-Frdctopyranose

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SYNTHESIS AND SWEETNESS OF PSEUDO-β-D AND L-FRUCTOPYRANOSE[1]

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ABSTRACT

Pseudo-β-D (D-2) and L-fructopyranose (L-2), 1(*S*) and (1*R*)-(1,2/-3,4)-4-*C*-hydroxymethyl-1,2,3,4-cyclohexanetetrol, have been synthesized, starting from optically active *endo*-adducts of furan and acrylic acid, following the modified procedure used for the preparation of the *racemic* modification. It has been demonstrated that the D and L-enantiomers are nearly as sweet as D-fructose, and the former is somewhat sweeter than the latter.

INTRODUCTION

Since pseudo-β-DL-glucopyranose has been shown to be as sweet as true D-glucose,[3] elucidation of sweetness and structure relationships for sugars has been extensively carried out by use of pseudo-sugars and related cyclitols as model compounds. Recently, pseudo-β-DL-fructopyranose has been shown to taste nearly as sweet as true D-fructose.[4,5]

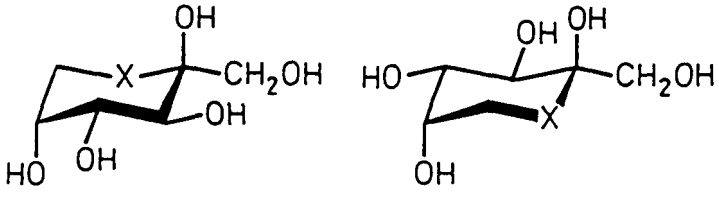
An interesting question that has remained unanswered is whether D and L-fructose have similar sweet taste. It may be difficult to prepare enough L-fructose for a proper comparison but an approximate comparison might be achieved by evaluation of the sweetness of the enantiomers of pseudo-β-fructose instead of those of β-fructopyranose.

We describe a synthesis of pseudo-β-D (D-2) and L-fructopyranose (L-2), starting from optically resolved *endo*-adducts of furan and

acrylic acid. The synthesis has been carried out following the modified procedure conducted for the racemic modification.

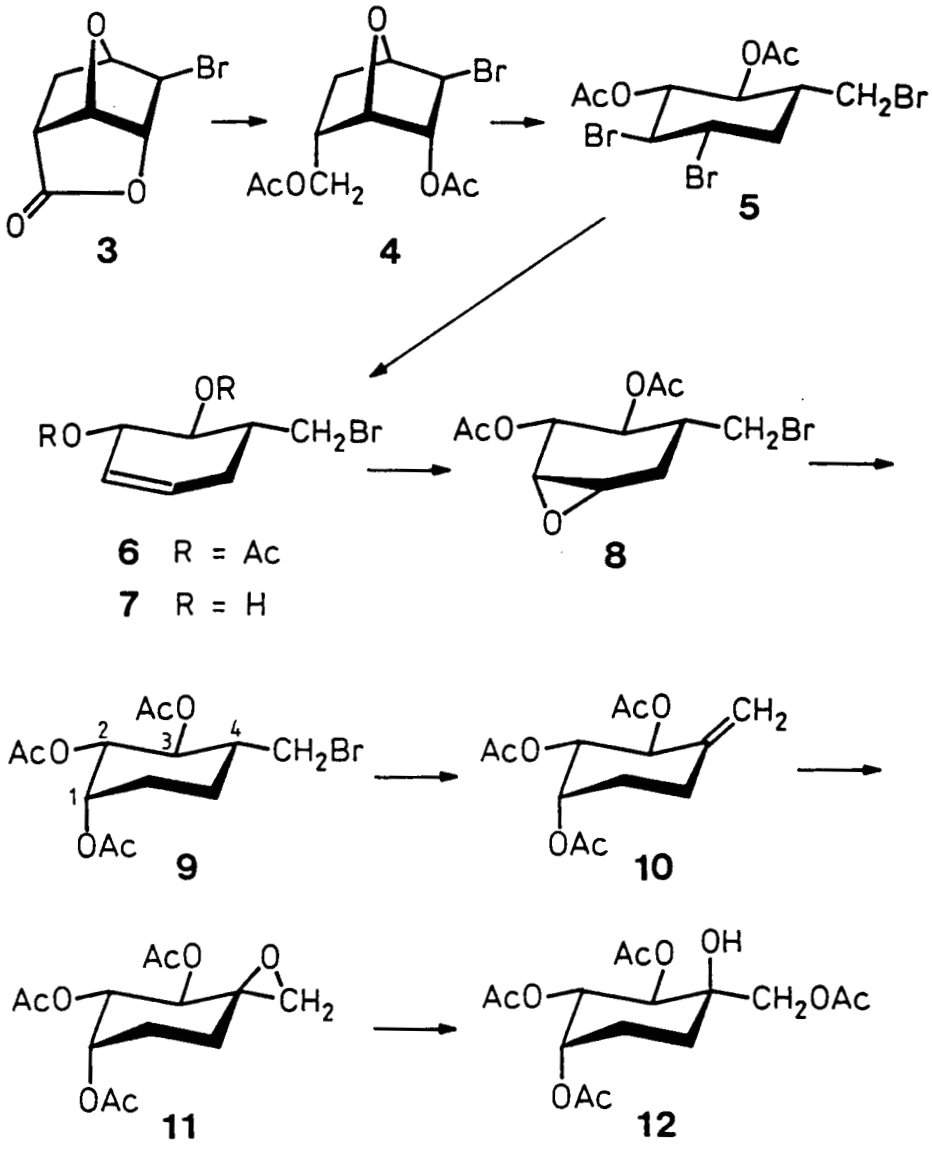
RESULTS AND DISCUSSION

Treatment of (*S*)-α-methylbenzylamine salt[6] of (2*R*)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid with bromine in water gave 96% of the bromolactone (L-3), which was reduced with lithium aluminum hydride in tetrahydrofuran (THF), followed by acetylation with acetic anhydride in pyridine to afford the diacetate (L-4) in 82% yield. Cleavage of the anhydro ring with hydrogen bromide in acetic acid gave the tribromide (L-5) in 67% yield. Debromination of L-5 with zinc dust in acetic acid gave 86% of the olefin (L-6), which was O-deacetylated with hydrochloric acid in ethanol to give the diol (L-7) in 78% yield. Oxidation of L-7 with *m*-chloroperbenzoic acid (MCPBA) proceeded selectively to give a single epoxide (L-8) in 55% yield. Regioselective reduction of L-8 was readily effected by treatment with diborane and sodium borohydride in THF to give, after acetylation, 82% yield of the triacetate (L-9), the ^{1}H NMR spectrum of which showed a triplet (δ 5.23, J = 10.2 Hz) and a doublet of doublets (δ 4.90, J = 3 and 10.2 Hz) due to coupled H-3 and H-2, respectively. Treatment of L-9 with silver fluoride in pyridine afforded the methylene compound L-10 in 92% yield. This compound could be converted selectively to a single epoxide L-11 (88%), treatment of which with sodium acetate in aqueous 10%



D-1 X = O **L-1** X = O
D-2 X = CH_2 **L-2** X = CH_2

2-methyoxyethanol at 70 °C, followed by acetylation, gave the crystalline tetraacetate (L-12), $[\alpha]_D$ +46° ($CHCl_3$), in 80% yield. *O*-Deacetylation of L-12 with methanolic sodium methoxide gave a syrupy free pseudosugar L-2, $[\alpha]_D$ +57° (methanol).



For convenience, the formulas (3 - 12) depict only one enantiomers corresponding to the L-series of pseudo-sugars.

Similarly, starting from the di-*O*-acetyl compound D-6,[7] the pseudo-β-D-fructopyranose tetraacetate (D-12), $[\alpha]_D$ -46° ($CHCl_3$), was obtained. Compound D-12 was converted to the free pseudo-sugar D-2, $[\alpha]_D$ -57° (methanol).

Sweetness of D and L-2 in comparison with that of D-fructose (D-1) was evaluated by five people by tasting ca. 10% aqueous solutions of

three compounds. All agreed that both enantiomers taste as sweet as D-fructose, and three judged that the D-enantiomer is somewhat sweeter than the L-enantiomer.

One pair of vicinal hydroxyl groups has been proposed to be the primary AH, B unit (distance 3 A) for constitution of sweet taste in the sugar series.[8,9] For β-D-fructopyranose, the anomeric hydroxyl group (HO-2) and O-1 were identified as AH and B, respectively, and the third component was assigned to the methylene ring carbon (C-6), which is a hydrophobic site (γ) deduced to be somewhat related to sweetness intensity.[10]

The present results suggest that the enantiomeric β-fructoyranoses possess similar behavior concerning sweetness. Small but observable difference in sweetness between the D and L-enantiomers of pseudo-β-fructopyranose might be due to some deformation of the proposed tripartite geostereochemistry.[11]

EXPERIMENTAL

General Methods. Melting points were obtained with a Buchi 510 capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-4 polarimeter. ^{1}H NMR spectra were recorded at 90 MHz with a Varian EM-390 spectrometer for solutions in $CDCl_3$ with reference to tetramethylsilane as the internal standard. TLC was performed on silica gel 60 F-254 (E. Merck, Darmstadt) with detection by charring with sulfuric acid. Column chromatography was conducted on silica gel 60 (70-230 mesh). Chromatographic solvent systems are designated as volume to volume ratios. Organic solutions were dried over anhydrous sodium sulfate and concentrated at <50 ^{o}C under reduced pressure. The structures of the optically active compounds were confirmed by comparison of their ^{1}H NMR spectra with those of the corresponding known racemic modifications.

(3R)-2-exo-Bromo-4,8-dioxatricyclo[4.4.1.0^{3,7}]nonan-5-one (L-3). To a stirred solution of (*S*)-(-)-α-methylbenzylamine salt[6] of (2*R*)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (200 mg, 0.77 mmol) in water (3.2 mL) was added bromine (40 μL, 0.78 mmol) at ambient temperature for 5 h. The mixture was diluted with water and extracted with ethyl acetate (15 mL). The extract was washed successively with saturated sodium hydrogencarbonate and brine, dried, and concentrated.

The residue was crystallized from ethyl acetate to give L-3 (161 mg, 96%) as needles: mp 114-115 °C, $[\alpha]_D^{30}$ -105° (c 1, H_2O.

Anal. Calcd for $C_7H_7BrO_3$: C, 38.39; H, 3.22. Found: C, 38.28; H, 3.28.

(1R)-3-endo-Acetoxy-5-endo-acetoxymethyl-2-exo-bromo-7-oxabicyclo-[2.2.1]heptane (L-4). To a solution of L-3 (11.5 g, 52 mmol) in THF (250 mL) was added LAH (2.38 g, 1.2 molar eq), and the mixture was stirred at ambient temperature for 3 h. The mixture was treated with ethyl acetate and water, and the precipitate was removed by filtration. The filtrate was concentrated and the residue was acetylated with acetic anhydride (100 mL) and pyridine (100 mL) at ambient temperature overnight. The excess reagents were removed by evaporation and the residue was crystallized from ethanol to give L-4 (13.1 g, 82%) as prisms: mp 73.5-74.5 °C, $[\alpha]_D^{28}$ -69° (c 1, chloroform).

Anal. Calcd for $C_{11}H_{15}BrO_5$: C, 43.02; H, 4.92. Found: C, 43.02; H, 4.84.

(1S)-(1,3/2,4,6)-1,2-Diacetoxy-3,4-dibromo-6-(bromomethyl)-cyclo-hexane (L-5). A mixture of L-4 (3.0 g, 9.8 mmol) and 15% hydrogen bromide in acetic acid (16 mL) was heated in a sealed tube at 85 °C for 15 h. The mixture was poured into ice-water (150 mL) and extracted with ethyl acetate (100 mL). The extract was processed in the usual way and the crude product was crystallized from ethanol to give L-5 (3.0 g, 67%) as prisms: mp 130-131 °C, $[\alpha]_D^{27}$ -0.8° (c 1, chloroform).

Anal. Calcd for $C_{11}H_{15}Br_3O_4$: C, 29.30; H, 3.30. Found: C, 29.39; H, 3.30.

(1S)-(1/2,6)-1,2-Diacetoxy-6-bromomethyl-3-cyclohexene (L-6). A mixture of L-5 (11.9 g, 26.3 mmol) was treated with zinc dust (12.1 g, 7 eq) in acetic acid (100 mL) at 70 °C for 20 min. An insoluble material was removed and the filtrate was concentrated. The residue was crystallized from ethanol to give L-6 (6.55 g, 86%) as prisms: mp 52-53 °C $[\alpha]_D^{21}$ +2.5° (c 1, chloroform).

Anal. Calcd for $C_{11}H_{15}BrO_4$: C, 45.38; H, 5.19. Found: C, 45.62; H, 5.03.

(1S)-(1/2,6)-6-Bromomethyl-3-cyclohexene-1,2-diol (L-7). A mixture of L-6 (5.88 g, 20.2 mmol) and ethanol (90 mL) containing concd hydrochloric acid (30 mL) was stirred at ambient temperature for 15 h. The mixture was neutralized with sodium hydrogencarbonate and then

concentrated. The product was purified on a column of silica gel with 2:5 ethyl acetate-hexane to give L-7 (3.24 g, 78%) as prisms: mp 76-77 °C, $[\alpha]_D^{21}$ -36° (c 1.1, chloroform).

Anal. Calcd for $C_7H_{11}BrO_2$: C, 40.60; H, 5.35. Found: C, 40.71; H, 5.20.

Similarly, the (1*R*)-enantiomer (D-7) was synthesized from D-6:[7] Yield 83%, mp 76-77 °C, $[\alpha]_D^{27}$ +29° (c 1, chloroform).

Anal. Found: C, 40.65; H, 5.31.

(1S)-(1,2,3,5/4)-3,4-Di-O-acetyl-1,2-anhydro-5-(bromomethyl)-cyclohexane (L-8). A mixture of L-7 (2.16 g, 10.4 mmol), MCPBA (3.1 g, ca. 1.2 eq), and dichloromethane (50 mL) was stirred at ambient temperature for 3 h. The mixture was concentrated and the residue was acetylated in the usual way. The product was purified on a column of silica gel to give L-8 (1.77 g, 55%) as needles: mp 125-126 °C, $[\alpha]_D^{27}$ +1.5° (c 1, chloroform).

Anal. Calcd for $C_{11}H_{15}O_5$: C, 43.02; H, 4.92. Found: C, 43.22; H, 4.87.

Similarly, the (1*R*)-enantiomer (D-8) was synthesized from D-7, yield 74%, mp 125-126 °C, $[\alpha]_D^{23}$ -3.6° (c 1, chloroform).

Anal. Found: C, 43.32; H, 4.88.

(1S)-(1,2,4/3)-1,2,3-Triacetoxy-4-(bromomethyl)cyclohexane (L-9). To a stirred solution of sodium borohydride (310 mg, 1.1 eq) in THF (45 mL) was added 1M diborane-THF (12.9 mL, 1.8 eq) solution and a solution of L-8 (2.21 g, 7.2 mmol) in THF (22 mL) in turn under argon, and the mixture was stirred at ambient temperature for 3 h. 1M sulfuric acid-THF (100 mL) was added to the mixture and then it was neutralized with sodium hydrogencarbonate. The mixture was concentrated and the residue was acetylated in the usual way. The product was purified on a silica gel column to give L-9 (2.1 g, 82%) as prisms: mp 115-116 °C, $[\alpha]_D^{27}$ -3.2° (c 0.4, chloroform); ^{1}H NMR δ 5.41 (m, 1 H, H-1), 5.23 (t, 1 H, J = 10.2 Hz, H-3), 4.90 (dd, 1 H, J = 3 and 10.2 Hz, H-2), 3.48 (dd, 1 H, J = 3.4 and 10.5 Hz) and 3.25 (dd, 1 H, J = 6.8 and 10.5 Hz) (CH_2Br), 2.02, 2.10, and 2.16 (3 s, each 3 H, 3 OAc).

Anal. Calcd for $C_{16}H_{19}BrO_6$: C, 44.46; H, 5.45. Found: C, 44.48; H, 5.36.

The (1*R*)-enantiomer D-9 was synthesized from D-8 in a similar way, yield 68%, mp 114-115 °C, $[\alpha]_D^{24}$ +3.8° (c 0.4, chloroform).

Anal. Found: C, 44.54; H, 5.33.

(1S)-(1,2/3)-1,2,3-Triacetoxy-4-(methylene)cyclohexane (L-10). A mixture of L-9 (2.13 g, 6.1 mmol), silver fluoride (2.05 g, 2.3 mmol), and pyridine (40 mL) was stirred at ambient temperature for 3 h. The product was purified on a short column of alumina with chloroform and crystallized from hexane to give L-10 (1.56 g, 92%) as prisms: mp 70.5-72.5 °C, $[\alpha]_D^{22}$ +38° (c 1.1, chloroform).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.59; H, 6.72.

Similarly, the (1*R*)-enantiomer D-10 was synthesized from D-9, yield 91%, mp 71-72.5 °C, $[\alpha]_D^{24}$ -47° (c 1, chloroform).

Anal. Found: C, 57.63; H, 6.76.

(1S)-(1,2/3,4)-1,2,3-Tri-O-acetyl-4,7-anhydro-4-C-hydroxy-methyl-1,2,3,4-cyclohexanetetrol (L-11). Compound L-10 (1.47 g, 5.45 mmol) was treated with MCPBA (3.8 g, ca. 2.8 eq) in dichloromethane (40 mL) at ambient temperature for 5 h. The product was purified on a column of silica gel with 2:5 ethyl acetate-hexane to give L-11 (1.37 g, 88%) as a syrup, $[\alpha]_D^{23}$ +37° (c 1.2, chloroform).

Anal. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.74; H, 6.32.

Similarly, the (1*R*)-enantiomer D-11 was prepared from D-10; yield 63%, $[\alpha]_D^{22}$ -43° (c 1.9, chloroform).

Anal. Found: C, 54.38; H, 6.30.

(1S)-(1,2/3,4)-1,2,3-Tri-O-acetyl-4-C-acetoxymethyl-1,2,3,4-cyclohexanetetrol (L-12). A mixture of L-11 (1.06 g, 3.7 mmol), anhydrous sodium acetate (3.2 g, 7 eq), and aqueous 10% 2-methyoxyethanol (20 mL) was stirred at 70 °C for 10 h. The mixture was concentrated and the residue was acetylated in the usual way. The product was purified on a column of silica gel with 5:9 ethyl acetate-hexane to give L-12 (1.02 g, 80%) as prisms, mp 113.5-114.5 °C, $[\alpha]_D^{24}$ +46° (c 1, chloroform).

Anal. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40. Found: C, 52.10; H, 6.30.

Compound L-12 was O-deacetylated with methanolic sodium methoxide to give a syrupy L-2, $[\alpha]_D^{23}$ +57° (c 4.9, methanol).

Similarly, D-12 was synthesized from D-11 in 64% yield, mp 111-112 °C, $[\alpha]_D^{21}$ -50° (c 1.2, chloroform).

Anal. Found: C, 52.32; H, 6.27.

Compound D-12 similarly gave a syrupy D-2, $[\alpha]_D^{22}$ -57° (c 1.2, methanol).

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