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Note

From D-xylose to terminal polyols: a simple synthetic route

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ABSTRACT

A simple and efficient synthetic approach toward different terminal alkyl tetraols and triols, starting from D-xylose, is described. The opening of the oxetane ring in a suitably protected 3,5-anhydro-D-xylose derivative with Grignard reagents leads to D-xylose-derived 5-deoxy-5-*C*-alkyl derivatives, which are suitable for reduction to terminal polyols after protecting group hydrolysis.

With the growing concern for environment protection, sugar-based surfactants have received much attention as solubilizers and emulsifying agents. Carbohydrates are generally considered readily available, cheap, biodegradable, and nontoxic materials.[1] Moreover, carbohydrate-based non-ionic detergents are considered non-denaturant and are widely used in the isolation of membrane proteins in their biologically active form.[2,3] The polar head group in carbohydrate-based surfactants is a sugar moiety to which a hydrophobic tail of choice is coupled.

Carbohydrate surfactants are, as a rule, glycosides.[4–6] The idea of elongating a carbohydrate (head group) by forming a bond between a carbohydrate carbon and an alkyl carbon of a deliberately chosen hydrophobic alkyl tail seems to be a straightforward solution for preparation of non-glycoside types of carbohydrate surfactants. However, general synthetic methods for the preparation of branched-chain carbohydrates do not exist; methods for the formation of carbon–carbon bond are always adapted to the particular reactivity of the carbohydrate moiety.[7] Herein, we report a simple method for the elongation of the D-xylose skeleton at C-5, with almost any chosen alkyl group. The general synthetic strategy consists in oxetane ring opening in easily obtainable 3,5-anhydro-D-xylose **1**[8,9] with Grignard reagents (Scheme 1).

The opening of oxetane rings with nucleophiles, including Grignard reagents, is a known and useful reaction in non-carbohydrate oxetanes. Ring cleavage with Grignard reagents and ring reduction with metal hydrides are regioselective reactions: cleavage occurs generally between the oxygen and the least-substituted ring alpha carbon.[10] In contrast to the numerous synthetic applications of oxetane ring opening with alkyl magnesium halogenides, the opening of carbohydrate-based oxetane rings with Grignard reagents has not been studied much previously, mainly due to the relatively limited number of known oxetane ring structures among carbohydrates. In line with the general reactivity of oxetanes, the Grignard reaction, when applied to **1**, enables a one-step synthesis of 5-*C*-alkyl-5-deoxy derivatives of D-xylose with a variety of alkyl chains. Ready elongation of the D-xylose skeleton with a deliberately chosen lipophilic alkyl chain and with simultaneous preservation of predefined D-xylose configuration on optically active sites is a promising simple synthetic route to different terminal tetraols.

According to our previous investigations, the opening of the oxetane ring in 3,5-anhydro-1,2-*O*-cyclohexylidene-α-D-xylofuranose (**1**) with various nucleophilic reagents (hydrohalogen acids,[9] acetyl haloganides,[11] primary or secondary amines including alkaloids[12]) always proceeds regioselectively and provides good yields of the corresponding 5-deoxy-5-halo-, 3-*O*-acetyl-5-deoxy-5-halo- and 5-deoxy-5-amino-D-xylofuranose derivatives, respectively. This regioselectivity of nucleophilic oxetane ring opening in **1** is demonstrated this time by hydride reduction of the 3,5-anhydro ring: the reaction proceeds almost quantitatively giving **2** in 97% isolated yield. No reduction product resulting from hydride approach to the xylose C-3, as confirmed by NMR data (Tables 1 and 2), was formed.

Further experimental confirmation of this general similarity in reactivity and regioselectivity among carbohydrate and non-car-

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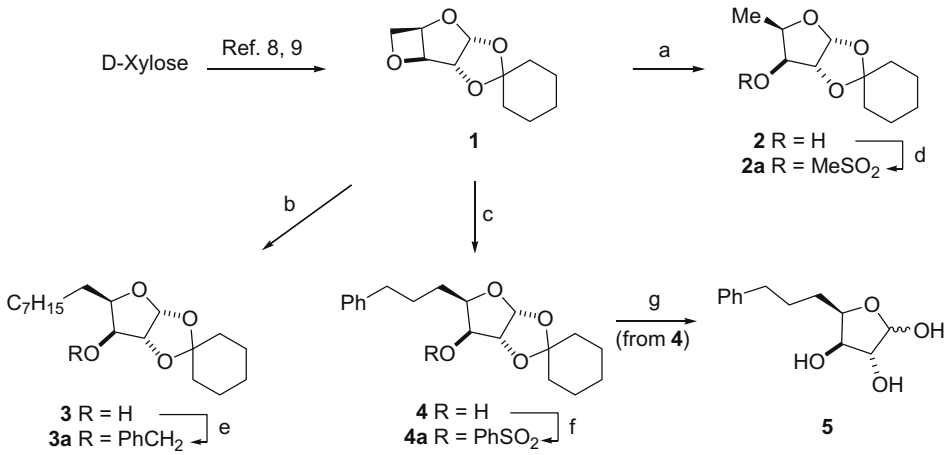

Scheme 1. Oxetane ring opening of 3,5-anhydro-1,2-*O*-cyclohexylidene-α-D-xylofuranose (**1**) with Grignard reagents. Reagents and conditions: (a) $LiAlH_4$,THF, reflux, 3 h; (b) $C_7H_{15}MgBr$, THF, reflux, 3 h; (c) $PhCH_2CH_2MgBr$, THF, reflux, 5 h; (d) MsCl, Py, $CHCl_3$, rt, 12 h; (e) BnCl, KOH, DMSO, 50 °C, 1 h; (f) $PhSO_2Cl$, Py, $CHCl_3$, +4 °C, 48 h; (g) 40% aq AcOH, reflux, 3 h.

bohydrate oxetanes has been obtained in the reaction of **1** with Grignard reagents: heptylmagnesium bromide and 2-phenylethyl magnesium bromide in reaction with **1** gave 5-deoxy-5-*C*-heptyl- and 5-deoxy-5-*C*-(2-phenylethyl)-derivatives **3** and **4**, respectively, as the only isolated products. From the standpoint of searching for terminal polyols, **2**–**4** represent promising starting compounds for the synthesis both terminal 1,2,3,4-alkyl tetraols and 1,2,4-alkyl triols. The alkylidene protecting group in C-5-elongated D-xylose derivatives is easily hydrolyzed with acid, as illustrated herein by hydrolysis of **4** to give the hemiacetal **5**. Because the starting anhydrosugar **1** is an easily obtainable compound, the proposed set of reactions consisting of oxetane ring opening in **1** with Grignard reagents represent a simple and general synthetic route toward terminal 1,2,3,4-alkyl tetraols and terminal 1,2,4-alkyl triols.

1. Experimental

1.1. General methods

Melting points were determined on a Büchi MP 50 apparatus and are not corrected. The NMR spectra were recorded on a Bruker AC250E instrument in $CDCl_3$ using $(CH_3)_4Si$ as an internal standard and are presented in Tables 1 and 2. Mass spectra were recorded with a Termo Finnigan Polaris Q (EIMS) or Finnigan MAT 8230BE spectrometer (CIMS). The first number when referring to the mass spectra denotes the *m/z* value, while the numbers in parenthesis correspond to the relative abundance of the mass peak. TLC was performed on Silica gel DC Alufolien (E. Merck, Darmstadt), with 4:1 toluene–EtOAc as the mobile phase. The polarity of the mobile phase was augmented by the addition of CH_3OH when necessary. Visualization of the spots was achieved by spraying 50% sulfuric acid followed by subsequent heating at 150 °C. Organic extracts were dried with anhydrous Na_2SO_4. Solutions were concentrated using a rotary evaporator under diminished pressure. Active carbon was used as the decolorizing agent.

1.1.1. 1,2-*O*-Cyclohexylidene-5-deoxy-α-D-xylofuranose (2)

Oxetane **1** (2.30 g, 10.8 mmol) was dissolved in THF (30 mL). At rt, $LiAlH_4$ (0.6 g, 15.7 mmol) was added to the solution in portions and the reaction mixture was heated at reflux for 3 h. After cooling, 10% sulfuric acid was added until the separation of layers; the organic layer was dried and evaporated to leave an oil that solidified upon standing. Crystallization from *iso*-octane gave **2** (2.25 g, 97%), mp 89.6 °C; EIMS: 213.9 (M^+, 28), 184.9 (32), 171 (58), 99.1 (58), 81.0 (62); Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.46. Found: C, 61.53; H, 8.43.

Table 1
^{1}H NMR Spectral data for **2**–**5**

	Chemical shifts (ppm), signal shape, and integrals of xylose protons					Coupling constants (Hz)				Other signals
	H-1	H-2	H-3	H-4	H-5	$J_{1,2}$	$J_{3,4}$	$J_{4,5}$	Other	
2	5.88, d, 1H	4.49, d, 1H	3.99, dd, 1H	4.29, qd, 1H	1.28, d, 3H	3.8	2.4	6.3	$J_{3,OH}$ 6.1	1.31–1.74, m, 10H, cy[a]; 2.13, br d, OH;
2a	5.91, d, 1H	4.74, d, 1H	4.88, d, 1H	4.44, qd, 1H	1.32, d, 3H	3.8	2.8	5.4		1.35–1.76, m, 10H, cy[a]; 3.07, s, 3H, Me from Ms;
3	5.89, d, 1H, H-1	4.49, d, 1H	4.06–4.13, m, 2H			3.8				1.18–1.78, 24H, 12 × CH_2 alkyl and cy[a]; 0.88, t, 3H, CH_3;
3a	5.93, d, 1H	4.62, d, 1H	3.80, d, 1H	4.14, td, 1H		3.9	3.0	7.0	CH_2Ph, J_{gem}12.0	0.91, t, 3H, CH_3; 1.14–1.85, m, 24H, 12 × CH_2 alkyl and cy[a]; 4.50 and 4.73, 2d, 2H, CH_2Ph; 7.25–7.41, m, 5H, Ar-H;
4	5.89, d, 1H	4.48, d, 1H	4.03, dd, 1H	4.12, td, 1H		3.8	2.4	6.6	$J_{3,OH}$ 6.6; CH_2Ph, *J* 6.8	1.32–1.84, m, 15H, 7 × CH_2 and OH; 2.68, t, CH_2Ph; 7.15–7.38, m, 5H, Ar-H;
4a	5.89, d, 1H	4.65, d, 1H	4.77, d, 1H	4.14, td, 1H		3.8	2.7	6.7		1.29–1.78, m, 14H, 7 × CH_2; 2.55, t, 2H, CH_2Ph; 7.08–7.97, m, 10H, Ar-H;
5	5.14, s, 1H, β anomer 5.41, d, 1H, α anomer	4.01–4.29, m, 6H, both anomers				4.1				1.50–1.83, m, CH_2-6 and CH_2-5 2.63–2.76, m, CH_2-7, both anomers

[a] cy = cyclohexylidene.

Table 2
^{13}C NMR data for **2**–**5** in $CDCl_3$.

	Chemical shifts (ppm) of xylose carbons					Other signals
	C-1	C-2	C-3	C-4	C-5	
2	103.86	85.00	76.30	75.92	12.70	23.49, 23.82,23.85, 35.54 and 36.14 cyclohexylidene; 112.02 Cq
2a	103.89	83.20	83.00	74.64	13.13	23.38, 23.71, 24.70, 35.55, 36.04, 5 × CH_2; 38.28, Me from Ms; 112.77 Cq
3	103.75	84.78	75.43	80.21		14.09 Me, 22.64, 23.55, 23.89, 24.93, 26.03, 27.60, 29.19, 29.43, 29.72, 31.85, 35.62, 36.19 (12 × CH_2); 112.03 Cq
3a	104.11	81.68	81.94	80.33		14.04, CH_3; 22.58, 23.51, 23.83, 24.89, 25.99, 27.76, 29.13, 29.39, 29.68, 31.80, 35.64, 36.24, 12 × CH_2; 71.59, CH_2Ph; 127.53, 127.68, 128.30, 137.65 (Ar-C); 111.73 Cq
4	103.74	84.74	75.43	80.05		23.53, 23.86, 24.89, 27.14, 27.76, 35.60, 35.81, 36.18 (8 × CH_2, cyclohexylidene and CH_2-5, CH_2-6, CH_2-7); 125.81, 128.39, 141.94 (Ar-C); 112.06 Cq
4a	103.70	82.76	82.84	78.68		23.34, 23.69, 24.70, 27.18, 27.24, 35.51, 35.53, 36.01, 8 × CH_2; 125.72, 127.71, 128.18, 128.26, 129.30, 134.09, 135.92, 141.58 (Ar-C); 112.62 Cq
5	98.38[a] 104.44[b]					29.95, 30.14, 30.65, 31.27, 37.71 (CH_2-5, CH_2-6, CH_2-7, both anomers); 77.97, 78.75, 79.08, 81.92, 83.68, 84.73 (C-2, C-3, C-4, both anomers); 124.63, 124.69, 128.77, 131.42, 145.65 Ar-C both anomers;

[a] α-Anomer.
[b] β-Anomer.

1.1.2. 1,2-*O*-Cyclohexylidene-5-deoxy-3-*O*–methanesulfonyl-α-D-xylofuranose (2a)

A solution of methanesulfonyl chloride (0.75 g, 6.5 mmol) in $CHCl_3$ (5 mL) was added to a solution of **2** (1.07 g, 5 mmol) in a mixture of $CHCl_3$ (5 mL) and pyridine (5 mL) in one portion at rt. After standing for 12 h, $CHCl_3$ (100 mL) was added and the mixture was washed with 10% aqueous hydrochloric acid and then with H_2O. The organic solution was dried and evaporated to a colored oil that solidified on standing. Crystallization from isopropanol gave **2a** (0.92 g, 63%), as silky crystals, mp 94 °C; EIMS: 291.8 (M^+, 24), 248.8 (54), 153.0 (30), 81.1 (25), 79.1 (22), 69.1 (20), 55.1 (100); Anal. Calcd for $C_{12}H_{20}O_6S$: C, 49.30; H, 6.90. Found: C, 49.46; H, 6.92.

1.1.3. 1,2-*O*-Cyclohexylidene-3-*O*-benzyl-5-deoxy-5-*C*-(2-heptyl)-α-D-xylofuranose (3a)

A crystal of iodine was added to magnesium turnings (1.46 g, 60 mmol) in dry THF (25 mL) and then heptyl bromide (10.74 g, 60 mmol) was added while stirring, in one portion at rt. Vigorous reaction started spontaneously and then the reaction mixture was cooled externally, and afterward was heated at reflux. The complete dissolution of magnesium was evident in 40 min. Oxetane **1** (8.5 g, 40 mmol) in THF (10 mL) was added dropwise. After the reaction mixture was heated at reflux for another 3 h, the reaction was assumed to be complete. The mixture was quenched by the addition of aqueous hydrochloric acid (10%) and products were extracted with hexane (3 × 80 mL). Evaporation of the combined extracts left a mass with a soapy-waxy appearance on standing. TLC showed a spot corresponding to a new compound and another faint spot that could be attributed to heptanol by comparison with an analytical sample. Attempts to crystallize the product were unsuccessful. The crude product was dissolved in hot CH_3OH (100 mL), and H_2O (150 mL) was added. After cooling and standing overnight a white soapy deposit (9 g) was formed. The mass was again dissolved in hot isopropanol (100 mL), and H_2O (150 mL) was added. Cooling resulted in white soapy-waxy deposit (8.2 g, 66% calculated on **1**), which was a single component according to TLC and melted at 40–45 °C, after drying. However, satisfactory elemental analysis could not be obtained. IR: 3450 sharp, hydroxyl group; ^1H NMR and ^{13}C NMR data were in accordance with proposed structure of 1,2-*O*-cyclohexylidene-5-deoxy-5-*C*-(2-heptyl)-α-D-xylofuranose (**3**), (see Tables 1 and 2).

To the mixture of crude **3** (1 g, 3.2 mmol), dimethylsulfoxide (5 mL) and benzyl chloride (0.6 g, 48 mmol) was added finely grounded sodium hydroxide (0.3 g) in one portion. The reaction mixture was stirred at 50 °C for 1 h, then poured into H_2O and extracted with CH_2Cl_2 (3 × 50 mL). Combined extracts were washed with H_2O (2 × 50 mL), dried, and evaporated to an oil. High vacuum distillation gave **3a** (0.8 g, 62%) as an oil, CI MS: M + 1 = 403 (100); Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.54; H, 9.29.

1.1.4. 1,2-*O*-Cyclohexylidene-5-deoxy-5-*C*-(2-phenylethyl)-α-D-xylofuranose (4)

A crystal of iodine was added to magnesium turnings (2.83 g, 116 mmol) covered with dry Et_2O. A solution of 2-bromoethyl benzene (20.35 g, 110 mmol) in dry Et_2O (80 mL) was added dropwise to the suspension. The reaction started easily and was complete after 2 h at reflux. The addition of oxetane **1** (23.3 g, 110 mmol in 80 mL of Et_2O) then commenced. During the addition, the reaction mixture tended to solidify and at this stage, dry benzene (80 mL) was added and the reaction flask was heated to distill off Et_2O until the temperature of distillate reached 55 °C. After 5 h at reflux, the reaction was assumed to be complete. Then aqueous hydrochloric acid (10%) was added until the organic and H_2O layers separated. The organic layer was washed with H_2O and concentrated. The addition of petroleum ether, followed by cooling, resulted in crystallization of **4** (21.5 g, 61%), mp 100–102 °C. EIMS: 317.9 (M^+, 53), 288.9 (26), 274.9 (29), 203.1 (36), 185.1 (100), 157.1 (58); Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.36; H, 8.30.

1.1.5. Attempted sulfonylation of 4: 3-*O*-Benzenesulfonyl-1,2-*O*-cyclohexylidene-5-deoxy-5-*C*-(2-phenylethyl)-α-D-xylofuranose (4a)

To a solution of **4** (2.0 g, 6.2 mmol) in a mixture of $CHCl_3$ (5 mL) and pyridine (3 mL) was added a solution of benzenesulfonyl chloride (1.2 g, 6.7 mmol) in $CHCl_3$ (5 mL) in one portion at rt. The reaction mixture was left for 48 h at 4 °C and then the mixture was diluted with $CHCl_3$ (100 mL), washed with hydrochloric acid (10%), and then with H_2O. Drying and evaporation of the solvent left **4a** as an oil (2.2 g, 77%). Satisfactory proof of **4a** purity (elemental analysis) could not be obtained, but MS and NMR analysis clearly support the proposed structure. EIMS $C_{25}H_{30}O_6S$: 458.0 (M^+, 85), 414.9 (48), 309.9 (92), 257.0 (43), 203.1 (64), 185.1 (100).

1.1.6. 5-Deoxy-5-*C*-(2-phenylethyl)-D-xylofuranose (5)

A solution of compound **4** (5.0 g, 16 mmol) was hydrolyzed in a mixture of acetic acid (40 mL) and H_2O (60 mL) at reflux for 3 h. Then, H_2O (150 mL) was added and the reflux condenser was changed for distillation. Part of the reaction mixture was distilled off (~100 mL) to diminish the quantity of acetic acid. The remaining was neutralized (aq sodium carbonate) and extracted with EtOAc (4 × 50 mL). Concentration of combined extracts and addition of petroleum ether resulted in crystallization of pure **5** (2.83 g, 74%), mp 108 °C; CI MS: 239 (M^++1, 42), 221 (45), 203 (40), 185

(100), 161 (65); Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.45; H, 7.56

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