Preparation of *Aldehydo* Sugars and Sugar Acids *via* Ozonolysis of Sugar Hydrazones

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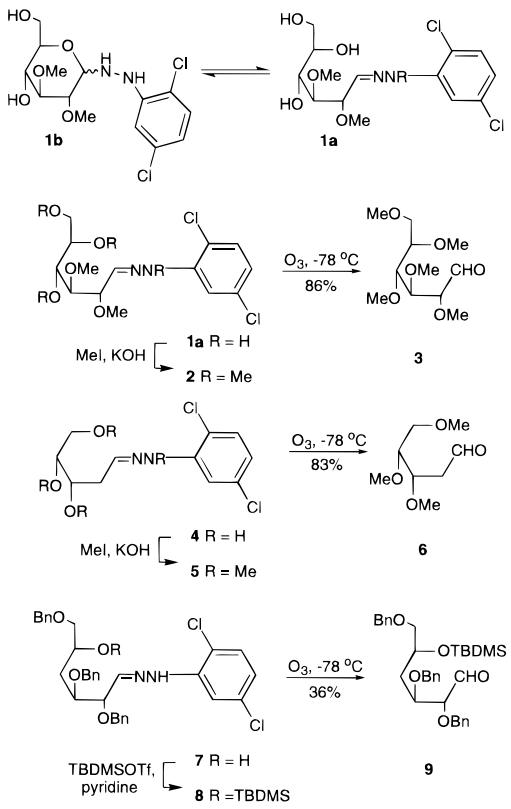
For a recent investigation into carbon chain shortening methodology, we required ready access to variously substituted gluconic acids. However, although *aldehydo* sugars are important intermediates in natural product synthesis,[1] no methodology existed for the preparation of acyclic sugar acids which were appropriately protected to avoid spontaneous lactonization. The common approach to acyclic carbohydrate derivatives, ring-opening *via* the dithioacetals,[2] was incompatible with protecting groups required for our subsequent investigations, and attempts to prepare the acid through hydrolysis of protected gluconolactones were unsuccessful. We now report that selectively protected gluconic acids can be prepared from cyclic sugars *via* formation of an acyclic hydrazone. It is interesting that, while sugar hydrazones have long been used as derivatives to characterize sugars,[3,4] they have not been well examined heretofore as synthetic intermediates in their own right.

Hydrazones are readily formed by heating a lactol with a hydrazine in alcohol.[5−7] The acyclic hydrazone (**1a**; ^{1}H NMR for H_1, *ca.* δ 7) and a cyclic hydrazine isomer (**1b**; ^{1}H NMR for H_1, *ca.* δ 4)[8,9] exist in facile equilibrium (Scheme 1) which is solvent dependent. Only the cyclic hydrazine isomer **1b** was observed in chloroform; in pyridine, H_1 was recorded as a sharp signal at δ 6.3, suggesting that **1a** and **1b** were in fast equilibrium with **1a** the dominant species. Methylation of the C-5 hydroxyl of **1a** gave **2**. Ozonolytic reactivity of hydrazone

Scheme 1



C=N double bonds is known to be *N*-substituent-dependent in simple cases.[10] In preliminary work, C-5 OH groups of sugar (2,5-dichlorophenyl)hydrazones **1a** and **4** were protected by reaction with methyl iodide, which resulted, as well, in *N*-methylation. The *N*-(2,5-dichlorophenyl)-*N*-methylhydrazone of glucose (**2**) or of 2-deoxyribose (**5**) readily underwent ozonolysis[9,10] to give aldehydes **3** and **6**, respectively (Scheme 1).

4-Deoxy compound **11**[12] was prepared from commercially available methyl 4,6-*O*-benzylideneglucopyranoside **10** in straightforward fashion (Scheme 2). Benzylation[13] followed by reductive ring opening of the benzylidene acetal gave methyl 2,3,6-tri-*O*-benzylglucopyranoside[15] in good yield. Reduction of the 4-*O*-triflate by $NaBH_4$[15] and acidic hydrolysis of the methyl glycoside gave **11**.[12] However, extending the hydrazone ozonolysis methodology described above to include more labile silyl ether protecting groups at C-5 OH was only moderately successful. In particular, silylation of (2,5-dichlorophenyl)-hydrazone **7** gave *O*-silylated **8**; no *N*-silylation was noted, and ozonolysis gave *aldehydo* sugar **9** in only 36% yield (see Scheme 1). To test the hypothesis that *N*,*N*-disubstitution might abet ozonolysis, **13** was prepared from **11** by reaction with ethanolic 1,1-dimethylhydrazine followed by silylation with TBDMS triflate in pyridine.

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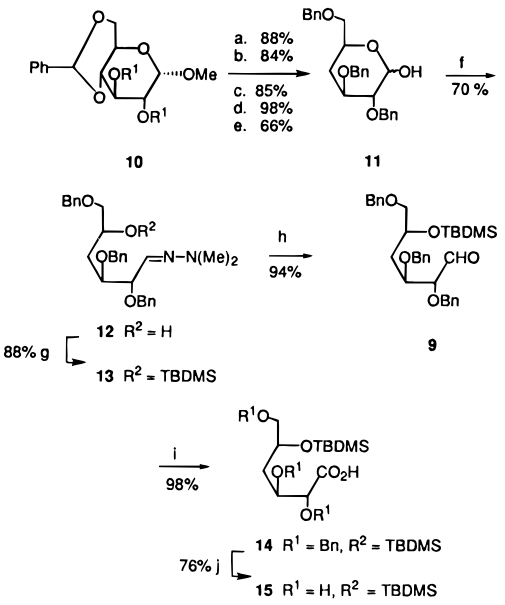
Scheme 2



Reagents and conditions: a. NaH, BnBr, DMF; b. $NaCNBH_3$, HCl, Et_2O; c. Tf_2O, pyridine; d. $NaBH_4$, CH_3CN; e. HOAc, HCl; f. 1,1-dimethylhydrazine, EtOH; g. TBDMSOTf, pyridine; h. (1) O_3, CH_2Cl_2, -78 °C; (2) Me_2S; i. $NaOCl_2$, NaH_2PO_4, 2-methyl-1-butene, ^tBuOH, H_2O;j. H_2, Pd-C, EtOH, C_6H_8

Indeed, ozonolysis gave **9** in high yield (94%); qualitatively, ozonolysis of **13** proceeded about five times faster than that of **2** or **5**.[16]

Oxidation of **9** to gluconic acid **14** required conditions that would tolerate the acid sensitive silyl ether protecting group. Initial attempts using Cr(VI) or permanganate reagents gave the desired carboxylic acid, but yields were variable, and tedious purification steps were required. Sodium chlorite oxidation[17,18] has been reported to tolerate a broad range of functionality and is compatible with carbohydrate substrates.[19,20] Indeed, **14** could be prepared (98%) simply by chlorite oxidation of **9** in buffered media. Debenzylation of the acid required a modified transfer hydrogenolysis procedure;[21,22] incomplete debenzylation was often noted under normal hydrogenolysis conditions.

The approach described herein for the synthesis of acyclic *aldehydo* sugars complements that for the preparation of sugar oximes.[23] While traditional preparations of acyclic sugars *via* dithioacetals involve reaction with alkanethiols in HCl,[2] hydrazones can be prepared under mild conditions. And, because hydrazones can be synthesized from variously protected aldoses,[24] ozonolysis of the hydrazone is an efficient route to a broad range of acyclic sugar aldehydes. Subsequent mild oxidation can then give the protected gluconic acids; both the sugar aldehydes and acids can be of importance for the further synthesis of elaborated glycoside species.[25]

Experimental Section

Materials were obtained from Aldrich Chemical Company and used without further purification. Ozone was generated using a Wellsbach Model T-408 Lab Ozonizer (100 V, 6.2 psi of O_2, flow rate = 1.5 L/min) and was bubbled through the solutions of the hydrazones until they were pale blue in color.

2,3-Di-*O*-benzylglucose (2,5-Dichlorophenyl)hydrazone (1). A solution of 2.44 g (6.78 mmol) 2,3-di-*O*-benzylglucose (prepared by benzylation of **10** followed by hydrolysis) and (2,5-dichlorophenyl)hydrazine (1.44 g, 8.14 mmol) in 200 mL of methanol was refluxed for 18 h. Workup and chromatography gave 3.54 g (quant yield) of product. ^{1}H NMR (CD_3CN): δ 7.44−7.27 (m, 11 H), 7.20 (d, J = 8.6 1 H), 6.70 (dd, J = 2.6, 8.6, 1 H), 6.45 (br s, 1 H), 4.92 (d, J = 10.9, 1 H), 4.86 (d, J = 11.2, 1 H), 4.81 (d, J = 11.2, 1 H), 4.73 (d, J = 10.9, 1 H), 4.66 (d, J = 10.2, 1 H), 4.09 (dd, J = 8.9, 10.2, 1 H), 3.75 (ddd, J = 3.0, 6.9, 11.9, 1 H), 3.52 (dt, J = 5.9, 11.8, 1 H), 3.46−3.38 (m, 3 H), 3.30 (t, J = 8.9, 1 H), 3.23 (ddd, J = 2.6, 5.9, 8.9, 1 H), 2.89 (dd, J = 2.6, 11.8, 1 H); ^{13}C (CD_3COCD_3): δ 147.1, 140.2, 139.6, 130.8, 128.9, 128.7, 128.6, 128.2, 128.1, 127.8, 118.8, 116.2, 114.4, 91.3, 86.6, 80.7, 78.1, 75.5, 75.4, 71.9; IR (KBr) 1596 cm^{-1} (C=N). Anal. Calcd for $C_{26}H_{28}Cl_2N_2O_5$: C, H, N.

2,3-Di-*O*-benzyl-4,5,6-tri-*O*-methylglucose *N*-(2,5-Dichlorophenyl)-*N*-methylhydrazone (2). To a KOH slurry (3.0 g; 53.6 mmol KOH in 20 mL of DMSO) were added **1** (2.23 g, 4.28 mmol) and methyl iodide (2.0 mL, 4.6 g, 32.4 mmol), and the resulting mixture was stirred overnight at room temperature. Workup and chromatography gave 2.42 g (98%) of the title compound. ^{1}H NMR (CD_3COCD_3): δ 7.44−7.15 (m, 13 H), 7.03 (d, J =6.9, 1 H), 4.85 (d, J = 10.9, 1 H), 4.73 (d, J = 12.2, 1 H), 4.62 (d, J = 10.9, 1 H), 4.57 (d, J = 12.1, 1 H), 4.44 (t, J = 6.9, 1 H), 3.94 (dd, J = 3.6, 6.9, 1 H), 3.71 (dd, J = 2.6,10.6, 1 H), 3.65 (dd, J = 3.6, 6.6, 1 H), 3.50 (ddd, J = 2.6, 4.6, 6.6, 1 H), 3.43 (dd, J = 4.6, 10.6, 1 H), 3.41 (s, 3 H), 3.33 (s, 3 H), 3.29 (s, 3 H), 3.22 (s, 3 H); ^{13}C (CD_3CN): δ 148.8, 140.0, 139.7, 138.0, 133.5, 129.3, 129.2, 129.0, 128.9, 128.5, 128.4, 126.6, 126.5, 126.3, 81.0, 80.9, 80.4, 75.1, 71.8, 71.1, 60.3, 59.1, 57.6, 39.8; IR (neat) 1605 cm^{-1} (C=N). For $C_{30}H_{36}Cl_2N_2O_5$, HRMS, 574.2001 (calculated), 574.1992 (measured).

2,3-Di-*O*-benzyl-4,5,6-tri-*O*-methyl-*aldehydo*-D-glucose (3). A solution of 411 mg (0.71 mmol) of **2** in ethyl acetate was cooled to −78 °C, and ozone was then bubbled through this solution (1 h). Dimethyl sulfide was added, and the mixture was concentrated. Chromatography (50% ether in hexanes) gave **3** (246 mg, 86%). ^{1}H NMR (CD_3COCD_3): δ 9.22 (s, 1 H), 7.45−7.25 (m, 10 H), 4.88 (d, J = 11.8, 1 H), 4.79 (d, J = 11.2, 1 H), 4.62 (d, J = 11.2, 1 H), 4.56 (d, J = 11.8, 1 H), 4.25 (d, J = 5.9, 1 H), 4.15 (dd, J = 2.6, 5.9, 1 H), 3.73 (dd, J = 1.6,10.2, 1 H), 3.54 (dd, J = 2.6, 7.6, 1 H), 3.47 (m, 1 H), 3.42 (dd, J = 3.6, 10.2, 1 H), 3.31 (s, 3 H), 3.28 (s, 3 H), 3.18 (s, 3 H); ^{13}C (CD_3CN): δ 200.7, 139.3, 139.2, 129.4, 129.2, 128.9, 128.8, 81.3, 80.8, 80.0, 79.1, 74.2, 73.7, 70.4, 59.9, 59.0, 57.4; IR (neat) 1729 cm^{-1} (C=O). For $C_{23}H_{30}O_6$, HRMS, 402.2042 (calculated), 402.1964 (measured).

2-Deoxyribose (2,5-Dichlorophenyl)hydrazone (4). A mixture of 2-deoxyribose (4.91 g, 36.6 mmol) and (2,5-dichlorophenyl)hydrazine (9.00 g, 50.8 mmol) in 100 mL of methanol was heated to reflux overnight. Workup and chromatography gave **4** (10.63 g, 99%) as product. ^{1}H NMR (CD_3COCD_3): δ 8.80 (br s, 1 H), 7.64 (t, J = 5.6, 1 H), 7.43 (d, J = 2.6, 1 H), 7.25 (d, J = 8.2, 1 H), 6.73 (dd, J = 2.6, 8.2 1 H), 3.98−3.52 (m, 7 H), 2.71 (ddd, J = 3.6, 5.6, 14.9, 1 H), 2.48 (ddd, J = 5.9, 8.6, 14.9, 1 H); ^{13}C (CD_3COCD_3): δ 146.6, 132.7, 130.3, 117.7, 114.8, 112.9,

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86.6, 67.8, 66.9, 66.8, 32.7; IR (KBr) 1597 cm^{-1} (C═N). Anal. Calcd for $C_{11}H_{24}Cl_2N_2O_3$: C, H, N.

2-Deoxy-3,4,5-tri-*O*-methyl-D-*erythro*-pentose *N*-(2,5-dichlorophenyl)-*N*-methylhydrazone (5). The title compound was prepared as for **2** (88%). ^1H NMR (CD_3COCD_3): δ 7.42 (d, J = 8.2, 1 H), 7.33 (d, J = 2.6, 1 H), 7.13 (dd, J = 2.6, 8.2, 1 H), 7.10 (t, J = 4.9, 1 H), 3.59−3.51 (m, 2 H), 3.47−3.40 (m, 2 H), 3.41 (s, 3 H), 3.38 (s, 3 H), 3.31 (s, 3 H), 3.12 (s, 3 H), 2.64−2.49 (m, 2 H); ^{13}C (CD_3CN): δ 149.7, 138.9, 133.4, 132.3, 126.1, 125.84, 125.81, 82.1, 80.1, 72.6, 59.1, 58.6, 58.2, 39.8, 34.5; IR (neat) 1582 cm^{-1} (C═N). For $C_{15}H_{22}Cl_2N_2O_3$: HRMS, 348.1007 (calculated), 348.1014 (measured).

2-Deoxy-3,4,5-tri-*O*-methyl-*aldehydo*-D-*erythro*-pentose (6). Ozonolysis as for **3** gave **6** (83%). ^1H NMR ($CDCl_3$): δ 9.75 (t, J = 2.3, 1 H), 3.83 (dt, J = 5.6, 6.3, 1 H), 3.51 (dd, J = 4.3, 10.5, 1 H), 3.44 (dd, J = 4.3, 10.5, 1 H), 3.35 (dt, J = 4.3, 5.6, 1 H), 3.41 (s, 3 H), 3.39 (s, 3 H), 3.35 (s, 3 H), 2.69 (ddd, J = 2.3, 5.6, 16.5, 1 H), 2.60 (ddd, J = 2.3, 5.6, 16.5, 1 H); ^{13}C (CD_3CN): δ 202.1, 81.9, 77.4, 72.3, 59.2, 58.7, 58.0, 45.6; IR (neat) 1724 cm^{-1} (C═O). For $C_8H_{16}O_4$: HRMS, (M − 1) 175.0970 (calculated), 175.0962 (measured).

2,3,6-Tri-*O*-benzyl-4-deoxy-D-*xylo*-hexose (2,5-Dichlorophenyl)hydrazone (7). The title compound was prepared as for **1**. ^1H NMR (pyridine-d_5): δ 7.86 (d, J = 2.6, 1 H), 7.67 (d, J = 8.2, 1 H), 7.55−7.22 (m, 15 H), 6.74 (dd, J = 2.6, 8.2, 1 H), 6.24 (d, J = 9.2, 1 H), 5.17 (d, J = 10.6, 1 H), 5.03 (d, J = 10.6, 1 H), 4.96 (s, 2 H), 4.77 (d, J = 11.9, 1 H), 4.71 (d, J = 11.9, 1 H), 4.38 (t, J = 8.9, 1 H), 3.87−3.57 (m, 4 H), 2.23 (ddd, J = 1.3, 4.9, 12.2, 1 H), 1.65 (m, 1 H).

2,3,6-Tri-*O*-benzyl-4-deoxy-5-*O*-(*tert*-butyldimethylsilyl)-D-*xylo*-hexose (2,5-Dichlorophenyl)hydrazone (8). The title compound was prepared as for **13**. ^1H NMR ($CDCl_3$) δ 7.81 (s, 1 H), 7.47 (d, J = 1.8, 1 H), 7.4−7.2 (m, 15 H), 7.18 (d, 8.3, 1 H), 7.04 (d, J = 7.2, 1 H), 6.77 (dd, J = 1.8, 8.2, 1 H), 4.74 (d, J = 11.4, 1 H), 4.68 (d, J = 12, 1 H), 4.58 (d, J = 11.5, 1 H), 4.55 (d, J = 12, 1 H), 4.49 (s, 2 H), 4.23 (dd, J = 5.8, 6.8, 1 H), 4.0−4.13 (m, 1 H), 3.96−3.91 (m, 1 H), 3.39 (d, J = 4.6, 2 H), 1.84−1.78 (2 H), 0.91 (s, 9 H), 0.07 (s, 2 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 141.55, 139.14, 138.88, 138.68, 134.54, 130.54, 130.40, 129.98, 128.82, 128.76, 128.56, 128.18, 127.92 120.36, 115.46, 114.65, 90.43, 77.73, 75.87, 73.84, 73.15, 71.77, 69.46, 36.86, 1.71, −2.26, −2.90, −3.02, −3.18, −4.03

2,3,6-Tri-*O*-benzyl-4-deoxy-5-*O*-(*tert*-butyldimethylsilyl)-*aldehydo*-D-*xylo*-hexose (9). From (dichlorophenyl)hydrazone **8**: Ozonolysis as for **3** gave **9** (36%). From dimethylhydrazone **13**: Ozonolysis of **13** (384 mg, 0.64 mmol) for 10 min gave **9** (333 mg; 94%) as a clear, colorless syrup. The aldehyde slowly oxidizes in air to give 2,3,6-tri-*O*-benzyl-4-deoxygluconic acid (**14**). ^1H NMR: ($CDCl_3$): δ 9.78 (d, J = 1.4, 1 H). 7.2−7.4 (m, 15 H), 4.75 (d, J = 11.8 Hz, 1 H), 4.61 (d, J = 4.0 Hz, 2 H), 4.60 (d, J = 11.8 Hz, 1 H), 4.44 (s, 2 H), 4.06−4.16 (m, 2 H), 3.96 (dd, J = 1.4, 4.3, 1 H) 3.42 (dd, J = 5.5, 9.7, 1 H), 3.38 (dd, J = 5.2, 9.7, 1 H), 1.88 (dd, J = 4.2, 7.6 Hz, 2 H), 0.932 (s, 3 H), 0.895 (s, 3 H), 0.992 (s, 3 H), 0.060 (s, 3 H), 0.051 (s, 3 H); ^{13}C (C_6D_6): δ 201.7, 138.4, 138.3, 137.6, 126.0, 125.97, 125.7, 125.6, 125.3, 76.2, 75.2, 72.9, 72.8, 72.6, 72.0, 68.8, 36.3, −4.0, −4.2, −4.9, −5.0, −5.1; IR (neat); 1732 (C═O). For $C_{33}H_{44}O_5Si$: MS (FAB): calculated: m/z 548 (100.00), 549 (42.97), 550 (13.26), 551 (2.89); found: 548 (100), 549 (42), 550 (13), 551 (2).

2,3,6-Tri-*O*-benzyl-4-deoxy-D-*xylo*-hexose *N,N*-Dimethylhydrazone (12). A solution of 880 mg (2.03 mmol) of **11** in 15 mL of ethanol was heated to reflux with 10 mg of *p*-toluenesulfonic acid monohydrate and 0.25 mL (3.29 mmol, 1.6 equiv) of *N,N*-dimethylhydrazine for 3 h. The solution was cooled, concentrated, and chromatographed (1:1 Et_2O/hexanes) to give **12** (678 mg; 70%) as a clear, colorless syrup. ^1H NMR (CD_3CN): δ 7.2−7.4 (m, 15 H), 6.43 (d, J = 7.2 Hz, 1 H), 4.72 (d, J = 11.2, 1 H), 4.57 (d, J = 11.87 Hz, 1 H), 4.53 (d, J = 10.9, 1 H), 4.48 (s, 2 H), 4.40 (d, J = 11.86, 1 H), 4.02 (dd, J = 5.93, 6.92 1 H), 3.94−3.83 (m, 2 H), 3.40 (dd, J = 4.45, 9.6, 1 H), 3.33 (dd, J = 6.59, 9.6, 1 H), 2.93 (d, J = 4.94, 1 H) 2.74 (s, 6 H), 1.62−1.52 (m, 2 H); ^{13}C (CD_3COCD_3) δ 139.3, 139.1, 138.9, 133.6, 83.0, 82.2, 77.5. 73.1, 67.5, 66.2, 42.5, 42.3, 35.6; IR (neat): 1498 cm^{-1} (C═N). Anal. Calcd for $C_{29}H_{36}O_4N_2$: C, H, N. HRMS: 476.2674 (calculated); 476.2691 (measured).

2,3,6-Tri-*O*-benzyl-4-deoxy-5-*O*-*tert*-butyldimethylsilyl-D-*xylo*-hexose *N,N*-Dimethylhydrazone (13). A solution of 860 mg (1.8 mmol) of **12** in 20 mL of anhydrous pyridine was stirred under N_2 overnight with 0.5 mL (2.2 mmol, 1.2 equiv) of TBDMSOTf. The mixture was poured into $CHCl_3$, washed first with 1 M HCl and then with water, and dried ($MgSO_4$). Concentration and chromatography (10% EtOAc in hexanes) gave **13** (930 mg; 88%) as a thick, yellow syrup. ^1H NMR ($CDCl_3$): δ 7.2−7.4 (m, 15 H), 6.38 (d, J = 7.25 Hz, H_1), 4.81 (d, J = 11.21, 1 H), 4.61 (d, J = 11.88 Hz, 1 H), 4.52 (d, J = 11.22, 1 H), 4.48 (d, J = 11.88, 1 H), 4.47 (s, 2 H), 4.07 (dd, J = 6.2, 7.26 H_2), 4.06 (t, J = 6, H_5), 3.88 (q, J = 6.2, H_3), 3.36 (d, J = 4.75, 2 × H_6), 2.78 (s, 6 H), 1.72−1.78 (m, 2 × H_4), 0.88 (s, 3 H), 0.87 (s, 3 H), 0.83 (s, 3 H), 0.034 (s, 3 H), 0.020 (s, 3 H); IR (neat): 1471 cm^{-1} (C═N). For $C_{35}H_{50}O_4NSi$, HRMS: 590.3539 (calculated); 590.3528 (measured).

2,3,6-Tri-*O*-benzyl-4-deoxy-5-*O*-(*tert*-butyldimethylsilyl)-D-*xylo*-hexonic Acid (14). A solution of 140 mg (0.26 mmol) of **9** in 5 mL of *tert*-butyl alcohol and 2 mL of water was stirred with 60 mg (0.50 mmol, 2 equiv) of NaH_2PO_4 and 0.1 mL of 2-methyl-1-butene (0.93 mmol, 3.5 equiv) for 5 min. To this, 70 mg (0.77 mmol, 3 equiv) of $NaOCl_2$ was added, and the mixture was stirred for 3 h. The reaction was quenched by addition of 3 mL of saturated Na_2SO_3 solution, and the reaction mixture was poured into 1 M HCl and extracted with CH_2Cl_2. The combined organic layers were washed (water and brine) and dried (Na_2SO_4). Concentration gave **14** (140 mg; 97%) as a pale yellow syrup. ^1H NMR: (C_6D_6): δ 7.0−7.32 (m, 15 H), 4.75 (d, J = 11.3 Hz, 1 H), 4.61 (d, J = 11.6 Hz, 1 H), 4.59 (d, J = 11.3 Hz, 1 H), 4.33 (dd, J = 4.1, 9.2 Hz, 1 H), 4.20 (s, 2 H), 4.17 (d, J = 11.7 Hz, 1 H), 4.10 (d, J = 4.2 Hz, 1 H), 3.10−3.29 (m, 3 H), 2.07 (ddd, J = 14, 9.2, 3.3, 1 H), 1.97 (ddd, J = 14, 9.2, 3.3, 1 H),).956 (s, 9 H), 0.081 (s, 3 H), 0.060 (s, 3 H); ^{13}C ($CDCl_3$): δ 174.28, 138.17, 137.89, 136.91, 128.35, 128.09, 127.98, 127.95, 127.868, 127.68, 75.05, 73.21, 72.96, 72.48, 36.16; IR (neat): 1725 cm^{-1} (C═O). Anal. Calcd for $C_{33}H_{44}O_6Si$, C, H.

4-Deoxy-5-*O*-(*tert*-butyldimethylsilyl)-D-*xylo*-hexonic Acid (15). A solution of 225 mg (0.40 mmol) of **14** in 10 mL of EtOH was stirred with 60 mg of 10% Pd on carbon and 500 μL of cyclohexene under H_2 for 5 days to give **15** (90 mg; 76%) as a clear colorless oil. ^1H NMR (D_2O): δ 4.05 (m, 1 H), 3.94 (m, 1 H), 3.80 (d, J = 2.58, 1 H), 3.53 (d, J = 5, 2 H), 1.70 (ddd, J = 3.1, 10.8, 14, 1 H), 1.56 (ddd, J = 1.8, 9, 14, 1 H), 0.82 (s, 9 H), 0.01 (s, 6 H); IR (neat): 1715 cm^{-1} (C═O).

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Supporting Information Available: ^1H NMR spectra for compounds **2**, **3**, **5**−**9**, **13**, and **15**. Complete elemental analysis data for compounds **1**, **4**, **12**, and **14** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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