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De Novo Asymmetric Synthesis of all D-, all L- and D-/L-Oligosaccharides Using Atom-less Protecting Groups

Ravula Satheesh Babu[†], **Qian Chen**[†], **Sang-Woo Kang**[†], **Maoquan Zhou**[†], and **George A. O'Doherty**[*]
Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115

Abstract

Oligosaccharide synthesis is hindered by the need for multiple steps as well as numerous selective protections and deprotections. Herein we report a highly efficient *de novo* route to various oligosaccharide motifs, of use for biological and medicinal structure activity studies. The key to the overall efficiency is the judicious use of asymmetric catalysis and synthetic design. These green principles include the bidirectional use of highly stereoselective catalysis (Pd(0)-glycosylation/post-glycosylation). In addition, the chemoselective use of C-C and C-O π-bonds functionality, as atom-less protecting groups as well as an anomeric directing group (via a Pd-π-allyl), highlights the atom economical aspects of the route to a divergent set of natural and unnatural oligosaccharides (*i.e.*, various D-/L-diastereomers of oligosaccharide as well as deoxysugars which lack *C*-2 anomeric directing groups). For example, in only 12 steps, the construction of a highly branched hepta-saccharide with 35 stereocenters was accomplished from an achiral acylfuran.

Of the biopolymers, the carbohydrates present the greatest synthetic challenges. In contrast to peptides and nucleic acids, there is a dearth of synthetic methods for the incorporation of unnatural monomers into oligosaccharide structures. While there are many methods for the de novo asymmetric synthesis of monosaccharides, the translation of these methods to oligosaccharides synthesis is severely limited.

Due to the stereochemical complexity, the hexoses have long stood as targets for synthesis.[1] In particular, they serve as test substrates for asymmetric catalysis.[2] As these *de novo* asymmetric routes evolved from flexible, albeit laborious, approaches to all eight hexoses[2] to quite efficient approaches to specific hexoses,[3] the utility of these catalytic asymmetric approaches have been limited to the synthesis of unnatural and rare monosaccharides.[4]

As the recognition of the importance of oligosaccharides to biological processes has grown,[5] the commensurate need for synthetic oligosaccharides intermediates has been largely met with traditional carbohydrate approaches, which draw from naturally occurring carbohydrate starting materials.[6] While these approaches have been widely successful for supplying natural oligosaccharide structural motifs for biological studies, they have limited potential for medicinal chemistry studies.[1,5,7] The obvious solution of merging of these two

Corresponding Author: G.O' Doherty@neu.edu.
[†]**Author Contributions**
These authors contributed equally to this work and are listed alphabetically.

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Supporting Information. Detailed experimental procedures and full compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

approaches, *de novo* monosaccharide synthesis followed by oligosaccharide assembly, is mired by the need for additional protection and deprotection steps that makes these processes uneconomical, not to mention un-atom economical.[8] Thus, more convenient and efficient methods are still needed.[9]

Oligosaccharide motifs, like the nona-saccharide Man-9, are involved in a variety of important biological functions (*e.g.*, protein and cellular recognition and signaling).[7] While multistep synthesis and isolation and semi-synthesis have provided access to these types of oligosaccharides for biological studies, these studies have been limited to the natural structural motifs.[10] For instance, having access to a hepta-saccharide motif with unnatural branching and its enantiomer (cf., **23**, Scheme 4) would enable structure activity relationship (SAR) studies of the role these complex oligosaccharide arrays (*e.g.*, Man-9) play in many biological processes. For instance, having access to both D- and L-glycoconjugates could allow for the differentiation of specific protein interaction from pharmacokinetic properties.[11]

To address this need, we have developed a complementary *de novo* approach to carbohydrates that is compatible with diversification and oligosaccharide assembly (Scheme 1).[12] Our approach allows for the facile incorporation of simple pyranyl-sugars (*i.e.*, under functionalized sugars) into various oligosaccharide motifs without the need for any protection/deprotection steps with complete stereocontrol.[13] The appeal of this approach is that: the double bond in pyranone glycosyl donor (**2a/2b**) serves as an anomeric directing group in the Pd(0)-catalyzed glycosylation; the enone functionality of the pyranone products (**3a/3b**) serves as atom-less protecting groups for the *C*-2 to *C*-4 triol portion of the hexose (**4a/4b**);[14] and the route has equal efficiency to access to various D- and L-isomer.[11,12,15]

Previously we have developed a diastereoselective Pd(0)-catalyzed glycosylation reaction and demonstrated its use in the *de novo* synthesis of all D- or all L-1,4- and 1,6-α-*manno*-trisaccharides.[11,12] Herein, we present our discovery of an expeditious route to various highly branched/all D-, all L-and mixed D-/L-oligosaccharides using asymmetric and diasteroselective catalysis for stereocontrol. These studies resulted in a synthesis of a library of enantiopure α-*rhamno/manno*-trisaccharide (Schemes 2 and 3), as well as a 12-step synthesis of a highly branched hepta-saccharide with up to 35 stereocenters from achiral starting materials. This greener approach to oligosaccharides not only reduces the number of chemical transformations it also limits the number of protecting groups used (one TBS-group/hexose for hepta-saccharide **23**).

We first explored the library synthesis of 1,4-α-*rhamno*-trisaccharides (*i.e.,* D-D-D, D-D-L, D-L-D, D-L-L trisaccharides, **12** to **15**). The route commenced with the allylic alcohol **D-5**, which was prepared from commercially available achiral acylfuran **1a** (Scheme 1).[16] Using a Pd-catalyzed glycosylation with pyranone **D-2a** and reduction, monosaccharide **D-5** was diastereoselectively elongated into the disaccharide **6** (Scheme 2). By changing the pyranone to its enantiomer (α-Boc pyranone **L-2a)** the diasteromeric D-L disaccharide **7** was prepared. Repeating this divergent diastereoselective elongation of disaccharides **6** and **7** (glycosylation/reduction) provided the four possible D-/L-diastereomeric trisaccharides **8**, **9**, **10** and **11**. These four diastereomeric routes occurred with almost the same synthetic efficiency and with virtually complete stereocontrol. A similarly diastereoselective osmium catalyzed global dihydroxylation of allylic alcohol **8**, **9**, **10** and **11** afforded the four desired diastereomeric 1,4-linked α-*rhamno*-pyranoses D-D-D-**12a**, D-D-L-**13a**, D-L-D-**14a**, D-L-L-**15a**. A final element of synthetic divergence can be employed with a global reduction of the double bonds in trisaccharide **8**, **9**, **10** and **11** with excess diimide[17] to give the α-1,4-linked 2,3-dideoxyoligosaccharides **12b**, **13b**, **14b** and **15b** in nearly quantitative yields. An important feature of this route is that the ketone reductions and alkene dihydroxylations

occur with complete stereocontrol with respect to the local pyran stereochemistry and not the stereochemistry of the adjacent pyran rings (a fundamental requirement for atom-less protecting groups).

To further explore the stereochemical robustness of this approach, we next explored the bidirectional glycosylation of the *C*-4 and *C*-6 alcohols. The desired diol **D-16** was prepared from Boc pyranone **D-2b** in 3 steps with 69% overall yield (Scheme 3). Subjecting alcohol **D-16** to our typical Pd-catalyzed glycosylation reaction conditions provided the trisaccharide precursor trispyran **17** in 75% yield. Diastereoselective 1,2-reduction of pyranone **17** with $NaBH_4$ and OsO_4/NMO oxidation of the resulting allylic alcohols afforded the branched mixed D-/L-trisaccharide **18** with α-*rhamno*/*manno*-stereochemistry as a single diastereomer in 68% yield. Alternatively, by switching the dihydroxylation conditions to diimide reduction, the branched mixed D-/L-trisaccharide **19** with two 2,3-dideoxy-α-*rhamno* and one 2,3-dideoxy-*manno*-pyranose rings was prepared as a single diastereomer.

Encouraged by the results, we were emboldened to try the application of this approach to the target hepta-oligomannoside **23** (Scheme 4). Gratifyingly, the preparation of hyper-branched hepta-saccharide occurred with the same efficiency and high degree of stereocontrol (cf., Schemes 2 and 3). Palladium catalyzed glycosylation of pyranone **L-2b** with the enantiomeric diol **L-16**, followed $NaBH_4$ reduction provided the allylic alcohol **20** in 65% yield (Scheme 4). Treatment of **20** with TBAF successfully removed the two TBS-groups and the resulting tetraol **21** then served as a glycosyl acceptor for per-glycosylation. Simply repeating the two-step protocol (glycosylation/reduction) on **21** gave the hepta-saccharide/tetra-allylic alcohol **22** in 49% yield. To our delight, per-dihydroxylation of **22** using the Upjohn conditions (OsO_4/NMO) gave exclusively the α-*manno*-hepta-saccharide **23** in 86% yield, which could be purified by simple silica gel chromatography (ether/MeOH). Similarly, a global reduction with excess diimide resulted in the 2,3-dideoxy-D-erythro-hexo-hepta-saccharide **24**, which was easily isolated in 74% yield. While a similarly short route to *ent*-**23** (*e.g.*, the all D-hepta-saccharide) can be envisioned using a traditional glycosylation strategy (Scheme S1), the route would require the use of significantly more protecting groups and offer no practical approach to the D-/L-stereoisomers and deoxy-congeners. It is important to note the acid sensitive of the glycosidic bonds in deoxy hepta-saccharides **23** and **24**, which might not survive the strongly acidic conditions of a traditional glycosylation.

In summary, a highly efficient, stereocontrolled and divergent route to various natural and unnatural oligosaccharide motifs has been developed via asymmetric catalysis. This *de novo* route featured the bidirectional use of a Pd(0)-catalyzed glycosylation/post-glycosylation transformations. The four possible D-/L-diastereomeric α-1,4-linked *rhamno*-trisaccharides and dideoxy-congeners were prepared in 10 steps starting from achiral acylfuran **1a**. Similarly, a highly branched hepta-saccharide was stereoselectively constructed from an achiral acylfuran **1b** in 12 steps. This approach is quite mild, amenable to the acid sensitive deoxysugars capable of being diversified into any of the D- and/or L-sugar diastereomers with complete stereocontrol. Finally, this new method enables the rapid assembly of unnatural oligosaccharide motifs (e.g., enantiomer, deoxysugars, D-/L-diastereomers) and in turn the possibility for numerous mode of action studies in glycobiology. Effort along these lines are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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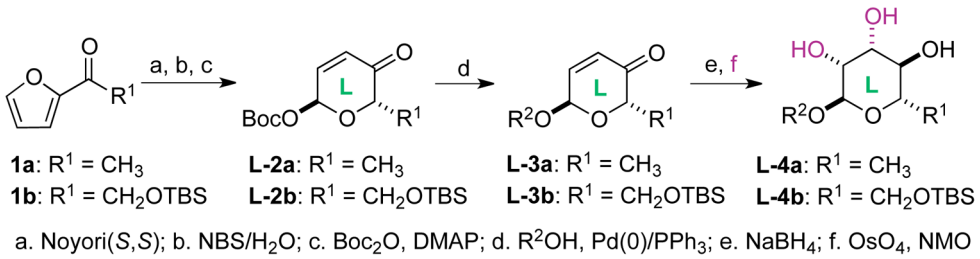
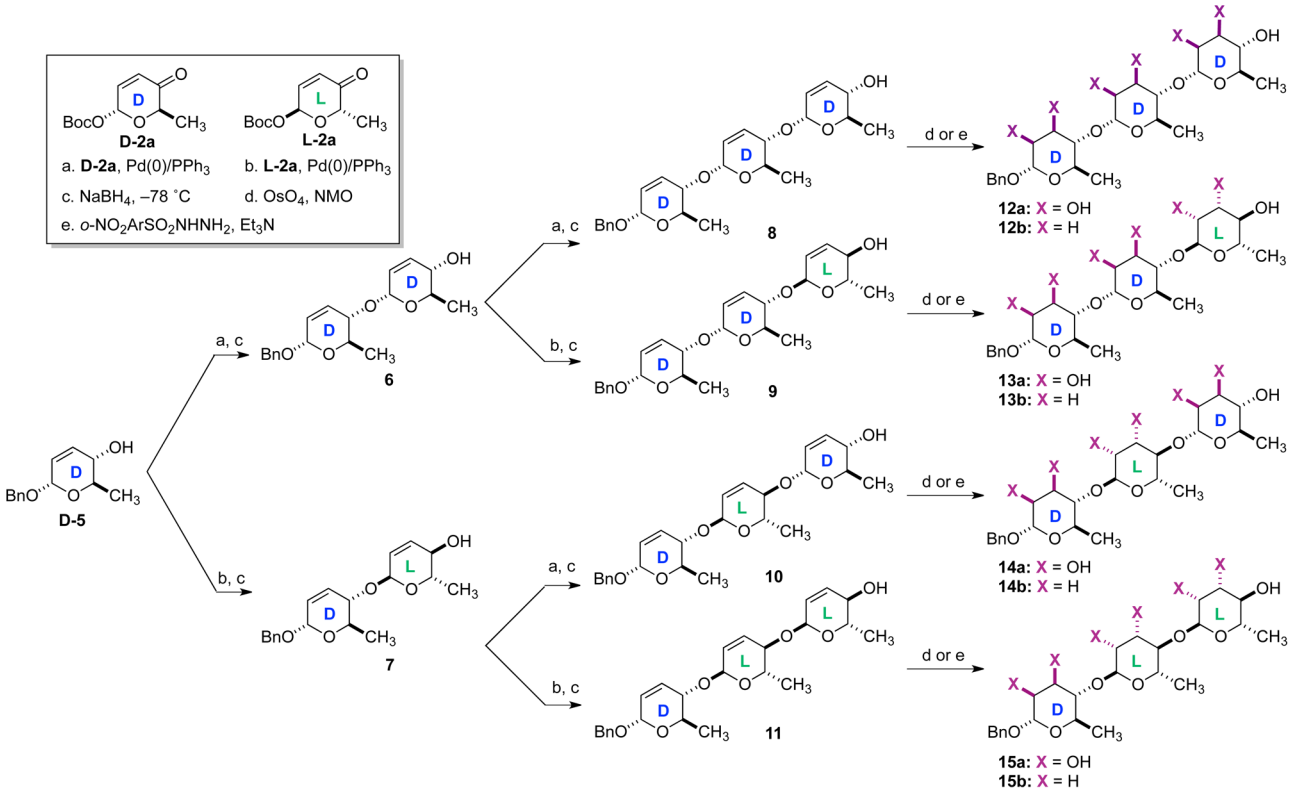
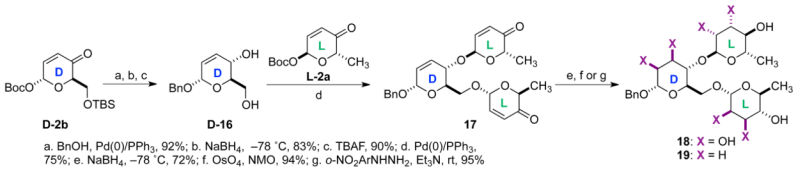


Scheme 1.
De Novo Achmatowicz Approach to the Hexoses

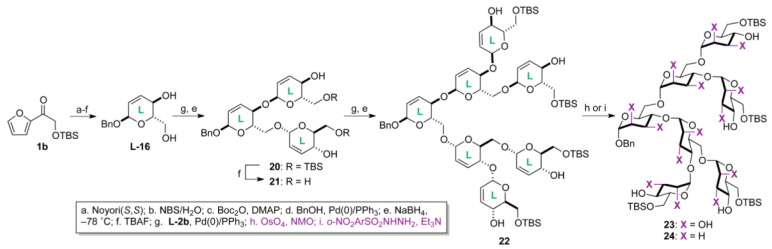


Scheme 2.

Synthesis of a Library of 1,4-Linked α-*Rhamno*-trisaccharides Containing both D- and L-Pyranoses



Scheme 3.
Synthesis of Branched α-*Rhamno*/*Manno*-trisaccharide Containing both D- and L-Pyranoses



Scheme 4.

A 12-Step Synthesis of Highly Branched All-L-α-*Manno*-hepta-pyranoside