Efficient "Dehomologation" of Di-*O*-isopropylidenehexofuranose Derivatives To Give *O*-Isopropylidenepentofuranoses by Sequential Treatment with Periodic Acid in Ethyl Acetate and Sodium Borohydride

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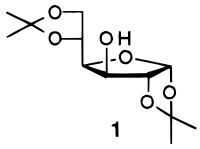
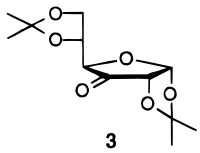
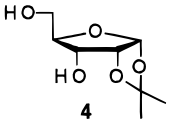
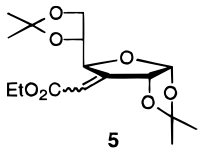
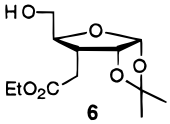
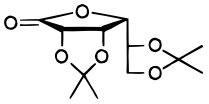
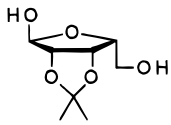
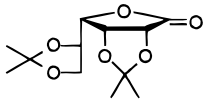
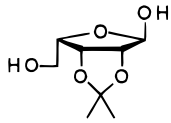
Cascade chemistry, "one-pot" sequential transformations in organic synthesis, provides convenient and efficient methods for the preparation of a variety of organic compounds,[1,2] and carbohydrates are a readily available source of chiral building blocks for the synthesis of biologically relevant molecules. It was recently reported that periodic acid in diethyl ether effected selective hydrolysis of the terminal *O*-isopropylidene group from acyclic carbohydrates that also contained internal acetals.[3a] Sequential oxidative cleavage of the exposed glycol then removed the terminal carbon with concomitant generation of an aldehyde.[3] We now report parallel results which extend the scope, provide improved reaction conditions, and add the reduction step. This sequence results in efficient "dehomologation" of di-*O*-isopropylidenehexofuranoses to give useful *O*-isopropylidenepentofuranoses without purification of intermediates.

This methodology is readily applicable to furanose diacetals. Ethyl acetate as solvent gives smoother conversions, and with a wider range of substrates, than diethyl ether (dichloromethane and tetrahydrofuran gave poor results). The mixture is filtered after selective hydrolysis/oxidation is complete, and the filtrate is evaporated. The syrupy residue is dissolved in ethanol and treated with sodium borohydride to reduce the terminal aldehyde and complete the overall dehomologation of hexofuranose diacetals to pentofuranose acetals.

Our results are summarized in Table 1. Sequential treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**, entry 1) gave 1,2-*O*-isopropylidene-α-D-xylofuranose (**2**, 95%). In entries 2 and 3, reduction to give **4** and **6** occurred stereoselectively from the β face (only the noted isomer was observed in ^{1}H and ^{13}C NMR spectra). Precedents exist for stereoselective reductions of ketones and conjugated esters via participation of the hydroxymethyl group in delivery of borohydride species at the β face.[4−6] Entries 4 and 5 also have apparent selectivity in harmony with participating delivery of the hydride and opposite to that expected on steric grounds from a bimolecular process. However, the anomeric structures of those hemiacetals are mobile and could represent the more thermodynamically stable diastereomers. The lactones **7** and **9** have low solubility in diethyl ether, and ethyl acetate as solvent was markedly advantageous. As expected, periodic acid in ethyl acetate functioned as a selective acid catalyst for hydrolysis of a 6-membered terminal isopropylidene acetal in the presence of a 5-membered anomeric acetal. Thus, treatment of 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**11**, Scheme 1) under our usual conditions gave 1,2-*O*-isopropylidene-α-D-xylofuranose (**2**, 96%). The products of the three-stage sequential conversions have been reported previously, except **6**, and their ^{1}H and ^{13}C NMR spectra are in agreement with literature values. The stereochemistry at C3 of **6** was confirmed by its parallel preparation from the known hexose derivative **12**[7] (Scheme 1).

Table 1. Sequential Hydrolysis, Oxidation,[a] and Reduction of Furanose Diacetal Derivatives

entry	substrate (1 mmol)	$NaBH_4$ (mmol)	product	yield (%)
1	 **1**	1.5	**2**	95
2	 **3**	2.5	 **4**	92
3	 **5**	3.0	 **6**	85
4	 **7**	1.0	 **8**	60
5	 **9**	1.0	 **10**	60

[a] All conversions employed 1.2 mmol of H_5IO_6.

In summary, selective acid-catalyzed hydrolysis of terminal *O*-isopropylidene acetals and oxidative cleavage of the exposed glycol with periodic acid followed by reduction of the resulting terminal aldehyde with sodium borohydride provides an efficient three-stage dehomologation of readily available hexofuranose diacetals to pentofuranose acetal derivatives. Ethyl acetate is an advantageous solvent for periodic acid and a number of carbohydrate derivatives.

Experimental Section

^{1}H (200 or 500 MHz) and ^{13}C (50 MHz) NMR spectra were recorded with solutions in TMS/$CDCl_3$. Low-resolution electron-impact mass spectra (MS) were determined at 20 eV. Com-

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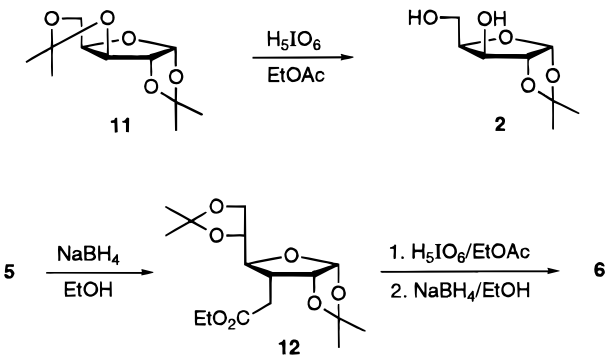
Scheme 1



pounds **1** and **11** were obtained from Aldrich, and **3**,[8] **5**,[9] **7**,[10] and **9**[10] were prepared as described. Products **2**,[11] **4**,[12] **8**,[13] **10**,[14] and intermediate **12**[7] were reported previously and have melting points and ^{1}H and ^{13}C NMR data in harmony with literature values.

General Method for Sequential Selective Hydrolysis, Oxidative Cleavage, and Reduction. A solution of the dried di-*O*-isopropylidene compound (1 mmol) and H_5IO_6 (1.2 mmol) in dried EtOAc (10 mL) was stirred for 2 h. The reaction mixture was filtered, and the filtrate was evaporated. The residue was dissolved in EtOH (abs, 15 mL), and $NaBH_4$ (Table 1) was added in small portions with vigorous stirring. Stirring was continued for 30 min, excess HOAc was added, and volatiles were evaporated. The residue was dissolved (EtOAc), the solution was washed (H_2O), dried (Na_2SO_4), and evaporated, and volatiles were removed in vacuo (oil pump) overnight to give the product with yields as noted.

1,2-*O*-Isopropylidene-α-D-xylofuranose (2). A solution of **11** (230 mg, 1.00 mmol) and H_5IO_6 (274 mg, 1.20 mmol) in EtOAc (10 mL) was stirred for 2 h. The mixture was filtered, and the filtrate was evaporated. The residue was dissolved (EtOAc), washed (H_2O), dried (Na_2SO_4), and evaporated to give **2**[11] (171 mg, 96%): ^{1}H NMR δ 5.97 (d, J = 3.7 Hz, 1H), 4.51 (d, J = 3.7 Hz, 1H), 4.31 (m, 1H), 4.25 (br, 1H), 4.15 (m, 1H), 4.04 (m, 2H), 3.26 (br, 1H), 1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR δ 112.2, 105.2, 85.8, 79.9, 76.4, 60.9, 27.1, 26.6.

3-Deoxy-3-C-[(ethoxycarbonyl)methyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (6). $NaBH_4$ (57 mg, 1.5 mmol) was added portionwise to a solution of **5**[9] (328 mg, 1.00 mmol) in EtOH (abs, 15 mL), and the mixture was stirred overnight. Excess HOAc was added, volatiles were evaporated, and the residue was dissolved (EtOAc). The solution was filtered and evaporated to give 3-deoxy-3-*C*-[(ethoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[7] (**12**, quantitative). Treatment of **12** with H_5IO_6/EtOAc (dried) as described in the general method gave **6** (oil; 234 mg, 90% from **5**). "Diffusion" crystallization[15] (EtOAc/hexanes) gave **6**: mp 37−39 °C; ^{1}H NMR ($CDCl_3$) δ 5.80 (d, J = 3.7 Hz, 1H), 4.77 (t, J = 3.8 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.81−3.91 (m, 2H), 3.70 (br s, 1H), 3.55 (dd, J = 13.2, 4.2 Hz, 1H), 2.60−2.74 (m, 1H), 2.30−2.50 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{1}H NMR (DMSO-d_6/D_2O) δ 5.77 (d, J = 3.7 Hz, 1, H1), 4.70 ("t", J = 4.2 Hz, 1, H2), 4.07 (q, J = 7.1 Hz, 2, OEt), 3.67 (dt, J = 9.9, 3.7 Hz, 1, H4), 3.56 (dd, J = 12.4, 3.0 Hz, 1, H5), 3.41 (dd, J = 12.4, 4.4 Hz, 1, H5'), 2.49 (d, J = 7.5 Hz, 2, CH_2CO), 2.15−2.28 (m, 1, H3), 1.40 (s, 3, Me), 1.25 (s, 3, Me), 1.21 (t, 3, OEt); irridiation at δ 2.21 (H3) caused simplification of the signals at δ 4.70 (H2) and 3.67 (H4); ^{13}C NMR ($CDCl_3$) δ 172.5, 111.7, 105.1, 81.7, 61.5, 60.9, 40.3, 30.0, 26.9, 26.6, 14.4; MS m/z 260 (M^+). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.54; H, 7.76.

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