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Enantioselective Route from Carbohydrates to Cyclooctane Polyols

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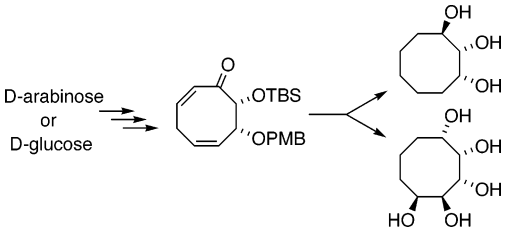
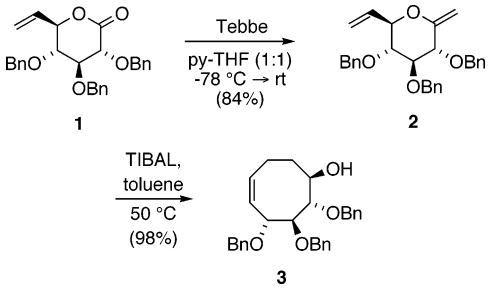
ABSTRACT



A synthetic route to select cyclooctane-1,2,3-triols and 1,2,3,4,5-pentaols has been defined. The starting materials are D-glucose or D-arabinose, and the key steps consist of a zirconocene-promoted ring contraction, a [3,3] sigmatropic rearrangement, and more extended functionalization of the resulting cyclooctadienone.

Polysaccharides are recognized to mediate a host of cell surface interactions, which include binding to toxins and pathogens, and to form much of the structural framework of cells and tissues. Such utilization of carbohydrates operates widely despite long-recognized disadvantages associated with unwelcomed hydrolytic instability, limitations linked to the adoption of specific unfavorable conformations, and degradability brought on by glycosidases. As a result, carbohydrate recognition events have been probed with polyhydroxylated carbocyclic mimetics originally consisting of five- and six-membered cyclitols.[1] More recently, attention has been increasingly accorded to eight-membered ring systems.[2−6] The general perception is that replacement of the endocyclic oxygen atom of a pyranoside ring by three methylene groups would provide for unprecedented conformational projections of the appended hydroxyl substituents while precluding degradation by carbohydrate-processing enzymes. The probing of inhibitory activities toward glycosidases could be meaningfully expanded as well.



Several years ago, our group reported on the discovery that triisobutylaluminum (TIBAL) is capable of promoting [3,3] sigmatropy within 2-methylene-6-vinyltetrahydropyrans as a general route to functionalized eight-membered rings.[7]

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(2) (a) Blériot, Y.; Giroult, A.; Mallet, J.-M.; Rodriguez, E.; Vogel, P.; Sinay, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2553. (b) Wang, W.; Zhang, Y.; Zhou, H.; Blériot, Y.; Sinaÿ, P *Eur. J. Org. Chem.* **2001**, 1053. (c) Wang, W.; Zhang, Y.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2466.

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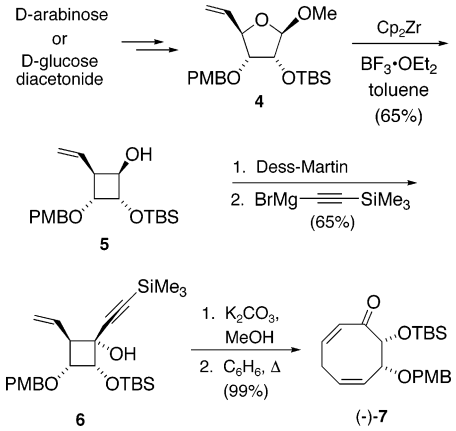
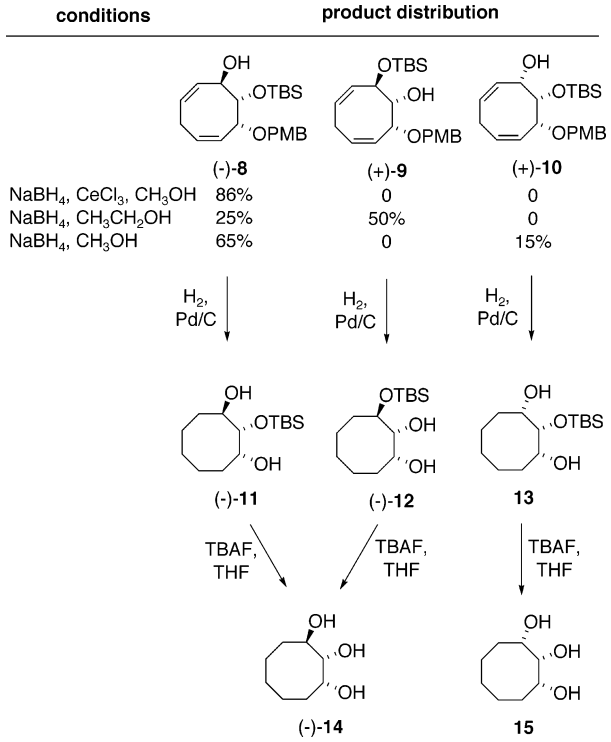
Scheme 1. Preparation of (−)-**7**



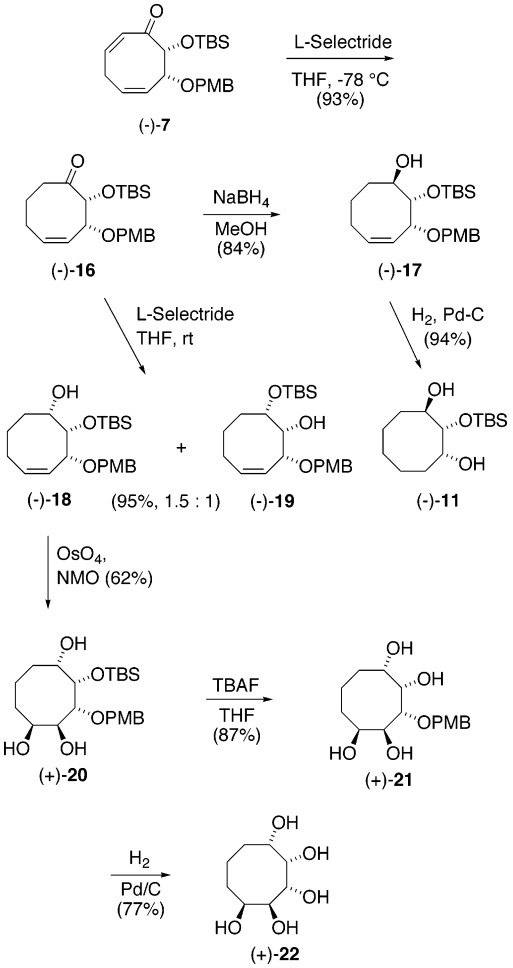
This process has been elegantly extended to cyclooctanoid carbasugars by Sinaÿ[2] and by van Boom[3] as exemplified by

Scheme 2. Sodium Borohydride Reduction of (−)-**7**



the conversion of **2** to **3**. Presently, we detail an entirely different approach to the rapid elaboration of polyhydroxylated cyclooctanes. This new technology takes advantage of the ease with which plentiful and inexpensive carbohydrates can be transformed into 4-vinylfuranosides, and the propensity of the latter to undergo deoxygenative ring contraction when treated with zirconocene[8,9] (Scheme 1). As in the case of **4**,[10] this transformation can be highly diastereocontrolled. The sequential oxidation of **5** so obtained to the substituted cyclobutanone and alkynyl Grignard addition then leads to **6**, which is notably responsive to chemoselective desilylation and thermal isomerization to give (−)-**7** quantitatively.

Scheme 3. Route to Polyol (+)-**21**



The more extended functionalization of **7** began with sodium borohydride reduction (Scheme 2). When $CeCl_3$ was present as a coreactant, exclusive conversion to **8** was observed. However, a sensitivity to solvent soon became evident. The continued use of methanol in the absence of the lanthanide furnished **8** and its epimer **10** in a 4.3:1 ratio. This dropoff in stereoselectivity was not noted in ethanol, but the silyl-migrated isomer **9** now emerged as the major product.[11] The structural assignments to **8**−**10** were secured

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(10) Paquette, L. A.; Kim, I. H.; Cunière, N. *Org. Lett.* **2003**, *5*, 221.

(11) For other examples of related silyl transfers, see: Paquette, L. A.; Hartung, R. E.; Hofferberth, J. E.; Vilotijevic, I.; Yang, J. *J. Org. Chem.* **2004**, *69*, 2454.

by sequential hydrogenation and desilylation. By this means, **8** and **9** were transformed into **14** whose cis,anti configuration was evident from its eight-line ^{13}C NMR spectrum and an $[\alpha]_D^{25}$ of −61.8 in $CHCl_3$ solution. The equally smooth conversion of **10** to **15** was punctuated by the complete loss of optical activity and the recording of only five carbon signals as a direct consequence of its C_s symmetry.[11]

Alternative treatment of **7** with L-Selectride in THF at −78 °C proceeded exclusively with 1,4-reduction to generate the levorotatory cyclooctenone **16** (93%, Scheme 3). This routing allows subsequent conversion to the β-configured carbinol **17**. Since MM3-based calculations show **17** and its epimer to be isoenergetic, the stereochemical course of the borohydride reduction is clearly conformationally controlled.[12] The match-up with **11** corroborated the assigned stereochemistry.

Advancement in the direction of pentahydroxy system **22** was realized by L-Selectride reduction of **16** in THF at room temperature. Under these conditions, the resulting hydroxyl group was oriented α as in **18**, and silyl transfer to give **19** operated as well. Dihydroxylation with OsO_4 in the presence of NMO produced **20**, thereby setting the stage for sequential fluoride-ion-induced desilylation and hydrogenolytic removal of the PMB group. Since **22** exhibited eight carbon signals and a positive optical rotation, the meso isomer had not been formed. The osmylation step had therefore necessarily taken place from the β face of the π-bond as shown.

In summary, the crafting of cyclooctane-1,2,3-triols and -1,2,3,4,5-pentaols from simple carbohydrate precursors has been accomplished. Six of the constituent ring carbons arise from the starting sugars and the remaining two are derived from trimethylsilylacetylene. The synthetic pathway underscores the potential offered by the zirconocene-promoted ring contraction for enhancing the scaffolding capacity of carbohydrates.

Note Added after ASAP Publication. The title of Scheme 3 was incorrect in the version published ASAP January 13, 2005; the corrected version was published ASAP January 13, 2005.

Supporting Information Available: Experimental procedures, ^1H NMR spectra, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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