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New oligomers of conduritol-F and *muco*-inositol. Synthesis and biological evaluation as glycosidase inhibitors

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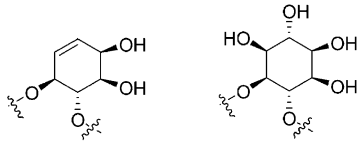
Abstract—Several oligomers possessing the configuration of conduritol-F and *muco*-inositol have been prepared and tested against six glycosidase enzymes. Electrochemical dehalogenation and reductive deprotection of cinnamyl ethers are featured in the reported syntheses. The synthesis, properties, and biological activities are investigated.

Unnatural saccharides, including oligosaccharides, have long been recognized as potential inhibitors of glycosidic enzymes and hence show promise in the investigation of antiviral agents.[1] Such compounds include carbasugars,[2] azasugars,[3] and various analogues that structurally and functionally resemble carbohydrates but fail to enter the natural metabolic pathways following their interaction with appropriate enzymes.[4]

A few years ago, we reported the synthesis of several oligoinositols, a new class of compounds whose structure in solution resembles that of oligosaccharides but which are not glycosidically labile. Consequently, these compounds are ideal carbohydrate surrogates, especially in view of the fact that there are more combinatorial possibilities in the oligomeric inositol series than for natural carbohydrates because of the presence of an additional chiral center.[5] Oligomers containing the elements of L-*chiro*- and *neo*-inositols[6] as well as those derived from naphthalene[7] displayed remarkable structural and biological properties, including the ability to sequester calcium ions from aqueous solutions.[6] Results in this area have been reviewed.[8] Recently we synthesized oxygen- and nitrogen-linked oligomers and tested them against common glycosidase enzymes, with promising results.[9] This paper describes the synthesis, structure, and biological evaluation of oligomers based on the motif of either conduritol-F (**1**) or *muco*-inositol (**2**). Both series of compounds were prepared in an iterative fashion from the known epoxide **4**,[6,10] as shown in Schemes 1 and 2.



Epoxide **4** is available in two steps (75% overall yield) from diol **3**, obtained in a reproducible yield of 12 g/L,[11] by the whole-cell fermentation of bromobenzene in a 15-L fermentor with *Escherichia coli* JM109 (pDTG601A), an organism overexpressing toluene di-oxygenase.[12] The epoxide was opened in the presence of a Lewis acid catalyst with cinnamyl alcohol and benzyl alcohol to provide, respectively, **5a** (73% yield) and **5b** (75% yield), which were used as nucleophilic partners in further coupling to epoxide **4**. Ether **6a** was subjected to dehalogenation, electrochemical deprotection of the cinnamyl group,[13] and hydrolysis to furnish conduritol-F dimer **7**. Another dimer **10**, having C-2 symmetry, was prepared via **9** by allowing *trans* diol **8** to open the epoxide.

The corresponding *muco*-inositol oligomer was prepared as shown in Scheme 2. Reduction of the halogen in **6b** gave **11**, which was subjected to epoxidation with dioxirane.[16] After much experimentation, treatment of **11** with methyl-(trifluoromethyl)dioxirane generated in situ

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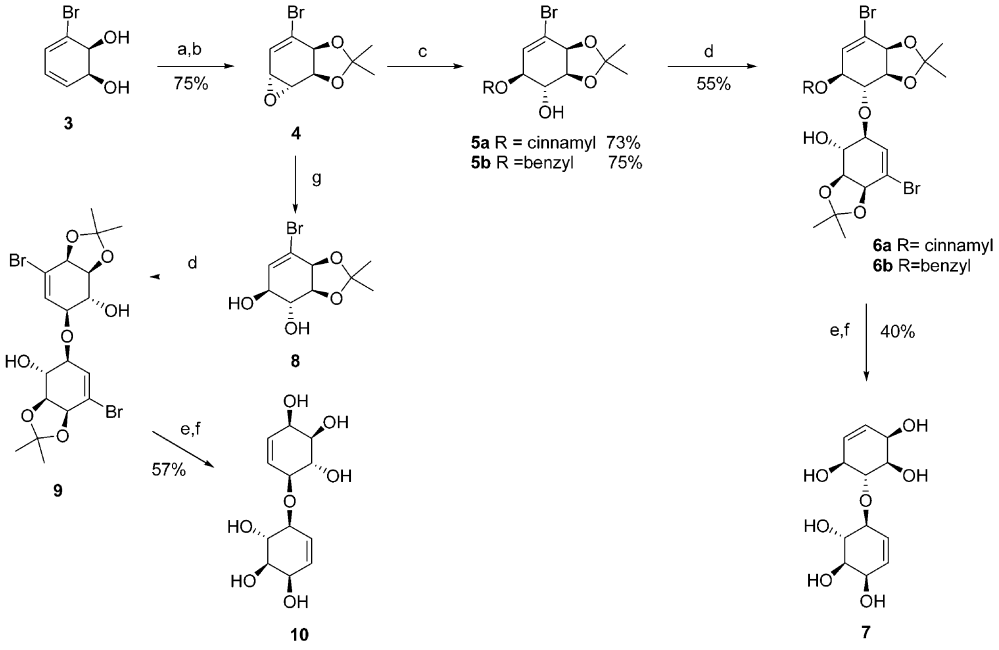
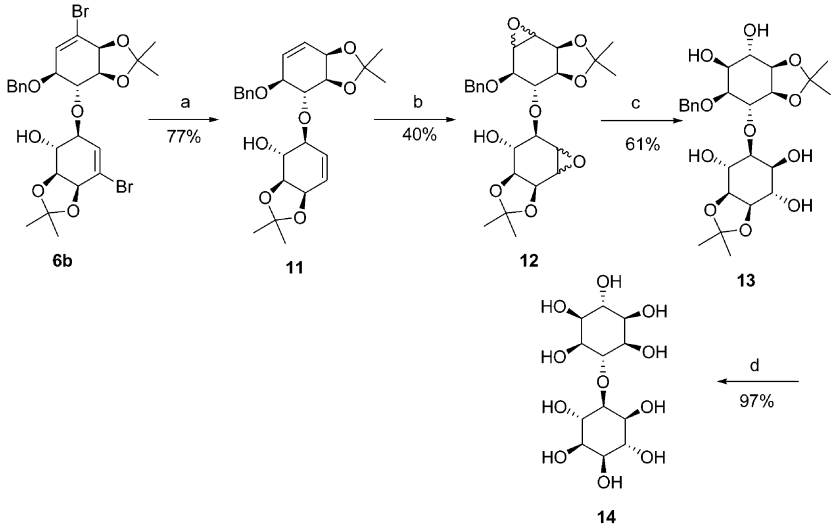
bis epoxide **12** as a mixture of diastereoisomers (40%). Hydrolysis of **12** proceeded as expected in a redundant fashion[17] providing a single isomer **13** via *trans*-diaxial opening. Treatment of **13** with palladium on activated carbon under a hydrogen atmosphere in acidic methanol afforded the *muco*-di-inositol **14** in 97%.

To evaluate their potential as glycosidase inhibitors, all compounds were screened against six commercially available enzymes. The data presented in Table 1 reveal promising inhibitory activity against some of the enzymes. Compounds (**7** and **10**) that preserved the conduritol-F motif proved to be stronger inhibitors compared to the monomers or the *muco*-inositol oligomer. We have previously shown that nitrogen-linked inositols and conduramines followed similar trends.[9] The conduritol motif resembles more closely the structure of the transition state assumed to operate in glycolysis,[4] and this may explain the higher inhibitory activity in comparison with the fully hydroxylated inositols.

Three-dimensional representations of the oligomers were obtained by modeling with the Spartan SGI software, available from Wavefunction, Inc.[18] The components of *muco*-di-inositol (**14**) appear to position themselves approximately ninety degrees from one another in order to avoid steric interactions between α-substituents. The structural arrangement of a higher order oligomer, hypothetical *muco*-inositol octamer **16**, was also calculated, showing interesting intramolecular



Scheme 1. Reagents and conditions: (a) dimethoxypropane, acetone, *p*TsOH; (b) *m*CPBA, CH_2Cl_2; (c) cinnamyl or benzyl alcohol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (d) **4**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (e) −3.0 V, Et_4NBr, MeCN; (f) trifluoroacetic acid:THF:H_2O (4:1:1); (g) H_2O.

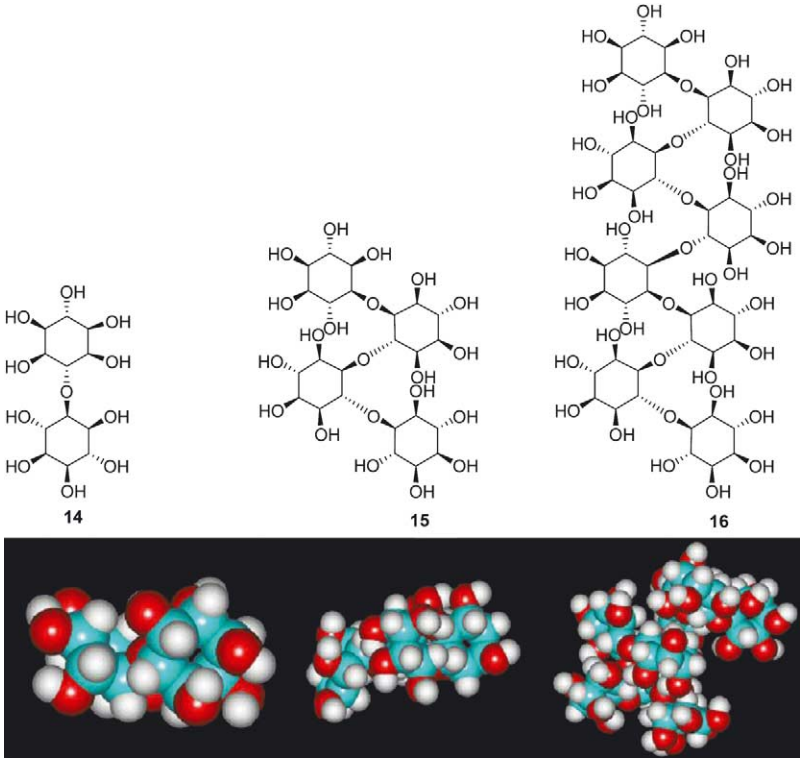


Scheme 2. Reagents and conditions: (a) −3.0 V, Et_4NBr, MeCN; (b) oxone, trifluoroacetone, $NaHCO_3$, MeCN, 0 °C; (c) Amberlyst A-27 resin (basic), H_2O; (d) H_2, Pd/C, acidic MeOH.

Table 1. Results of inhibition studies[a]

	α-Glucosidase	β-Glucosidase	α-Galactocosidase	β-Galactocosidase	α-Mannosidase	β-Mannosidase
Conduritol-F[14]	I	I	I	600 μM	I	I
muco-Inositol[15]	I	I	I	I	I	I
7	60 μM	I	850 μM	190 μM	I	I
10	I	I	275 μM	250 μM	I	1.50 mM
14	800 μM	I	I	600 μM	I	I

[a] Each value shown is the average of two experiments; I = inactive.



hydrogen-bonding similar to that observed for the octamer of L-*chiro*-inositol,[9] which has been shown to prefer a helical arrangement.

All oligomers made up of inositol components contain a *trans* linkage and therefore maintain a β-turn in their secondary structure. The three dimensional shape is defined by the stereochemistry of the monomeric units. We describe these oligomers as 'homogeneous' as they contain identical repeating units. Future endeavors will examine 'heterogeneous' oligomers in which the shape is 'programmed' by rationally alternating different monomers, for example, L-*chiro*, *neo*, *muco*. Such compounds may find use as templates for asymmetric synthesis or in the design of catalysts. The results of these endeavors will be reported in due course.

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17. For a definition of redundant operations, see ref 8.
18. All results were calculated by means of Monte-Carlo simulation to find the minimum energy conformations. These structures were further optimized by semi-empirical (AM1) methods. All calculations were performed with parameters for gas phase medium.