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Rhodium-Catalyzed Decarbonylation of Aldoses

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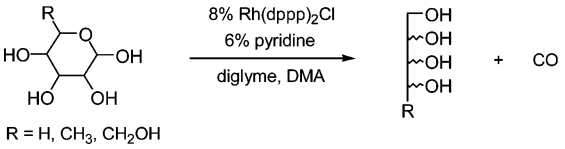
Received August 14, 2007



A catalytic procedure is described for decarbonylation of unprotected aldoses to afford alditols with one less carbon atom. The reaction is performed with the rhodium complex $Rh(dppp)_2Cl$ in a refluxing diglyme−DMA solution. A slightly improved catalyst turnover is observed when a catalytic amount of pyridine is added. Under these conditions most hexoses and pentoses undergo decarbonylation into the corresponding pentitols and tetrols in isolated yields around 70%. The reaction has been applied as the key transformation in a five-step synthesis of L-threose from D-glucose.

Extending or shortening the carbon chain in unprotected aldoses has been a subject in carbohydrate chemistry for more than a century.[1] Although many methods are known for chain elongation of aldoses[2] there are only a few procedures for shortening the carbon chain. The Ruff degradation converts salts of aldonic acids into one carbon shorter aldoses.[3] The reaction is performed with hydrogen peroxide in the presence of iron(III) or copper(II) salts and often occurs in a moderate yield. Another oxidative degradation reaction converts aldoses into salts of aldonic acids with loss of one carbon atom.[4] This reaction is carried out with molecular oxygen in an alkaline solution and gives rise to a good yield in most cases. Moreover, these procedures for shortening the carbon chain both involve stoichiometric amounts of inorganic salts.

Aldoses are aldehydes that can undergo a C−H insertion reaction with a metal followed by decarbonylation. This transformation converts C_n aldoses into C_{n-1} alditols. Andrews and co-workers exploited this transformation with stoichiometric amounts of Wilkinson's catalyst ($Rh(PPh_3)_3Cl$).[5] The decarbonylation was performed in *N*-methyl-2-pyrrolidinone (NMP) at 130 °C and afforded alditols in isolated yields ranging from 37% to 87%.[5] The high temperature is due to the fact that only a minute amount of the aldose is present as the free aldehyde in solution. Ketohexoses underwent decarbonylation under the same conditions, but in this case the main product was furfuryl alcohol since ketohexoses are easily dehydrated into 5-hydroxymethylfurfural.[6] The reactions are stoichiometric since $Rh(PPh_3)_3Cl$ is converted into $Rh(CO)(PPh_3)_2Cl$, which will not perform the decarbonylation unless the temperature is raised to about 200 °C. However, if additives are added the decarbonylation of D-glucose can be achieved with 5−10% of $Rh(PPh_3)_3Cl$ in an NMP solution.[7] The additives are either diphenylphosphoryl azide,[8] sodium azide (both at 50 °C for 24 h), or a 1,ω-bis(diphenylphosphino)alkane (alkane = ethane, butane, hexane, at 130 °C for 24 h). In all cases, the conversion was rather slow and only a 30−49% HPLC yield of D-arabinitol was obtained in 24 h.[7]

Earlier work has shown that catalytic decarbonylations of aldehydes can be carried out with rhodium catalysts containing a bidentate phosphine ligand.[9] The complex $Rh(dppp)_2Cl$ (dppp = 1,3-bis(diphenylphosphino)propane) has been shown to decarbonylate simple aldehydes in neat solution.[9] Unfortunately, $Rh(dppp)_2Cl$ is not very soluble in organic solvents and has only found limited use as a decarbonylation catalyst. Recently, we reinvestigated the application of $Rh(dppp)_2Cl$ in this reaction and found that the decarbonylation of a wide range of aldehydes could be effectively achieved in refluxing diglyme and that the active catalyst could be generated in situ from commercially available $RhCl_3 \cdot 3H_2O$ and dppp.[10]

Herein, we describe the catalytic decarbonylation of unprotected aldoses by the use of $Rh(dppp)_2Cl$. The reaction gives easy access to a number of chiral polyols which can be used as building blocks for further synthesis. Furthermore, the decarbonylation has been applied as the key step in a concise synthesis of L-threose from D-glucose.

The initial experiments were performed with D-glucose as the substrate. It soon became clear that the decarbonylation could not be achieved with an in situ generated catalyst. When glucose, $RhCl_3 \cdot 3H_2O$, and dppp were mixed in refluxing diglyme the reaction immediately turned black due to precipitation of rhodium metal. Our earlier work has shown that Rh(III) is reduced to Rh(I) by dppp,[10] but glucose is also a reducing agent and is probably responsible for the further reduction to Rh(0). It was also attempted to form the active catalyst by mixing $RhCl_3 \cdot 3H_2O$ and dppp in refluxing diglyme and then adding glucose. However, these experiments mainly led to decomposition of the carbohydrate. As a result, it was decided to use a preformed catalyst, $Rh(dppp)_2Cl$, which can be prepared in two

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(2) For recent examples, see: (a) Palmelund, A.; Madsen, R. *J. Org. Chem.* **2005**, *70*, 8248. (b) Hotchkiss, D.; Soengas, R.; Simone, M. I.; van Ameijde, J.; Hunter, S.; Cowley, A. R.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 9461. (c) Hunter, D. F. A.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3831. (d) Jørgensen, M.; Iversen, E. H.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4625.

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10.1021/jo7017729 CCC: $37.00
Published on Web 11/03/2007

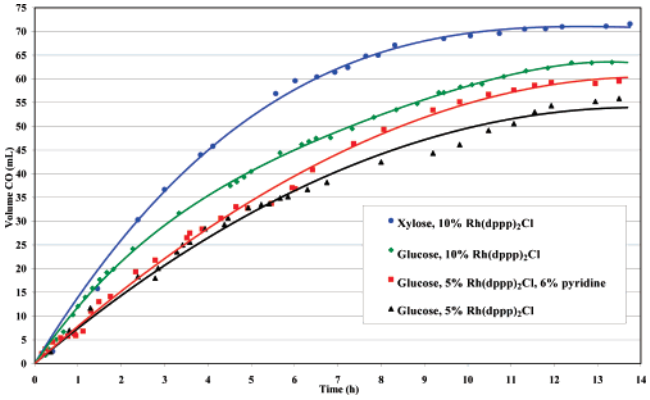


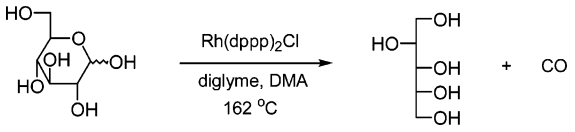
FIGURE 1. CO evolution during the course of the decarbonylation (see the Experimental Section for details).

steps from $RhCl_3 \cdot 3H_2O$.[11] The reaction with this catalyst gave D-arabinitol as the main product, but the decarbonylation was still accompanied by significant decomposition due to the poor solubility of glucose in diglyme. Several cosolvents were investigated and it was found that smaller amounts of water, NMP, or *N*,*N*-dimethylacetamide (DMA) gave rise to a homogeneous reaction mixture. Unfortunately, water forms an azeotrope with diglyme with a boiling point of 99 °C, which is much lower than the boiling point of diglyme (162 °C). The decarbonylation requires a rather high temperature in order to proceed at a reasonable rate and the reactions in diglyme−water mixtures proceeded too slowly and were highly dependent on the diglyme−water ratio and the scale. NMP was used in the earlier decarbonylations with $Rh(PPh_3)_3Cl$[5−7] and we have shown that simple aldehydes could be decarbonylated in NMP with a catalyst generated from $RhCl_3 \cdot 3H_2O$ and dppp.[10] Glucose also underwent decarbonylation with $Rh(dppp)_2Cl$ in a diglyme−NMP mixture, but it was difficult to remove the high-boiling NMP (bp 202 °C) in the workup. DMA (bp 165 °C), on the other hand, was easier to remove and gave similar results as NMP. We therefore selected a mixture of diglyme and DMA for the decarbonylations of monosaccharides. The progress of the reaction could be monitored by measuring the evolution of carbon monoxide (Figure 1). The solvents were removed in the workup by diluting the reaction with water and washing the mixture with dichloromethane. This afforded D-arabinitol in 71% isolated yield from D-glucose with 10% of $Rh(dppp)_2Cl$ (Table 1, entry 1). The major byproduct was 1,4-anhydro-D-arabinitol, which was isolated in 20% yield and characterized as the corresponding triacetate. Only traces were observed of 2,5-anhydro-D-arabinitol (1,4-anhydro-D-lyxitol) and both anhydro sugars are probably formed from the parent arabinitol due to the high reaction temperature. It was not possible to obtain 1,4-anhydro-D-arabinitol as the major product by increasing the reaction time since these experiments were accompanied by significant decomposition.

The decarbonylation still required a rather high catalyst loading due to the tiny amount of the free aldehyde at equilibrium.[12] A lower catalyst loading gave a lower yield due to incomplete conversion and decomposition (Table 1, entry 2 and Figure 1). It is known, however, that the mutarotation of aldoses can be accelerated by acid or base.[13] Therefore, several experiments were performed in the presence of acetic acid or pyridine (Table 1, entries 3−6). Both additives had a beneficial effect and made it possible to obtain higher yields with a shorter reaction time. Pyridine gave the best result and it was therefore decided to carry out the decarbonylation in the presence of 6% of pyridine (Figure 1). Under these conditions complete conversion of glucose was achieved with 8% of $Rh(dppp)_2Cl$ in 8 h (Table 1, entry 7).

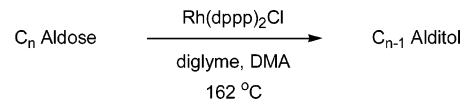
The reaction was then applied to a number of other monosaccharides (Table 2). The experiments were performed in the presence and in the absence of pyridine to illustrate the effect of the added base. The pentoses generally reacted slightly faster than the hexoses (Table 2 and Figure 1). Arabinose, ribose, xylose, mannose, and rhamnose gave similar yields as glucose

TABLE 1. Decarbonylation of D-Glucose into D-Arabinitol



entry	amount of $Rh(dppp)_2Cl$, %	additive	reaction time, h	isolated yield, %
1	10	none	9	71
2	5	none	11	44
3	5	7% AcOH	9.5	39
4	5	15% AcOH	9	51
5	5	6% pyridine	9.5	55
6	5	13% pyridine	9.5	58
7	8	6% pyridine	8	71

TABLE 2. Decarbonylation of Pentoses and Hexoses



entry	aldose	method[a]	reaction time, h	alditol	isolated yield, %
1	D-arabinose	A	9	erythritol	68
2	D-arabinose	B	6.5	erythritol	70
3	D-ribose	A	8	erythritol	71
4	D-ribose	B	6.5	erythritol	76
5	D-xylose	A	8	D-threitol	70
6	D-xylose	B	7.5	D-threitol	74
7	D-mannose	A	9	D-arabinitol	69
8	D-mannose	B	8	D-arabinitol	72
9	L-rhamnose	A	11	5-deoxy-L-arabinitol	66
10	L-rhamnose	B	10	5-deoxy-L-arabinitol	71
11	D-galactose	A	9	D-arabinitol	39
12	D-galactose	B	8	D-arabinitol	56
13	*N*-acetyl-D-glucosamine	A	16	1-acetylamino-1-deoxy-D-arabinitol	42
14	*N*-acetyl-D-glucosamine	B	14.5	1-acetylamino-1-deoxy-D-arabinitol	40[b]

[a] A: 10% $Rh(dppp)_2Cl$. B: 8% $Rh(dppp)_2Cl$, 6% pyridine. [b] 15% of pyridine was used.

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(12) Glucose exists as a mixture of the free aldehyde (0.019%), the hydrated aldehyde (0.022%), two pyranose forms (98.6%), and two furanose forms (1.29%) in an aqueous solution at 82 °C; see: Maple, R. R.; Allerhand, A. *J. Am. Chem. Soc.* **1987**, *109*, 3168.

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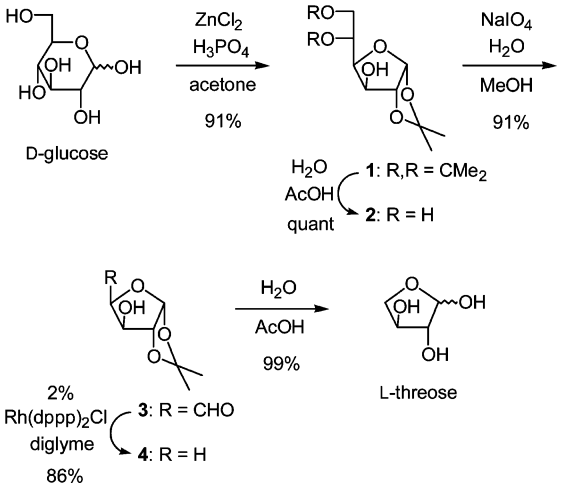
SCHEME 1



while the yields with galactose and *N*-acetylglucosamine were lower. Galactose is less soluble in diglyme−DMA than the other aldoses while *N*-acetylglucosamine is known to decarbonylate slowly due to coordination with the *N*-acetyl group.[5] The long reaction time and the high temperature did result in some decomposition of *N*-acetylglucosamine during the course of the reaction. In all cases, however, the addition of pyridine gave a faster transformation and made it possible to use slightly less of the rhodium catalyst. As in the case of the initial experiments with glucose, the major byproducts were C_{n-1} 1,4-anhydroalditols. For example, 1,4-anhydro-D-arabinitol was isolated in 20% yield from the experiment in entry 8 while 1,4-anhydro-5-deoxy-L-arabinitol was obtained in 17% yield from the reaction in entry 10.

The reaction can also be applied to partially protected carbohydrate substrates. We envisioned that the tetrose L-threose could be prepared from D-glucose in a few steps by using the decarbonylation as the key step. L-Threose is a useful chiral starting material,[14] but is not available from natural sources. It has previously been prepared by oxidative degradation of other carbohydrates[15] and from L-tartaric acid.[16] However, none of these routes takes advantage of the most abundant carbohydrate, D-glucose.

The synthesis of L-threose began by converting glucose into diisopropylidene glucofuranose **1**[17] (Scheme 1). The more labile 5,6-*O*-isopropylidene acetal was selectively hydrolyzed in aqueous acetic acid followed by evaporation of the solvent. The crude triol **2** was then subjected to periodate cleavage to afford aldehyde **3**.[18] Previously, periodic acid (H_5IO_6) in dry ether has been shown to affect acetal hydrolysis and glycol cleavage in one step.[19] Unfortunately, when we applied this procedure to **1** we only obtained **3** in 40−50% yield, which is much lower than the 91% yield for the two-step procedure. Aldehyde **3** crystallizes as the dimer, but slowly equilibrates in aqueous solution to form the monomer. Contrary to the unprotected aldoses, aldehyde **3** is easy to dissolve in pure diglyme. Again, it was not possible to conduct the decarbonylation with an in situ generated catalyst from $RhCl_3 \cdot 3H_2O$ and dppp since this experiment only led to precipitation of rhodium metal. However, when aldehyde **3** was submitted to 2% of $Rh(dppp)_2Cl$, clean decarbonylation occurred into 1,2-*O*-isopropylidene-*β*-L-threofuranose (**4**). Subsequent removal of the acetal then afforded L-threose in an overall yield of 71% from D-glucose. L-Threose is a syrup and exists as an almost equal mixture of the α- and the *β*-anomer together with a small amount of the hydrate of the aldehyde.

In conclusion, we have developed a catalytic procedure for decarbonylation of unprotected and partially protected carbohydrate aldehydes. This transformation will open new possibilities for using carbohydrates as chiral starting materials in synthetic chemistry.

Experimental Section

General Procedure for Decarbonylation of Unprotected Aldoses. To the aldose (400−650 mg, 2.78 mmol) were added $Rh(dppp)_2Cl$ (214 mg, 0.22 mmol), DMA (3 mL), diglyme (20 mL), and freshly distilled pyridine (14.5 *μ*L, 0.18 mmol). The mixture was thoroughly degassed under high vacuum and then stirred at reflux (162 °C) under a nitrogen atmosphere until TLC (acetone/BuOH/H_2O = 5:4:1) showed full conversion to the corresponding alditol (6−16 h). The solution was cooled to room temperature followed by addition of water (50 mL). The mixture was washed with CH_2Cl_2 (4 × 50 mL) and the combined organic phases were extracted with water (2 × 10 mL). The combined aqueous phases were concentrated and the residue co-concentrated with EtOH. The resulting residue was further purified by either flash column chromatography (CH_2Cl_2/MeOH/H_2O = 4:1:0 to 65:25:4) or reverse phase column chromatography (H_2O). The reaction could also be monitored by measuring the evolution of carbon monoxide. In this case, the reaction flask was connected to a burette filled with water. The bottom of the burette was further connected to a water reservoir with a large surface area. At rt (25 °C) full conversion of the aldose corresponds to 68 mL of carbon monoxide.

D-Arabinitol. White crystals. R_f 0.49 (acetone/BuOH/H_2O = 5:4:1). $[\alpha]^{22}_D$ −10.3 (*c* 0.2, MeOH) (lit.[20] $[\alpha]^{19}_D$ −12 (*c* 1, MeOH)). Mp 98−99 °C (MeOH) (lit.[21] mp 101−102 °C (EtOH)). ^{1}H NMR (300 MHz, D_2O) *δ* 3.86 (ddd, *J* = 2.0, 5.3, 7.3 Hz, 1H), 3.77 (dd, *J* = 2.7, 11.5 Hz, 1H), 3.68 (ddd, *J* = 2.7, 6.2, 8.8 Hz, 1H), 3.58 (m, 3H), 3.50 (dd, *J* = 2.0, 8.3 Hz, 1H). ^{13}C NMR (75 MHz, D_2O) *δ* 72.3, 71.8, 71.7, 64.5, 64.4. Anal. Calcd for $C_5H_{12}O_5$: C, 39.47; H, 7.95. Found: C, 39.55; H, 7.65.

Erythritol. White crystals. R_f 0.47 (acetone/BuOH/H_2O = 5:4:1). Mp 116−117 °C (MeOH/heptane) (lit.[22] mp 120−121 °C). ^{1}H NMR (300 MHz, D_2O) *δ* 3.74−3.65 (m, 2H), 3.62−3.49 (m, 4H). ^{13}C NMR (75 MHz, D_2O) *δ* 73.3, 64.0. Anal. Calcd for $C_4H_{10}O_4$: C, 39.34; H, 8.25. Found: C, 39.05; H, 8.00.

D-Threitol. White crystals. R_f 0.52 (acetone/BuOH/H_2O = 5:4:1). $[\alpha]^{22}_D$ −7.5 (*c* 0.5, MeOH) (lit.[23] $[\alpha]^{23}_D$ −7.0 (*c* 0.9, MeOH)). Mp 89−91 °C (MeOH) (lit.[24] mp 90−91 °C (BuOH)). ^{1}H NMR

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(300 MHz, D_2O) δ 3.69−3.51 (m, 6H). ^{13}C NMR (75 MHz, D_2O) δ 72.9, 63.9. Anal. Calcd for $C_4H_{10}O_4$: C, 39.34; H, 8.25. Found: C, 39.19; H, 8.05.

5-Deoxy-L-arabinitol. Colorless syrup. R_f 0.68 (acetone/BuOH/H_2O = 5:4:1). $[\alpha]^{22}_D$ +11.7 (*c* 3.8, MeOH). $[\alpha]^{22}_D$ +13.1 (*c* 0.5, H_2O) (reported for the enantiomer[25] $[\alpha]^{23}_D$ −10.6 (H_2O)). ^1H NMR (300 MHz, D_2O) δ 3.85−3.74 (m, 2H), 3.64−3.53 (m, 2H), 3.38−3.28 (m, 1H), 1.17 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, D_2O) δ 74.6, 70.7, 67.1, 63.1, 18.3. Anal. Calcd for $C_5H_{12}O_4$: C, 44.11; H, 8.88. Found: C, 43.85; H, 8.59.

1-Acetylamino-1-deoxy-D-arabinitol. White crystals. R_f 0.49 (acetone/BuOH/H_2O = 5:4:1). $[\alpha]^{22}_D$ +23.5 (*c* 0.5, H_2O) (lit.[26] $[\alpha]^{22}_D$ +23 (H_2O)). Mp 142−143 °C (MeOH) (lit.[26] mp 146.5−147.5 °C). ^1H NMR (300 MHz, D_2O) δ 3.81 (t, J = 6.7 Hz, 1H), 3.67 (dd, J = 2.6, 11.4 Hz, 1H), 3.57 (ddd, J = 4.4, 7.8, 7.7 Hz, 1H), 3.48 (dd, J = 6.2, 11.5 Hz, 1H), 3.32 (d, J = 8.5 Hz, 1H), 3.25−3.11 (m, 2H), 1.85 (s, 3H). ^{13}C NMR (75 MHz, D_2O) δ 175.4, 71.7, 71.7, 69.1, 63.9, 43.3, 22.8. Anal. Calcd for $C_7H_{15}NO_5$: C, 43.52; H, 7.83; N, 7.25. Found: C, 43.67; H, 7.56; N, 7.18.

1,2-*O*-Isopropylidene-β-L-threofuranose (4). To 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**3**) (500 mg, 2.66 mmol) were added $Rh(dppp)_2Cl$ (51 mg, 0.053 mmol) and a degassed solution of diglyme (10 mL). The mixture was thoroughly degassed and then stirred at reflux (162 °C) in a preheated oil bath for 26 h. The solvent was removed under high vacuum at 70 °C to give a black residue, which was purified by flash column chromatography eluting with ether/pentane = 2:3 to 4:1 to afford **4** (366 mg, 86%) as white crystals. R_f 0.35 (EtOAc/heptane = 3:2). $[\alpha]^{22}_D$ +13.1 (*c* 0.8, acetone) (lit.[15b] $[\alpha]_D$ +13 (*c* 1, acetone)). Mp 80−81 °C (ether) (lit.[15b,27] mp 84−85 °C (ether/hexane)). ^1H NMR (300 MHz, CD_3OD) δ 5.78 (d, J = 3.7 Hz, 1H), 4.35 (d, J = 3.7 Hz, 1H), 4.04 (d, J = 2.8 Hz, 1H), 3.92 (dd, J = 2.9, 9.8 Hz, 1H), 3.68 (dd, J = 1.0, 9.8 Hz, 1H), 1.32 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (50 MHz, CD_3OD) δ 112.7, 106.7, 86.4, 75.9, 73.9, 27.1, 26.4. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.79; H, 7.47.

L-Threose. 1,2-*O*-Isopropylidene-β-L-threofuranose (**4**) (100 mg, 0.62 mmol) was dissolved in 30% aqueous AcOH (10 mL) and heated to reflux for 4 h. The liquids were removed in vacuo and the residue was purified by reverse-phase column chromatography eluting with H_2O to give L-threose (74 mg, 99%) as a colorless oil consisting of a 14:11:5 mixture of the α- and β-furanose forms and the hydrate. R_f 0.57 (acetone/BuOH/H_2O = 5:4:1). $[\alpha]^{22}_D$ +12.3 (*c* 2.0, H_2O) (lit.[15b] $[\alpha]_D$ +12 (*c* 1, H_2O)). ^1H NMR (300 MHz, D_2O) δ 5.33 (d, J = 4.2 Hz), 5.17 (d, J = 1.1 Hz), 4.94 (d, J = 6.3 Hz), 4.50−3.36 (m, 4H). ^{13}C NMR (75 MHz, D_2O), α-anomer: δ 103.4, 81.9, 76.4, 74.3; β-anomer: δ 97.9, 77.4, 76.1, 71.8; hydrate: δ 91.0, 74.5, 72.1, 64.2. Anal. Calcd for $C_4H_8O_4$: C, 40.00; H, 6.71. Found: C, 40.74; H, 6.72. HRMS calcd for $C_4H_8O_4Na$ $[M + Na]^+$ *m*/*z* 143.0320, found *m*/*z* 143.0327. ^1H and ^{13}C data are in accordance with literature values.[28]

Acknowledgment. Financial support from the Lundbeck Foundation is gratefully acknowledged. The Center for Sustainable and Green Chemistry is sponsored by the Danish National Research Foundation.

Supporting Information Available: General experimental methods, characterization of 1,4-anhydro-D-arabinitol and 1,4-anhydro-5-deoxy-L-arabinitol, synthesis of **2** and **3**, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7017729

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