Concise syntheses of 1,2-L-*chiro*-inositol conjugates and oligomers–a novel class of saccharide mimics with promising molecular properties

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Calcium complexes with novel amino-inositol conjugates to form secondary extended helical structures are reported.

Unnatural mono- and oligo-saccharides, where either the glycosidic oxygen or the endocyclic oxygen have been replaced by a methylene unit, continue to attract attention[1] because of their biological activities ranging from simple inhibition of glycosidic enzymes[2a] to possible activity in cell adhesion and communication pathways.[2b] Our research in the general design of carbohydrates has yielded unique saccharide derivatives, initially destined for their examination of their insulin mediating properties.[3] We recently reported the synthesis of L-*chiro*-inositol-*proto*-quercitol conjugate **3** by Lewis-acid catalysed coupling of nucleophilic and electrophilic partners, such as **1** and **2** respectively, derived from cyclohexadiene-*cis*-diols (Fig. 1).[4]

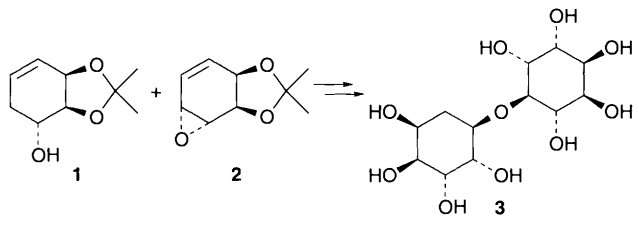
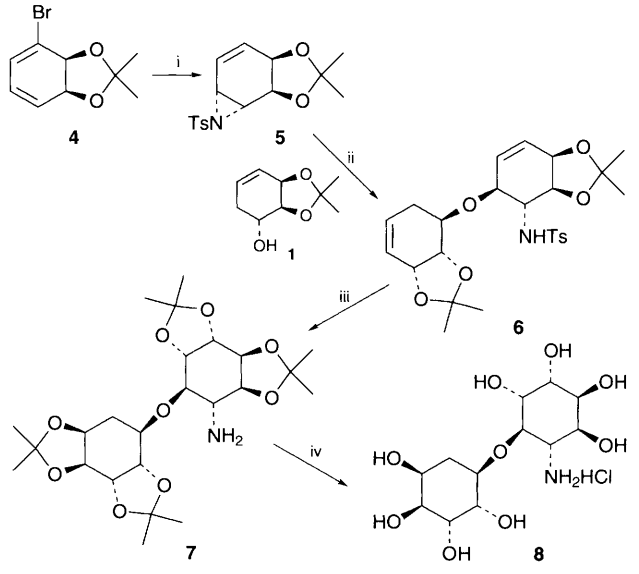


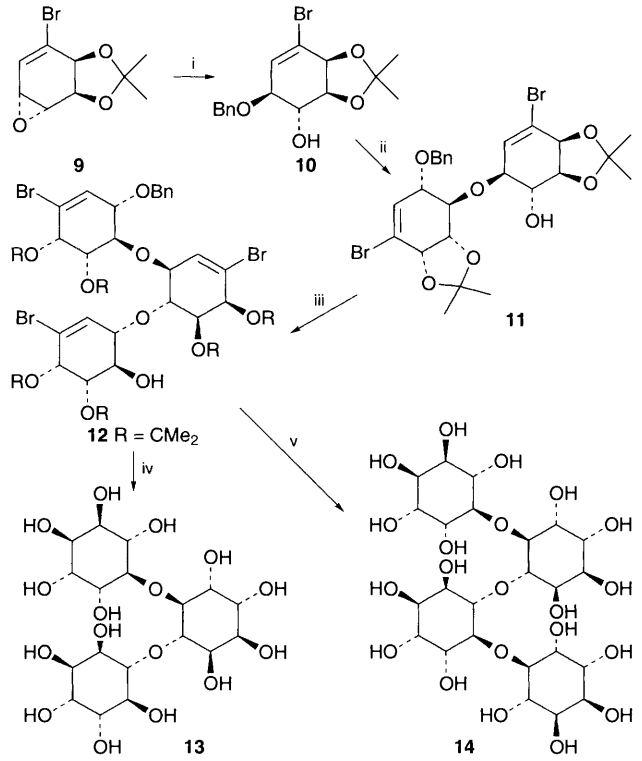
Fig. 1

Here we highlight the preparation of several higher oligomers of L-*chiro*-inositol conjugated to other inositols or aminocyclitols and report on the interesting properties of this novel class of compounds.

The amino-inositol **8** was synthesized on a multi-gram scale in several steps as shown in Scheme 1. Conversion of the known diene[5] **4** to the tosyl aziridine[6] **5** was effected using recently disclosed aziridination procedures[7] which provided the desired crystalline aziridine **5** in moderate yield. Upon treatment of aziridine **5** with the secondary alcohol[5] **1** under acid catalysis,[4] the conjugate **6** was isolated in 52% yield. Following oxidation of the bis-diene with osmium tetroxide, removal of the amino



Scheme 1 *Reagents and conditions:* i, (*a*) C_6H_5I = NTs, cupric acetylacetonate; (*b*) Bu_3Sn, AIBN, THF, heat, 2 h, 85%; ii, BF_3Et_2O, CH_2Cl_2, −20 °C, 24 h, 52%; iii, (*a*) OsO_4, NMO, acetone, H_2O, Bu^{t}OH, room temp., 15 h, 89%; (*b*) 2,2-dimethoxypropane, acetone, *p*-TsOH, room temp., 1 h, 78%; (*c*) Na, $NH_{3(l)}$, −78 °C, 1 h, 92%; iv, HCl, MeOH, room temp., 24 h, quant.



Scheme 2 *Reagents and conditions:* i, benzyl alcohol, CSA, CH_2Cl_2, room temp., 1.5 h, 58%; ii, **9**, BF_3·Et_2O, CH_2Cl_2, −20 °C, 30 min, 79%; iii, **9**, BF_3·Et_2O, CH_2Cl_2, −20 °C, 30 min, 55%; iv, (*a*) Bu_3Sn, AIBN, THF, heat, 3 h, 81%; (*b*) OsO_4, NMO, acetone, H_2O, Bu^{t}OH, room temp., 24 h, 93%; (*c*) 2,2-dimethoxypropane, acetone, *p*-TsOH, room temp., 3 h, 89%; (*d*) Pd (10% on C), H_2, MeOH, room temp., 3 h, 68%; (*e*) HCl, MeOH, room temp., 16 h, quant.; v, (*a*) **9**, BF_3·Et_2O, CH_2Cl_2, −20 °C, 30 min, 54%; (*b*) Bu_3Sn, AIBN, THF, heat, 3 h, 81%; (*c*) OsO_4, NMO, acetone, H_2O, Bu^{t}OH, room temp., 24 h, 90%; (*d*) 2,2-dimethoxypropane, acetone, *p*-TsOH, room temp., 2 h, 82%; (*e*) Pd (10% on C), H_2, MeOH, room temp., 3 h, 71%; (*f*) HCl, MeOH, room temp., 16 h, quant.

protecting functionality gave the amine **7** which was converted to the amine hydrochloride **8** upon deprotection.

The tri- and tetra-meric inositol oligomers, **13** and **14** respectively, were produced in a linear fashion utilizing successive coupling transformations and oxidative sequences (Scheme 2) that furnished deprotected oligomers **13** and **14** obtained in four steps each.

Conjugates **3** and **8** were assayed for β-glucosidase inhibition by monitoring the *p*-nitrophenyl-β-D-glucopyranoside hydrolysis catalysed by this enzyme.[8] Only the amino derivative **8** displayed any activity, albeit weak, with an observed 12% inhibition of this enzyme at 3.5 mmol concentrations of amine.

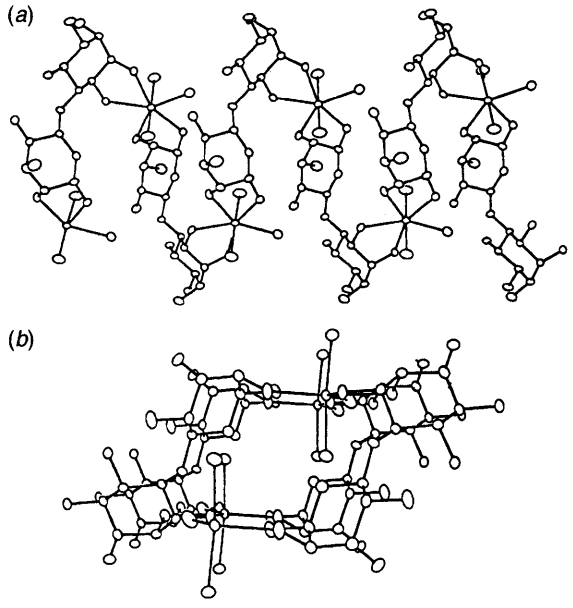


Fig. 2 Thermal ellipsoids drawing of the extended secondary helical structure shown along (*a*) the *b*-axis and (*b*) down the *b*- axis

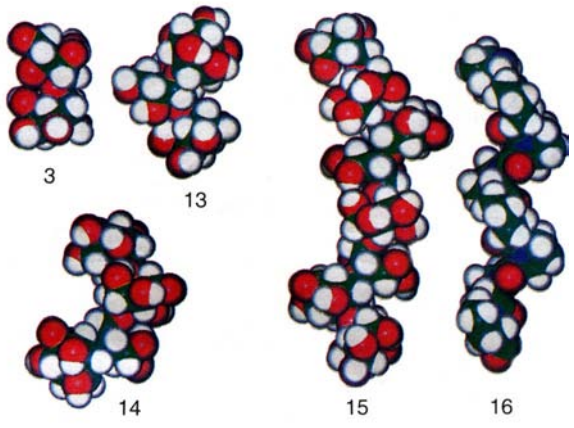


Fig. 3

The metal chelating potential of the amino conjugate **8** was tested through doping of an aqueous solution of the amine hydrochloride with an equimolar aqueous solution of calcium chloride.[9] Following slow evaporation of the solvent at room temperature, the resulting crystals were analysed by single crystal X-ray diffraction and shown to possess a striking extended secondary helical structure, shown in Fig. 2, exhibiting an ordered array of calcium ions bridging two amino residues. The calcium ions have pentagonal bipyramidal coordination consisting of two hydroxide groups from each amino residue and a water molecule in the equatorial plane, and two water molecules in the axial positions. The crystal structure exhibits a 3-dimensional network of H-bonding. Both chloride ions as well as a water molecule of crystallization link the amino residues in chains and between chains.

Molecular modelling of trimer **13** and tetramer **14** suggest a tendency, Fig. 3, towards a β-turn secondary structure which becomes especially evident in higher oligomers, such as the hypothetical octamer **15** here compared to that of proline **16**.

Compounds of this type have not been previously synthesized and thus constitute a novel class of unnatural saccharides which promise to have fascinating chemical and biological properties. Furthermore, the method of assembly lends itself to combinatorial technology that will lead to libraries of oligomers containing any compositions or combinations for eventual biological evaluation.

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Footnotes

† To whom questions concerning X-ray crystallography results should be addressed.

‡ Undergraduate research participant 1995.

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