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Synthesis of Septanosides through an Oxyglycal Route

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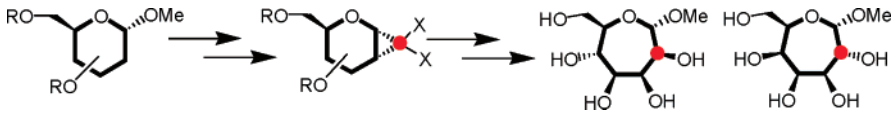

A new route to synthesize septanoside derivatives from protected 2-hydroxyglycals is reported. Ring expansion of a pyranoside to a septanoside was achieved through key reactions of a cyclopropanation, ring opening, oxidation, and reduction. Methyl septanoside derivatives, namely, methyl α-D-*glycero*-D-*talo*-septanoside and methyl α-D-*glycero*-L-*altro*-septanoside, were synthesized in an overall yield of 35% and 46%, respectively, from the corresponding protected 2-hydroxy glycals.

Introduction

The seven-membered cyclic sugar derivatives, namely, septanoses and septanosides, are less commonly known sugar homologues.[1] Studies of the acid-catalyzed formation of acetonides from unsubstituted free sugars, by Stevens and coworkers, have demonstrated the first instance of a preparative method to isolate the septanoside derivatives.[2] Synthesis of cyclic seven-membered sugars, namely, septanoses, arise interest, partly due to the desire to identify the configurational and conformational features of septanoses, and the attendant possibilities to explore their chemical and biological properties.[3] A few methods of septanoside formation are the following: (i) hemiacetal or acetal formation from a linear precursor containing aldehyde and appropriately positioned hydroxyl group;[2,4,5] (ii) pyridinium chloride mediated ring-opening of a protected glucopyranoside;[6] (iii) condensation of dialdehydes with active methylene compounds;[7] (iv) ring-closing metathesis reactions of appropriately installed diene derivatives;[8] (v) expansion of a glycal via cyclopropanation and ring opening;[9] and (vi) Baeyer−Villiger oxidation of inositol derivatives.[10] We desired that 2-hydroxyglycals would form as suitable substrates for ring expansion, leading to the formation of septanoside derivatives, retained with hydroxyl groups in each carbon of the septanoside. With this intention, we have explored a ring expansion reaction, wherein a cyclic six-membered sugar derivative is converted directly to a cyclic seven-membered sugar derivative, through a methylene insertion, oxidation, and reduction reactions on oxyglycal precursors. Syntheses of septanosides, starting from oxyglycal derivatives of gluco-and galactopyranosides, are presented herein.

Results and Discussion

(a) Synthesis of Methyl α-D-*glycero*-D-*talo*-Septanoside. The synthesis was initiated from methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**). The *O*-benzyl-protected oxyglycal **4** was synthesized analogous to a procedure reported for the corresponding *O*-acetyl- and *O*-benzoyl-protected oxyglycals.[11] Acetolysis of the benzyl derivative **1**, followed by treatment with HBr/AcOH, led to the formation of bromide **2** (Scheme

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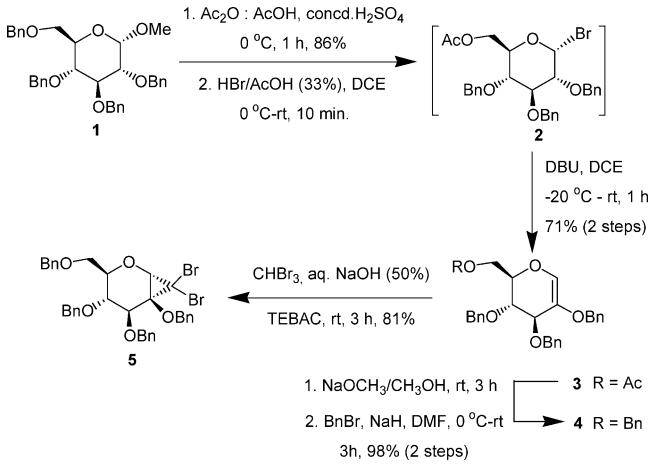
SCHEME 1



1). Dehydrohalogenation of **2** was performed by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[11] in DCE to obtain 2-hydroxyglucal **3**, in an overall yield of 60%. The hydroxyglycal ethers and esters are known in a number of reactions,[12] including the cyclopropanation reaction.[13] The acetate group in **3** was replaced with a benzyl protecting group, providing 2,3,4,6-tetra-*O*-benzyl 1,5-anhydro-D-*arabino*-hex-1-enitol (**4**) (Scheme 1). Compounds **3** and **4** are obtained previously through different synthetic procedures.[13−15] Methylene insertion in **4** was conducted by using dibromocarbene, prepared in situ by treatment of $CHBr_3$ with aq NaOH (50%) under phase transfer conditions, and the dibromocyclo adduct **5** was obtained as a single diastereomer. By following the rationale that bulky dibromocarbene would approach the olefin from a face less-hindered to the C-3 benzyloxy group,[9a] the cyclopropyl group was assigned to occupy an α-configuration at the anomeric center.

The cyclopropyl derivative **5** was subjected to methanolysis (NaOMe/PhMe) and the fully functionalized oxepine **6** was obtained in an excellent yield and only one anomer formed exclusively. An α-configuration at the anomeric center of **6** was assigned tentatively. It was desired to have a vinyl ether derivative devoid of the halide moiety, so as to instal the hydroxy groups at C-2 and C-3. Treatment of bromide **6** with n-BuLi/THF and quenching with MeOH afforded oxepine **7**, in a good yield (Scheme 2).

With the observation that oxepine **7** was unstable for longer periods, it was subjected immediately upon its preparation to an oxidation with use of dimethyldioxirane.[16] The epoxidation reaction was efficient and, under the aqueous alkaline reaction conditions, epoxide converted to the α-hydroxy ketone **8** in a good yield. The presence of the newly formed functionalities, namely, the keto and the hydroxyl groups, was identified from their IR spectral frequencies at 1737 and 3417 cm^{-1}, respectively. Reduction of the keto functionality in **8** with use of $NaBH_4$ led to isolation of **9**. The reduction occurred with high stereoselectivity. Deprotection of the benzyl groups by hydrogenolysis afforded D-*glycero*-D-*talo*-septanoside **10**, in a good yield (Scheme 3).

The anomeric proton in **10** resonated as a doublet in the ^1H NMR spectrum (4.52 ppm, $J = 6.5$ Hz). On the other hand, the H-3 proton resonated as a narrow doublet (3.97 ppm, $J = 1.5$ Hz). The structural and stereochemical assignments were performed further with the aid of HMQC and NOESY spectrum. The C-1 nucleus in **10** resonated at 102.6 ppm. The α-configuration was confirmed on the basis of the observed anomeric geminal C−H coupling constant ($^1J_{C1-H1}$) of 167.9 Hz, measured from the ^{13}C coupled HMQC experiment. This $^1J_{C1-H1}$ value agrees with that reported by Peczuh and co-workers,[8c] for other septanoside derivatives. The through-space proximities were identified by the presence of cross-peaks between the pair H2−H4 and H2−H6 in the NOESY spectrum and these cross-peaks indicated the distance between these protons to be ∼4 Å. From the *J* value of ∼1.5 Hz between H-2−H-3 and H-3−H-4 protons, cis-relationships of the hydroxyl groups were identified.

(b) Synthesis of Methyl α-D-*glycero*-L-*altro*-Septanoside (16). Establishing the protocol for the D-*glycero*-D-*talo*-septanoside **10** warranted that the strategy be extended to the corresponding galacto-derivative. However, as detailed below, modification of the reaction protocol was required to suit galactose. The vinyl ether synthon **11** was prepared according to a known synthesis.[11] Cyclopropanation of **11** was effective only with dichlorocarbene and the dichloroadduct **12** was obtained as a single isomer in a good yield. Reaction of **11** with dibromocarbene, as exercised in the case of the oxyglycal **4**, was unsuccessful even after several attempts. Decomposition of **11** was observed in the reaction. It is probable that the C-4 axial orientation of the substituent in **11** provides a facile approach to less bulky dichlorocarbene than that to dibromocarbene. Solvolytic ring opening of **12** was carried out under a reflux condition, using NaOMe in 1,4-dioxane, and the ring-opened chloro-oxepine derivative **13** was obtained in an excellent yield (Scheme 4).

The anomeric carbon in **13** exhibited a resonance at 101.9 ppm, whereas the olefinic carbons were ascertained from the resonances 120.2 and 152.2 ppm in the ^{13}C NMR spectrum. Mass spectral analysis further confirmed the constitution of **13**. Introduction of oxygen functionalities at C-2 and C-3 in **13** was attempted through dehalogenation and the epoxidation strategy, as applied with the oxepine **7** in the gluco-derivative as described above. However, the reactions were unsuccessful. After several attempts to introduce the oxygen functionalities across the olefin in **13**, the RuO_4-mediated oxidation[17] was conducted and the diketo derivative **14** was obtained in a moderate yield. The appearance of a signal at 203 ppm in the ^{13}C NMR spectrum and the presence of a peak at 1740 cm^{-1} in the IR spectrum confirmed the presence of keto groups in **14**. The corresponding absence of olefinic carbon signals was also confirmed for the derivative **14**. The mass spectrum of **14** indicated that one keto group was retained in the hydrated form. Reduction of the ketone ($NaBH_4$/MeOH) led to the formation of diol **15** (Scheme 5).

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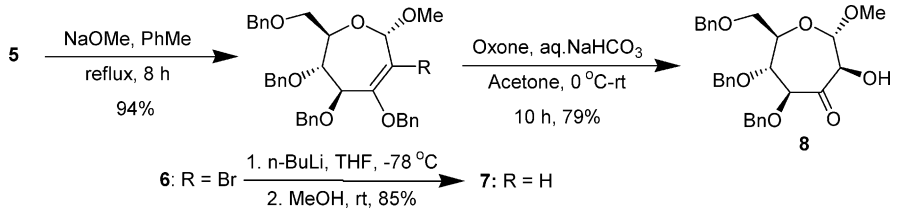
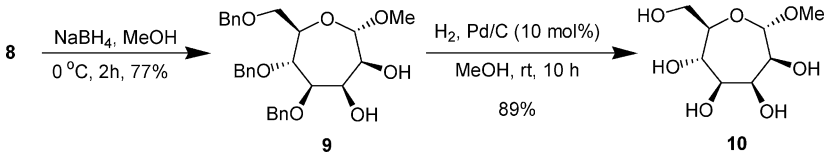
SCHEME 2



SCHEME 3



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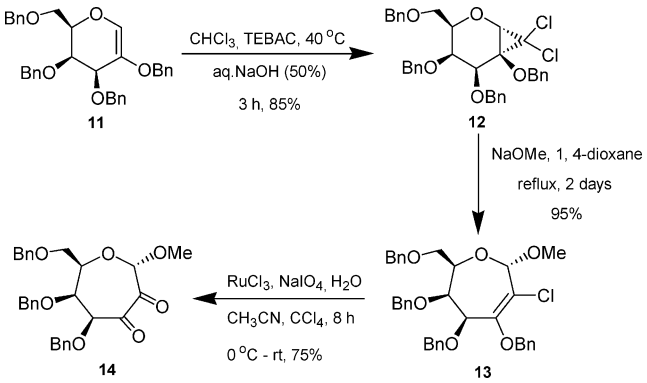


The reaction occurred with high selectivity and a single diastereomer was obtained in a good yield. The *O*-benzyl groups were deprotected in the final stage to secure the free hydroxyl groups containing D-*glycero*-L-*altro*-septanoside derivative **16**, in an excellent yield.

The constitution and configuration of **16** were confirmed by NMR spectroscopy and mass spectrometry. The structural assignments were performed through heteronuclear multiple quantum correlation (HMQC) and *J*-coupled correlation spectroscopy (COSY).

In the ^{1}H NMR spectrum of **16**, protons other than methyl and H-1 protons appeared as three sets of multiplets, namely, H-2 and H-3 (4.01−3.96 ppm), H-4, H-5 and H-6 (3.90−3.86 ppm), and H-7a and H-7b (3.59−3.50 ppm). A sharp doublet at 4.73 ppm with a J_{H1-H2} value of 3 Hz indicated a cis-relationship between H-1 and H-2. In the ^{13}C NMR spectrum of **16**, anomeric carbon appeared at 100.1 ppm. Here again the $^1J_{C1-H1}$ coupling value ($^1J_{C1-H1}$ = 167.8 Hz) was measured by utilizing ^{13}C-coupled HMQC experiment, which proved further the α-anomeric configuration. Since the resonances corresponding to H-2 and H-3 protons in the ^{1}H NMR spectrum of **16** were complex, the homonuclear decoupling experiments were conducted further on the partially protected derivative **15**. Selective irradiation of H-1 in **15** eliminated the doublet of doublet pattern of H-2 and the J_{H2-H3} value was identified to be 6.7 Hz (Figure 1). Irradiations on appropriate protons led to identifying the coupling constants J_{H1-H2} = 3.9 Hz and J_{H3-H4} ≈ 1 Hz. From these *J* values, the configurations were assigned for C-1, C-2, and C-3, as presented in Scheme 5.

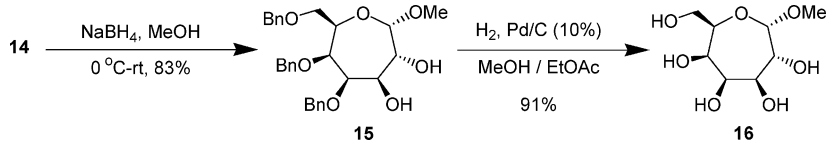
In conclusion, a new methodology is developed to prepare unnatural septanoside derivatives. The carbene insertions of an oxyglycal substrate, ring opening of cyclopropyl moiety, oxidation, and reduction reactions are utilized to expand the six-membered pyranoses to seven-membered septanosides. The methodology is applied to obtain two configurationally different septanosides, namely, the methyl α-D-*glycero*-D-*talo*-septanoside and methyl α-D-*glycero*-L-*altro*-septanoside. The features of this method are that the intermediates such as the seven-membered vinyl halides, vinyl ethers, the diketones, and the diols are potential sites for many other functionalizations, in principle. These features will be explored further in functionalizing the newly formed septanosides.

Experimental Section

6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide (2). To a solution of **1** (4 g, 7.2 mmol) in AcOH:Ac_2O medium (1:1, 40 mL) was added concentrated H_2SO_4 (0.8 mL) dropwise at 0 °C then the solution was stirred at room temperature for 30 min, diluted with water (100 mL), and extracted with $CHCl_3$ (2 × 50 mL). The organic layer was washed with aq.$NaHCO_3$ solution (3 × 150 mL) and water (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified (hexane:EtOAc = 8:2) to afford 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (9:1, α:*β* mixture) (3.3 g, 86%) as a pale yellow oil. R_f 0.51 (7:3 hexane/EtOAc); HRMS *m*/*z* $C_{31}H_{34}O_8Na$ calcd 557.2151, found 557.2161. To a solution of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (2 g, 3.7 mmol) in DCE (25 mL) was added HBr/AcOH (33%, 4.2 mL, 16.8 mmol) dropwise slowly at 0 °C, then the solution was stirred for 10 min while warming to room temperature, poured over ice, diluted, and extracted with $CHCl_3$ (2 × 50 mL). The organic layer was washed with aq $NaHCO_3$ solution (2 × 50 mL) and water (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The bromo compound **2** was used as such for the next step without further purification.

1,5-Anhydro-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (3). To a solution of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide (**2**) (2.1 g, 3.7 mmol) in DCE (25 mL) was added DBU (0.73 mL, 4.8 mmol) dropwise at −20 °C, then the solution was stirred in the dark for 30 min and allowed to warm to room temperature. The reaction mixture was diluted with $CHCl_3$ (100 mL), washed with aq HCl (5%) (3 × 30 mL), water (2 × 50 mL), and aq $NaHCO_3$ solution (2 × 50 mL), and dried (Na_2SO_4) and the solvents were removed in vacuo. The crude product was purified (hexane:EtOAc = 8:2) to afford **3** (1.26 g, 71%) as a colorless oil. R_f 0.57 (4:1 hexane/EtOAc); $[\alpha]_D$ +12 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.35−7.21 (m, 15H), 6.26 (s, 1H), 4.81−4.57 (m, 6H), 4.39−4.30 (m, 2H), 4.25 (d, *J* = 4.8 Hz, 1H), 4.12−4.07 (m, 1H), 3.81 (dd, *J* = 6.6, 4.8 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.7, 139.2, 138.1, 137.5, 137.0, 128.4, 128.3, 127.9, 126.8, 75.1, 74.6, 73.9, 72.6, 72.5, 70.9, 62.5,

SCHEME 5



20.8; HRMS *m*/*z* $C_{29}H_{30}O_6Na$ calcd 497.1940, found 497.1960. Compound **3** was converted to **4**[13] by (i) de-*O*-acetylation under Zemplén condition and (ii) *O*-benzylation with use of BnBr in DMF, in the presence of NaH.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1,2-*C*-(dibromomethylene)-α-D-*glycero*-D-*galacto*-hexitol (5). To a solution of **4** (0.192 g, 0.367 mmol) and benzyltriethylammonium chloride (cat.) in $CHBr_3$ (1 mL) was added aq NaOH (50%, 1 mL) then the solution was stirred for 15 min, diluted with brine solution (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was purified (hexane:EtOAc = 9:1) to afford **5** (0.21 g, 81%) as a pale yellow oil. R_f 0.57 (9:1 hexane/EtOAc); $[\alpha]_D$ +47 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.19 (m, 20H), 4.95−4.88 (m, 3H), 4.68−4.59 (m, 3H), 4.44 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.19−4.05 (m, 2H), 4.02 (s, 1H), 3.92−3.89 (m, 1H), 3.61 (dd, J = 10.5, 3.1 Hz, 1H), 3.47 (dd, J = 10.5, 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 138.0, 137.6, 137.4, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 126.9, 80.7, 79.0, 74.5, 73.9, 73.5, 72.7, 71.0, 70.6, 64.3, 64.0, 42.6; HRMS *m*/*z* $C_{35}H_{34}Br_2O_5Na$ calcd 715.0671, found 715.0692.

Methyl 2-bromo-2-deoxy-3,4,5,7-tetra-*O*-benzyl-α-D-*arabino*-hept-2-enoseptanoside (6). A solution of **5** (0.07 g, 0.1 mmol) in PhMe (5 mL) was admixed with NaOMe/CH_3OH (0.5 M, 2 mL), refluxed for 8 h, diluted with EtOAc (20 mL), washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified (hexane:EtOAc = 9:1) to afford **6** (0.061 g, 94%) as a pale yellow oil. R_f 0.50 (9:1 hexane/EtOAc); $[\alpha]_D$ −38 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.07 (m, 20H), 5.24 (s, 1H), 4.73−4.69 (m, 2H), 4.61−4.55 (m, 2H), 4.52−4.41 (m, 2H), 4.33−4.13 (m, 4H), 3.72 (dd, J = 8.4, 2.1 Hz, 1H), 3.62−3.56 (m, 1H), 3.52−3.51 (m, 1H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 138.2, 137.7, 137.2, 136.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 114.3, 101.1, 80.3, 77.3, 73.0, 72.1, 72.0, 71.3, 71.2, 70.7, 56.3; HRMS *m*/*z* $C_{36}H_{37}BrO_6Na$ calcd 667.1671, found 667.1672.

Methyl 2-deoxy-3,4,5,7-tetra-*O*-benzyl-α-D-*arabino*-hept-2-enoseptanoside (7). *n*-BuLi (1.6 M, 0.1 mL, 1.1 mmol) was added dropwise to a solution of **6** (0.060 g, 0.093 mmol) in THF (5 mL) at −78 °C. After 4 h, the reaction mixture was quenched by dropwise addition of MeOH (2 mL), solvents were removed in vacuo, and the resulting residue was diluted with EtOAc (20 mL), washed with water (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified (hexane:EtOAc = 9:1) to afford **7** (0.045 g, 85%) as a colorless oil. R_f 0.40 (9:1 hexane/EtOAc); $[\alpha]_D$ +21 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.11 (m, 20H), 5.38 (s, 1H), 4.78−4.58 (m, 5H), 4.51−4.39 (m, 3H), 4.21 (d, J = 11.1 Hz, 1H), 4.13−4.08 (m, 2H), 3.68 (dd, J = 9, 1.5 Hz, 1H), 3.65−3.59 (m, 1H), 3.56−3.51 (m, 1H), 3.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 138.5, 138.1, 137.6, 136.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 100.2, 100.1, 80.4, 79.2, 77.3, 72.8, 71.6, 71.1, 70.9, 69.5, 55.0; HRMS *m*/*z* $C_{36}H_{38}O_6Na$ calcd 589.2566, found 589.2584.

Methyl 4,5,7-tri-*O*-benzyl-α-D-*manno*-sept-3-uloside (8). To a stirred solution of oxepine **7** (0.040 g, 0.071 mmol) in acetone (4 mL) was added aq $NaHCO_3$ (0.031 g in 1 mL water) at 0 °C. After 10 min, Oxone (0.114 g, 0.185 mmol) was added in portion, and the reaction mixture was stirred for 10 h at room temperature, diluted with EtOAc (15 mL), washed with water (2 × 20 mL), dried (Na_2SO_4), concentrated in vacuo, and purified (hexane:EtOAc

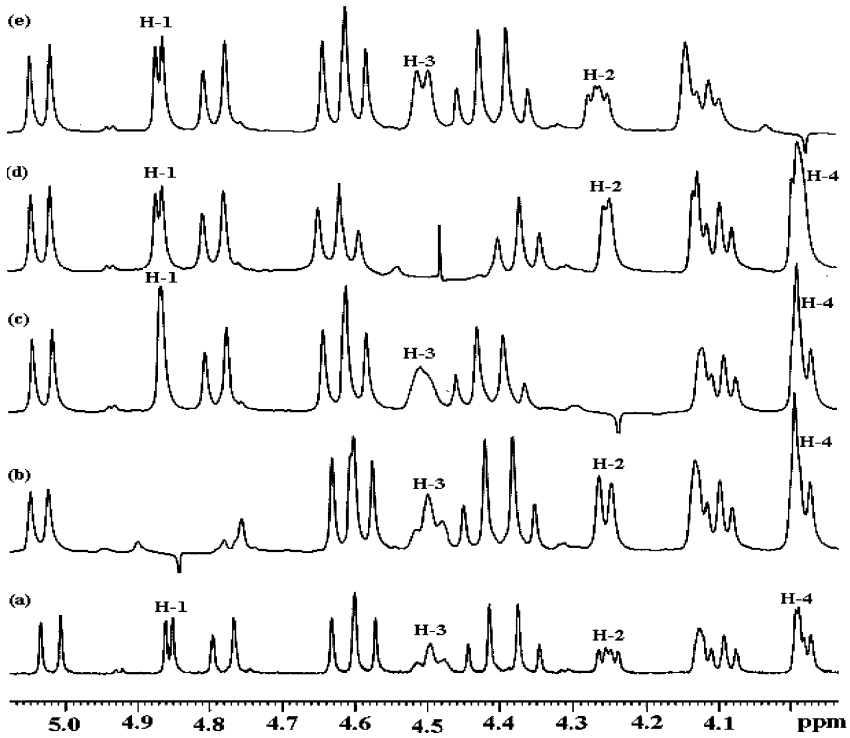


FIGURE 1. (a) Partial ^{1}H NMR spectrum of **15**; (b) partial ^{1}H NMR spectrum of **15** upon H-1 irradiation; (c) partial ^{1}H NMR spectrum of **15** upon H-2 irradiation; (d) partial ^{1}H NMR spectrum of **15** upon H-3 irradiation; (e) partial ^{1}H NMR spectrum of **15** upon H-4 irradiation.

= 8:2) to afford **8** (0.027 g, 79%) as a colorless oil. R_f 0.30 (5:1 hexane/EtOAc); $[\alpha]_D$ +19 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.14 (m, 15H), 4.86 (d, J = 10.4 Hz, 1H), 4.78 (d, J = 13.6, 2H), 4.59−4.51 (m, 3H), 4.45−4.32 (m, 3H), 3.80−3.62 (m, 3H), 3.45 (s, 3H), 3.36 (d, J = 7.6 Hz, 1H), 2.6 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 137.8, 137.1, 137.0, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 104.1, 88.7, 78.3, 76.3, 75.2, 73.4, 73.2, 70.2, 70.1, 56.4; HRMS *m*/*z* calcd $C_{29}H_{32}O_7Na$ 515.2046, found 515.2025.

Methyl 4,5,7-tri-*O*-benzyl-α-D-*glycero*-D-*talo*-septanoside (9). To a solution of **8** (0.027 g, 0.055 mmol) in MeOH (2 mL) was added $NaBH_4$ (0.010 g, 0.274 mmol) at 0 °C then the solution was stirred for 2 h, solvents were removed in vacuo, and the resulting residue was dissolved in EtOAc (3 × 10 mL) and washed with brine (10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo and purified (hexane:EtOAc = 1:1) to afford **9** (0.021 g, 77%) as a colorless oil. R_f 0.26 (1:1 hexane/EtOAc); $[\alpha]_D$ +32 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.16 (m, 15H), 4.76 (d, J = 11.3 Hz, 1H), 4.73 (d, J = 5.6 Hz, 1H), 4.69 (s, 2H), 4.59 (d, J = 11.5 Hz, 1H), 4.52−4.48 (m, 2H), 4.2 (br s, 1H), 3.86 (d, J = 3.6 Hz, 2H), 3.72−3.68 (m, 3H), 3.63−3.61 (m, 1H), 3.43 (s, 3H), 2.84 (br s, 1H), 2.56 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 138.0, 137.6, 128.5, 128.4, 128.3, 128.0, 127.7, 127.6, 102.7, 85.3, 77.2, 74.6, 74.5, 73.3, 73.1, 71.6, 71.1, 70.6, 56.0; HRMS *m*/*z* $C_{29}H_{34}O_7Na$ calcd 517.2202, found 517.2214.

Methyl α-D-*glycero*-D-*talo*-Septanoside (10). To a solution of **9** (0.020 g, 0.040 mmol) in MeOH (15 mL) was added Pd/C (10%, 0.030 g), then the solution was stirred at room temperature under a pressure of hydrogen gas for 10 h. The reaction mixture was filtered over a celite pad and washed with MeOH (3 × 15 mL), and solvents were removed in vacuo to afford **10** (0.008 g, 89%) as a colorless oil. R_f 0.58 (1:1 CH_3OH/ $CHCl_3$); $[\alpha]_D$ +51 (*c* 1.00, CH_3OH); ^1H NMR (500 MHz, D_2O) δ 4.52 (d, J = 6.5 Hz, 1H), 3.97 (d, J = 1.5 Hz, 1H), 3.78−3.76 (m, 2H), 3.64 (dd, J = 13.5, 3.5 Hz, 1H), 3.58−3.49 (m, 3H), 3.41(s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 102.6, 76.3, 76.0, 72.1, 71.5, 70.3, 62.0, 55.6; HRMS *m*/*z* $C_8H_{16}O_7Na$ calcd 247.0794, found 247.0794.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1,2-*C*-(dichloromethylene)-α-D-*glycero*-L-*altro*-hexitol (12). To a stirred solution of oxygalactal **11**[11] (0.198 g, 0.327 mmol) and benzyltriethylammonium chloride (cat.) in $CHCl_3$ (1 mL) was added aq NaOH (50%, 1.1 mL) dropwise at room temperature, then the solution was stirred at 40 °C for 2 h, diluted with brine (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo, and the resulting residue was purified (hexane:EtOAc = 9:1) to afford **12** (0.195 g, 85%) as a colorless oil. R_f 0.64 (9:1 hexane/EtOAc); $[\alpha]_D$ +9 (*c* 1.00, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.17 (m, 20H), 5.03−4.97 (m, 3H), 4.68−4.56 (m, 3H), 4.48−4.36 (m, 2H), 4.08 (d, J = 2.1 Hz, 1H), 3.95 (s, 1H), 3.92−3.90 (m, 2H), 3.57−3.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.1, 138.0, 128.8, 128.7, 128.5, 128.4, 128.2, 127.8, 77.8, 75.5, 74.4, 73.9, 73.8, 72.3, 71.2, 69.2, 67.2, 63.2, 62.3; HRMS *m*/*z* $C_{35}H_{34}Cl_2O_5Na$ calcd 627.1681, found 627.1679.

Methyl 2-chloro-2-deoxy-3,4,5,7-tetra-*O*-benzyl-α-D-*lyxo*-hept-2-enoseptanoside (13). To a stirred solution of **12** (0.102 g, 0.168 mmol) in dioxane (5 mL) was added NaOMe/CH_3OH (0.5 M, 2 mL), then the reaction mixture was refluxed for 48 h and solvents were removed in vacuo. The resulting residue was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (20 mL), dried (Na_2SO_4), concentrated in vacuo, and purified (hexane:EtOAc = 9:1) to afford **13** (0.101 g, 95%) as a colorless oil. R_f 0.47 (9:1 hexane/EtOAc); $[\alpha]_D$ −39 (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.19 (m, 20H), 5.18 (s, 1H), 4.84 (d, J = 2.4 Hz, 2H), 4.78 (d, J = 11.7 Hz, 1H), 4.63−4.41 (m, 6H), 4.30−4.26 (m, 1H), 3.90 (d, J = 3.0 Hz, 1H), 3.78−3.70 (m, 2H), 3.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 138.2, 137.9, 137.7, 136.9, 128.4, 128.3, 128.1, 128.0, 127.6, 127.5, 120.2, 102.0, 79.3, 76.7, 73.4, 73.3, 71.1, 70.1, 57.1; HRMS *m*/*z* $C_{36}H_{37}ClO_6Na$ calcd 623.2176, found 623.2153.

Methyl 4,5,7-tri-*O*-benzyl-α-D-*lyxo*-sept-2,3-diuloside (14). To a stirred solution of chloro-oxepine **13** (0.090 g, 0.150 mmol) in MeCN:CCl_4 (5 mL, 1:1) at 0 °C was added a solution of $RuCl_3$ (cat.) and $NaIO_4$ (0.080 g, 0.375 mmol) in water (2 mL) dropwise. After 8 h of stirring at room temperature, the reaction mixture was diluted with EtOAc (10 mL) and CH_2Cl_2 (10 mL), filtered through a pad of silica gel, and washed with EtOAc (2 × 20 mL) and the solvents were removed in vacuo. The resulting residue was purified (hexane:EtOAc = 7:3) to afford **14** (0.055 g, 75%), in the hydrated form, as a colorless oil. R_f 0.48 (1:1 hexane/EtOAc); $[\alpha]_D$ +20 (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.21 (m, 15H), 5.16 (s, 1H), 4.95−4.89 (m, 2H), 4.73−4.67 (m, 2H), 4.54 (d, J = 11.3 Hz, 1H), 4.47 (d, J = 11.3 Hz, 1H), 4.40 (d, J = 7.1 Hz, 1H), 4.36 (m, 1H), 4.15−4.10 (m, 1H), 3.56−3.49 (m, 2H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 137.6, 137.4, 137.0, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 100.6, 93.2, 85.0, 77.8, 74.4, 73.5, 71.2, 68.7, 56.8; HRMS *m*/*z* $C_{29}H_{30}O_7Na{\cdot}H_2O$ calcd 531.1995, found 531.2003.

Methyl 4,5,7-tri-*O*-benzyl-α-D-*glycero*-L-*altro*-septanoside (15). To a solution of **14** (0.050 g, 0.102 mmol) in MeOH (4 mL) at 0 °C was added $NaBH_4$ (0.019 g, 0.510 mmol), then the mixture was stirred for 2 h, solvents were removed in vacuo, the resulting residue was dissolved with EtOAc (3 × 15 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo, and the crude product was purified (hexane:EtOAc = 6:4) to afford **15** (0.042 g, 83%) as a colorless oil. R_f 0.39 (1:1 hexane/EtOAc); $[\alpha]_D$ +29 (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.26 (m, 15H), 5.02 (d, J = 11.5 Hz, 1H), 4.85 (d, J = 3.9 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 4.63−4.57 (m, 2H), 4.50−4.48 (m, 1H), 4.44−4.34 (m, 2H), 4.27−4.24 (dd, J = 6.7, 3.9 Hz, 1H), 4.15−4.07 (m, 2H), 3.99−3.98 (m, 2H), 3.51−3.47 (m, 1H), 3.45 (s, 3H), 3.42−3.38 (m, 1H), 2.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.0, 129.9, 128.7, 128.5, 127.9, 127.7, 99.1, 79.3, 77.8, 75.7, 73.4, 73.1, 71.8, 71.7, 69.8, 69.6, 55.7; HRMS *m*/*z* $C_{29}H_{34}O_7Na$ calcd 517.2202, found 517.2211.

Methyl α-D-*glycero*-L-*altro*-Septanoside (16). To a stirred solution of **15** (0.040 g, 0.081 mmol) in MeOH (20 mL) was added Pd/C (10%, 0.023 g) with continued stirring at room temperature under a pressure of hydrogen gas for 12 h. The reaction mixture was then filtered through a celite pad and washed with MeOH (3 × 15 mL), and solvents were removed in vacuo to afford **16** (0.016 g, 91%) as a colorless oil. R_f 0.45 (1:1 CH_3OH/$CHCl_3$); $[\alpha]_D$ +54 (*c* 1.00, CH_3OH); ^1H NMR (500 MHz, D_2O) δ 4.73 (d, J = 3 Hz, 1H), 4.0 (dd, J = 6.5, 3 Hz, 1H), 3.97−3.95 (m, 1H), 3.90−3.86 (m, 3H), 3.58−3.55 (dd, J = 11.5, 7 Hz, 1H), 3.54−3.50 (dd, J = 11.5, 5.5 Hz, 1H), 3.34 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 100.1, 74.5, 73.2, 71.9, 71.5, 69.3, 61.7, 55.8; HRMS *m*/*z* $C_8H_{16}O_7Na$ calcd 247.0794, found 247.0793.

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Supporting Information Available: General experimental procedure and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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