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Chemical Synthesis of 1-Deoxy-L-fructose and L-Sorbose Through Carbonyl Translocation

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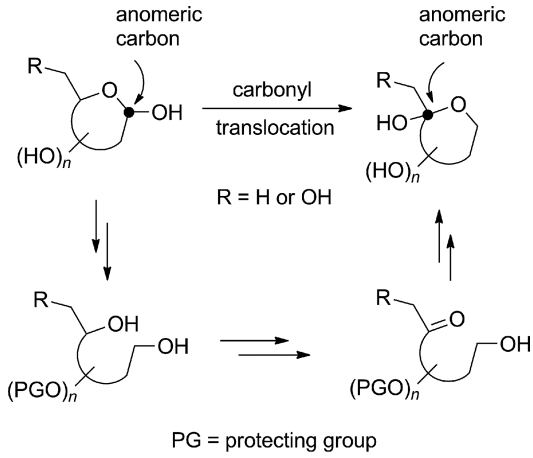
Two rare sugars – 1-deoxy-L-fructose and L-sorbose – were synthesized from inexpensive starting materials by a carbonyl translocation method developed in our laboratory. Reduction of a known starting compound gave a 1,5-diol derivative. Selective protection of the corresponding primary alcohol and oxidation of the secondary alcohol provided the desired product in acyclic, protected form. Subsequent deprotection resulted in the production of 1-deoxy-L-fructose from the known starting material in five steps and in a total yield of 42 %. This approach represents the first report of a chemical synthesis of 1-deoxy-L-fructose. A similar strategy was applied to convert inexpensive D-glucose into L-sorbose, which was prepared in five steps from a known starting material in a total yield of 55 %. The synthetic methods represent a complementary method to biological approaches for the synthesis of vitamin C.

Introduction

Deoxysugars, an important class of carbohydrates, occur widely in nature. They are found in liposaccharides, glycoproteins, and glycolipids on bacterial cell surfaces.[1] 2-Deoxy-D-ribose is, of course, a component of DNA. Synthesis[2] of its L-configured counterpart, 2-deoxy-L-ribose, is important because it is used in studies involving nucleic acid recognition[3] and antitumor agents.[4] A number of synthetic and biochemical methods for preparing rare deoxysugars have been developed.[5] However, most involve considerable labor or the use of expensive starting materials and reagents,[6] thus making them poorly amenable for use in an industrial production process. Hence, a general and practical method for the synthesis of rare sugars from inexpensive starting materials would be highly desirable.

A synthetic methodology for preparation of the rare 2-deoxy-L-ribose through carbonyl translocation has recently been developed in this laboratory.[2a] The method is based on a radical process involving carbonyl translocation and represents an alternative and efficient approach to the synthesis of rare 2-deoxy-L-sugars from inexpensive starting materials: namely, D-sugars. However, to prepare other rare non-deoxysugars by this carbonyl translocation process, a new synthetic approach that does not involve the use of the radical process was needed. A schematic representation of a highly efficient and simple method involving carbonyl translocation for the synthesis of rare sugars is shown in Scheme 1. To achieve such a carbonyl translocation, the masked carbonyl carbon (anomeric carbon) of the sugar has to be reduced to give a diol derivative. Selective protection of the corresponding primary alcohol, oxidation of the secondary alcohol, and subsequent deprotection affords the desired rare sugars.



Scheme 1. A new synthetic method involving carbonyl translocation.

Here we report on the synthesis of two examples – 1-deoxy-L-fructose and L-sorbose – by this new synthetic methodology.

1-Deoxy-D-fructose has been shown to serve as a potential metabolic inhibitor and an antimetabolite.[7] Its synthesis from D-arabinose was successfully developed by Fleet and co-workers.[7b] Although the same strategy could also be applied to prepare 1-deoxy-L-fructose from L-arabinose, an alternative synthetic approach for an efficient synthesis of 1-deoxy-L-fructose could lead to the development of additional potential inhibitors. The current methods for

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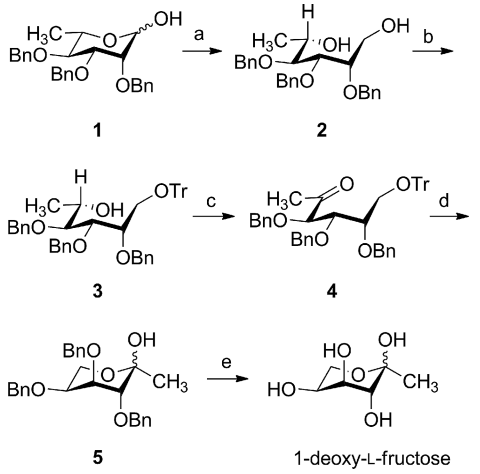
preparing 1-deoxy-L-fructose involve biochemical procedures,[8] and although the synthesis involves a fermentation step, the process also involves the use of toxic Raney nickel.

L-Sorbose is the starting material for the bioproduction of vitamin C. The current industrial processes for preparing L-sorbose are based on bioproduction with use of D-sorbitol as the starting material.[9] From an industrial point of view, the main problem associated with this process is the substrate concentration [10–20% (w/v)], which limits the efficiency of production. Therefore, the development of a chemical process for the production of L-sorbose would be desirable.[10] By our new methodology, 1-deoxy-L-fructose and L-sorbose were prepared from inexpensive L-rhamnose and D-glucose, respectively, as starting materials.

Results and Discussion

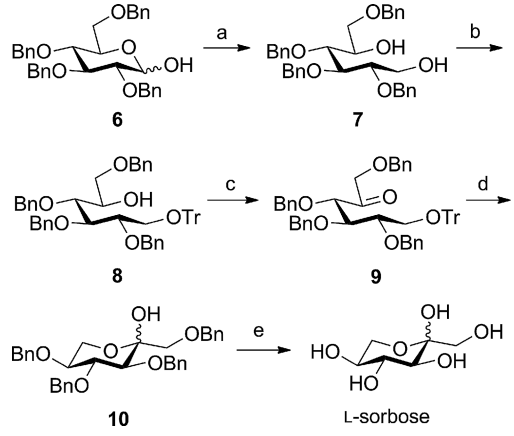
The synthesis of 1-deoxy-L-fructose is shown in Scheme 2. The synthesis started from the known intermediate **1**, which was readily prepared in three steps from commercially available L-rhamnose.[11] LAH reduction[12] gave the 1,5-diol derivative **2**, and selective protection of the primary hydroxy group with a trityl group[13] generated compound **3**. A Swern oxidation[14] of the remaining secondary hydroxy group produced **4**, an acyclic and protected form of 1-deoxy-L-fructose. Removal of the trityl group by treatment with formic acid in a diethyl ether solution[15] gave the 1-deoxy-L-fructose derivative **5** in the pyranose form. Benzyl-protected 1-deoxy-L-fructose derivative **5** may also be used as a convenient synthon for further synthetic manipulation. Finally, removal of the benzyl groups under high-pressure conditions (50 psi) successfully afforded 1-deoxy-L-fructose.



Scheme 2. *Reagents and conditions:* (a) $LiAlH_4$, THF, 0 °C to r.t., 16 h, 80%; (b) TrCl, DMAP, DBU, toluene/CH_2Cl_2 (1:2, *v*/*v*), 60 °C, 2 d, 79%; (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C, 1 h, 87%; (d) HCO_2H/diethyl ether (1:1, *v*/*v*), room temp., 2 h, 95%; (e) Pd/C, H_2, EtOH, 50 psi, 24 h, 80%.

1-Deoxy-L-fructose was thus prepared from the known intermediate **1** in five steps and in a total yield of 42%.[16] The methodology represents the first report of a chemical synthesis of 1-deoxy-L-fructose. The overall synthesis avoided the need for expensive reagents and would be amenable for use in an industrial process.

The carbonyl translocation methodology was also applied to the synthesis of L-sorbose, the synthesis of which from an inexpensive D-glucose derivative is shown in Scheme 3. The synthesis started from the known intermediate **6**, which was prepared in two steps from commercial available methyl D-glucopyranoside.[17] Reduction of **6** with LAH afforded 1,5-diol derivative **7**,[12] and selective protection with a trityl group gave compound **8**.[18] An oxidation reaction provided the acyclic L-sorbose derivative **9**,[18] and two deprotection steps resulted in the production of L-sorbose. The L-sorbose was thus obtained from the known intermediate **6** in five synthetic steps in a total yield of 55%.[19] Current industrial production of L-sorbose relies on biosynthesis, whereas here a complementary and efficient chemical synthesis has been successfully explored. This simple and inexpensive method provides an alternative and potentially useful industrial process for the synthesis of vitamin C.



Scheme 3. *Reagents and conditions:* (a) $LiAlH_4$, THF, 0 °C to room temp., 16 h, 95%; (b) TrCl, DMAP, DBU, toluene/CH_2Cl_2 (1:2, *v*/*v*), 60 °C, 2 d, 84%; (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C, 1 h, 94%; (d) HCO_2H/diethyl ether (1:1, *v*/*v*), room temp., 15 min, 77%; (e) Pd/C, H_2, EtOH, 50 psi, 24 h, 95%.

Conclusions

A new synthetic methodology based on carbonyl translocation without the need for a radical process has been successfully developed and allows conversion of inexpensive starting materials into rare sugars. No expensive reagents or harsh conditions were required for the synthesis. 1-Deoxy-L-fructose was prepared from the known intermediate **1** in five steps in a total yield of 42% (or eight steps from L-rhamnose). This represents the first report of a chemical synthesis of 1-deoxy-L-fructose in which no toxic reagents are used. Meanwhile, L-sorbose was synthesized from the known intermediate **6** in five steps in a total yield of 55% (or seven steps from methyl D-glucopyranoside). The synthesis of L-sorbose represents a complementary chemical

method to the bioproduction of L-sorbose. This efficient and inexpensive method provides an alternative and potential industrial process for the synthesis of vitamin C. Furthermore, this new synthetic approach is sufficiently general and efficient that many other rare sugars could also be prepared from inexpensive starting materials. Such studies are currently underway.

Experimental Section

General: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Bruker Avance 300 MHz instrument. NMR spectra were recorded in $CDCl_3$, CD_3OD, or D_2O. Chloroform (δ = 7.26 ppm in ^{1}H NMR; δ = 77.0 ppm in ^{13}C NMR), methanol (δ = 3.31 ppm in ^{1}H NMR; δ = 49.00 ppm in ^{13}C NMR), and D_2O (acetone as internal standards, δ = 2.22 ppm in ^{1}H NMR; δ = 30.9 ppm in ^{13}C NMR) were used as internal standards, respectively. Splitting patterns are reported as follows: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. Coupling constants (J) are reported in Hz. IR spectra were recorded with a Perkin–Elmer Spectrum 100 FT-IR spectrometer and are reported in cm^{-1}. High-resolution mass spectrometry (HRMS) was recorded with a Shimadzu LCMS-IT-TOF spectrometer (ESI-MS). Optical rotations were measured with a Horiba SEPA-300 Digital polarimeter. TLC (Merck Art. 60 F_{254}, 0.25 mm) precoated sheets were used. Reaction products were isolated by flash chromatography performed on Merck Art. Geduran Si 60 (0.040–0.063 mm) silica gel, yields of products refer to chromatographically purified products unless otherwise stated. THF and toluene were distilled over traces of sodium metal with use of benzophenone as indicator under N_2. Dichloromethane, DMSO, DBU, and triethylamine were dried with CaH_2 and then distilled. Ethanol was dried with magnesium and iodine and then distilled. Formic acid was distilled before use. All reactions were performed under a blanket of N_2 or Ar.

2,3,4-*O*-Tribenzyl-L-rhamnitol (2): LAH (39.7 mg) was added to a solution of **1** (0.13 g, 0.31 mmol) in THF (3.0 mL). The reaction mixture was stirred for 16 h at room temp. After the reaction was completed, water (49 μL) was added, 5 min later $NaOH_{(aq.)}$ (15%, 49 μL) was added, and 5 min later water (98 μL) was added, and the mixture was then stirred for another 20 min. A white precipitate formed, and the reaction mixture was then filtered and washed with diethyl ether. The filtrate was concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes 1:1 as eluent to give a white solid (0.11 g, 80%), m.p. 64.9–66.9 °C. $[\alpha]_D^{24}$ = –7.70 (c = 1.29, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.20 (m, 15 H), 4.81–4.71 (two d overlapped at 4.78 and 4.74, J = 11.4 Hz, 2 H), 4.70–4.56 (m, 3 H), 4.49 (d, J = 11.4 Hz, 1 H), 4.06 (q, J = 5.7 Hz, 1 H), 4.00–3.90 (m, 2 H), 3.89–3.80 (m, 1 H), 3.74 (q, J = 4.5 Hz, 1 H), 3.51 (dd, J = 5.7, 3.9 Hz, 1 H), 2.71 (d, J = 5.3 Hz, 1 H, OH), 2.48 (t, J = 5.3 Hz, 1 H, OH), 1.26 (d, J = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9 (s), 137.8 (s), 128.4 (d), 128.3 (d), 128.1 (d), 127.8 (d), 127.7 (d), 82.1 (d), 79.5 (d), 78.4 (d), 74.0 (t), 73.4 (t), 71.8 (t), 67.3 (d), 60.4 (t), 19.6 (q) ppm. IR (neat): $\tilde{\nu}$ = 3440 (OH), 3089, 3066, 3012, 2936, 2880, 2403, 2316, 1953, 1879, 1812, 1606, 1587, 1497, 1454, 1396, 1329, 1216, 1062, 1028, 917, 882, 849, 697, 667, 615 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{32}KO_5$ $[M + K]^+$ 475.1887; found 475.1816.

2,3,4-*O*-Tribenzyl-1-*O*-trityl-L-rhamnitol (3): DBU (0.62 mL, 4.12 mmol), a catalytic amount of DMAP (28.0 mg, 0.23 mmol), and TrCl (0.96 g, 3.44 mmol) were added to a solution of **2** (1.00 g, 2.29 mmol) in a co-solvent system (CH_2Cl_2/toluene 2:1, 22.0 mL). The reaction mixture was stirred at 60 °C for 2 d and then worked up by addition of water. The resulting mixture was extracted with CH_2Cl_2 (60 mL×3). The combined organic layers was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes 2:8 as eluent to give a white solid (1.23 g, 79%), m.p. 71.5–73.4 °C. $[\alpha]_D^{24}$ = –32.17 (c = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.45 (m, 6 H), 7.44–7.29 (m, 22 H), 7.14–7.06 (m, 2 H), 4.85 (d, J = 11.7 Hz, 1 H), 4.67–4.47 (m, 5 H), 4.08–3.94 (m, 2 H), 3.89 (td, J = 5.6, 2.9 Hz, 1 H), 3.64 (dd, J = 10.5, 2.9 Hz, 1 H), 3.57 (dd, J = 5.6, 4.2 Hz, 1 H), 3.45 (dd, J = 10.5, 5.6 Hz, 1 H), 2.57 (s, 1 H, OH), 1.24 (d, J = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0 (s), 138.4 (s), 138.3 (s), 138.1 (s), 128.8 (d), 128.3 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.7 (d), 127.6 (d), 127.5 (d), 126.9 (d), 86.9 (s), 82.2 (d), 79.1 (d), 78.5 (d), 73.6 (t), 73.4 (t), 72.6 (t), 67.5 (d), 63.2 (t), 19.5 (q) ppm. IR (neat): $\tilde{\nu}$ = 3464 (OH), 3087, 3062, 3031, 2932, 2878, 1959, 1813, 1598, 1494, 1450, 1395, 1329, 1217, 1181, 1155, 1089, 1069, 1029, 1003, 900, 850, 759, 698, 668, 643, 633, 617, 606 cm^{-1}. HRMS (ESI): calcd. for $C_{46}H_{46}NaO_5$ $[M + Na]^+$ 701.3243; found 701.3245.

2,3,4-*O*-Tribenzyl-1-*O*-trityl-L-fructitol (4): A solution of DMSO (63.9 μL, 0.10 mmol) in CH_2Cl_2 (0.15 mL) was added dropwise at –78 °C to a solution of oxalyl chloride (65 μL, 0.75 mmol) in CH_2Cl_2 (0.15 mL), and the reaction mixture was then stirred for 30 min followed by addition of a solution of **3** (69.3 mg, 0.10 mmol) in CH_2Cl_2 (0.55 mL) at the same temperature. The resulting mixture was stirred for another 30 min, then quenched by dropwise addition of Et_3N (0.21 mL, 1.5 mmol) in CH_2Cl_2 (0.15 mL) at –78 °C, and allowed to warm up gradually to room temp. The mixture was diluted with CH_2Cl_2 (10 mL), washed with water (3 mL) and brine (3 mL), dried with $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes 15:85 as eluent to give a yellow oil (59 mg, 87%). $[\alpha]_D^{24}$ = –48.46 (c = 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.44 (m, 6 H), 7.40–7.15 (m, 22 H), 6.92 (dd, J = 7.2, 1.8 Hz, 2 H), 4.76 (d, J = 11.4 Hz, 1 H), 4.55 (d, J = 11.4 Hz, 1 H), 4.45–4.35 (m, 3 H), 4.32–4.23 (one d at 4.29, J = 3.0 Hz, 1 H, overlapped with one t at 4.26, J = 4.9 Hz, 1 H), 4.18 (d, J = 3.6 Hz, 1 H), 3.88–3.79 (m, 1 H), 3.71 (dd, J = 10.5, 8.7 Hz, 1 H), 3.25 (dd, J = 10.5, 3.7 Hz, 1 H), 2.14 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.1 (s), 143.9 (s), 138.3 (s), 137.7 (s), 137.3 (s), 128.8 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.6 (d), 127.4 (d), 127.3 (d), 127.0 (d), 86.7 (s), 86.1 (d), 79.6 (d), 77.9 (d), 74.4 (t), 73.5 (t), 71.9 (t), 62.0 (t), 27.6 (q) ppm. IR (neat): $\tilde{\nu}$ = 3088, 3063, 3023, 2875, 2776, 2403, 2315, 1958, 1881, 1812, 1710 (C=O), 1598, 1493, 1448, 1396, 1353, 1332, 1260, 1217, 1184, 1154, 1087, 1074, 1028, 943, 900, 847, 750, 697, 668, 643, 632, 603 cm^{-1}. HRMS (ESI): calcd. for $C_{46}H_{44}NaO_5$ $[M + Na]^+$ 699.3087; found 699.3088.

2,3,4-Tri-*O*-benzyl-1-deoxy-L-fructose (5): Formic acid (0.66 mL) was added to a solution of **4** (90 mg, 0.13 mmol) in diethyl ether (0.66 mL). The reaction mixture was stirred at room temp. for 2 h. The solution was diluted with diethyl ether and neutralized with $NaHCO_{3(aq.)}$ until the pH was 7. The resulting mixture was washed with water (10 mL×3) and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes 3:7 as eluent to give a yellow oil (55 mg, 95%). *A mixture of anomers in a ratio of 1.4:1 was obtained.* Due to difficulties in ^{1}H and ^{13}C NMR analysis, we can only provide the following data. $[\alpha]_D^{24}$ = +47.29 (c = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.15 (m, 36 H, $H_{major+minor}$), 5.63 (s, 1 H, H_{minor}), 5.02 (d, J = 10.8 Hz, 1.4 H,

H_{major}), 4.80 (d, J = 12.3 Hz, 2.4 H, $H_{major+minor}$), 4.71 (d, J = 10.8 Hz, overlapped with d at 4.69, J = 12.6 Hz, 3.4 H), 4.64–4.56 (m, 4.2 H), 4.52 (d, J = 12.0 Hz, 2 H, H_{minor}), 4.48–4.40 (m, 2.4 H), 4.07–3.88 (m, 3.4 H), 3.87–3.69 (m, overlapped with d at 3.82, J = 7.5 Hz, 8.4 H), 3.40 (d, J = 3.3 Hz, 1 H, H_{minor}), 2.69 (br. s, 1 H, H_{minor}, OH), 1.47 (s, 4.2 H, H_{major}), 1.34 (s, 3 H, H_{minor}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, mixture): δ = 138.4, (s), 138.2 (s), 138.1 (s), 137.3 (s), 137.1 (s), 128.6 (d), 128.5 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.8 (d), 127.6 (d), 97.9 (s, anomeric carbon, major), 97.1 (s, anomeric carbon, minor), 79.8 (d), 79.1 (d), 77.3 (d), 75.8 (t), 74.6 (d), 74.1 (t), 73.4 (t), 72.9 (d), 71.8 (t), 71.6 (d), 71.6 (t), 71.2 (t), 60.8 (t), 57.6 (t), 26.6 (q), 24.3 (q) ppm. IR (neat): $\tilde{\nu}$ = 3443 (OH), 3088, 3064, 3031, 2987, 2877, 2247, 1956, 1879, 1813, 1724, 1606, 1586, 1497, 1454, 1425, 1397, 1373, 1351, 1309, 1259, 1235, 1206, 1177, 1092, 1064, 1027, 948, 910, 876, 838, 815, 697, 648, 617 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{30}NaO_5$ [M + Na]$^+$ 457.1991; found 457.2000.

1-Deoxy-L-fructose: Compound **5** (84.6 mg, 0.19 mmol) and Pd/C (25 wt.-% 21.2 mg) were added to a flask containing 2 mL of EtOH (2.0 mL). The air inside the metal reaction vessel was removed by vacuum and replaced with H_2 gas, with the pressure of the reaction kept at 50 psi. The reaction mixture was stirred at room temp. for 24 h. After TLC analysis indicated that starting material had been consumed completely, the reaction mixture was filtered and concentrated to give a crude product, which was purified by flash chromatography with CH_2Cl_2/MeOH 4:1 as eluent to give a colorless liquid (25.6 mg, 80%). Due to difficulty of ^{1}H and ^{13}C NMR analysis, we can only provide the following data.

Note: Comparison of our ^{1}H and ^{13}C spectra with the literature data (ref.,[7b] spectra obtained from Prof. Fleet and Dr. Wormald, University of Oxford) is shown in the Supporting Information. $[\alpha]_D^{26}$ = +81.43 (c = 0.85, H_2O). Lit.: $[\alpha]_D^{20}$ = +85.5 (c = 1.4, H_2O) was reported in ref.;[8b] for the enantiomer 1-deoxy-D-fructose, $[\alpha]_D^{21}$ = –80.5 (c = 1.0, H_2O) was reported in ref.[7b] HRMS (ESI): calcd. for $C_6H_{12}NaO_5$ [M + Na]$^+$ 187.0583; found 187.0580.

2,3,4,6-*O*-Tetrabenzyl-D-glucitol (7):[12] LAH (0.29 g, 7.55 mmol) was added at 0 °C to a solution of **6** (1.20 g, 2.20 mmol) in THF (14.6 mL). The reaction mixture was stirred for 16 h at room temp. After the reaction was complete by TLC analysis, water (354 μL) was added, 5 min later $NaOH_{(aq.)}$ (15%, 354 μL) was added, and 5 min later further water (709 μL) was added, and the mixture was continuously stirred for another 20 min. A white precipitate formed, and the reaction mixture was then filtered and washed with diethyl ether. The filtrate was concentrated to give a colorless liquid (1.19 g, 95%), which was pure enough for the next step. $[\alpha]_D^{26}$ = +14.55 (c = 3.87, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.17 (m, 20 H), 4.73 (d, J = 11.4 Hz, 2 H), 4.67 (d, J = 10.5 Hz, 1 H), 4.65 (d, J = 13.7 Hz, 1 H), 4.59 (d, J = 13.7 Hz, 1 H), 4.57 (d, J = 10.5 Hz, 1 H), 4.52 (d, J = 11.4 Hz, 2 H), 4.10–4.00 (m, 1 H), 3.91 (dd, J = 6.3, 3.0 Hz, 1 H), 3.85–3.69 (m, 3 H), 3.65 (d, J = 4.8 Hz, 2 H), 3.62–3.51 (m, 1 H), 3.00 (d, J = 5.6 Hz, 1 H, OH), 2.18 (t, J = 5.6 Hz, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1 (s), 138.0 (s), 137.8 (s), 128.4 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.7 (d), 79.5 (d), 79.1 (d), 77.4 (d), 74.5 (t), 73.2 (t), 73.1 (t), 71.1 (t), 70.7 (d), 61.8 (t) ppm. IR (neat): $\tilde{\nu}$ = 3438 (OH), 3089, 3063, 3030, 2874, 2334, 1954, 1878, 1812, 1606, 1586, 1496, 1453, 1425, 1397, 1355, 1308, 1237, 1208, 1086, 1065, 1027, 911, 819, 732, 695, 600 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{39}O_6$ [M + H]$^+$ 543.2747; found 543.2741.

2,3,4,6-*O*-Tetrabenzyl-1-*O*-trityl-D-gluctiol (8):[18] DBU (0.48 mL, 3.18 mmol), a catalytic amount of DMAP (25.9 mg, 0.21 mmol), and TrCl (0.89 g, 3.18 mmol) were added to a solution of **7** (1.15 g, 2.12 mmol) in a co-solvent system (CH_2Cl_2/toluene 2:1, 21.0 mL). The reaction mixture was stirred at 60 °C for 2 d and then worked up by addition of water (20 mL). The resulting mixture was extracted with CH_2Cl_2 (70 mL×3). The combined organic layers was washed with brine (70 mL), dried with $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes 2:8 as eluent to give a pale yellow oil (1.40 g, 84%). $[\alpha]_D^{25}$ = +10.83 (c = 13.84, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.41 (m, 6 H), 7.40–7.19 (m, 27 H), 7.09–7.02 (m, 2 H), 4.72 (d, J = 10.5 Hz, 2 H), 4.66 (d, J = 11.7 Hz, 1 H), 4.60 (d, J = 11.7 Hz, 1 H), 4.52 (d, J = 12.9 Hz, 1 H), 4.48 (d, J = 12.9 Hz, 1 H), 4.40 (d, J = 11.4 Hz, 1 H), 4.18 (d, J = 11.4 Hz, 1 H), 4.10 (t, J = 4.2 Hz, 1 H), 3.94 (br. d, J = 4.2 Hz, 2 H), 3.69–3.55 (m, overlapped with one d at 3.59, J = 3.9 Hz, 3 H), 3.47 (dd, J = 10.5, 3.3 Hz, 1 H), 3.24 (dd, J = 10.3, 5.0 Hz, 1 H), 2.93 (d, J = 3.9 Hz, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9 (s), 138.4 (s), 138.2 (s), 138.1 (s), 128.7 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.5 (d), 127.4 (d), 126.9 (d), 86.7 (d), 79.1 (d), 78.5 (d), 77.6 (d), 74.3 (t), 73.3 (t), 73.1 (t), 73.0 (t), 71.2 (t), 70.7 (d), 63.0 (t) ppm. IR (neat): $\tilde{\nu}$ = 3654, 3571 (OH), 3086, 3059, 3029, 2865, 2315, 2244, 1956, 1877, 1811, 1596, 1491, 1449, 1397, 1352, 1313, 1250, 1211, 1183, 1154, 1065, 1027, 1001, 944, 899, 846, 816, 763, 732, 695, 631 cm^{-1}. HRMS (ESI): calcd. for $C_{53}H_{52}NaO_6$ [M + Na]$^+$ 807.3662; found 807.3656.

1,3,4,5-*O*-Tetrabenzyl-6-*O*-trityl-L-sorbose (9):[18] A solution of DMSO (45 μL, 0.63 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise at –78 °C to a solution of oxalyl chloride (46 μL, 0.53 mmol) in CH_2Cl_2 (0.3 mL) and the reaction mixture was then stirred for 30 min, followed by addition of a solution of **8** (0.16 g, 0.21 mmol) in CH_2Cl_2 (1.2 mL) at the same temperature. The resulting mixture was stirred for another 30 min, then quenched by dropwise addition of Et_3N (0.15 mL, 1.05 mmol) in CH_2Cl_2 (0.3 mL) at –78 °C, and allowed to warm up gradually to room temp. The mixture was diluted with CH_2Cl_2 (30 mL), washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes 15:85 as eluent to give a yellow oil (0.15 g, 94%). $[\alpha]_D^{26}$ = –5.32 (c = 7.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.40 (m, 5 H), 7.38–7.18 (m, 26 H), 7.16–7.11 (m, 2 H), 7.05–7.00 (m, 2 H), 4.65 (d, J = 12.0 Hz, 2 H), 4.56 (d, J = 11.3 Hz, 1 H), 4.44 (d, J = 11.3 Hz, 1 H), 4.36 (d, J = 12.0 Hz, 1 H), 4.30 (d, J = 11.7 Hz, 1 H), 4.27 (d, J = 11.1 Hz, 1 H), 4.19 (dd, J = 6.6, 6.0 Hz, 1 H), 4.14 (d, J = 8.7 Hz, 2 H), 4.01 (d, J = 3.9 Hz, 1 H), 3.97–3.87 (m, overlapped with one d at 3.95, J = 11.4 Hz, 2 H), 3.47 (dd, J = 10.3, 3.6 Hz, 1 H), 3.14 (dd, J = 10.3, 5.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.4 (s, C=O), 143.8 (s), 138.3 (s), 137.8 (s), 137.4 (s), 136.9 (s), 128.7 (d), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.0 (d), 86.7 (s), 82.7 (d), 79.9 (d), 78.7 (d), 74.6 (t), 74.3 (t), 73.6 (t), 73.2 (t), 62.8 (t) ppm. IR (neat): $\tilde{\nu}$ = 3086, 3060, 3030, 2935, 2866, 1957, 1878, 1812, 1730 (C=O), 1597, 1493, 1450, 1397, 1334, 1249, 1211, 1176, 1154, 1154, 1109, 1069, 1046, 1027, 1002, 945, 901, 808, 763, 735, 695, 632 cm^{-1}. HRMS (ESI): calcd. for $C_{53}H_{50}NaO_6$ [M + Na]$^+$ 805.3505; found 805.3500.

1,3,4,5-*O*-Tetrabenzyl-L-sorbose (10):[6] Formic acid (0.35 mL) was added to a solution of **9** (57.4 mg, 0.07 mmol) in diethyl ether (0.35 mL). The reaction mixture was stirred at room temp. for 15 min. The solution was diluted with diethyl ether (10 mL) and then neutralized with $NaHCO_{3(aq.)}$ until the pH was 7. The organic layer was then washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes

25:75 as eluent to give a yellow oil (31 mg, 77%). $[\alpha]_D^{26}$ = –17.33 (*c* = 2.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.22 (m,18 H), 7.20–7.15 (m, 2 H), 4.97 (d, *J* = 10.7 Hz, 1 H), 4.86 (d, *J* = 10.5 Hz, 1 H), 4.83 (d, *J* = 10.5 Hz, 1 H), 4.72 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.58–4.44 (m, 3 H), 3.95 (t, *J* = 9.3 Hz, 1 H), 3.81–3.69 (m,2 H), 3.69–3.55 (m, 1 H), 3.48 (d, *J* = 9.3 Hz, 1 H), 3.40 (d, *J* = 9.3 Hz, 1 H), 3.30 (d, *J* = 11.7 Hz, overlapped with s at 3.28, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6 (s), 138.2 (s), 137.7 (s), 137.3 (s), 128.4 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.6 (d), 97.4 (s, anomeric C), 82.7 (d), 78.6 (d), 78.4 (d), 75.7 (t), 75.6 (t), 73.7 (t), 71.8 (t), 61.0 (t) ppm. IR (neat): $\tilde{\nu}$ = 3429 (OH), 3088, 3063, 3030, 2873, 1953, 1877, 1812, 1725, 1605, 1586, 1542, 1496, 1453, 1361, 1331, 1308, 1253, 1206, 1157, 1072, 1027, 902, 842, 818, 734, 695, 605 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{36}KO_6$ $[M + K]^+$ 579.2149; found 579.2123.

L-Sorbose: Compound **10** (0.15 g, 0.28 mmol) and Pd/C (25 wt.-% 38.0 mg) were added to a flask containing 2.8 mL of EtOH (2.8 mL). The air inside the metal reaction vessel was removed by vacuum and replaced with H_2 gas, with the pressure of the reaction kept at 50 psi. The reaction mixture was stirred at room temp. for 24 h. After TLC analysis indicated that starting material had been consumed completely, the reaction mixture was filtered, and then concentrated to give a white solid (48 mg, 95%). Due to difficulty of ^1H and ^{13}C NMR analysis, we can only provide the following data.

Note: Comparisons of our ^1H and ^{13}C spectra with reference spectra (sample obtained from TCI Chemicals) are shown in the Supporting Information, m.p. 164.1–166.2 °C. $[\alpha]_D^{26}$ = –37.69 (*c* = 1.53, H_2O). Lit.: $[\alpha]_D^{27}$ = –42.8 (*c* = 4, H_2O) and $[\alpha]_D^{19}$ = –42.9 ± 2 (*c* = 1.6, H_2O) were reported in ref.[10a] and ref.[10b] HRMS (ESI): calcd. for $C_6H_{12}NaO_6$ $[M + Na]^+$ 203.0532; found 203.0529.

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[19] Specific rotation of L-sorbose obtained by our methodology is $[\alpha]_D^{24}$ = –37.69 (*c* = 1.53, H_2O). $[\alpha]_D^{27}$ = –42.8 (*c* = 4, H_2O) and $[\alpha]_D^{19}$ = –42.9 ± 2 (*c* = 1.6, H_2O) are reported in ref.[10a,10b].

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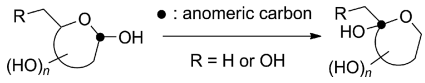
Unusual Sugars

Two rare sugars – 1-deoxy-L-fructose and L-sorbose – were synthesized from inexpensive starting materials by a carbonyl translocation method.



Keywords: Synthetic methods / Carbohydrates / Deoxysugars / Rare sugars

