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SYNTHESIS OF L-FRUCTOSE*

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ABSTRACT

L-Sorbose (**1**) was converted into methyl 4,6-*O*-isopropylidene-α-L-sorbofuranoside, which was tosylated to give methyl 4,6-*O*-isopropylidene-1,3-di-*O*-*p*-tolylsulfonyl-α-L-sorbofuranoside. Removal of the isopropylidene protecting group and formation of a 3,4-anhydro-ring afforded methyl 3,4-anhydro-1-*O*-*p*-tolylsulfonyl-α-L-tagatofuranoside, which was converted into L-fructose (**7**) by acid hydrolysis. In an alternative, facile synthesis, **1** was converted, in the presence of tin(II) chloride as a catalyst, into 1,2:4,6-di-*O*-isopropylidene-α-L-sorbofuranose. Selective removal of the 4,6-*O*-isopropylidene group, followed by formation of a 3,4-anhydro ring afforded 3,4-anhydro-1,2-*O*-isopropylidene-α-L-tagatofuranose. Opening of the anhydro ring by base catalysis and removal of the 1,2-*O*-isopropylidene group yielded **7**.

INTRODUCTION

L-Fructose, not found in Nature, was synthesized for the first time by Fischer[1]. DL-Glucose phenylosazone was prepared from α-acrose and hydrolyzed to glycosulose, which was reduced to DL-fructose. L-Fructose was isolated from the mixture. L-Fructose was later synthesized by Wolfrom and Thompson from L-arabinonic acid in five steps[2].

Recently, L-fructose was prepared by aldol condensation[3]. DL-Glyceraldehyde condensation with 1,3-dihydroxy-2-propane, catalyzed by Dowex 1 (OH^-) resin, gave a hexulose mixture. Crystallization of the mixture from methanol yielded 54% of DL-fructose. Treatment of the DL-fructose mixture with baker's yeast gave a product from which 62% of 2,3:4,5-di-*O*-isopropylidene-β-L-fructopyranose was isolated after isopropylidenation. When L-glyceraldehyde was used as starting material, 2,3:4,5-di-*O*-isopropylidene-β-L-fructopyranose was isolated in 60–65% yield after isopropylidenation of the hexulose mixture. L-Fructose has been prepared enzymically from L-mannose by an isomerase present in cell-free

*Dedicated to Professor Rezső Bognár in the year of his 75th birthday.

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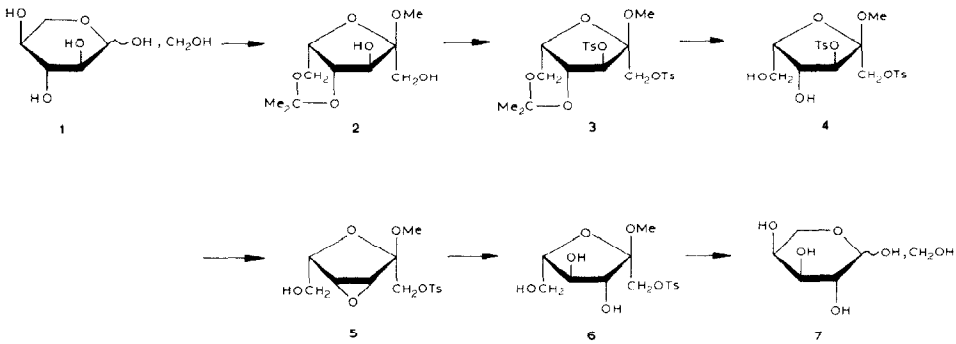
extracts of *Aerobacter aerogenes* grown on L-mannose to give L-fructose in 28–32% yield[4].

Both chemical and enzymic procedures are either too elaborate or require relatively expensive starting material. We report herein two simple methods for the synthesis of L-fructose starting with L-sorbose, a relatively inexpensive industrial chemical. The key step is to form a 3,4-anhydro ring in the L-sorbose molecule, and to open the anhydro ring so as to give the desired configuration.

RESULTS AND DISCUSSION

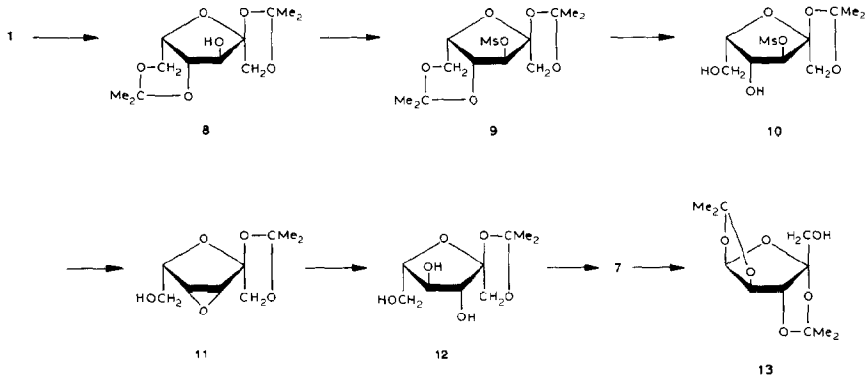
In one synthetic route, L-fructose was prepared from L-sorbose *via* methyl 4,6-*O*-isopropylidene-α-L-sorbofuranoside (**2**). Compound **2** was prepared in one step following the method of Maeda *et al.*[5]. Tosylation of **2** gave methyl 4,6-*O*-isopropylidene-1,3-di-*O*-*p*-tolylsulfonyl-α-L-sorbofuranoside (**3**) and a trace proportion of methyl 4,6-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-α-L-sorbofuranoside.



The isopropylidene group of **3** was readily removed in 60% acetic acid solution to give methyl 1,3-di-*O*-*p*-tolylsulfonyl-α-L-sorbofuranoside (**4**). The reaction mixture was made alkaline to form a 3,4-anhydro ring by intramolecular nucleophilic displacement of the sulfonyloxy group. The alkali concentration and the proportion of methanol in the reaction mixture were critical. For example, when a solution of **4** in methanol (100 mL) and M sodium hydroxide (70 mL) was heated for 5 h at 45°, only a very small portion of **4** was converted to methyl 3,4-anhydro-1-*O*-*p*-tolylsulfonyl-α-L-tagatofuranoside (**5**). Conditions required for alkaline scission of three-membered anhydro rings are, in general, more drastic than the conditions used for ring closure. No anhydro ring opening was detected under the alkaline conditions used in this latter reaction. Under mild, acidic conditions, **5** was converted into methyl 1-*O*-*p*-tolylsulfonyl-α-L-fructofuranoside (**6**). The anhydro ring was hydrolyzed, but the glycosidic bond and the sulfonyl ester linkage survived. The *p*-toluenesulfonyl ester linkage is relatively resistant to acid hydrolysis and the glycosidic bond stabilized by the inductive effect from the

adjacent sulfonyl ester group. Because of the difficulty in cleavage of the sulfonyl ester linkage, a high concentration of sulfuric acid (5M) was employed, and the anhydro ring was opened exclusively at C-4. These conditions apparently favor the development of a positive charge at C-4 rather than at C-3 because of the inductive effect from the substituents at C-1 and C-2. The major product from the acid hydrolysis was L-fructose (**7**). Some minor by-products were also detected. Crystalline **7** showed an optical rotation of $\sim +60°$ within 30 min after dissolution. The optical rotation indicated that the crystalline material was the α-L anomer. L-Fructose (**7**) was subjected to a tasting panel for sweetness and found to be as sweet as D-fructose.

Although the synthesis is simple, compound **2** was obtained in only 3.1% yield, which caused the end product to be rather costly. Thus, a second method was developed. L-Fructose was again prepared from L-sorbose, but each intermediate in this procedure was formed in high yield. L-Sorbose was converted into 1,2:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**8**), which is formed normally in ~5% yield[6]. However, when tin(II) chloride was used as a catalyst, **8** could be obtained in >80% yield, as indicated by t.l.c. The optical rotation and m.p. of **8** agreed with those reported by Tokuyama *et al.*[6], but differed from those by Patil *et al.*[7]. The reaction was slow unless a small amount of 1,2-dimethoxyethane or acetone was present to improve the solubility of tin(II) chloride. 1,2-Dimethoxyethane was preferred for the highest yield. Mesylation of **8** gave 1,2:4,6-di-*O*-isopropylidene-3-*O*-mesyl-α-L-



sorbofuranose (**9**) in 83% yield. Compound **9** crystallizes readily from the reaction mixture upon the addition of water. Preferably, compound **9** is prepared from L-sorbose without isolation of the intermediate, **8**. The 4,6-*O*-isopropylidene protecting group of **9** was selectively removed either in a mixture of acetone and 0.25% aqueous sulfuric acid at 25°, or in 60% acetic acid at 40°. A small amount of by-product, most likely 3-*O*-mesyl-L-sorbose, was also deteced in the 0.25% sulfuric acid medium. 1,2-*O*-Isopropylidene-3-*O*-mesyl-α-L-sorbofuranose (**10**) crystallized from the reaction mixture after most of the acetone had been removed.

L-Fructose was prepared from the crude product obtained by selective removal of the 4,6-*O*-isopropylidene group of **9**. Formation of the 3,4-anhydro ring was readily achieved in alkaline condition at 25°, to give 3,4-anhydro-1,2-*O*-isopropylidene-α-L-tagatofuranose (**11**), but opening of the anhydro ring by base catalysis was difficult. Ring opening was complete in strong, aqueous alkaline solution after a 3-day heating at 70–80°; a small amount of by-product was detected. On the other hand, a solution of **10** in 5% aqueous potassium hydroxide solution at reflux for 3 h gave 1,2-*O*-isopropylidene-α-L-fructofuranose (**12**) as a single product. Removal of the 1,2-*O*-isopropylidene group by acid hydrolysis gave **7** as the major product and isopropylidenation of **7** according to Morgenlie's procedure[3] gave **13** having the same m.p. and optical rotation as the compound previously reported[3].

EXPERIMENTAL

Methyl 4,6-O-isopropylidene-α-L-sorbofuranoside (**2**). — L-Sorbose (**1**, 40 g) was refluxed in 2,2-dimethoxypropane (100 mL) containing *p*-toluenesulfonic acid (500 mg) for 2 h. The mixture was made neutral with a slight excess of methanolic sodium methoxide and concentrated to a syrup. The syrup was extracted with benzene (2 × 50 mL) and the benzene fraction extracted with water (3 × 50 mL). The aqueous fraction, saturated with NaCl, was extracted with chloroform (3 × 100 mL). The chloroform was evaporated and the residue chromatographed on a silica gel column, eluted with 9:1 (v/v) hexane–acetone, to give **2** as a crystalline material (1.6 g, 3.1%), R_F (t.l.c. on silica gel in 9:1, v/v, chloroform–acetone) 0.26, which was recrystallized from ether, m.p. 109–110°; lit.[5] m.p. 108–109°.

Anal. Calc. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.98; H, 7.99.

Methyl 4,6-O-isopropylidene-1,3-di-O-p-tolylsulfonyl-α-L-sorbofuranoside (**3**). — A solution of **2** (1.2 g) in pyridine (1.8 mL) was cooled in an ice bath and *p*-toluenesulfonyl chloride (3.3 g) in pyridine (5 mL) was added slowly. After storage for 2 days at 25°, ice was added and the mixture extracted with chloroform (2 × 20 mL). The organic layer was washed twice with water, dried (Na_2SO_4), and evaporated to a syrup. Traces of pyridine in the residue were removed by co-evaporation with toluene to give **3** as a syrup (2.9 g, 100%), which was chromatographically pure; $[\alpha]_D^{25}$ +6° (*c* 2.5, chloroform); R_F (t.l.c. on silica gel in 9:1, v/v, chloroform–acetone) 0.80; ^{1}H-n.m.r. ($CDCl_3$): δ 7.85–7.20 (m, 8 H, 2 $C_6H_4CH_3$), 4.63–3.60 (m, 7 H, H-1,3,4,5,6), 3.17 (s, 3 H, OCH_3), 2.43, 2.41 (s, s, 6 H, 2 $C_6H_4CH_3$), and 1.25, 1.15 (s, s, 6 H, CMe_2); m.s.: *m/z* (largest fragment ion) 527 ($M - CH_3$).

Anal. Calc. for $C_{24}H_{30}O_{10}S$: C, 53.13; H, 5.57; S, 11.82. Found: C, 53.21; H, 5.51; S, 11.74.

Methyl 1,3-di-O-p-tolylsulfonyl-α-L-sorbofuranoside (**4**). — Compound **3** (2.3 g) was stirred in 60% acetic acid solution (23 mL) for 2.5 h at 55°. The pH of the solution was raised to 5–6 with 10M sodium hydroxide solution, and the mixture extracted with chloroform (2 × 50 mL). The chloroform was evaporated to give **4**

as a syrup (2 g, 94%); $[\alpha]_D^{25}$ −46° (*c* 1.8, chloroform), R_F (t.l.c. on silica gel in 9:1, v/v, chloroform–acetone) 0.25; ^{1}H-n.m.r. ($CDCl_3$): δ 7.85–7.06 (m, 8 H, 2 $C_6H_4CH_3$), 4.80–3.40 (m, 7 H, H-1,3,4,5,6), 3.20 (s, 3 H, OCH_3), and 2.40, 2.37 (s, s, 6 H, 2 $C_6H_4CH_3$).

Anal. Calc. for $C_{21}H_{26}O_{10}S_2$: C, 50.19; H, 5.22; S, 12.76. Found: C, 50.39; H, 5.48; S, 12.90.

Methyl 3,4-anhydro-1-O-p-*tolylsulfonyl-α*-L-*tagatofuranoside* (**5**). — To a solution of **4** (1.43 g) in methanol (1 mL) was added 2M NaOH solution (1 mL). After 2 h at 40°, **4** was converted into a single product, which showed a positive vicinal-epoxide test[8]. Methanol (20 mL) was added and the solution made neutral with 2.5M H_2SO_4. The salt was filtered off and water (10 mL) added. After evaporating the methanol, the aqueous solution was extracted with chloroform (2 × 50 mL). The chloroform was evaporated off to give **5** as a syrup (0.85 g, 90%), $[\alpha]_D^{25}$ −27° (*c* 2.5, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.87–7.10 (m, 4 H, $C_6H_4CH_3$), 4.30–3.50 (m, 7 H, H-1,3,4,5,6), 3.17 (s, 3 H, OCH_3), and 2.40 (s, 3 H, $C_6H_4CH_3$).

Anal. Calc. for $C_{14}H_{18}O_7S$: C, 50.90; H, 5.49; S, 9.17. Found: C, 50.76; H, 5.84; S, 9.47.

Methyl 1-O-p-*tolylsulfonyl-α*-L-*fructofuranoside* (**6**). — A solution of **5** (0.29 g) in a small amount of methanol was acidified with 0.5M H_2SO_4 to pH 2–3. After storage for 2 days at 25°, **5** was converted into a single product. The mixture was made neutral with M NaOH and extracted with chloroform. The organic fraction was evaporated and the residue chromatographed on a silica gel column. Elution with 9:1 (v/v) chloroform–acetone gave **6** as a syrup (0.29 g, 95%); ^{1}H-n.m.r. ($CDCl_3$): δ 7.83–7.10 (m, 4 H, $C_6H_4CH_3$), 4.30–3.40 (m, 7 H, H-1,3,4,5,6), 3.23 (s, 3 H, OCH_3), and 2.43 (s, 3 H, $C_6H_4CH_3$); m.s.: *m/z* (largest fragment ion) 317 (M − OCH_3).

1,2:4,6-Di-O-*isopropylidene-α*-L-*sorbofuranose* (**8**). — α-L-Sorbose (**1**, 8.24 g) was suspended in 1,2-dimethoxyethane (25 mL) containing $SnCl_2$ (10 mg), and 2,2-dimethoxypropane (13.4 mL) was added. The mixture was refluxed with stirring for 2 h until the solution was clear. A drop of pyridine was added and the mixture concentrated to a syrup. The syrup was dissolved in chloroform and washed with water. The chloroform fraction was dried (Na_2SO_4) and evaporated to a syrup which was extracted with hot petroleum ether. Crystallization occurred from the cooled extract. Recrystallization from petroleum ether gave **8** (4.88 g, 41%), m.p. 71–73°, $[\alpha]_D^{25}$ −24.7° (*c* 1.029, acetone); m.s.: *m/z* (largest fragment ion) 245 (M − CH_3); lit.[6] m.p. 72–73°, $[\alpha]_D^{25}$ −23.9°.

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 54.93; H, 7.67.

1,2:4,6-Di-O-*isopropylidene-3*-O-*mesyl-α*-L-*sorbofuranose* (**9**). — (*a*) To a solution of **8** (0.7 g) in pyridine (1 mL), cooled in an ice bath, was added methanesulfonyl chloride (0.31 mL). After 1 h, ice was added and the white crystalline material was washed with water to give **9** (0.76 g, 83.5%).

(*b*) L-Sorbose (30 g) was suspended in 2,2-dimethoxypropane (90 mL) and

1,2-dimethoxyethane (3 mL) containing $SnCl_2$ (150 mg) was added. The mixture was refluxed with stirring for 2 h until the solution was clear, and then evaporated to a syrup. A solution of the syrup in pyridine (60 mL) was cooled in an ice bath and methanesulfonyl chloride (19.4 mL) was added. After storage in a refrigerator overnight and for 4 h at 25°, water (1 L) was added. The crystals were collected by filtration (28.9 g, 51%). Recrystallization from ethanol gave **9** as colorless needles, m.p. 123–124°.

Anal. Calc. for $C_{13}H_{22}O_8S$: C, 46.14; H, 6.56; S, 9.48. Found: C, 46.25; H, 6.70; S, 9.11.

*1,2-O-Isopropylidene-3-O-mesyl-α-*L*-sorbofuranose* (**10**). — Compound **9** (1 g) was dissolved in acetone (10 mL) and 0.24% H_2SO_4 (10 mL) was added. After storage for 16 h at 25°, the solution was made neutral with solid $NaHCO_3$ and filtered. Acetone was removed by evaporation until crystallization occurred to give **10** (0.55 g, 63%). Recrystallization from ethanol gave **10** as colorless needles, m.p. 103–104°.

Anal. Calc. for $C_{10}H_{18}O_8S$: C, 40.26; H, 6.08; S, 10.75. Found: C, 40.32; H, 6.45; S, 10.95.

L-*Fructose* (**7**). — (*a*) *From* **5**. To a solution of **5** (7.5 g) in ethanol (50 mL) was added 5M H_2SO_4 (125 mL). The mixture was heated for 1 h at 70° and made neutral with 10M NaOH. After addition of ethanol and filtering off the salts, the filtrate was evaporated. The residue was chromatographed on a silica gel column. Elution with 40:10:7 (v/v) ethyl acetate–methanol–water gave **7** as a syrup (3.6 g, 88%), which was de-ionized through a column of Amberlite MB-1 ion-exchange resin and eluted with water. The effluent was evaporated to a syrup that crystallized from ethanol. Recrystallization from water–ethanol gave **7**, m.p. 89–90°, $[\alpha]_D^{25}$ +88° (*c* 1.5, water); ^{1}H-n.m.r. (D_2O, 1% sodium 4,4-dimethyl-4-silapentane-1-sulfonate): δ 4.13–3.37 (m); lit.[2] $[\alpha]_D^{25}$ +93° (water).

Anal. Calc. for $C_6H_{12}O_6 \cdot 0.25\ H_2O$: C, 39.02; H, 6.82. Found: C, 39.00; H, 6.87.

Compound **7** had the same mobility as D-fructose, but lower mobility than L-sorbose on silica gel t.l.c. (3:1:1, v/v, methyl ethyl ketone–methanol–acetic acid). The peracetylated derivatives[9] of D-fructose and compound **7** also had an identical mobility on silica gel t.l.c.(9:1, v/v, chloroform–acetone).

(*b*) *From* **9**. Compound **9** (2.5 g) was dissolved in acetone (20 mL) and 0.25% H_2SO_4 (15 mL) was added. After storage for 20 h at 25°, the solution was made alkaline with 9M NaOH (2 mL), heated for 48 h at 70–80°, acidified with 9M H_2SO_4 (pH ~10), heated for 20 min at 70–80°, and then made neutral with 2M NaOH. The mixture was taken to dryness and the residue extracted with ethanol (40 mL). The ethanol solution was concentrated to a syrup (0.97 g) which contained a small proportion of by-products having a lower mobility than L-fructose on silica gel t.l.c. The mixture was chromatographed on a silica gel column (40:10:7, v/v, ethyl acetate–methanol–water) to give **7** as a syrup (0.83 g, 62%).

*2,3:4,5-Di-O-isopropylidene-α-*L*-fructopyranose*[3] (**13**). — Syrup **7** (1.21 g)

was treated with 2.5% H_2SO_4 in acetone (45.5 mL) for 3.5 h. The solution was made neutral with solid $NaHCO_3$, filtered, and concentrated to a syrup. This was dissolved in 70% aqueous acetic acid (30 mL) and kept for 90 min at 50–55°, and then overnight at 25°. The solvent was removed and the residue partitioned between chloroform and water. The chloroform fraction was dried (Na_2SO_4) and then evaporated to a syrup. Crystallization from petroleum ether gave **13** (0.36 g, 21.2%), m.p. 95–97°, $[\alpha]_D^{25}$ +23.2° (c 2, chloroform); lit.[3] m.p. 96–97°, $[\alpha]_D^{25}$ +23°.

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.32; H, 8.10.

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