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Application of a phase transfer reaction to the synthesis of L-fructose

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Abstract

L-Fructose was prepared in five steps from L-sorbose (**1**). 1,2-*O*-Isopropylidene-α-L-sorbopyranose (**2**), prepared from **1**, was selectively tosylated using phase transfer catalysis to give 1,2-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-L-sorbopyranose (**3**). Formation of a 3,4-anhydro ring, followed by its base-catalyzed opening to effect overall inversion of configuration at both C-3 and C-4 gave 1,2-*O*-isopropylidene-α-L-fructopyranose (**5**), which was deacetonated to yield L-fructose (**6**).

Keywords: Phase transfer catalysis; Synthesis of L-fructose; Fructose, L-

1. Introduction

L-Sugars are reported to have the same degree of sweetness as their enantiomers [1] and are presumably nonmetabolizable [2]. D-Fructose is absorbed by facilitated diffusion [3], i.e., its entry mechanism is carrier-mediated (but energy independent); therefore, the L enantiomer, L-fructose, may not bind to the carrier and may not be carried into intestinal cells, the first step in absorption. Because it has been reported that L-glucose is fermented anaerobically [4], it is likely that L-fructose would also be fermented and would, therefore, be partially caloric via the indirect route of subsequent absorption of short chain acids. If so, it is likely that it would cause intestinal discomfort as well. An economical supply of L-fructose is needed for feeding studies to establish its nutritive value and physiological effects.

D-Fructose is the sweetest of the simple sugars [1]. L-Fructose, not yet detected in nature, was first synthesized by Fischer [5], who isolated "α-acrosazone" (DL-glucose phenylosazone) from a mixture obtained by the action of alkali upon either dibromoacrolein [6] or

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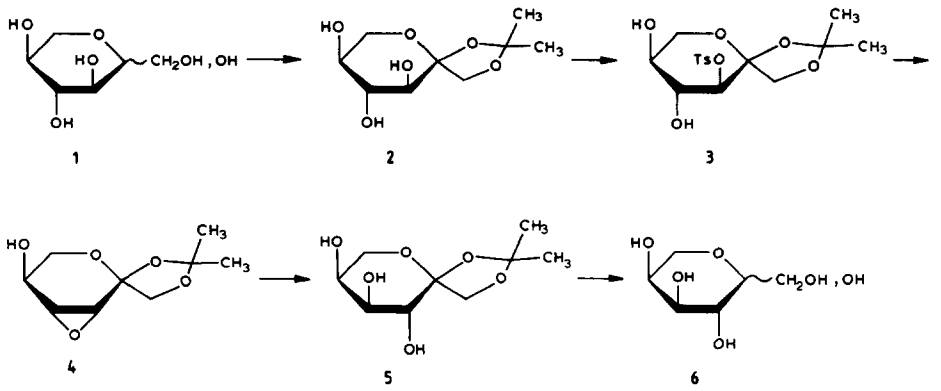
glycerol [7], then hydrolyzed it to D-*arabino*-hexos-2-ulose, which was reduced to DL-fructose. Treatment of the latter with yeast removed D-fructose, leaving the L-fructose. Crystalline DL-fructose was obtained by Schmitz [8] by the action of very dilute alkali on crystalline DL-glyceraldehyde (aldose–ketose isomerization followed by aldol condensation). Morgenlie [9] employed the same reaction catalyzed by Dowex 1(OH^-) resin and obtained DL-fructose in 54% yield after crystallization from methanol. Treatment of DL-fructose with bakers' yeast gave a product from which 2,3:4,5-di-*O*-isopropylidene-β-L-fructopyranose was obtained. Wolfrom and Thompson [10] synthesized L-fructose from L-arabinonic acid in five steps. L-Mannose [11] was isomerized to L-fructose by an enzyme present in a cell-free extract of *Aerobacter aerogenes* grown on L-rhamnose (6-deoxy-L-mannose). Chen and Whistler [12] prepared L-fructose from L-sorbose in seven steps by protecting non-involved hydroxyl groups, formation of the 3,4-anhydro ring, and ring opening to the desired configuration.

Previous syntheses of L-fructose, except that of Chen and Whistler [12], have used expensive starting materials and/or have been laborious and inefficient. Enzymic preparation of L-fructose [11], while promising, also requires an expensive starting material. Application of phase transfer catalysis (PTC) to obtain regio- [13,14] and stereo- [15,16] selective reactions prompted us to apply PTC in a modification of the scheme of Chen and Whistler for the synthesis of L-fructose. The hope was that PTC might allow omission of at least some blocking and deblocking steps. In this paper, we present an alternative route to L-fructose (**6**) starting with L-sorbose (**1**), a readily available intermediate in the synthesis of L-ascorbic acid.

2. Results and discussion

Crystalline 1,2-*O*-isopropylidene-α-L-sorbopyranose (**2**) was prepared by the method of Patil and Bose [17]. This compound was chosen because it has OH-3 and OH-4 unblocked, and because it was presumed to have better organic-solvent solubility and be easier to deblock than the methyl glycoside, for example. Selective tosylation of **2** to give 1,2-*O*-isopropylidene-3-*O*-(*p*-tolylsufonyl)-α-L-sorbopyranose (**3**) was done under PTC conditions. The catalyst of choice was tetrabutylammonium hydrogensulfate because of its hydrophobic cation and its nonnucleophilic counter anion and the fact that it could be used in a variety of organic solvents.

Of the secondary hydroxyl groups, the one next to the anomeric center has been found to be most reactive to *p*-toluenesulfonylation, presumably because it is the most acidic [18]. The regioselectivity of the phase transfer-catalyzed reaction seems likely to be a result of this acidity [13,14]. Formation of **3** was followed by TLC using a standard obtained by selective hydrolysis of 1,2:4,5-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-L-sorbopyranose. 1,2:4,5-Di-*O*-isopropylidene-α-L-sorbopyranose was prepared by the method of Brady [19]. Compound **3** crystallized after column chromatography. Its structure was established from ^1H,^{13}C, HOMO- and HETERO-COSY, APT, and proton HOMO-decoupled NMR spectra. Comparison of the ^{13}C NMR spectra of **3** with **2** indicated a downfield shift of 9 ppm of C-3 of **3** as compared to **2**, confirmation of the site of tosylation. In addition to **3**, two minor products were observed (by TLC).



Treatment of **3** with hydroxide ion in methanol resulted in the formation of 3,4-anhydro-1,2-*O*-isopropylidene-α-L-tagatopyranose (**4**). The configuration of **4** was confirmed using the same NMR techniques employed to confirm the structure of **3**. In **4**, $J_{4,5} \approx 0$ Hz, indicating a *trans* relationship [20] between H-4 and H-5. The formation of **4** also confirmed the regioselective tosylation of O-3. Tosylation at O-4 would have resulted in an epoxide with H-4 and H-5 in a *cis* relationship, the latter expected to have $J_{4,5} > 2$ Hz [20].

Base-catalyzed opening of the 3,4-anhydro ring was somewhat difficult, requiring a high concentration of base and heating for 2 days. The stereochemistry of the 3,4-anhydro ring opening to form 1,2-*O*-isopropylidene-α-L-fructopyranose (**5**) followed the Fürst–Plattner rule [21], which was confirmed by the smaller H-4–H-5 coupling constant of **5** as compared to that of **2**. Treatment of **5** with acid under mild conditions yielded L-fructose (**6**), which had the same R_f value as D-fructose and an optical rotation and melting point that agreed with the values previously reported [10,12]. None of the yields were optimized. Compound **3** can be converted into **5**, and even into **6**, in one-pot reactions without isolation of intermediates.

3. Experimental

General methods.—Melting points were determined on a Fisher–Johns melting point apparatus (Fisher Scientific). Optical rotations were measured at room temperature on a Perkin–Elmer 241 polarimeter. NMR experiments were done using a QE 300 NMR spectrometer (General Electric Co.). TLC was performed on Silica Gel 60 precoated aluminum sheets (E. Merck). Detection involved spraying the chromatogram with a solution of 10% H_2SO_4 in 95% EtOH and heating the plate for several minutes at ca. 150°C. Separation of the compounds by column chromatography was done with silica gel 60 (230–400 mesh, E. Merck).

1,2-O-Isopropylidene-α-L-sorbopyranose (**2**).—Anhydrous $CuSO_4$ (20 g) was suspended in dry acetone (160 mL); pure anhydrous L-sorbose (**1**) (2.0 g, 11.1 mmol) was added, and the mixture was heated at 50°C under vigorous stirring for 5 h. The cooled mixture was filtered and made alkaline by dropwise addition of 17.5% NaOH. Acetone was removed under reduced pressure. Anhydrous ether was added to the syrupy residue, and

the mixture was seeded with pure **2**. After refrigeration overnight, crystalline **2** was obtained; yield 0.99 g (4.5 mmol, 40%); mp 142–143°C; $[\alpha]_D$ −85.7° (*c* 2.0, H_2O); (lit. [22] mp 142°C; $[\alpha]_D$ −88.7°); ^1H NMR data [D_2O, 0.75% 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt]: δ 4.20–3.97 (q, 2 H, H-1,1′), 3.79–3.75 (m, 1 H, $J_{4,5}$ 7.8 Hz, H-5), 3.68–3.58 (m, 3 H, H-4,6,6′), 3.5 (d, 1 H, H-3), 1.53–1.45 (d, 6 H, CMe_2); ^{13}C NMR data (same solvent): δ 113 (CMe_2), 69.3 (C-1), 105.4 (C-2), 74.5 (C-3), 69.9 (C-4), 71.05 (C-5), 62.6 (C-6). Anal. Calcd for $C_9H_{16}O_6$: C, 49.13; H, 7.33. Found: C, 48.84; H, 6.94.

1,2-O-Isopropylidene-3-O-(p-tolylsulfonyl)-α-L-sorbopyranose (**3**).—Tetrabutylammonium hydrogensulfate (60 mg) and *p*-toluenesulfonyl chloride (0.19 g, 0.98 mmol) were dissolved in CH_2Cl_2, then aq NaOH (5%, 3 mL) and compound **2** (0.22 g, 1.0 mmol) were added to the solution in that order. After stirring for 25 min at room temperature, all starting material was converted to products (TLC, 4:1 toluene–acetone). The organic phase was separated, washed with water, and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure, and the resulting syrup was chromatographed on a Silica Gel 60 column using 4:1 toluene–acetone as the eluant. Compound **3** crystallized on evaporation of the solvent; yield 0.17g (0.45 mmol, 45%); mp 73–76°C; ^1H NMR data ($CDCl_3$, 1% Me_3Si): δ 7.85–7.20 (q, 4 H, C_6H_4-CH_3), 4.67 (q, 1 H, $J_{4,5}$ 6.5 Hz, H-4), 4.62 (d, 1 H, $J_{3,4}$ 6.6 Hz, H-3), 4.29 (m, 1 H, H-5), 4.02, 3.79 (q, 2 H, H-1,1′), 3.87, 3.81 (m, 2 H, H-6,6′), 2.55–2.45 (s, 3 H, $C_6H_4CH_3$) and 1.45–1.25 (d, 6 H, CMe_2); ^{13}C NMR data (same solvent): δ 69.9 (C-1), 106.7 (C-2), 83.5 (C-3), 74.6 (C-4), 76.9 (C-5), 61.75 (C-6). Anal. Calcd for $C_{16}H_{22}O_8S$: C, 51.38; H, 5.93; S, 8.53. Found: C, 51.08; H, 6.17; wS, 8.42.

3,4-Anhydro-1,2-O-isopropylidene-α-L-tagatopyranose (**4**).—Compound **3** (1.5 g, 4.0 mmol) was dissolved in MeOH (1.5 mL), and aq 2 M NaOH (1.5 mL) was added. After stirring for 2.5 h at 45°C, all starting material was converted to product. The solution was made neutral, diluted with water (15 mL), and extracted with $CHCl_3$. Removal of the solvent gave syrupy **4**; yield 0.73 g (3.4 mmol, 85%); ^1H NMR data ($CDCl_3$, 1% Me_3Si): δ 4.26, 3.99 (q, 2 H, H-1,1′), 4.11 (t, 1 H, $J_{5,6}$ 5.3, $J_{4,5}$ 0 Hz, H-5), 3.8 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-4), 3.78 (d, 2 H, $J_{5,6}$ 5.3 Hz, H-6), 3.61 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 1.45–1.42 (d, 6 H, CMe_2); ^{13}C NMR data (same solvent): δ 68.7 (C-1), 107.0 (C-2), 57.1 (C-3), 56.2 (C-4), 77.0 (C-5), 61.9 (C-6).

1,2-O-Isopropylidene-α-L-fructopyranose (**5**).—To a solution of **4** (2.5 g, 12.4 mmol) in acetone (20 mL), 5 M NaOH (3.5 mL) was added dropwise and the solution was stirred at 70°C for 52 h. The cooled mixture was neutralized with 4.5 M H_2SO_4 and evaporated. The syrupy residue was extracted with warm excess $CHCl_3$, and the solvent mixture was kept at room temperature overnight to give crystalline **5**; yield 2.0 g (9.0 mmol, 73%); mp 83–85°C; ^1H NMR data [D_2O, 0.75% 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt]: δ 4.35–3.45 (m, 7 H, $J_{4,5} \approx 3.5$ Hz, H-1,3,4,5,6), 1.75–1.65 (d, 6 H, CMe_3). Anal. Calcd for $C_9H_{16}O_6$: C, 49.13; H, 7.33. Found: C, 48.76; H, 7.49.

L-*Fructose* (**6**).—Compound **5** (2.0 g, 11.1 mmol) was dissolved in MeOH (15 mL) and the solution was acidified to pH 2 with 0.5 M H_2SO_4. The acidic solution was stirred for 2 h at ca. 50°C, cooled, and neutralized. After removing the solvent, the residue was extracted with EtOH, from which compound **6** crystallized; yield 1.09 g (6.0 mmol, 67%). Compound **6** had the same TLC mobility as D-fructose in 3:2:1 EtOAc–MeOH–water; mp

90–94°C; $[\alpha]_D$ +94.4° (*c* 1.8, H_2O); (lit. [10,11] mp 93–95°C; $[\alpha]_D$ +93°). Anal. Calcd for $C_6H_{12}O_6$: C, 40.04 H, 6.72. Found: C, 39.72; H, 7.06.

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