

Synthesis of Structurally Diverse and Defined Bivalent Mannosides on Saccharide Scaffolding

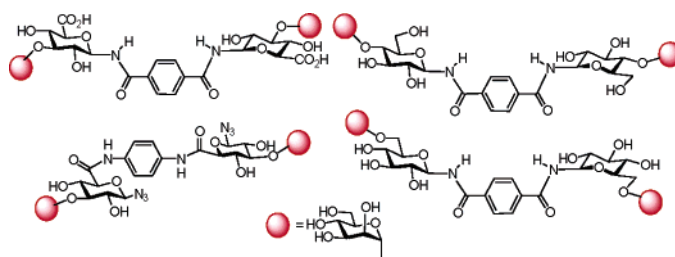
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ABSTRACT



The synthesis of bivalent mannosides by the grafting of α -D-mannopyranoside onto monosaccharide acceptors and conjugation to terephthalic acid or phenylenediamine is described. Computational methods were used to predict accessible orientations and distances between the mannose units.

Cells communicate through complex interaction of carbohydrate polymers with their receptors.¹ Such biopolymers constitute a high-density coding system. Multivalent carbohydrates^{2,3} form part of this polymer class and are important in generating high-affinity binding, mediating cell–cell recognition, adhesion, and modulation of signal transduction. Synthetic multivalent ligands have proven to be useful in defining new biological mechanisms.⁴ Mechanisms of binding of such ligands to receptors are diverse; for example, cross-linking of lectins by multivalent ligands⁵ as well as chelate effects operate. Opportunities exist for the development of therapeutics⁶ and vaccines.⁷ Small glyoclusters can

exhibit interesting properties. For example a synthetic compound can be identified, from a series of rigidified multivalent ligands, each exposing the same headgroup (lactose), that exhibits selective blocking of one galectin when evaluated against a panel of galectins.⁸ This suggests more generally that detailed three-dimensional structure–activity relationships of multivalent ligands will be interesting. These have not been explored to date, although crystal structures of ligand–receptor complexes are known and relationships

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between architecture and biological activity have been described (e.g., small clusters versus dendrimers versus polymers). For many glycocluster structures, it may be difficult to define the bioactive conformations that the ligands adopt if flexible scaffolding is used for display of the recognition component. Herein we describe synthesis of ligands with potential to cross-link mannose receptors and exploration of their conformation by computational methods.

Scaffolds^{9,10} based on glycosylamides **1** (Figure 1) have been synthesized and their structure investigated.^{11,12} We

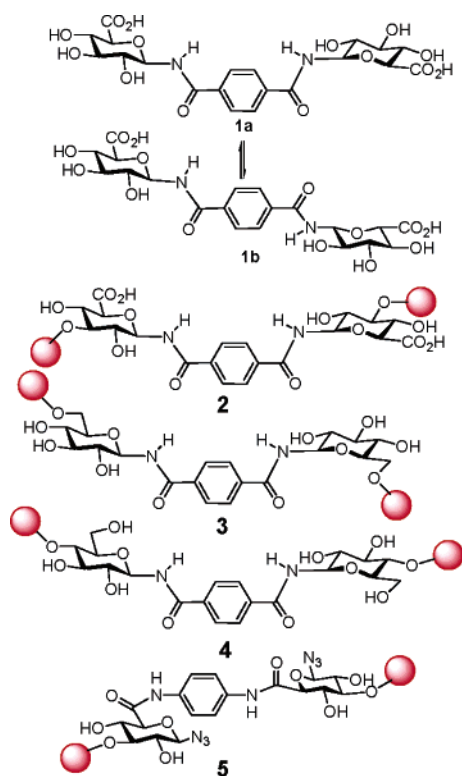


Figure 1. Two-dimensional structures of **1**–**5**. Red sphere = α -D-mannopyranoside.

envisaged grafting the α -D-mannopyranoside headgroup onto hydroxyl groups of the core structure **1** or its related glucose analogue to generate **2**–**4** (Figure 2) with potential to cross-link mannose receptors. Because of a limited number of degrees of conformational freedom, it is possible to predict or determine the spatial relationships between their mannose residues. In addition, we designed **5**, a dimer built on a phenylenediamine unit.¹³ A prediction of the preferred conformations of **2**–**4** was first undertaken by computational

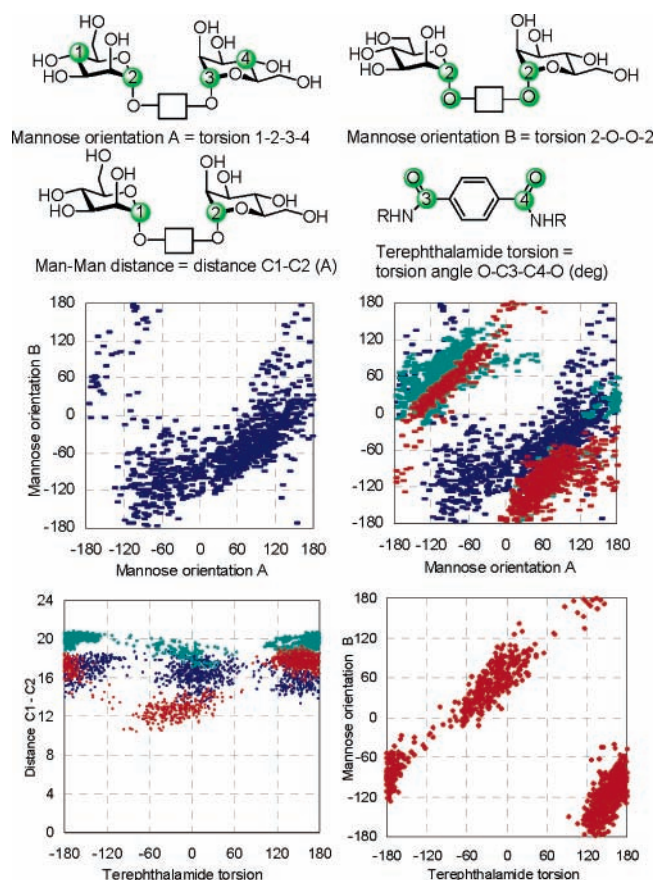


Figure 2. Top graphs show mannose orientation A plotted vs mannose orientation B for 1000 conformers of **2**–**4** sampled during stochastic dynamics simulations. The profile for **2** is blue, that for **3** is green, and that for **4** is red. The distance between mannose residues (\AA) as a function of terephthalamide torsion is shown bottom left. The mannose orientation B as a function of terephthalamide torsion for **4** is shown at the bottom right. The Man–Man distance for **3** is 16–20 \AA and that for **4** is 10–14 \AA , when similar orientations of mannose are found for **3** and **4** (i.e., when terephthalamide torsion is $0 \pm 60^\circ$).

methods (Macromodel 8.5)¹⁴ before synthesis of the compounds. All calculations were carried out using the GB/SA solvation model¹⁵ for water and the OPLS-AA force field.¹⁶ First, the favored angles for the dihedrals Φ and Ψ ¹⁷ for the glycosidic linkage between the mannose and glucose/glucuronic acid residues were calculated by systematic exploration of Φ and Ψ space and also by conformational searching techniques, of model disaccharides.^{18,19} The glycosidic torsion angles for the lowest energy structures agreed with related disaccharides calculated previously.²⁰

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Scheme 1

(i) LiOH, THF/H₂O/MeOH
(ii) Ac₂O, 85°C, 2 h, 91%

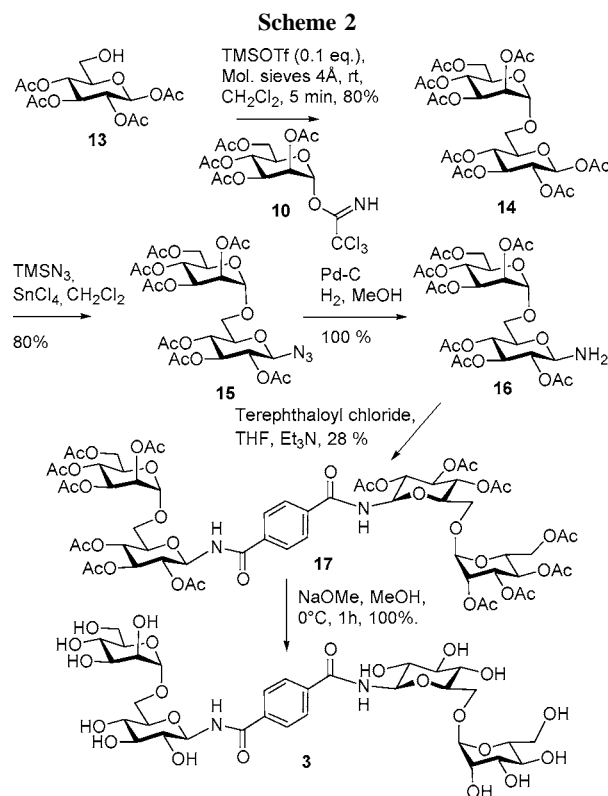
MeOH, 60°C, 2h, 90%

Allyl alcohol (2 eq.), THF, Mol. sieves 4Å, 65°C, 20h, 68%

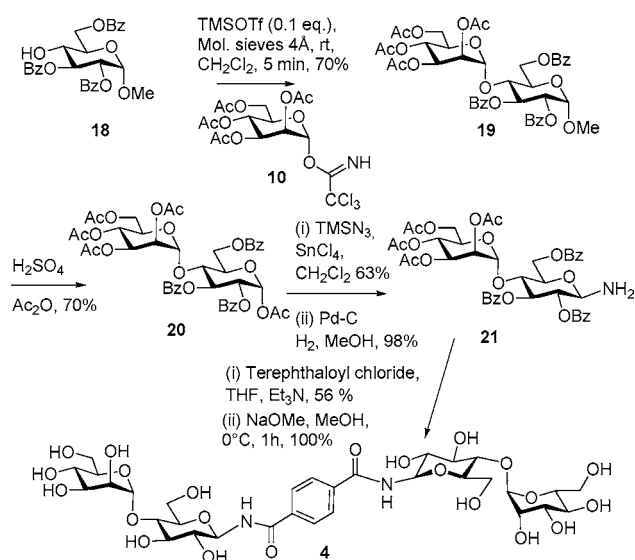
TMSOTf (0.1 eq.), Mol. sieves 4Å, 0°C, CH₂Cl₂, 30 min, 35%

Terephthaloyl chloride (0.5 eq.), PPh₃-polystyrene (1.3 eq.), 6%

NaOMe, MeOH, 0°C, 1h, 95%



Scheme 3

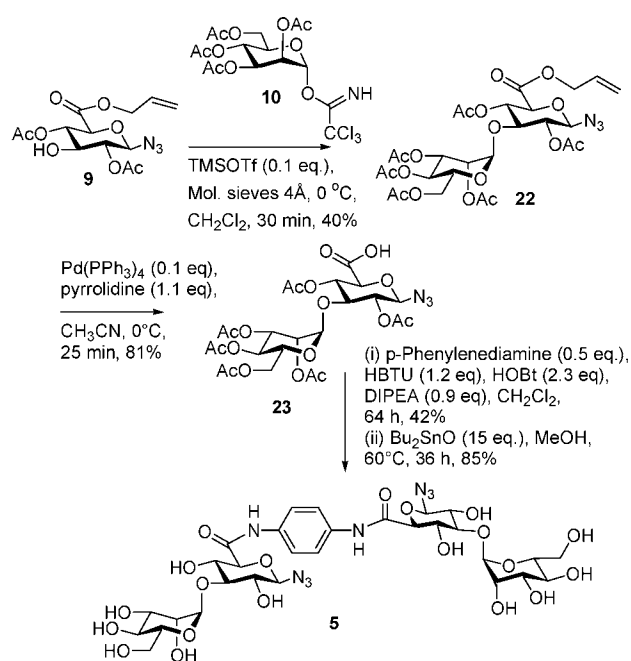


by reaction with acetic anhydride gave the 6,3-lactone **7**. This lactone reacted readily with alcohols to give **8** or **9**. The Schmidt glycosidation of **8** with imidate **10**²⁶ gave **11**, which was subsequently converted, in very low yield,²⁷ to the dimer **12** on reaction with terephthaloyl chloride promoted by a polymer-supported aryl phosphine. Removal of the protecting groups from **12** gave **2**.

The tetraacetate **13**²⁸ was reacted with **10** as above to give **14**. This was converted to azide **15** using SnCl₄ and azidotrimethylsilane. The amine **16** was prepared from **15** by catalytic hydrogenation, and its subsequent reaction with terephthaloyl chloride in the presence of triethylamine in THF gave the dimer **17** (28%). This was converted to **3** by Zemplen deacetylation (Scheme 2). The synthesis of **4** was achieved via the tribenzoate **18**,²⁹ which on glycosidation gave disaccharide **19**. Acetolysis gave **20**, and this product was converted to amide **21** via a glycosyl azide. Reaction of **21** with terephthaloyl chloride in THF in the presence of triethylamine followed by removal of the protecting groups gave **4** (Scheme 3).

The divalent mannoside **5** was prepared as shown in Scheme 4.³⁰ The Schmidt glycoside coupling reaction of **9** with **10** gave **22**. The allyl ester protecting group was removed by palladium catalysis³¹ to give acid **23**. Coupling

Scheme 4



of **23** with *p*-phenylenediamine promoted by HBTU/HOBt gave, after prolonged reaction time, the protected divalent compound. Removal of the acetate protecting groups by the standard methods (NaOMe/MeOH, LiOH, hydrazine) was unexpectedly problematic and gave a mixture containing unidentified products, but the use of dibutyltin oxide³² in methanol proved to be satisfactory and gave **5**.³³

In summary, we described synthesis of structurally diverse bivalent mannosides on saccharide scaffolding. Mannose—mannose orientations and distances were determined by location on the scaffold and preferred glycosidic and terephthalamide torsions. Each compound showed a distinct three-dimensional structural profile. A comparison of the biological properties of **2–5** will be reported in due course.

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Supporting Information Available: Analytical data for **2–5** and ¹H and ¹³C-NMR spectra for all new compounds and selected additional conformational analysis on **2–4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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