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Synthesis of 3-Deoxy-L-ketohexoses through Group Transfer

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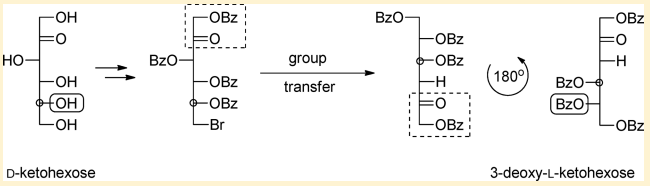
Supporting Information

ABSTRACT: A practical method for the synthesis of 3-deoxy-L-ketohexoses is described. Both D- and L-ketohexoses can be transformed into rare 3-deoxy-L-ketohexoses in six steps through a group transfer process. The key step involves a radical cyclized onto a carbonyl group, followed by a fragmentation reaction, eventually resulting in the group transfer of an α-oxy carbonyl group. The process involves tin-free and environmentally benign radical conditions (TTMSS/AIBN/toluene). The acyclic form of 3-deoxy-L-fructose was prepared in only three steps from the inexpensive starting material, D-fructose. A further modification by preparing a dithioacetal derivative was accomplished, which could serve as a convenient sugar synthon for further synthetic applications. Removal of the dithioacetal protecting group results in the formation of the rare 3-deoxy-L-fructose in a total yield of 42%. This methodology could be further extended to the synthesis of other deoxy-L-ketohesoses, such as 3-deoxy-L-sorbose.

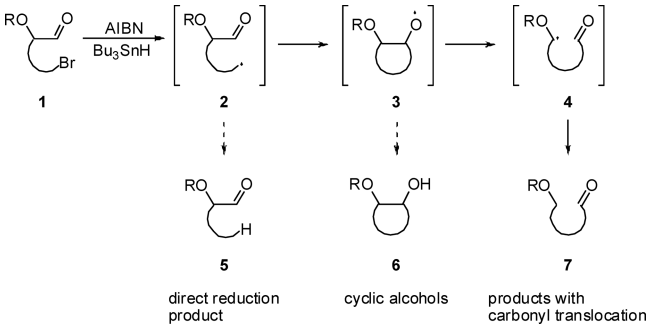


INTRODUCTION

Rare deoxy-L-sugars are an important class of carbohydrates, which are found in many important natural products.[1] Deoxy-L-sugars are involved in a wide range of research areas, ranging from nutritional science to the pharmaceutical industry.[2] They also serve as key building blocks for the preparation of antitumor and antiviral agents,[3] as well as L-DNA and L-nucleosides.[4] Due to their limited availability in nature and an increasing demand in related research, several chemical[5] and biochemical[6] methods for the synthesis of deoxy-L-sugars have been explored. Among these efforts, the synthesis of deoxy-L-ketohexoses has been less studied, compared to the synthesis of deoxy-L-aldohexoses. Currently available methods for the chemical synthesis of L-ketohexoses from inexpensive D-sugars as starting materials largely rely on the isomerization/conversion of an aldohexose, the chain extension of an aldopentose, or OH group inversion from another ketohexose.[5] Regarding deoxy-L-ketohexoses, an efficient method for the chemical synthesis of deoxy-L-ketohexoses directly from inexpensive D-sugars as starting materials would be interesting for organic chemists. To achieve this, it would be necessary to first convert the sugar from the D configuration to the L configuration, followed by selective deoxygenation of the specific hydroxyl group. However, current available methods are tedious and time-consuming. To the best of our knowledge, a practical method for the synthesis of 3-deoxy-L-ketohexoses has not been reported.

Radical cyclization reactions of carbonyl compounds represent one of the most efficient methods for the construction of ring systems under relatively neutral conditions.[7] Regarding the formation of ring systems, several methods have been developed to produce the desired cyclic products.[8] Positioned with an α-oxy group (compound **1**), the radical **2** cyclizes onto the carbonyl group to give the resulting alkoxy radical **3**, as shown in Scheme 1. Depending on the reaction conditions, this alkoxy radical **3** either abstracts a hydrogen atom to give cyclic alcohols **6** or undergoes fragmentation to afford carbonyl translocation products **7**. Several attempts have been made to exclusively produce either cyclic alcohols or the products with carbonyl translocation.[9] Among these previous reports, it was not feasible to obtain only carbonyl translocation products in acyclic systems. However, a novel and highly efficient radical process involving only carbonyl translocation was developed recently in this laboratory.[10] The assistance of a geminal dialkyl effect or a conformationally rigid system was not required when a benzoyl group was used as the protecting group, and the product distribution in radical cyclization reactions of α-oxy carbonyl compounds was dramatically changed. In our model studies, the substrate is assisted by positioning a benzoyl group α to the

Scheme 1



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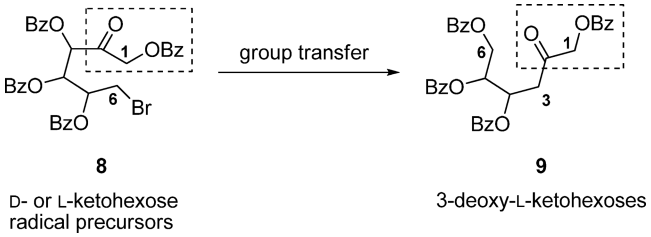
carbonyl group, and the radical cyclization process leads exclusively to the formation of carbonyl translocation products.[11]

Synthetic Plan. We report herein on the synthesis of 3-deoxy-L-ketohexoses through a group transfer process, as shown in Scheme 2. The key step involves a group transfer process of an α-oxy carbonyl group, which is initiated under environmentally benign radical conditions. Under this radical process, the α-oxy carbonyl group is transferred from the head to the tail of this acyclic carbohydrate system **8** in a single synthetic step, eventually resulting in the formation of 3-deoxy-L-ketohexoses **9**. This synthetic methodology is unique and sufficiently practical that it could be used to transform both D- and L-ketohexoses into 3-deoxy-L-ketohexoses.

Scheme 2. Synthetic Plan

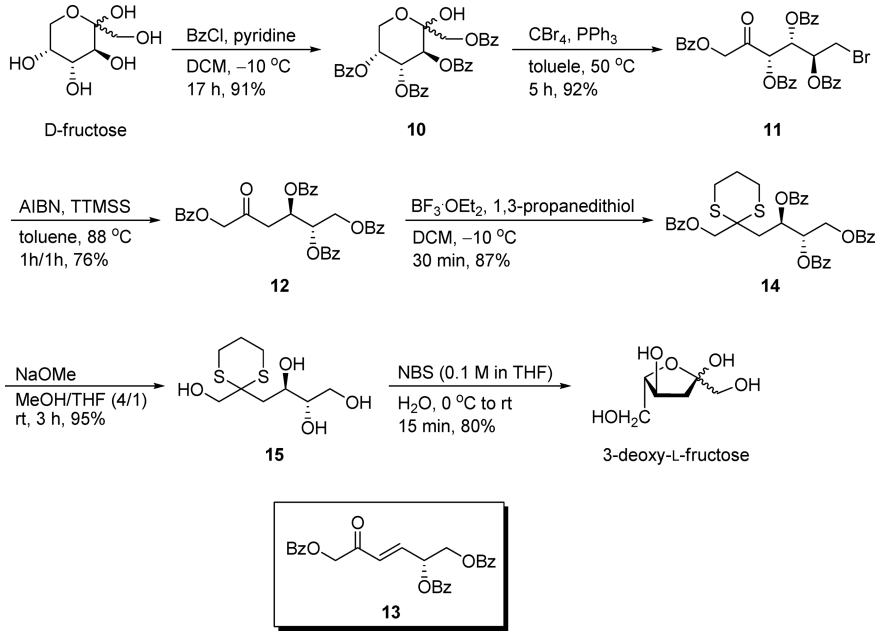


RESULTS AND DISCUSSION

The methodology for preparing 3-deoxy-L-fructose is shown in Scheme 3. Starting from the inexpensive D-fructose, selective benzoylation at a low temperature (−10 °C) resulted in the formation of the tetrabenzoate **10** with a free anomeric hydroxyl group.[12] Bromination using carbon tetrabromide (CBr_4) and triphenylphosphine (PPh_3) successfully afforded the radical precursor **11** in just two synthetic steps. Initiated under environmentally benign radical conditions (TTMSS/AIBN/toluene),[13] a group transfer process was performed to give the benzoyl-protected 3-deoxy-L-fructose **12** in 76% yield without column chromatography. To verify that this product is indeed a 3-deoxy-L-fructose derivative, the stereochemistry of compound **12** was confirmed by its X-ray crystal structure. The obtained crystal structure indicated that the 3-deoxy-L-fructose derivative **12** with a (4*R*,5*S*) stereochemistry was indeed produced. To the best of our knowledge, this is one of the most efficient methods currently available for preparing deoxy-L-sugars (three synthetic steps). Attempts to directly remove the benzoyl protecting groups to give the free 3-deoxy-L-fructose were not successful, and an elimination reaction to release benzoic acid was observed to give a conjugate side product **13**. However, to further extend this methodology for further application, treatment of this key intermediate **12** with 1,3-propanedithiol (PDT) in the presence of boron triflouride diethyl etherate ($BF_3{\cdot}OEt_2$)[14] gave the dithioacetal **14**. Successful removal of the benzoyl protecting groups generated compound **15**, which is an important building block for sugar dithiolacetal chemistry.[15] The dithiane protecting group was removed by treatment with NBS in THF/H_2O solution[16] to give the free 3-deoxy-L-fructose in six steps in a total yield of 42%. This synthetic approach represents one of the most efficient methods for the synthesis of rare deoxy-L-sugars and represents a practical procedure for the synthesis of 3-deoxy-L-ketohexoses.[17] Furthermore, this synthetic approach is sufficiently practical and concise that it has the potential for use in the commercial production of 3-deoxy-L-ketohexoses. Since 3-deoxy-D-fructose (3-DF) is a metabolite found in human plasma and urine from diabetes patients,[18] its L-enantiomer would be useful in related research. Furthermore, with this synthetic approach in hand and an appropriate structural design, the key building block **15** could be used as a starting material for the preparation of potential inhibitors of the enzyme fructose bis-phosphate aldolase (FBA).[19]

To further extend this methodology to the synthesis of other 3-deoxy-L-ketohexoses, the chemical transformation of an L-ketohexose into a 3-deoxy-L-ketohexose was also explored, as shown in Scheme 4. Under similar conditions, L-sorbose was transformed into the radical precursor **17** in two synthetic

Scheme 3. From D-Fructose to 3-Deoxy-L-fructose



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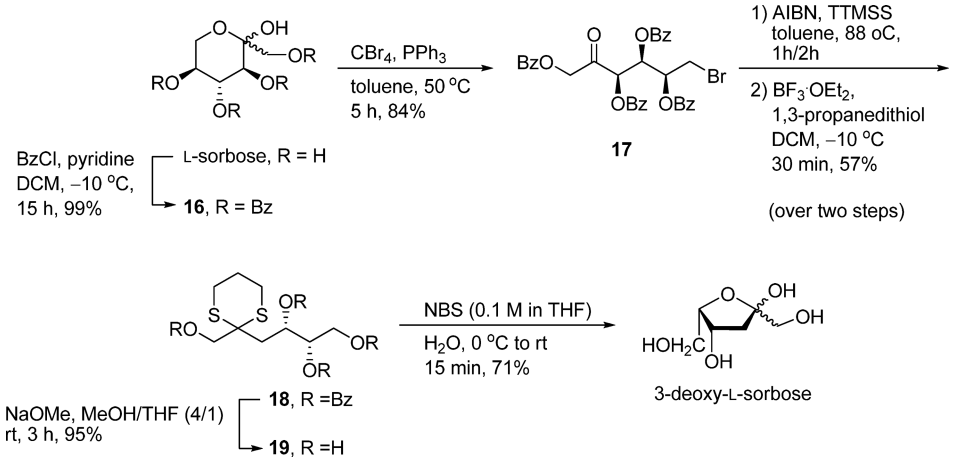
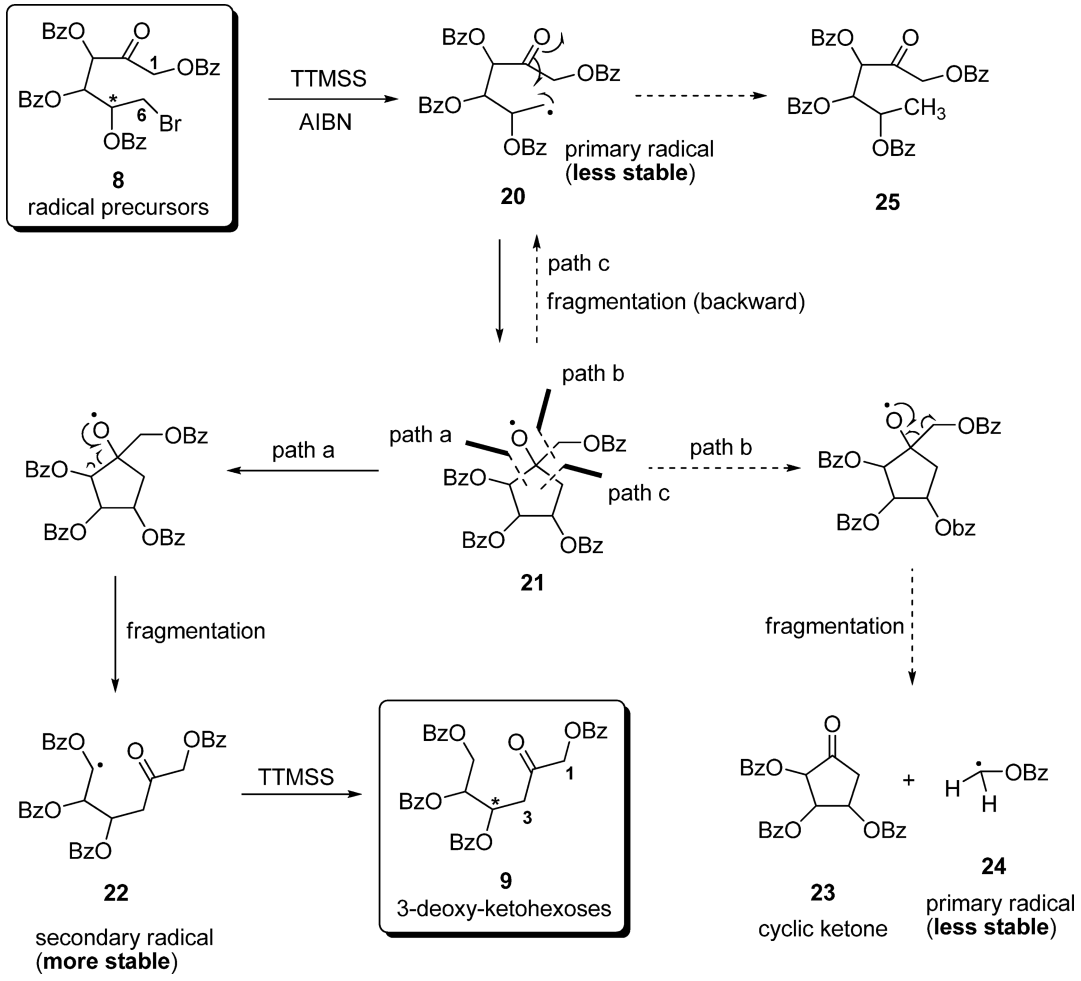
Scheme 4. From L-Sorbose to 3-Deoxy-L-sorbose



Scheme 5. Proposed Mechanism for the Group Transfer Process



steps. To shorten the overall process, the radical-initiated group transfer was followed by direct dithioacetal formation, successfully resulting in the formation of compound **18**. Removal of the benzoyl protecting groups afforded the dithiane sugar synthon **19**. Since L-sorbose is a crucial starting material for the production of vitamin C[20] and a key precursor for the synthesis of a variety of potent glycosidase inhibitors,[21] this sugar synthon **19** could be a building block for synthetic applications in numerous research areas. To generate 3-deoxy-L-sorbose, compound **19** was treated with NBS in THF/H_2O solution[16] to give the desired product in five steps in a total yield of 32%. To the best of our knowledge, the synthesis of 3-deoxy-L-sorbose was successfully developed.

A proposed mechanism for this group transfer process is shown in Scheme 5. Tris(trimethylsilyl)silyl radical,[13] generated from TTMSS and AIBN, reacts with the radical precursor **8** to give a primary alkyl radical **20**. This primary alkyl radical **20** cyclizes onto the carbonyl group to give a cycloalkoxy radical

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21. To regenerate the carbonyl group, there are three options (paths a, b, and c) for the β-fragmentation process of this cycloalkoxy radical **21**. Through path a, the β-fragmentation reaction occurs to give an α-oxy secondary alkyl radical **22** (more stable). Upon the abstraction of a hydrogen atom from TTMSS, 3-deoxy-L-ketohexoses are produced and the TTMSS radical is regenerated to continue the catalytic cycle. However, in path b, the β-fragmentation reaction would occur to generate a cyclic ketone **23** and an α-oxy primary alkyl radical **24** (less stable). In the path c, the reaction would go backward (or fragment) to give the original primary alkyl radical **20** (less stable). Upon the abstraction of a hydrogen atom from TTMSS, the direction reduction product **25** would be obtained, which was not observed in the reaction mixtures. Due to the stability of these radicals, we conclude that the β-fragmentation reaction of the cycloalkoxy radical occurs exclusively though path a to give the 3-deoxy-L-ketohexoses upon hydrogen abstraction, as expected.

CONCLUSIONS

The synthesis of 3-deoxy-L-ketohexoses was successfully developed. Through a radical group transfer process, both D- and L-ketohexoses can be transformed into rare 3-deoxy-L-ketohexoses in six steps. This process involves a radical cyclization onto the carbonyl group, followed by a fragmentation step, and results in the group transfer of an α-oxy carbonyl group. This novel process was initiated by tin-free and environmentally benign radical conditions (TTMSS/AIBN/toluene). The acyclic and benzoyl-protected 3-deoxy-L-fructose can be prepared in three steps from the inexpensive starting material, D-fructose. A further modification could be made to prepare the dithioacetal derivative, which could serve as a convenient sugar synthon for further application. Removal of the dithioacetal protecting group affords the rare 3-deoxy-L-fructose in a total yield of 42%. This synthetic methodology could be further extended to the synthesis of other deoxy-L-ketohesoses, such as 3-deoxy-L-sorbose (five steps from L-sorbose, total yield of 32%). This novel process is concise and has the potential for use in the commercial production of 3-deoxy-L-ketohexoses from both D- and L-ketohexoses. With this synthetic methodology in hand, the development of potential inhibitors for various glycosidases is currently underway.

EXPERIMENTAL SECTION

General. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 MHz machine. COSY spectra were recorded on a 500 MHz machine. The NMR spectra were recorded in $CDCl_3$ or CD_3OD. Chloroform (δ = 7.26 ppm in ^{1}H NMR; δ = 77.0 ppm in ^{13}C NMR) and methanol (δ = 3.31 ppm in ^{1}H NMR; δ = 49.00 ppm in ^{13}C NMR) were used as internal standards, respectively. Splitting patterns were reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constant (J) was reported in Hz. IR were recorded on a FT-IR spectrometer and reported in cm^{-1}. High-resolution mass spectrometry (HRMS) was recorded on a LCMS-IT-TOF spectrometer (ESI-MS). Optical rotations were measured on a digital polarimeter. Crystallographic data were obtained from a single-crystal XRD. Elementary analysis (EA) was recorded on a cube spectrometer. TLC (Merck Art. 60 F_{254}, 0.25 mm) precoated sheet was used. The 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 was distilled by refluxing it over traces of sodium metal using benzophenone as indicator under N_2. Toluene was distilled by refluxing it over traces of sodium metal under N_2. Dichloromethane and pyridine were dried over CaH_2 and then distilled. Methanol was dried over magnesium/iodine and then distilled. Benzoyl chloride and $BF_3{\cdot}OEt_2$ were distilled before use. The toluene used for radical cyclizations was deoxygenated by passing a gentle stream of argon through for 30 min before use. All reactions were performed under a blanket of N_2 or Ar.

1,3,4,5-*O*-Tetrabenzoyl-D-fructopyranose (10). To a solution of D-fructose (1.00 g, 5.55 mmol) and pyridine (3.30 mL, 41.2 mmol) in dry CH_2Cl_2 (6.90 mL) was added dropwise benzoyl chloride (2.6 mL, 22.5 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 17 h and then worked up by addition of water. The resulting mixture was diluted with CH_2Cl_2 (200 mL), washed with 0.1 N HCl (40 mL), saturated $NaHCO_{3(aq)}$ (40 mL), water (40 mL), and brine (40 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes =35/65 to give the desired product **10** (3.01 g, 91%) as a colorless oil. $[\alpha]^{26}_D$ − 176.48 (c = 1.69, $CHCl_3$); IR (neat) 3424 (OH), 1723 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (t, J = 6.5 Hz, 4H), 7.98 (d, J = 7.3 Hz, 2H), 7.83 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.44−7.30 (m, 6H), 7.30−7.20 (m, 4H), 6.25 (d, J = 10.5 Hz, 1H, H_3), 5.99 (dd, J = 10.5, 3.4 Hz, 1H, H_4), 5.79 (d, J = 1.5 Hz, 1H, H_5), 4.63 (d, J = 11.7 Hz, 1H, H_{1a}), 4.49 (d, J = 11.7 Hz, 1H, H_{1b}), 4.44 (d, J = 13.0 Hz, 1H, H_{6a}), 4.04 (dd, J = 13.0, 1.5 Hz, 1H, H_{6b}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 165.8 (C), 165.7 (C × 2), 133.3 (CH), 133.2 (CH), 133.1 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH × 2), 128.2 (CH), 96.8 (C, anomeric), 70.1 (CH), 69.4 (CH), 68.4 (CH), 66.1 (CH_2), 61.6 (CH_2); HRMS (ESI$^+$): m/z calcd for $C_{34}H_{28}O_{10}K$ $[M+K]^+$: 635.1314; found 635.1313, $C_{34}H_{28}O_{10}Na$ $[M + Na]^+$: 619.1580; found 619.1564; Anal. Calcd for $C_{34}H_{28}O_{10}$: C, 68.45; H, 4.73; found: C, 68.54; H, 4.61.

(3*S*,4*S*,5*S*)-1,3,4,5-*O*-Tetrabenzoyl-6-bromo-6-deoxy-D-fructose (11). To a solution of tertiary alcohol **10** (2.21 g, 3.70 mmol) and triphenylphosphine (1.70 g, 6.47 mmol) in 25 mL of dry toluene was added a solution of tetrabromomethane (1.84 g, 5.54 mmol) in 12 mL of dry toluene in one portion. The reaction mixture was stirred at 50 °C for 5 h and then concentrated to dryness in vacuum. The residue was dissolved in EtOAc (200 mL) and then washed with water (60 mL × 3) and brine (60 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 35/65 to give the desired product **11** (2.24 g, 92%) as a pale yellow oil: $[\alpha]_D^{26}$ +33.33 (c = 1.77, $CHCl_3$); IR (neat) 1725 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20−8.03 (m, 6H), 7.91 (d, J = 7.2 Hz, 2H), 7.67−7.40 (m, 10H), 7.40−7.28 (m, 2H), 6.35 (dd, J = 8.4, 2.1 Hz, 1H), 6.00 (d, J = 2.1 Hz, 1H), 5.84 (dt, J = 7.9, 4.0 Hz, 1H), 5.24 (d, J = 17.1 Hz, 1H, H_{1a}, AB), 5.16 (d, J = 17.1 Hz, 1H, H_{1b}, AB), 3.92 (dd, J = 11.7, 3.3 Hz, 1H, H_{6a}), 3.78 (dd, J = 11.7, 4.2 Hz, 1H, H_{6b}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9 (C), 165.3 (C), 165.2 (C), 165.1 (C), 165.0 (C), 133.9 (CH), 133.8 (CH), 133.6 (CH), 133.5 (CH), 130.0 (CH × 2), 129.8 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 74.2 (CH), 70.6 (CH), 69.6 (CH), 67.5 (CH_2), 31.3 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{34}H_{28}{}^{79}BrO_9$ $[M + H]^+$ 659.0917; found 659.0903, $C_{34}H_{28}{}^{81}BrO_9$ $[M + H]^+$ 661.0896; found 661.0891. Anal. Calcd for $C_{34}H_{27}BrO_9$: C, 61.92; H, 4.13. Found: C, 61.95; H, 4.35.

(4*R*,5*S*)-1,4,5,6-*O*-Tetrabenzoyl-3-deoxy-L-fructose (12). To a refluxed solution of the radical precursor **11** (2.09 g, 3.16 mmol) in 53 mL of toluene at 88 °C was added a solution of AIBN (0.10 g, 0.63 mmol) and TTMSS (1.50 mL, 4.75 mmol) in 53 mL of toluene over 1 h via a syringe pump. The resulting solution was continuously stirred at the same temperature for another 1 h. The solution was then cooled and directly concentrated to give a crude residue, which was washed by ether. The filtrate was removed, and the precipitate was collected to give the desired product **12** (1.40 g, 76%) as a white solid. No column chromatography or extraction was needed: mp 138.5−141.0 °C; $[\alpha]_D^{26}$ −4.27 (c = 0.45, $CHCl_3$); IR (neat) 1727 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08−7.92 (m, 8H), 7.60−7.48 (m, 4H), 7.44−7.32 (m, 8H), 6.06 (q, J = 5.8 Hz, 1H, H_4), 5.84 (q, J = 5.0 Hz, 1H, H_5), 4.91 (d, J = 16.8 Hz, 1H, H_{1a}), 4.86 (d, J = 16.8 Hz, 1H, H_{1b}),

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4.78 (dd, J = 12.2, 3.8 Hz, 2H, H_{6a}), 4.58 (dd, J = 12.2, 6.1 Hz, 2H, H_{6b}), 3.18 (dd, J = 17.0, 7.0 Hz, 1H, H_{3a}), 3.13 (dd, J = 17.0, 5.0 Hz, 1H, H_{3b}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1 (C), 166.0 (C), 165.6 (C), 165.4 (C), 165.3 (C), 133.5 (CH), 133.4 (CH), 133.2 (CH), 129.8 (CH), 129.7 (CH), 129.3 (CH), 129.2 (CH × 2), 128.9 (CH), 128.4 (CH), 72.0 (CH), 68.5 (CH_2), 68.4 (CH), 62.6 (CH_2), 40.0 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{34}H_{29}O_9$ $[M + H]^+$ 581.1812; found 581.1808. Anal. Calcd for $C_{34}H_{28}O_9$: C, 70.34; H, 4.86. Found: C, 70.63; H, 4.69.

(3*E*,5*R*)-1,5,6-*O*-Tribenzoylhex-3-en-2-one (13). To a refluxing solution of the radical precursor **11** (0.20 g, 0.30 mmol) in 5 mL of toluene at 88 °C was added a solution of AIBN (9.96 mg, 0.06 mmol) and TTMSS (0.14 mL, 0.45 mmol) in 5 mL of toluene over 1 h via a syringe pump. The resulting solution was continuously stirred at the same temperature for another 1 h. The solution was then cooled and directly concentrated to give a crude residue, which was dissolved in THF (3.1 mL). To this THF solution was added Et_3N (90 μL), and the resulting solution was stirred at rt for 1 h. After the reaction was complete, as evidenced by TLC analysis, the mixture was concentrated to give a crude product, which was purified by flash chromatography with EtOAc/hexanes = 25/75 as the eluent to give the desired product **13** (0.17 g, 95%) as a colorless oil: $[\alpha]_D^{26}$ −148.25 (c = 1.29, $CHCl_3$); IR (neat) 1717 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12−7.97 (m, 6H), 7.63−7.52 (m, 3H), 7.49−7.37 (m, 6H), 7.10 (dd, J = 16.1, 4.7 Hz, 1H, H_4), 6.62 (dd, J = 16.1, 1.5 Hz, 1H, H_3), 6.15−6.06 (m, 1H, H_5), 5.07 (s, 2H, H_1), 4.70 (dd, J = 11.7, 4.1 Hz, 1H, H_{6a}), 4.59 (dd, J = 11.7, 6.3 Hz, 1H, H_{6b}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8 (C), 165.9 (C), 165.7 (C), 165.2 (C), 140.8 (CH), 133.5 (CH), 133.4 (CH), 133.3 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 126.4 (CH), 70.8 (CH), 67.7 (CH_2), 64.3 (CH_2); HRMS (EI$^+$) m/z calcd for $C_{27}H_{22}O_7$ $[M]^+$ 458.1366; found 458.1365. Anal. Calcd for $C_{27}H_{22}O_7$: C, 70.73; H, 4.84. Found: C, 70.80; H, 4.73.

(4*R*,5*S*)-1,4,5,6-*O*-Tetrabenzoyl-3-deoxy-L-fructose Propane-1,3-diyl Dithioacetal (14). To a solution of **12** (0.65 g, 1.11 mmol) in dry CH_2Cl_2 (2.20 mL) were added 1,3-propanedithiol (0.12 mL, 1.17 mmol) and $BF_3{\cdot}OEt_2$ (1.10 mL, 8.89 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 30 min and then worked up by addition of saturated $NaHCO_{3(aq)}$. The solution was diluted with CH_2Cl_2 (120 mL) and then neutralized with saturated $NaHCO_{3(aq)}$ until the pH value was 7. The organic layer was then washed with water (40 mL × 3) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 3/7 to give the desired product **14** (0.65 g, 87%) as a pale yellow oil: $[\alpha]_D^{26}$ −8.50 (c = 3.46, $CHCl_3$); IR (neat) 1718 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11−7.96 (m, 8H), 7.60−7.47 (m, 4H), 7.46−7.30 (m, 8H), 6.19−6.13 (m, 1H, H_4), 5.83 (dt, J = 7.8, 3.8 Hz, 1H, H_5), 4.87−4.72 (m, 3H, H_{1a}, H_{1b}, H_{6a}), 4.66 (dd, J = 12.0, 6.9 Hz, 1H, H_{6b}), 3.06 (td, J = 12.0, 3.9 Hz, 2H, H_{3a}, H_{3b}), 2.77−2.48 (m, overlapped with dd at 2.70, J = 15.6, 8.7 Hz, 4H), 2.12−1.97 (m, 1H), 1.92−1.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 165.7 (C), 165.5 (C), 165.4 (C), 133.2 (CH), 133.1 (CH × 2), 129.8 (CH), 129.7 (CH × 2), 129.4 (C × 2), 128.3 (CH), 73.0 (CH), 69.1 (CH), 64.4 (CH_2), 62.5 (CH_2), 50.5 (C), 39.0 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 24.3 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{37}H_{34}O_8S_2$ $[M + Na]^+$ 693.1587; found 693.1576. Anal. Calcd for $C_{37}H_{34}O_8S_2$: C, 66.25; H, 5.11; S, 9.56. Found: C, 65.93; H, 4.92; S, 9.51.

3-Deoxy-L-fructose Propane-1,3-diyl Dithioacetal (15). To a solution of compound **14** (0.52 g, 0.77 mmol) in a cosolvent system (THF/MeOH = 1/4, 7.5 mL) was added NaOMe (0.17 g, 3.07 mmol). The resulting mixture was stirred at rt for 3 h. To the reaction mixture was added acetic acid to neutralize the solution until a pH value was 7 and then directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of CH_2Cl_2/MeOH = 8/1 to give the desired product **15** (0.19 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ +18.23 (c = 1.39, CH_3OH); IR (neat) 3320 (OH) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 3.94 (dd, J = 6.3, 1.8 Hz, 1H, H_5), 3.93 (d, J = 12.0 Hz, 1H, H_{1a}), 3.77 (d, J = 12.0 Hz, 1H, H_{1b}), 3.71 (dd, J = 11.1, 3.9 Hz, 1H, H_{3a}), 3.57 (dd, J = 11.1, 6.5 Hz, 1H, H_{3b}), 3.44 (td, J = 6.3, 3.9 Hz, 1H, H_4), 3.01−2.82 (m, 2H), 2.79−2.65 (m, 2H), 2.41 (dd, J = 15.3, 0.8 Hz, 1H, H_{6a}), 2.08−1.77 (m, overlapped with dd at 1.83, J = 15.3, 9.3 Hz, H_{6b}, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 76.4 (CH), 70.0 (CH), 66.8 (CH_2), 64.6 (CH_2), 54.4 (C), 43.1 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 26.4 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_9H_{18}O_4NaS_2$ $[M + Na]^+$ 277.0539; found 277.0538. Anal. Calcd for $C_9H_{18}O_4S_2$: C, 42.50; H, 7.13; S, 25.21. Found: C, 42.13; H, 6.85; S, 23.38.

3-Deoxy-L-fructose. To a solution of compound **15** (0.12 g, 0.49 mmol) in water (25 mL) was added dropwise a solution of *N*-bromosuccinide (0.52 g, 2.94 mmol) in THF (29 mL) at 0 °C until the yellow color remained. After being stirred at rt for 15 min, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (60 mL × 4). The pH value of the aqueous phase was adjusted to 7 with Amberlyst A-26 ion-exchange resin (OH^- form). The solution was filtered, and water was removed by lyophilization to give a crude product, which was purified by flash chromatography with the eluent of CH_2Cl_2/MeOH = 4/1 to give the desired product (64 mg, 80%) as a pale yellow oil: $[\alpha]_D^{23}$ +40.61 (c = 0.13, H_2O); the specific rotation of 3-deoxy-D-fructose is $[\alpha]_D$ −43.8 (2 min) to −40.0 (40 min) (c = 1.6, H_2O);[17a] $[\alpha]_D^{24}$ −69 (4 min) to −43.5 (40 min) (c = 1.0, H_2O);[17b] $[\alpha]_D^{21}$ −70.1 (3 min) to −42.5 (40 min) (c = 1.0, H_2O);[17c] $[\alpha]_D^{25}$ −41.0 (c = 1.0, H_2O);[17d] $[\alpha]_D^{23}$ −44 (c = 1.0, H_2O);[17e] $[\alpha]_D^{23}$ −48 (c = 4.2, H_2O);[17f] ^{1}H NMR (300 MHz, CD_3OD) δ 4.62 (br s), 4.37 (td, J = 6.8, 5.1 Hz), 4.30 (d, J = 3.3 Hz), 4.22 (dt, J = 7.8, 4.6 Hz), 4.15−3.98 (m), 3.98−3.86 (m), 3.78−3.36 (m), 2.75 (dd, J = 15.8, 4.2 Hz), 2.61 (dd, J = 15.8, 8.9 Hz), 2.44 (dd, J = 13.5, 7.5 Hz), 2.17 (dd, J = 6.9, 1.8 Hz), 2.01 (dd, J = 14.4, 3.9 Hz), 1.96 (s), 1.94−1.84 (m), 1.71 (dd, J = 12.6, 5.1 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 211.6 (C), 107.1 (C), 106.9 (C), 98.6 (C), 97.6 (C), 88.5 (CH), 87.4 (CH), 76.1 (CH), 73.0 (CH), 72.9 (CH), 69.8 (CH), 69.7 (CH_2), 69.6 (CH_2), 69.3 (CH × 2), 68.6 (CH_2), 68.0 (CH), 67.4 (CH_2), 67.0 (CH_2), 66.8 (CH), 65.3 (CH_2), 64.5 (CH_2), 64.4 (CH_2), 63.1 (CH_2), 60.6 (CH_2), 43.7 (CH_2), 43.4 (CH_2), 43.3 (CH_2), 36.2 (CH_2), 34.3 (CH_2); HRMS (FAB$^+$) m/z calcd for $C_6H_{12}O_5$ $[M]^+$ 164.0685; found 164.0682.

1,3,4,5-*O*-Tetrabenzoyl-L-sorbopyranose (16). To a solution of L-sorbose (1.00 g, 5.55 mmol) and pyridine (3.30 mL, 41.2 mmol) in dry CH_2Cl_2 (6.90 mL) was added dropwise benzoyl chloride (2.6 mL, 22.5 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 15 h and then worked up by addition of water. The resulting mixture was diluted with CH_2Cl_2 (200 mL), washed with 0.1 N HCl (40 mL), saturated $NaHCO_{3(aq)}$ (40 mL), water (40 mL), and brine (40 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 3/7 to 35/65 to give the desired product **16** (3.28 g, 99%) as a colorless oil: $[\alpha]_D^{26}$ +9.20 (c = 0.34, $CHCl_3$); IR (neat) 3430 (OH), 1727 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02−7.96 (m, 6H), 7.89 (dd, J = 8.2, 1.2 Hz, 2H), 7.54−7.46 (m, 2H), 7.44−7.36 (m, 5H), 7.35−7.22 (m, 5H), 6.32 (t, J = 9.9 Hz, 1H, H_4), 5.80 (d, J = 10.0 Hz, 1H, H_3), 5.50 (td, J = 9.9, 6.4 Hz, 1H, H_5), 4.68 (br s, 1H, OH), 4.58 (d, J = 1.0 Hz, 2H, H_1), 4.26−4.14 (m, 2H, H_6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 165.8 (C), 165.6 (C × 2), 133.4 (CH), 133.1 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH × 2), 128.4 (CH), 128.3 (CH × 2), 96.1 (C, anomeric), 71.7 (CH), 70.8 (CH), 70.3 (CH), 67.3 (CH_2), 59.8 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{34}H_{28}O_{10}Na$ $[M + Na]^+$ 619.1575; found 619.1567. Anal. Calcd for $C_{34}H_{28}O_{10}$: C, 68.45; H, 4.73. Found: C, 68.81; H, 4.64.

(3*S*,4*S*,5*R*)-1,3,4,5-*O*-Tetrabenzoyl-6-bromo-6-deoxy-L-sorbose (17). To a solution of tertiary alcohol **16** (3.02 g, 5.05 mmol) and triphenylphosphine (2.32 g, 8.84 mmol) in 35 mL of dry toluene was added a solution of tetrabromomethane (2.51 g, 7.58 mmol) in 15 mL of dry toluene in one portion. The reaction mixture was stirred at 50 °C for 5 h and then concentrated to dryness in vacuum. The residue was dissolved in EtOAc (240 mL) and then washed with water (80 mL × 3) and brine (80 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 3/7 to give the desired product **17** (2.79 g, 84%) as a pale yellow oil: $[\alpha]_D^{26}$

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+26.06 (c = 2.69, $CHCl_3$); IR (neat) 1725 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10−7.92 (m, 8H), 7.63−7.48 (m, 4H), 7.48−7.31 (m, 8H), 6.32 (t, J = 4.8 Hz, 1H), 6.00 (d, J = 4.2 Hz, 1H), 5.81 (q, J = 5.3 Hz, 1H), 5.21 (d, J = 17.4 Hz, 1H, H_{1a}), 5.14 (d, J = 17.1 Hz, 1H, H_{1b}), 3.76 (dd, J = 10.8, 5.0 Hz, 1H, H_{6a}), 3.71 (dd, J = 10.8, 4.7 Hz, 1H, H_{6b}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3 (C), 165.4 (C), 165.3 (C × 2), 165.2 (C), 134.0 (CH), 133.7 (CH), 133.5 (CH), 133.4 (CH), 130.1 (CH), 129.9 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 74.1(CH), 71.1 (CH), 70.7 (CH), 67.0 (CH_2), 29.5 (CH_2); HRMS (ESI^+) m/z calcd for $C_{34}H_{28}{}^{79}BrO_9$ $[M + H]^+$ 659.0917; found 659.0911, $C_{34}H_{28}{}^{81}BrO_9$ $[M + H]^+$ 661.0896; found 661.0895. Anal. Calcd for $C_{34}H_{27}BrO_9$: C, 61.92; H, 4.13. Found: C, 61.91; H, 4.40.

(4*S*,5*S*)-1,4,5,6-*O*-Tetrabenzoyl-3-deoxy-L-sorbose Propane-1,3-diyl Dithioacetal (18). To a refluxed solution of the radical precursor **17** (2.19 g, 3.32 mmol) in 55 mL of toluene at 88 °C was added a solution of AIBN (0.11 g, 0.66 mmol) and TTMSS (1.54 mL, 4.98 mmol) in 55 mL of toluene over 1 h via a syringe pump. The resulting solution was continuously stirred at the same temperature for another 1 h. The solution was then cooled and directly concentrated to give a crude residue, which was directly used for the next step without purification.

To a solution of the previous crude residue (1.93 g, 3.32 mmol) in CH_2Cl_2 (3.30 mL) were added 1,3-propanedithiol (0.67 mL, 6.64 mmol) and $BF_3{\cdot}OEt_2$ (3.28 mL, 26.56 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 30 min and then worked up by addition of saturated $NaHCO_{3(aq)}$. The solution was diluted with CH_2Cl_2 (180 mL) and then neutralized with saturated $NaHCO_{3(aq)}$ until the pH value was 7. The organic layer was then washed with water (60 mL × 3) and brine (60 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 25/75 to 3/7 to give the desired product **18** (1.27 g, 57%, over two steps) as a pale yellow oil: $[\alpha]_D{}^{22}$ −13.92 (c = 1.08, $CHCl_3$); IR (neat) 1721 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 4H), 8.01−7.93 (m, 4H), 7.58−7.46 (m, 4H), 7.42−7.30 (m, 8H), 6.19−6.08 (m, 1H, H_4), 5.87−5.76 (m, 1H, H_5), 4.81 (d, J = 11.9 Hz, 1H, H_{1a}), 4.75 (dd, J = 12.2, 4.2 Hz, 1H, H_{6a}), 4.70 (d, J = 11.9 Hz, 1H, H_{1b}), 4.59 (dd, J = 12.2, 6.8 Hz, 1H, H_{6b}), 3.04 (t, J = 12.3 Hz, 2H, H_{3a}, H_{3b}), 2.70−2.52 (m, 4H), 2.11−1.97 (m, 1H), 1.91−1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (C), 165.6 (C), 165.4 (C), 165.3 (C), 133.2 (CH), 133.1 (CH), 133.0 (CH), 129.8 (CH × 2), 129.6 (CH), 129.4 (C), 129.3 (C), 128.3 (CH × 2), 72.1 (CH), 68.3 (CH), 64.6 (CH_2), 62.8 (CH_2), 50.6 (C), 39.3 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 24.2 (CH_2); HRMS (ESI^+) m/z calcd for $C_{37}H_{34}O_8NaS_2$ $[M + Na]^+$ 693.1587; found 693.1584. Anal. Calcd for $C_{37}H_{34}O_8S_2$: C, 66.25; H, 5.11; S, 9.56. Found: C, 66.43; H, 4.87; S, 9.91.

3-Deoxy-L-sorbose Propane-1,3-diyl Dithioacetal (19). To a solution of compound **18** (0.89 g, 1.33 mmol) in a cosolvent system (THF/MeOH = 1/4, 13 mL) was added NaOMe (0.29 g, 5.33 mmol). The resulting mixture was stirred at rt for 3 h. The reaction mixture was added acetic acid to neutralize the solution until the pH value was 7 and then directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of CH_2Cl_2/MeOH = 8/1 to give the desired product **19** (0.32 g, 95%) as a colorless oil: $[\alpha]_D{}^{24}$ −14.43 (c = 1.38, CH_3OH); IR (neat) 3327 (OH) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.05 (d, J = 8.7 Hz, 1H, H_5), 3.94 (d, J = 12.0 Hz, 1H, H_{1a}), 3.78 (d, J = 12.0 Hz, 1H, H_{1b}), 3.71−3.46 (m, 3H, H_{3a}, H_{3b}, H_4), 3.05−2.82 (m, 2H), 2.80−2.61 (m, 2H), 2.16 (dd, J = 15.0, 1.5 Hz, 1H, H_{6a}), 2.09−1.79 (m, overlapped with dd at 2.01, J = 15.0, 9.0 Hz, H_{6b}, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 76.4 (CH), 68.9 (CH), 66.5 (CH_2), 64.4 (CH_2), 54.3 (C), 43.3 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 26.4 (CH_2); HRMS (ESI^+) m/z calcd for $C_9H_{18}O_4NaS_2$ $[M + Na]^+$ 277.0539; found 277.0539.

3-Deoxy-L-sorbose. To a solution of compound **19** (0.12 g, 0.48 mmol) in water (24 mL) was added dropwise a solution of *N*-bromosuccinide (0.41 g, 2.31 mmol) in THF (29 mL) at 0 °C until the yellow color remained. After being stirred at rt for 15 min, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (60 mL × 4). The pH value of the aqueous phase was adjusted to 7 with Amberlyst A-26 ion-exchange resin (OH^- form). The solution was filtered and water was removed by lyophilization to give a crude product, which was purified by flash chromatography with the eluent of CH_2Cl_2/ MeOH = 4/1 to give the desired product (56 mg, 71%) as a pale yellow oil: $[\alpha]_D{}^{23}$ −45.13 (c = 0.23 H_2O); ^1H NMR (300 MHz, CD_3OD) δ 4.62 (br s), 4.43−4.36 (m), 4.26 (td, J = 6.3, 1.8 Hz), 4.19−4.10 (m), 3.39−3.71 (m), 3.67−3.56 (m), 3.55−3.46 (m), 3.46−3.33 (m), 2.72 (dd, J = 15.8, 8.9 Hz), 2.58 (dd, J = 15.8, 4.2 Hz), 2.36 (dd, J = 13.5, 5.4 Hz), 2.21−2.15 (m), 2.12 (d, J = 3.3 Hz), 1.98 (dd, J = 12.9, 5.1 Hz), 1.69 (dd, J = 14.1, 3.9 Hz), 1.57 (dd, J = 12.9, 11.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 211.2 (C), 107.3 (C), 106.7 (C), 98.7 (C), 98.0 (C), 85.9 (CH), 83.7 (CH), 76.3 (CH), 75.4 (CH), 73.2 (CH), 70.8 (CH), 69.7 (CH_2), 69.3 (CH_2), 69.3 (CH), 69.1 (CH), 69.0 (CH_2), 67.3 (CH_2), 66.9 (CH_2), 64.3 (CH_2), 62.9 (CH_2), 62.7 (CH_2), 62.3 (CH_2), 62.1 (CH_2), 45.2 (CH_2), 43.3 (CH_2), 43.2 (CH_2), 39.3 (CH_2), 32.7 (CH_2); HRMS (FAB^+) m/z calcd for $C_6H_{12}O_5$ $[M]^+$ 164.0685; found 164.0683.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02257.

^1H, ^{13}C/DEPT NMR spectra of **10**−**19**, 3-deoxy-L-fructose, and 3-deoxy-L-sorbose; COSY of **10**−**19** (PDF)
X-ray data of **12** (CCDC deposition number 1052966) (CIF)

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Notes

The authors declare no competing financial interest.

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