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Iodomethyl Group as a Hydroxymethyl Synthetic Equivalent: Application to the Syntheses of D-*manno*-Hept-2-ulose and L-Fructose Derivatives

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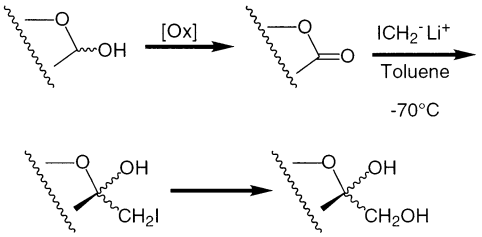
Abstract: The one-carbon elongation of aldoses to ketoses using iodomethyllithium as the key reagent in the homologation step is exemplified by the preparation of two carbohydrates of chemical and biological interests: D-*manno*-hept-2-ulose from D-mannose and L-fructose from L-arabinose.

The elongation of carbohydrates from the reducing end allows a net aldose to ketose homologation;[1] we now show this transformation to be feasible using the iodomethyl group as a hydroxymethyl equivalent (Scheme 1); this is exemplified by the preparation of two ketoses, D-*manno*-hept-2-ulose and L-fructose, which have been selected for their chemical and biological interests.

D-*manno*-Hept-2-ulose, 1. The effects of this seven-carbon ketose[2] on insulin secretion have been known for a long time,[3] and **1** has been shown to be a high-affinity inhibitor of glucokinase in pancreatic β-cells[4] and tumor cells;[5] it has been proposed that **1** is transported across the plasma membrane at the specific intervention of GLUT-2, an isoform of the human carbohydrate transport proteins.[6] *manno*-Hept-2-ulose, which is no longer commercially available, can be isolated from certain varieties of avocado[7] or after isomerization of D-*glycero*-D-*galacto*-heptose.[8] Condensation of 1,3-dihydroxypropanone with an erythrose derivative[9] and of nitroethanol with arabinose derivatives[10] have also yielded **1** as well as a molybdic acid induced rearrangement of 2-*C*-hydroxymethyl-D-glucose.[11] Since these procedures require separation of epimers, the addition of a 1-carbon synthon to an hexose, such as the addition of benzyloxymethylmagnesium chloride to mannonolactone **2**, has been proposed.[12] This procedure gave **1** in 28% overall yield, with 38% recovery of **2**, this yield being based on reacted lactone. Therefore, we considered that a more reactive species was necessary for this homologation reaction.

SCHEME 1



When reacted with diiodomethane/samarium, esters are converted to cyclopropanols[13] but the addition of an iodomethyl group to the carbonyl group can be accomplished by reaction with iodomethyllithium.[14] Due to its thermal instability, ICH_2Li is generated at low temperature from diiodomethane/MeLi, lithium/iodine exchange taking preference over metalation; this can be effected in the presence of the lactone partner;[14] no addition of methyllithium on the carbonyl group is observed.[15]

Thus, after reacting the readily available mannofuranonolactone **2**[16] with iodomethyllithium at low temperature, **3** was isolated in 92% yield (Scheme 2); this yield compares favorably with those observed for other lactones[14] and can be explained by internal coordination of the organometallic species by the oxygens of the acetals of **3**, which all lie on the same side of the furanose ring. As shown by an nOe effect between H-3 and the hydroxyl group, **3** exists mostly in solution as the α-anomer (>95%), which is also the form that could be crystallized (Philouze, C., unpublished results). Attempts to get **4** using reagents which are known to convert hindered halides to hydroxyl groups, such as superoxide anion,[17] hydrated alumina,[18] or TEMPO-mediated free-radical substitution followed by reduction[19] were ineffective; however, **4**[12] could be obtained after treatment with potassium hydroxide. Noteworthy is the outcome observed when iodide **3** was treated with a strong base (DBU) in aprotic solvent, pyranone **5** (73%) being the only

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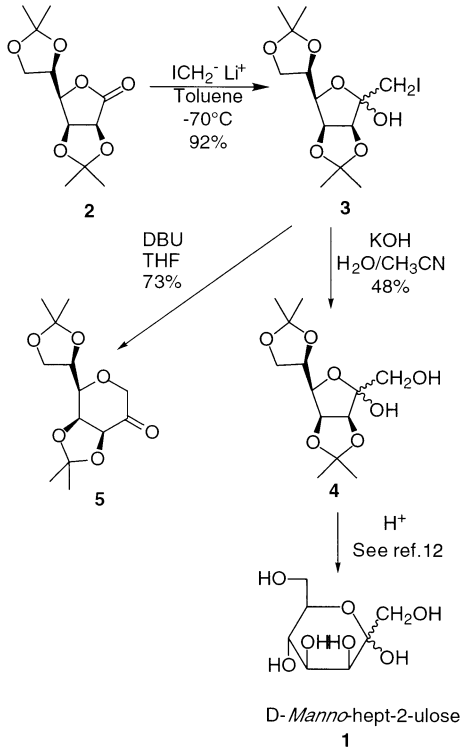
SCHEME 2



product (this can be explained by displacement of the iodide by the alkoxide at position-5 arising from the open-chain form of the carbohydrate). Deprotection of the acetals of **4** was then effected conventionally[12] which gave D-*manno*-hept-2-ulose **1** in 40% overall yield from **2**. This compares favorably with literature procedures and thus sets up a practical preparation.

L-Fructose, 7. Ketone **6** is a chiral auxiliary which has found important synthetic applications in asymmetric epoxidation[20,21] and enantioselective oxidation of *vic*-diols.[22] Other fructose-derived acetals have been shown to be effective in enantioselective cyclopropanations[23] or Diels−Alder cycloadditions.[24] However, the high price of L-fructose, **7**, the non-natural enantiomer, brings some limitations to the applicability of these otherwise efficient procedures.

Syntheses of L-fructose and derivatives have been elaborated from L-carbohydrates and they include elongation of arabinonic acid,[25] arabinose,[26] or glyceraldehyde,[27] inversion of the 4-OH of sorbose,[21,28] or enzymatic methods such as isomerization of mannose[29] or bacterial oxidation of mannitol.[30]

To get L-fructose we considered the addition of iodomethyllithium to a suitably protected arabinonolactone, since we have shown during the synthesis of **1** that an iodomethyl group could be considered as a hydroxymethyl equivalent. Our approach (Scheme 3) begins with the readily available acetal **8**,[31] which was first oxidized to **9** by bromine,[32] in the presence of barium carbonate as a buffer,[33] then benzylated to give lactone **10**.[34] When reacted with iodomethyllithium, **10** gave the expected iodohydrin **11**.

Displacement of the neopentylic iodide by hydroxyde proceeded in better yield (77%) than for the *manno*-heptulose series, and **12** thus formed was next converted to acetal **13**.[35] Completion of the synthesis involved removal of the benzyl group (to give alcohol **14**[21]) and then hydrolysis to **7**.

Besides this scheme providing a preparation of L-fructose, we believe its main advantage lies in an access to **14** and related chiral auxiliaries, and in particular to **15** (whose enantiomer, **6**, is known under the trademark Epoxone) as, by making them available under the L-form, this should expand their uses in asymmetric reactions.[36]

Experimental Section

Toluene was distilled over sodium and stored over 4 Å molecular sieves, diiodomethane was distilled and stored over copper turnings, acetone was distilled over calcium sulfate, and acetonitrile was distilled over calcium hydride and stored over 4 Å molecular sieves. ^{1}H spectra are referenced from tetramethylsilane or from the residual peak of $CHCl_3$ ($\delta_H = 7.24$ ppm) and are reported as follows: chemical shift (ppm), multiplicity, integration, coupling constants (Hz) and assignments. Chemical shifts for ^{13}C spectra are referenced from $CDCl_3$ resonance ($\delta_C = 77.0$ ppm).

1-Deoxy-3,4:6,7-di-*O*-isopropylidene-1-iodo-D-*manno*-hept-2-ulose (3). Under argon, to a solution of lactone **2**[16] (6.80 g, 26.5 mmol) and diiodomethane (10.71 g, 40.0 mmol) in dry toluene (180 mL) cooled to −70 °C was added dropwise a solution of methyllithium in diethyl ether (19.7 mL of a 1.6 M solution; 31.5 mmol). The solution was maintained at −70 °C for 20 min and quenched with a saturated solution of ammonium chloride in water (50 mL). The organic layer was decanted, and the aqueous layer was extracted with chloroform (3 × 50 mL); the combined organic layers were dried over sodium sulfate and the solvents evaporated under reduced pressure to give **3** (9.79 g, 24.5 mmol, 92%) as a pale yellow solid which can be used in the next step without purification. An analytical sample was obtained by recrystallization from ethyl acetate/*n*-hexane: mp (AcOEt/*n*-hexane) 87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.72 (s, 1H, O*H*), 3.45 and 3.54 (AB q, 2H, $J = 11$ Hz, H-1), 4.02−4.11 (m, 3H, H-5, H-7 and H-7′), 4.32−4.40 (m, 1H, H-6), 4.62 (d, 1H, $J_{3,4} = 6$ Hz, H-3), 4.95 (dd, 1H, $J_{4,5} = 4$ Hz, $J_{3,4} = 6$ Hz, H-4); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.2 (C-1), 24.8 (*C*H_3), 25.7

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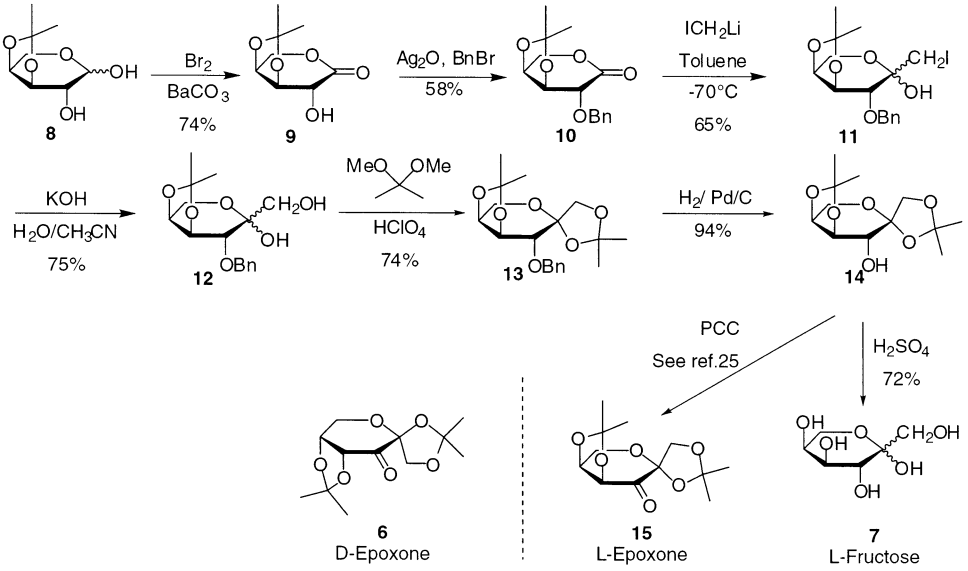
SCHEME 3



(CH_3), 26.2 (CH_3), 27.3 (CH_3) 66.7 (C-7), 76.5, 80.4, 81.1, 83.6 (C-3, C-4, C-5, C-6), 102.6 (C-2), 109.2 ($C(CH_3)_2$), 113.2 ($C(CH_3)_2$); $[\alpha]^{25}_D$ −8 (5 min) → −11 (24 h) (*c* 1, $CHCl_3$). Anal. Calcd for $C_{13}H_{21}IO_6$: C, 39.01; H, 5.29; I, 31.71. Found: C, 38.84; H, 5.52; I, 31.57.

3,4:6,7-Di-*O*-isopropylidene-D-*manno*-hept-2-ulose (4). A 1 M aqueous solution of NaOH (50 mL, 1.9 equiv) was added to a solution of iodide **3** (10.3 g, 25.7 mmol, 1 equiv) in a mixture of acetonitrile (150 mL)/water (50 mL), and the resulting solution was stirred for 35 min. The aqueous phase was extracted with 3 × 50 mL of AcOEt. The resulting organic phase was dried over magnesium sulfate and concentrated under vacuum to afford 5.20 g of an oil which was chromatographed over silica gel (eluant: *n*-hexane/ethyl acetate, from 6/4 to 4/6) to afford 3.55 g (12.2 mmol, 48%) of diol **4** as a white solid:

mp 85 °C (toluene/pentane) (lit.[12] mp 88 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.97 (m, 1H, CH_2OH), 3.15 (s, 1H, 2-O*H*), 3.70−3.83 (m, 2H, 1-H), 3.98−4.10 (AB part of an ABX system, 2H, J_{AB} = 9 Hz, H-7 and H-7′), 4.13 (dd, 1H, $J_{4,5}$ = 4 Hz, $J_{5,6}$ = 8 Hz, H-5), 4.35−4.41 (m, 1H, H-6), 4.60 (d, 1H, $J_{3,4}$ = 6 Hz, H-3), 4.92 (dd, 1H, $J_{4,5}$ = 4 Hz, $J_{5,6}$ = 6 Hz, H-4). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.3 (CH_3), 25.1 (CH_3), 25.7 (CH_3), 26.8 (CH_3), 64.4 (C-1), 66.6 (C-7), 73.1 (C-6), 79.5 (C-5), 80.3 (C-4), 85.0 (C-3), 104.7 (C-2), 109.1 ($C(CH_3)_2$), 112.9 ($C(CH_3)_2$); $[\alpha]^{25}_D$ +25 (5 min.) → +17 (24 h) (*c* 1, $CHCl_3$) (lit.[12] $[\alpha]_D$ +20.4 (*c* 1, $CHCl_3$)).

1-Deoxy-3,4:6,7-di-*O*-isopropylidene-2-keto-D-*manno*-heptopyranose (5). DBU (75μL, 0.5 mmol) was added to a solution of iodide **3** (200 mg, 0.5 mmol, 1 equiv) in dry THF (5 mL), and the reaction mixture was stirred for 3 h. Water (2 mL) was added, the reaction mixture was extracted with methylene chloride, the organic phase was dried over sodium sulfate, and the solvents were evaporated under vacuum to afford 164 mg of an oil which was chromatographed over silica gel (eluant: *n*-hexane/ethyl acetate, 3/1) to afford 100 mg (0,37 mmol, 73%) of heptose **5** as white solid: mp 58 °C (pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3,51 (dd, 1H, *J* = 2, 8 Hz, H-5), 3.96−4.10 (m, 3H, H-1 and H-7′), 3.96−4.37 (m, 3H, H-1, H-3 and H-7), 4.64 (dd, 1H, *J* = 2, 7 Hz, H-4); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.5 (CH_3), 26.1 (CH_3), 27.1 (CH_3), 27.4 (CH_3), 67.3 (C-1) 73.8 (C-7), 74.3(C-3 or C-6), 76.3 (C-4), 77.8 (C-3 or C-6), 77.9 (C-5), 110.0 ($C(CH_3)_2$), 112.3 ($C(CH_3)_2$), 204.4 (C=O); $[\alpha]^{25}_D$ −41 (*c* 1, $CHCl_3$).

3,4-*O*-Isopropylidene-L-arabinono-1,5-lactone (9). Bromine (1.998 g, 12.5 mmol) was added dropwise to a mixture of lactol **8** (950 mg, 5.0 mmol) and barium carbonate (1.184 g, 6.0 mmol) in water (10 mL) and dioxane (5 mL). The reaction mixture was stirred in the dark for 3 h, and the reaction was quenched by addition of a saturated aqueous solution of sodium thiosulfate. The mixture was extracted with ethyl acetate (3 × 20 mL), the organic phase was dried over sodium sulfate, and the solvents were evaporated under vacuum to yield lactone **9** (695 mg, 3.7 mmol, 74%), which was used in the next step without further purification.

An analytical sample was purified by rapid chromatography over silica gel (too long a chromatography results in opening of the lactone to the acid−alcohol), eluting with ethyl acetate/*n*-hexane (2/1) and recrystallized from petroleum ether.

The ^{1}H and ^{13}C NMR spectra are in accordance with the ones reported in the literature:[37] mp (petroleum ether) 92 °C (lit.[37] mp 95 °C); $[\alpha]^{25}_D$ −70 (*c* 1.8, MeOH) (lit.[37] $[\alpha]^{22}_D$ −9.8 (*c* 1.8, MeOH), lit.[38] $[\alpha]_D$ −1 (*c* 3, $CHCl_3$)).

2-*O*-Benzyl-3,4-*O*-isopropylidene-L-arabinono-1,5-lactone (10). Under argon, to a solution of lactone **9** (1.750 g, 9.3 mmol) in dry acetonitrile (40 mL) was added freshly prepared silver(I) oxide[39] (9.264 g, 40.0 mmol) followed by benzyl bromide (8.545 g, 50.0 mmol), and the resulting suspension was stirred in the dark overnight. The mixture was filtered over a pad of Celite, which was rinsed with methylene chloride, and the solvents were removed under vacuum. The oil thus obtained was purified by chromatography over silica gel (methylene chloride/methanol, 9/1) and the product recrystallized in *n*-hexane to give benzyl ether **10** as a white solid (1.500 g, 5.4 mmol, 58%): mp 76−77 °C (*n*-hexane). The ^{1}H NMR is in accordance with the one reported in the literature:[34] ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.0 (CH_3), 25.9 (CH_3), 67.4 (C-5), 72.6 (CH_2Ph), 71.2, 74.9, 75.6, (C-2, C-3, C-4) 110.4 ($C(CH_3)_2$), 128.2. 128.3, 128.5 (*C*H Ar), 136.1 (*C ipso* Ar), 167.7 (C=O); $[\alpha]^{23}_D$ +123 (*c* 1, $CHCl_3$).

3-*O*-Benzyl-1-deoxy-1-iodo-4,5-*O*-isopropylidene-L-fructopyranose (11). Under argon, to a solution of lactone **10** (1.50 g, 5.4 mmol) and diiodomethane (2.169 g, 8.1 mmol) in dry toluene (60 mL) cooled to −70 °C was added dropwise methyllithium (4.3 mL of a 1.6 M solution in diethyl ether, 6.9 mmol) at a rate such as to maintain the internal temperature between −70 and −60 °C. The solution was kept at −70 °C for 20 min and quenched with an aqueous saturated solution of ammonium chloride (20 mL). The organic layer was decanted, the aqueous layer was extracted with chloroform (2 × 50 mL), the combined organic phases were dried over sodium sulfate, and the solvents

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were evaporated under reduced pressure. The crude oil was purified by flash chromatography over silica gel (*n*-hexane/ethyl acetate, 9/1) to give **11** as an oil (1.47 g, 3.5 mmol, 65%).

Spectral data for the major anomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.14 (s, 1H, O*H*), 3.23 and 3.47 (AB q, 2H, J_{AB} = 10 Hz, H-1), 3.60 (d, 1H, $J_{3,4}$ = 7 Hz, H-3), 3.87 (A part of ABM, 1H, $J_{6,6'}$ = 12 Hz, H-6), 3.98−4.03 (m, 1H, H-6′), 4.10 (dd, 1H, $J_{5,6}$ = 2 Hz, $J_{4,5}$ = 6 Hz, H-5), 4.28 (t, 1H, $J_{4,5}$ = 6 Hz, H-4), 4.61 and 4.85 (AB q, 2H, J_{AB} = 11 Hz, CH_2Ph), 7.23−7.27 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.9 (C-1), 26.1 (*C*H_3), 28.0 (*C*H_3), 60.3 (C-6), 73.2 (*C*H_2Ph), 73.5 76.7, 77.2 (C-3, C-4, C-5), 94.5 (C-2), 109.2 (*C*$(CH_3)_2$), 128.1, 128.4 (*C*H Ar), 137.4 (*C ipso* Ar); $[\alpha]^{25}_D$ +35.5 (5 min) δ + 32.6 (24 h) (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}IO_5$: C, 45.73; H, 5.04. Found: C, 45.63; H, 5.27.

3-*O*-Benzyl-4,5-*O*-isopropylidene-L-fructopyranose (12). To a solution of **11** (840 mg, 2 mmol) in acetonitrile (15 mL) was added an aqueous solution of KOH (4 mL of a 1 M solution, 4 mmol), and the mixture was stirred for 1 h. The pH was adjusted to 8 by addition of 1 N HCl, the acetonitrile evaporated, and the aqueous mixture extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over sodium sulfate and the solvent evaporated to give diol **12** (480 mg, 1.5 mmol, 75%) as a white solid which was used in the next step without purification. An analytical sample was obtained by recrystallization from *n*-hexane/dichloromethane (8/3): mp 101 °C (*n*-hexane/dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.98 (X part of ABX, 1H, O*H*-1), 3.50 and 3.64 (AB part of ABX, 2H, $J_{1,1'}$ = 11 Hz, H-1, H-1′), 3.51 (s, 1H, O*H*-2), 3.59 (d, 1H, $J_{3,4}$ = 6 Hz, H-3), 3.94 and 4.14 (AB part of ABX, 2H, $J_{6,6'}$ = 13 Hz, H-6, H-6′), 4.24−4.27 (m, 1H, H-5), 4.47 (t, 1H, *J* = 6 Hz, H-4), 4.67 and 4.90 (AB q, 2H, J_{AB} = 12 Hz, CH_2-Ph), 7.34−7.36 (m, 5H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.0 (*C*H_3), 27.8 (*C*H_3), 59.9 (C-6), 65.9 (C-1), 73.1 (*C*H_2Ph), 73.3, 76.0, 76.2 (C-3, C-4, C-5), 96.1 (C-2), 109.06 (*C* $(CH_3)_2$), 127.9, 128.2, 128.3 (*C*H Ar), 137.4 (*C ipso* Ar); $[\alpha]^{25}_D$ +56.4 (5 min) → 38.8 (24 h) (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.90; H, 7.38.

3-*O*-Benzyl-1,2:4,5-di-*O*-isopropylidene-β-L-fructopyranose (13). To a solution of diol **12** (155 mg, 0.50 mmol) in dry acetone (5 mL) were added 2,2-dimethoxypropane (185 μL, 1.49 mmol) and $HClO_4$ (22 μL, 0.25 mmol of a 70% aqueous solution), and the resulting dark red solution was stirred for 4 h and then poured into concentrated ammonium hydroxide. The volatiles were evaporated under reduced pressure, and the solution was extracted with methylene chloride (3 × 15 mL). The organic layer was dried over sodium sulfate and the solvent removed in vacuo. The crude product was purified by flash chromatography over silica gel (toluene/ethyl acetate, 100/5) to give **13** (130 mg, 0.37 mmol, 74%) as an oil.

The ^{1}H spectrum is in accordance with the one reported in the literature:[35] ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.0 (*C*H_3), 26.2 (*C*H_3), 26.9 (*C*H_3), 28.1 (*C*H_3), 60.2 (C-6), 71.9 (*C*H_2), 73.0 (*C*H_2), 73.8, 76.0, 77.8 (C-3, C-4, C-5), 104.4 (C-2), 109.0 (*C*$(CH_3)_2$), 112.1 (*C*$(CH_3)_2$), 127.5, 127.7, 128.2 (*C*H Ar), 138.2 (*C ipso* Ar); $[\alpha]^{23}_D$ +87 (*c* 2, $CHCl_3$) (lit.[35] $[\alpha]_D^{22.5}$ −89.6 (*c* 2.22, $CHCl_3$) for the D-isomer).

1,2:4,5-Di-*O*-isopropylidene-β-L-fructopyranose (14). To a solution of benzyl ether **13** (55 mg, 0.16 mmol) in ethanol (2.5 mL) was added 5% Pd/C (20 mg). The flask was placed under an hydrogen atmosphere and the mixture stirred overnight. The flask was flushed with argon and filtered over Celite and the solvent removed in vacuo to afford pure alcohol **14** (40 mg, 0.15 mmol, 98%) as a white solid.

The spectral data are in accordance with those reported in the literature:[21] mp 117 °C (hexane/dichloromethane) (lit.[21] mp 118 °C); $[\alpha]^{23}_D$ +143 (*c* 1, $CHCl_3$) ($[\alpha]_D$ −144.2 (*c* 1, $CHCl_3$) for the D-isomer).[21]

L-Fructose (7). A solution of 1,2:4,5-di-*O*-isopropylidene-β-L-fructopyranose **14** (26 mg, 0.1 mmol) in ethanol (1.5 mL) was acidified to pH = 1 by addition of 2 N sulfuric acid and heated at 40 °C overnight. The solution was cooled to room temperature and the pH adjusted to 7−8 by addition of 2 N sodium hydroxide. After addition of ethanol and filtration of the salts, the solvents were evaporated and the residue chromatographed over silica gel using a mixture of AcOEt/MeOH/H_2O (40/10/7) as the eluent to give L-fructose **7** (13 mg, 0.072 mmol) in 72% yield.

The NMR data are identical with those recorded for D-fructose: $[\alpha]^{23}_D$ +87 (*c* 0.21, H_2O) (lit.[28a] $[\alpha]^{23}_D$ +88 (*c* 1.5, H_2O), lit.[28b] $[\alpha]^{23}_D$ +94.4 (*c* 1.8, H_2O), lit.[27] $[\alpha]^{23}_D$ +87.2 (*c* 2.1, H_2O), lit.[29] $[\alpha]^{23}_D$ +91 (*c* 2.5, H_2O), lit.[30] $[\alpha]^{23}_D$ +86 (*c* 1, H_2O), lit.[25] $[\alpha]^{23}_D$ +93 (*c* 9.5, H_2O),).

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