JOC*Note*

Chain Elongation of Aldoses by Indium-Mediated Coupling with 3-Bromopropenyl Esters

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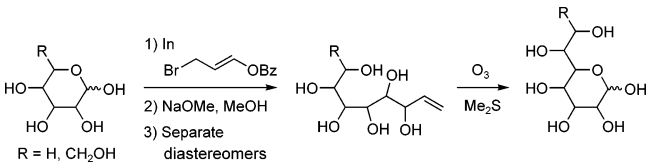

A procedure is described for acyloxyallylation of unprotected aldoses with two functionalized reagents: 3-bromopropenyl acetate and 3-bromopropenyl benzoate. The reaction is performed in ethanol or a dioxane/water mixture in the presence of indium metal. The products are deesterified in the workup to afford unsaturated polyols, which are isolated as mixtures of two diastereomers. The major diastereomers are subjected to ozonolysis to afford new aldoses, which have been elongated by two carbon atoms compared to the starting materials. The new aldoses all have lyxo configuration at positions 2, 3, and 4.

Extending the carbon chain in unprotected aldoses in a diastereoselective fashion has been a challenge in carbohydrate chemistry for more than a century. The classical methods for one-carbon extension involve addition of hydrogen cyanide or nitromethane to the carbonyl group of an aldose.[1] Two-carbon elongation of unprotected aldoses can be achieved by combining a Wittig reaction with a diastereocontrolled dihydroxylation.[2] Extending unprotected aldoses with three carbon atoms can be performed by a tin- or indium-mediated reaction with allyl bromide.[3] This allylation has been exploited in the synthesis of several naturally occurring higher carbon sugars.[4] Furthermore, we have employed indium-mediated allylation for the preparation of carbohydrate-derived dienes that can be cyclized by olefin metathesis.[5]

Recently, 3-bromopropenyl esters **A** and **B** were introduced and used for α-hydroxyallylation of aldehydes and ketones in the presence of zinc or indium metal.[6] We speculated that **A** and **B** could also be utilized for elongating unprotected aldoses. Subsequent ozonolysis of the terminal double bond in the allylation products would then give new aldoses with an additional two carbon atoms. Given the importance of higher carbon sugars, we believe that this procedure would be a very useful alternative to the existing methods for extending the carbon chain in aldoses. Herein, we report our results on the acyloxyallylation of unprotected aldoses with **A** and **B**.

Reagents **A** and **B** are prepared by treatment of acrolein with acetyl or benzoyl bromide at room temperature.[6a] Acetate **A** is isolated by distillation as a 3:1 (*E*)/(*Z*) mixture, while benzoate **B** is obtained by crystallization from pentane/ether as the pure (*E*)-isomer. The initial experiments were performed with D-arabinose and acetate **A**. It was soon discovered that the desired elongation proceeded in ethanol at 50 °C in the presence of indium metal (1.5 equiv). The product, an unsaturated polyol, was isolated in 85% yield as a 2.5:1 mixture of diastereomers after treatment of the crude mixture with base (Table 1, entry 1). The acetate was removed in the workup due to competing migration of this group in the product. The unsaturated polyol was purified by chromatography on a reverse-phase column, and the major diastereomer was isolated by crystallization. At this point, however, the absolute stereochemistry of the two stereoisomers was not known (vide infra). In addition to ethanol, the reaction also proceeded well in a 7:1 mixture of dioxane and water. Adding more water or changing to a mixture of water and ethanol gave slower conversion. Moreover, the reaction proceeded poorly in pure dioxane or THF due to the low solubility of the aldose. Several other metals were also investigated under the Barbier conditions in a dioxane/water mixture: Zn, Sn, Bi, Sb, Mg, and Al. However, none of these metals gave more than trace amounts of the desired elongation product. Attempts to make the transformation catalytic in indium by using 5% of indium metal together with a stoichiometric amount of zinc or aluminum were not successful either. Thus, the use of indium metal in ethanol seems to give the best results.

The reaction was then performed with the other three pentoses (Table 1, entries 3, 5, and 7). The results were similar to the ones obtained with arabinose. Only two out of the four possible diastereomers were observed with selectivities ranging from 1.5:1 to 4:1. In the lyxose reaction the product was purified by reverse-phase chromatography and the major diastereomer was isolated by

(1) Györgydeák, Z.; Pelyvás, I. F. *Monosaccharide Sugars: Chemical Synthesis by Chain Elongation, Degradation, and Epimerization*; Academic Press: San Diego, CA, 1998.

(2) Jørgensen, M.; Iversen, E. H.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4625.

(3) (a) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (b) Prenner, R. H.; Binder, W. H.; Schmid, W. *Liebigs Ann. Chem.* **1994**, 73.

(4) (a) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7937. (b) Gao, J.; Härter, R.; Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1994**, *59*, 3714. (c) Chan, T.-H.; Lee, M.-L. *J. Org. Chem.* **1995**, *60*, 4228. (d) Prenner, R. H.; Schmid, W. *Monatsh. Chem.* **1996**, *127*, 1045. (e) Warwel, M.; Fessner, W.-D. *Synlett* **2000**, 865.

(5) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444.

(6) (a) Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 997. (b) Lombardo, M.; Morganti, S.; d'Ambrosio, F.; Trombini, C. *Tetrahedron Lett.* **2003**, *44*, 2823. (c) Lombardo, M.; Gianotti, K.; Licciulli, S.; Trombini, C. *Tetrahedron* **2004**, *60*, 11725.

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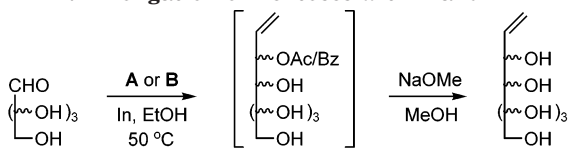
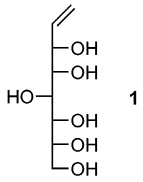
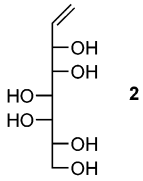
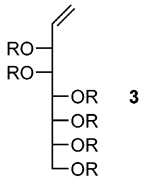
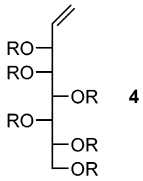
TABLE 1. Elongation of Pentoses with A and B



Entry	Pentose	Reagent	Yield	Diastereo-selectivity	Major diastereomer	#
1	D-arabinose	**A**	85%[a]	2.5:1		**1**
2	D-arabinose	**B**	67%[a]	4.0:1		
3	D-lyxose	**A**	60%[a]	4.0:1		**2**
4	D-lyxose	**B**	60%[a]	8.5:1		
5	D-ribose	**A**	82%[b]	1.5:1		**3**
6	D-ribose	**B**	77%[b]	3.5:1		
7	D-xylose	**A**	78%[b]	2.5:1		**4**
8	D-xylose	**B**	75%[b]	4.5:1		

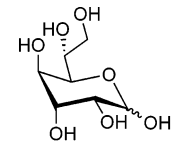
a: R = Ac
b: R = H

[a] Yield of polyol (two diastereomers). [b] Yield of peracetate (two diastereomers).

crystallization. With ribose and xylose, the two diastereomeric polyols could not be separated by crystallization. In these two reactions, the crude products were acetylated and the polyols were isolated as their peracetates. The diastereomers were then separated by silica gel chromatography, and the major diastereomers were subsequently obtained after deacetylation under Zemplén conditions. In all cases, the stereochemistry of the major diastereomer was determined after the ozonolysis reaction.

The four acyloxyallylations were then performed with the more stable and sterically demanding reagent **B** (Table 1, entries 2, 4, 6, and 8). Notably, the diastereoselectivities improved giving rise to the same two diastereomers as with **A**, but with selectivities ranging from 3.5:1 to 8.5:1. Again, the best result was obtained with lyxose, while ribose gave rise to a moderate selectivity. A similar difference in diastereomeric ratio was also observed in the earlier indium-mediated elongations of pentoses with allyl bromide.[3b]

The four major diastereomers were then subjected to ozonolysis and converted into the corresponding heptoses. The products were purified on a reverse-phase column and isolated in yields larger than 90%. The heptoses all had lyxo configuration at positions 2, 3, and 4: D-*glycero*-D-*gulo*-heptose (**5**) was isolated from the reaction with arabinose, D-*glycero*-L-*manno*-heptose (**6**) was obtained from the lyxose experiment, D-*glycero*-D-*manno*-heptose (**7**) was derived from ribose, while D-*glycero*-L-*gulo*-heptose (**8**) came from xylose. Heptoses **5**, **6**, and **7** have previously been prepared by elongation of D-glucose, D-galactose, and D-altrose, respectively.[1] It was not possible to find adequate characterization data for heptose **8**. The structure of this compound was determined by reduction to the corresponding heptitol, which has previously been studied by NMR. Heptose **7** is a common constituent of cell surface lipopolysaccharides in Gram negative bacteria.[7]



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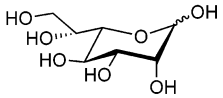

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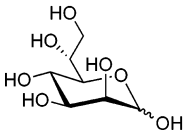

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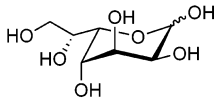

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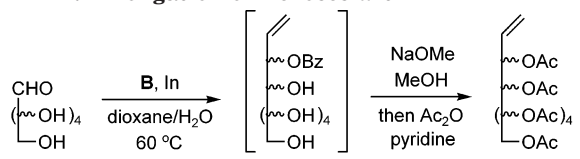
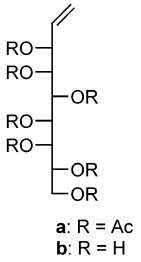
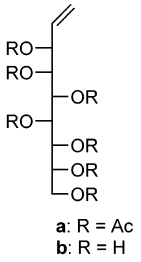
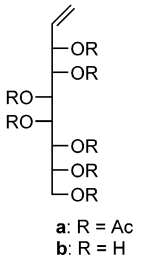
The elongation procedure was then extended to the cheap hexoses galactose, glucose, and mannose. In this case, the reaction was only performed with reagent **B**. Unfortunately, the hexoses turned out to be less reactive than the pentoses. Treatment of D-galactose with **B** and indium in ethanol at 50 °C gave very little of the desired product. Instead, ethyl galactoside was formed as a result of an acid-catalyzed Fischer glycosylation. To avoid this reaction, the solvent was changed to a mixture of dioxane and water. In this media, the coupling between galactose and **B** took place at 60 °C. However, it was never possible to achieve full conversion of the hexose, which hampered the purification of the final product. Several conditions were tried to improve the transformation, including ultrasound and various additives, but the reaction always stalled at about 70% conversion of the hexose. As a result, we decided to change the indium source to a more finely dispersed indium powder (60 mesh). This turned out to have a significant impact on the coupling reaction, and virtually complete conversion of galactose was now achieved. The product was debenzoylated and obtained as a 3.5:1 mixture of two diastereomers, which could not be separated at this time. Therefore, the diastereomers were acetylated to give the peracetates in 90% overall yield from galactose (Table 2, entry 1). D-Glucose and D-mannose were treated with reagent **B** under the same conditions to give a similar mixture of two diastereomers after debenzoylation and peracetylation (entries 2 and 3). In all three cases, only two out of the four possible diastereomers were observed.

(7) Brisson, J.-R.; Crawford, E.; Uhrín, D.; Khieu, N. H.; Perry, M. B.; Severn, W. B.; Richards, J. C. *Can. J. Chem.* **2002**, *80*, 949.

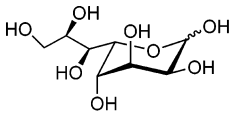
TABLE 2. Elongation of Hexoses with B



Entry	Hexose	Yield of peracetate	Diastereo-selectivity	Major diastereomer	#
1	D-galactose	90%	3.5:1	 **a**: R = Ac **b**: R = H	**9**
2	D-glucose	71%	3.5:1	 **a**: R = Ac **b**: R = H	**10**
3	D-mannose	71%	3.0:1	 **a**: R = Ac **b**: R = H	**11**

The major stereoisomers **10a** and **11a** were isolated in pure form by flash chromatography and deacetylated to furnish the unsaturated polyols **10b** and **11b**, respectively. In the reaction with galactose, it was not possible to separate **9a** from its diastereomer by flash chromatography. In this case, the mixture of the two peracetates was deacetylated and the polyol **9b** could now be obtained pure by crystallization. The three polyols **9b**, **10b**, and **11b** were then treated with ozone to afford the corresponding octoses in good yield. Once more, the higher carbon sugars were found to have lyxo configuration at positions 2, 3, and 4: D-*threo*-L-*gulo*-octose (**12**) was obtained from the reaction with galactose, D-*erythro*-L-*gulo*-octose (**13**) was isolated from the experiment with glucose, while D-*erythro*-L-*manno*-octose (**14**) was derived from mannose. Octoses **12** and **14** have previously been prepared by elongation of galactose and mannose in several steps,[8,9] while octose **13** is a new compound. The structure of **13** was determined by reduction to the corresponding octitol, which is a symmetric compound.

In summary, we have developed a simple protocol for the synthesis of higher carbon sugars by two-carbon chain elongation of pentoses and hexoses. The stereochemical outcome is predictable, and the method gives rise to higher sugars featuring the lyxo configuration at the reducing end. This procedure complements our previously developed protocol based on a Wittig dihydroxylation sequence.



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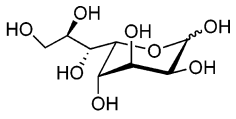

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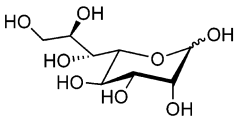

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Experimental Section

Acyloxyallylation of Pentoses. To a solution of the pentose (500 mg, 3.33 mmol) in EtOH (50 mL) at 50 °C was added acetate **A** (0.81 mL, 6.66 mmol) or benzoate **B** (1.61 g, 6.66 mmol) followed by indium (powder containing 1% magnesium, 574 mg, 5.00 mmol). The reaction was stirred vigorously at 50 °C until TLC showed complete consumption of the pentose (15−60 min). The mixture was filtered into Et_2O (100 mL) and extracted with water (100 mL + 2 × 50 mL). The combined aqueous layers were concentrated, and the residue was coevaporated twice with toluene. The crude product was dissolved in MeOH (50 mL), followed by addition of a freshly prepared 0.5 M NaOMe solution in MeOH until pH > 12 (about 30 mL). The mixture was stirred at room temperature until TLC showed full conversion (8−24 h). The solution was neutralized by addition of Amberlite IR-120 (H^+) ion-exchange resin. The resin was filtered off and washed with MeOH. The filtrate was concentrated. With arabinose and lyxose, the residue was purified by reverse-phase flash chromatography (H_2O). With ribose and xylose the residue was coevaporated with toluene, dissolved in pyridine (30 mL) and Ac_2O (30 mL), and then stirred at room temperature until TLC showed full conversion (1−2 h). The solution was diluted with Et_2O and washed with ice-cold 4 M aqueous HCl and water. The organic phase was dried and concentrated. The acetylated product was isolated by flash chromatography (hexane/Et_2O = 2:3).

Benzoyloxyallylation of Hexoses. The hexose (500 mg, 2.78 mmol) was dissolved in water (3.0 mL) at 60 °C followed by addition of dioxane (24 mL). To the solution was added benzoate **B** (2.01 g, 8.34 mmol), followed by indium (60 mesh, 637 mg, 5.55 mmol). The reaction was stirred vigorously at 60 °C for 1 h when TLC revealed more than 95% conversion. Most of the indium was removed by decanting the solution into another flask. The solvent was removed in vacuo, followed by coevaporation with toluene. MeOH (50 mL) was added, which resulted in a suspension to which a freshly prepared 0.5 M NaOMe solution in MeOH was added until pH > 12 (about 30 mL). The solution was stirred at reflux overnight, after which TLC revealed full conversion. The mixture was cooled to room temperature, neutralized with Ac_2O, and concentrated. The residue was coevaporated with toluene and then suspended in pyridine (20 mL). Ac_2O (20 mL) was added, and the mixture was stirred at room temperature until TLC showed full conversion (2−4 h). Excess Ac_2O was quenched by addition of ice-cold water (50 mL) and stirring at 0 °C for 20 min. The solution was extracted with CH_2Cl_2, and the combined organic phases were washed with 4 M aqueous HCl and water, dried, and concentrated. The residue was filtered through a plug of silica gel eluting with heptane/Et_2O = 3:2 to remove impurities followed by heptane/Et_2O = 1:4 to elute the diastereomeric product mixture. In the reaction with glucose and mannose, the major

(8) Hann, R. M.; Merrill, A. T.; Hudson, C. S. *J. Am. Chem. Soc.* **1944**, *66*, 1912.
(9) Karabinos, J. V.; Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1953**, *75*, 4320.

diastereomer could be isolated by flash chromatography (heptane/Et_2O = 1:1). It was not possible to separate the two diastereomers in the reaction with galactose.

Preparation of Heptoses by Ozonolysis. The 1,2-dideoxy-oct-1-enitol (300 mg, 1.44 mmol) was dissolved in MeOH (30 mL) and cooled to −78 °C, while N_2 was bubbled through the solution. Ozone was then bubbled through until the solution became deep blue. The treatment with ozone was continued for an additional 15 min, and N_2 was then bubbled through until the blue color had disappeared. Me_2S (1.0 mL, 13.6 mmol) was added, and the solution was allowed to reach room temperature and stirred for 16 h. The mixture was concentrated and purified by reverse-phase flash chromatography (H_2O).

Preparation of Octoses by Ozonolysis. The 1,2-dideoxy-non-1-enitol (0.80 to 1.44 mmol) was dissolved in water (5 mL) followed by addition of MeOH (30 mL). The solution was treated with ozone at −40 °C and worked up as described above.

1,2-Dideoxy-D-*glycero*-D-*gulo*-oct-1-enitol (1). White crystals; R_f 0.62 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ −8.6 (*c* 2.0, H_2O); mp 98−101 °C (EtOH).

1,2-Dideoxy-D-*glycero*-L-*manno*-oct-1-enitol (2). White crystals; R_f 0.62 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ −10.5 (*c* 2.0, H_2O); mp 170−172 °C (EtOH).

3,4,5,6,7,8-Hexa-*O*-acetyl-1,2-dideoxy-D-*glycero*-D-*manno*-oct-1-enitol (3a). Colorless syrup; R_f 0.41 (hexane/Et_2O = 1:3); $[\alpha]^{22}_D$ +35.0 (*c* 2.0, $CHCl_3$).

1,2-Dideoxy-D-*glycero*-D-*manno*-oct-1-enitol (3b). Hexaacetate **3a** was deacetylated with NaOMe in MeOH to give **3b** in 93% yield after filtration through a plug of reverse-phase silica gel. White crystals; R_f 0.63 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +12.0 (*c* 2.0, H_2O); mp 96−98 °C (EtOH/hexane).

3,4,5,6,7,8-Hexa-*O*-acetyl-1,2-dideoxy-D-*glycero*-L-*gulo*-oct-1-enitol (4a). White crystals; R_f 0.46 (hexane/Et_2O = 1:3); $[\alpha]^{22}_D$ +30.4 (*c* 2.0, $CHCl_3$); mp 76−77 °C (Et_2O/hexane).

1,2-Dideoxy-D-*glycero*-L-*gulo*-oct-1-enitol (4b). Hexaacetate **4a** was deacetylated with NaOMe in MeOH to give **4b** in 82% yield after filtration through a plug of reverse-phase silica gel. Colorless syrup; R_f 0.63 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +8.6 (*c* 2.0, H_2O).

D-*glycero*-D-*gulo*-Heptose (5). Isolated in 91% yield after ozonolysis of **1**. White crystals; R_f 0.37 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ −17.9 (*c* 2.0, H_2O) (lit.[10] $[\alpha]^{22}_D$ −20 (*c* 3.5, H_2O)); mp 190−191 °C (H_2O/EtOH) (lit.[8] mp 191−192 °C).

D-*glycero*-L-*manno*-Heptose (6). Isolated in 97% yield after ozonolysis of **2**. White foam; R_f 0.45 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ −11.0 (*c* 2.0, H_2O) (lit.[7] $[\alpha]_D$ −14 (*c* 0.2, H_2O)).

D-*glycero*-D-*manno*-Heptose (7). Isolated in 99% yield after ozonolysis of **3b**. White foam; R_f 0.39 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +16.2 (*c* 2.0, H_2O), $[\alpha]^{22}_D$ +17.1 (*c* 1.0, MeOH) (lit.[7] $[\alpha]_D$ +22 (*c* 2, MeOH)).

D-*glycero*-L-*gulo*-Heptose (8). Isolated in 90% yield after ozonolysis of **4b**. Colorless syrup; R_f 0.27 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +19.0 (*c* 2.0, H_2O).

3,4,5,6,7,8,9-Hepta-*O*-acetyl-1,2-dideoxy-D-*threo*-L-*gulo*-non-1-enitol (9a). Colorless syrup; isolated as a 3.5:1 mixture of diastereomers that could not be separated by chromatography. For the major isomer **9a**: R_f 0.28 (heptane/Et_2O = 1:3); $[\alpha]^{22}_D$ +10.1 (*c* 2.0, $CHCl_3$).

1,2-Dideoxy-D-*threo*-L-*gulo*-non-1-enitol (9b). The 3.5:1 mixture of heptaacetate **9a** and its diastereomer (1.47 g) was dissolved in MeOH (40 mL), and a 0.5 M solution of NaOMe in MeOH was added until pH > 12. The solution was stirred for 4 h and then neutralized with Amberlite IR-120 (H^+) ion-exchange resin. The resin was filtered off and rinsed with MeOH. The filtrate was concentrated and purified by reverse-phase flash chromatography (H_2O). Concentration gave a semicrystalline residue that was recrystallized from EtOAc/MeOH to afford **9b** (356 mg, 54%). White crystals; R_f 0.49 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +10.0 (*c* 2.0, H_2O); mp 142−144 °C (EtOAc/MeOH).

3,4,5,6,7,8,9-Hepta-*O*-acetyl-1,2-dideoxy-D-*erythro*-L-*gulo*-non-1-enitol (10a). White crystals; R_f 0.25 (heptane/Et_2O = 1:3); $[\alpha]^{22}_D$ +49.8 (*c* 2.0, $CHCl_3$); mp 106−107 °C (EtOAc/hexane).

1,2-Dideoxy-D-*erythro*-L-*gulo*-non-1-enitol (10b). Heptaacetate **10a** was deacetylated with NaOMe in MeOH to give **10b** in 82% yield after filtration through a plug of reverse-phase silica gel. White crystals; R_f 0.49 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +6.4 (*c* 2.0, H_2O); mp 107−109 °C (EtOH/hexane).

3,4,5,6,7,8,9-Hepta-*O*-acetyl-1,2-dideoxy-D-*erythro*-L-*manno*-non-1-enitol (11a). White crystals; R_f 0.29 (heptane/Et_2O = 1:3); $[\alpha]^{22}_D$ +0.8 (*c* 2.0, $CHCl_3$); mp 127−128 °C (EtOAc/hexane).

1,2-Dideoxy-D-*erythro*-L-*manno*-non-1-enitol (11b). Heptaacetate **11a** was deacetylated with NaOMe in MeOH to give **11b** in 94% yield after filtration through a plug of reverse-phase silica gel. White crystals; R_f 0.63 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ −10.0 (*c* 2.1, H_2O); mp 199−201 °C (H_2O).

D-*threo*-L-*gulo*-Octose (12). Isolated in 87% yield after ozonolysis of **9b**. White crystals; R_f 0.18 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +19.0 (*c* 2.0, H_2O) (lit.[8] $[\alpha]^{20}_D$ +19.2 (*c* 2, H_2O)); mp 172−174 °C (MeOH) (lit.[8] mp 187−188 °C).

D-*erythro*-L-*gulo*-Octose (13). Isolated in 79% yield after ozonolysis of **10b**. White foam; R_f 0.23 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ +16.0 (*c* 2.0, H_2O).

D-*erythro*-L-*manno*-Octose (14). Isolated in 95% yield after ozonolysis of **11b**. Colorless syrup; R_f 0.33 (H_2O/acetone/BuOH = 1:5:4); $[\alpha]^{22}_D$ −8.6 (*c* 2.0, H_2O) (lit.[9] $[\alpha]^{20}_D$ −7.5 (*c* 2, H_2O)).

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Supporting Information Available: General experimental methods and further characterization data for compounds **1**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Wolfrom, M. L.; Wood, H. B. *J. Am. Chem. Soc.* **1951**, *73*, 2933.