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De Novo Synthesis of Oligosaccharides Using a Palladium-Catalyzed Glycosylation Reaction

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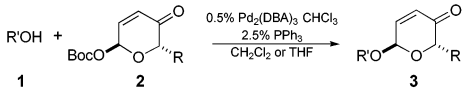
Oligosaccharide structures possess unique molecular scaffolding which at a cellular level can serve as molecular flags.[1] New synthetic methods applicable for the assembly of diverse oligosaccharide-based structures are essential for furthering our comprehension of carbohydrate structural activity in biological systems.[2] In particular, synthetic access to unnatural sugar analogues of these oligosaccharides will be critical to build the necessary probes for the study of oligosaccharide interactions.[1,2]

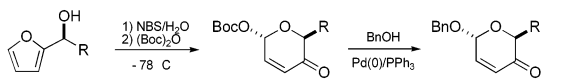
Previously we have developed an alternative de novo approach to the hexoses.[3] Our initial approach relied upon the use of the Achmatowicz reaction[4] in conjunction with the catalytic asymmetric synthesis of furan alcohols. A final improvement involved the development of a diastereoselective palladium catalyzed glycosylation reaction[5] (coupling of **1** and **2** to give **3**) to control coupling at the anomeric center (Scheme 1).[6] Herein we describe our strategy for the de novo synthesis of α-linked 1,4- and 1,6-oligosaccharides using this palladium (Pd)-catalyzed glycosylation reaction. In addition, we demonstrate that the oligo-pyranone products can be transformed into oligosaccharides by a simple reduction/oxidation sequence, which results in highly efficient syntheses.

Scheme 1. Palladium-Catalyzed Glycosylation Reaction



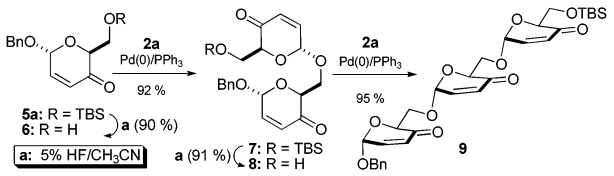
Our approach is quite mild and equally amenable to the glycosyl transfer of either a D- or L-sugar, because our glycosyl acceptors, pyranones **2a** and **2b**, can be prepared from furfuryl alcohols **4a** and **4b** in only two steps.[6a] The first Pd-catalyzed glycosylation reaction was performed to protect the reducing end of the oligosaccharide as a benzyl ether. Thus using only 1−5 mol % palladium, the pyranones **2a** and **2b** were coupled with benzyl alcohol (1.2 equiv) providing 6-benzyloxy pyranones **5a** and **5b** in 95% and 93% yields, respectively (Scheme 2).

Scheme 2. Synthesis of Pyranone and Glycosylation Reaction



For 1,6-oligosaccharide assembly, the glycosyl donor **6** with a free hydroxyl group at the C-6 was required. This was easily accomplished by removal of the TBS group of **5a** using HF/CH_3CN (90% yield). Subjecting alcohol **6** to our typical Pd catalyzed glycosylation reaction conditions[6a] (1.2 equiv of **2a**, 2.5% $Pd_2(DBA)_3 \cdot CHCl_3$, and 10% PPh_3) provided the disaccharide precursor bis-pyranone **7** in 92% yield (Scheme 3). Simply repeating the two-step process on **7** gave trisaccharide precursor tris-pyranone **9** in equally high yields (86% for the two steps). Because the initial

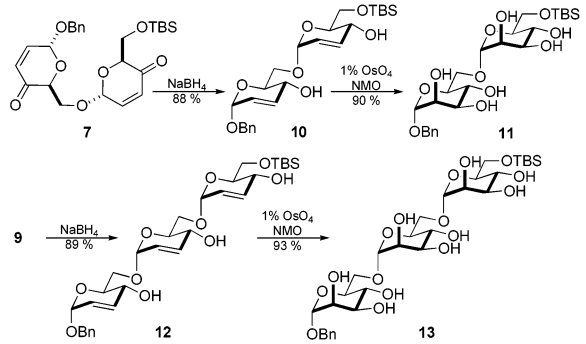
Scheme 3. Synthesis of 1,6-Disaccharides and 1,6-Trisaccharides



furan alcohols were prepared in optically pure form, these glycosylation reactions provide both **7** and **9** as single diastereoisomers.

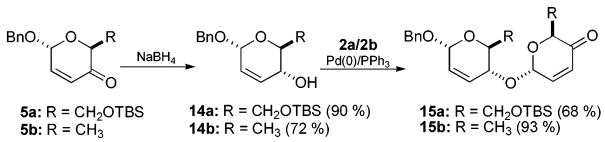
To demonstrate the utility of this process, the di- and trisaccharide precursors **7** and **9** were diastereoselectively converted into the all-*manno* di- and trisaccharides **11** and **13** (Scheme 4).[7] The bis-1,2-reduction of **7** with $NaBH_4$ gave alcohol **10** in 88% yield. Subsequent tandem double-bond oxidation with OsO_4/NMO afforded the 1,6-di-α-L-*manno*-pyranose **11** in 90% yield.[8] Similarly, diastereoselective keto-reduction of **9** afforded allylic alcohol **12** in 89% yield**.** The OsO_4/NMO oxidation of **12** afforded 1,6-tri-α-L-*manno*-pyranose **13** in 93% yield (Scheme 4).[8]

Scheme 4. Diastereoselective Reductions and Dihydroxylations



With successful de novo syntheses of 1,6-oligosaccharides, we next explored the glycosylation reaction of the C-4 secondary alcohol in pyrans **14a/b** for the synthesis of 1,4-oligosaccharides. Diastereoselective 1,2-reduction of the pyranones **5a/b** with $NaBH_4$ afforded exclusively the C-4 equatorial alcohols **14a/b**. These alcohols **14a/b** were used as glycosyl donors in the Pd-catalyzed glycosylation reactions with their similarly C-6 substituted glycosyl acceptors **2a/b**,[9] which afforded the C-4 glycosylated disaccharides **15a/b** in good yields and with excellent stereocontrol (Scheme 5).[10,11]

Scheme 5. Synthesis of 1,4-Disaccharides



Once again, the highly diastereoselective 1,2-reduction of the keto-group in pyranones **15a/b** afforded allylic alcohols **16a/b**

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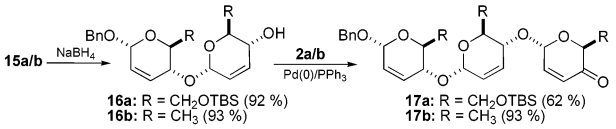
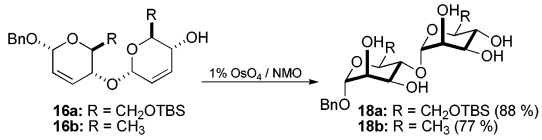
Scheme 6. Synthesis of 1,4-Trisaccharides



(Scheme 6). The C-4 alcohols in **16a/b** were used as glycosyl donors with their corresponding glycosyl acceptor pyranones **2a/b**[9] to fashion the 1,4-linked trisaccharides **17a/b** with excellent stereocontrol and overall yield (57% and 86% for the two steps).[10,11]

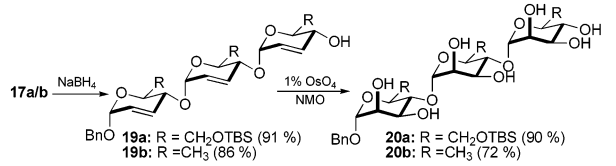
As with the 1,6-linked pyranones (Scheme 4), the OsO_4/ NMO oxidation of allylic alcohols **16a/b** afforded the 1,4-bis-α-*manno*-pyanoses **18a/b** both as single diastereomers in 88% and 77% yields, respectively (Scheme 7).[8,12] Thus, 10 stereocenters were selectively installed in **18a/b** in only 10 and 8 steps from achiral furfural and 2-acylfuran, respectively.[13]

Scheme 7. Conversion to 1,4-α-*manno*-Disaccharides



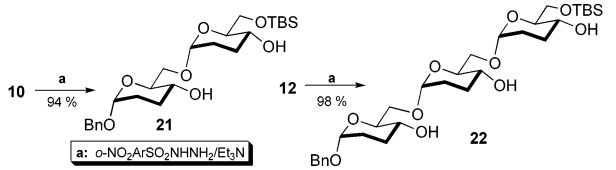
This high degree of stereocontrol remained at the 1,4-trisaccharide level (Scheme 8). Thus, diastereoselective 1,2-reduction of the ketone in **17a/b** with $NaBH_4$ followed by double-bond oxidation with OsO_4/NMO afforded the 1,4-tri-α-*manno*-pyranoses **20a/b** in good overall yields.[8] Amazingly, the 15 stereocenters of **20a** and **20b** were induced in only 12 and 10 steps from achiral furfural and 2-acylfuran, respectively.

Scheme 8. Conversion to 1,4-α-*manno*-Trisaccharides



Dideoxy-oligosaccharides can be prepared by employing a diimide reduction on the 1,6-linked di- and tripyrans **10** and **12**.[14] Thus, the 1,6-bis-α-2,3-deoxy-L-*manno*-pyranose **21** and 1,6-tri-α-2,3-deoxy-L-*manno*-pyranose **22** were prepared from exhaustive reduction of allylic alcohols **10** and **12**, using excess triethylamine and *o*-nitrophenylsulfonylhydrazide as a diimide precursor (Scheme 9).[15]

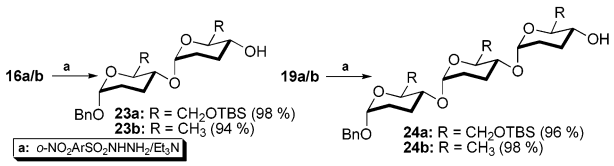
Scheme 9. Synthesis of 2,3-Deoxy-1,6-α-oligosaccharides



This diimide methodology also worked perfectly for the preparation of 1,4-linked 2,3-dideoxyoligosaccharides. Two 2,3-dideoxy-disaccharides (1,4-di-α-2,3-deoxymannose **23a/b**) and two 2,3-dideoxy-trisaccharides (1,4-tri-α-2,3-deoxymannose **24a/b**) were prepared in nearly quantitative yields by exposing the allylic alcohols **16a/b** and **19a/b** to excess diimide precursor and base (Scheme 10).[13]

In summary, we have synthesized natural and unnatural 1,4- and 1,6-α-*manno*-disaccharides as well as 1,4- and 1,6-α-*manno*-tri-

Scheme 10. Synthesis of 2,3-Deoxy-1,4-α-oligosaccharides



saccharides from furan alcohols by the iterative use of a Pd-catalyzed glycosylation reaction.[5] This new route was also used for the preparation of 2,3-dideoxy-oligosaccharides. The 1,4- and 1,6-α-*manno*-disaccharides were achieved in 8 or 10 total steps starting from achiral 2-acylfuran or furfural, respectively. Similarly, 1,4- and 1,6-α-*manno*-trisaccharides were also synthesized in 10 or 12 total steps using a sequential Pd-catalyzed glycosylation reaction. Key to the overall efficiency of this process was the use of highly diastereoselective 1,2-reductions and dihydroxylations. This three-step protocol allows for the rapid incorporation of either D- or L-pyranoses in oligosaccharides in good yields and with complete stereocontrol.[13] We believe this route is amenable to multigram-scale preparation of various natural and unnatural oligosaccharides.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) Ichikawa, Y.; Halcomb, R. L.; Wong, C.-H. *Chem. Br.* **1994**, *30*, 117−118. (b) Wong, P. G.; Bertozzi, C. R., Eds. *Glycochemistry. Principles, Synthesis and Applications*; Marcel Dekker: New York, 2001. (c) Bertozzi, C. R. *Chem. Biol.* **1995**, *2*, 703−708.

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(4) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165−176.

(5) While the diastereoselective transfer of a pyranone ring to an alcohol is an uncommon glycosylation reaction because the pyranone ring is at the same oxidation state as a traditional sugar (one OH per carbon atom), we feel this transfer of a bis-anhydro-sugar is as much a glycosylation reaction as other common glycosylation reactions (e.g. the transfer of a deoxysugar).

(6) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407. (b) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714−8715. (c) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336−1337.

(7) Important to the successful execution of this process, both reactions must occur with virtually complete diastereocontrol.

(8) While the dihydroxylation products were easily purified by silica gel chromatography, no efforts were taken to detect for trace levels of osmium.

(9) For glycosylation at the C-4 position we found that the best yields were obtained when a 2:1 ratio of glycosyl donor to acceptor was used.

(10) Not surprisingly, the glycosylation reaction consistently occurs in higher yields with the substrates having the smaller C-6 methyl substituents.

(11) The Pd-catalyzed glycosylation was significantly slower and occurred in lower yields (**14a** to **15a** and **16a** to **17a**), when using a pyranone with a C-1 pivaloate-leaving group.

(12) Using a different retrosynthetic bond disconnection, Sinou used a palladium-allylation reaction to prepare 1,4-disaccharides, see: Sinou, D.; Frappa, I.; Lhoste, P.; Porwanski, S.; Kryczka, B. *Tetrahedron Lett.* **1995**, *36*, 1251−1254.

(13) To demonstrate the generality of this process we prepared **18b, 20b, 23b** and **24b** in the all D-enantiomeric form.

(14) For a related alterative approach to 2-deoxysugars, see: (a) McDonald, F. E.; Reddy, K. S.; Diaz, Y., *J. Am. Chem. Soc.* **2000**, *122*, 4304−4309. (b) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979−3981.

(15) We have found *o*-nitrophenylsulfonylhydrazide/triethylamine to be an excellent diimide precursor, ideal for reducing pyrans of this type, see: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771−1774.

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