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One-pot Synthesis of Divalent and Trivalent Cluster Mannosides *via* Ugi Four-component Reaction

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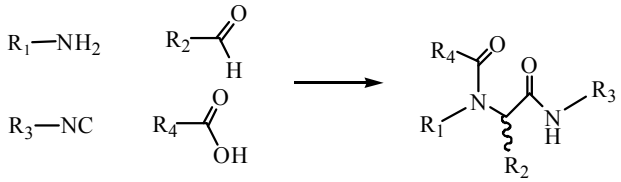
Abstract: The Ugi four-component reaction (U-4CR) was utilized to prepare divalent and trivalent cluster mannosides. Thus, two target compounds **6** and **8** were obtained efficiently using carboxymethyl 2, 3, 4, 6-tetra-*O*-acetyl-α-D-mannopyranoside **4** as acid component, and 1, 6-hexanediamine or tris(2-aminoethyl)amine as the multivalent scaffolds.

Keywords: Ugi reactions, cluster mannosides, glycocluster.

Although protein-carbohydrate interactions are essential to many biological processes, individual interactions usually exhibit weak binding affinities (K_d values usually ranging from mmol/L to μmol/L), as well as relatively low selectivities among similar carbohydrate ligands. The simultaneous formation of multiple protein-carbohydrate interaction is a binding mode, which was employed to achieve the necessary affinity. In this respect, the development of strategies for the preparation of structurally well defined multivalent (di-, tri- and higher order) glycoconjugate, named glycocluster, is highly desirable from the pharmaceutical point of view[1].

Multicomponent reactions (MCR) such as the Ugi reaction (**Scheme 1**) have generated much interest because of their synthetic potential, applications in combinatorial chemistry, and the generation of molecular diversity. The potential importance of the MCR reaction in carbohydrate chemistry has been recognized recently by other researchers[2,3].

Scheme 1



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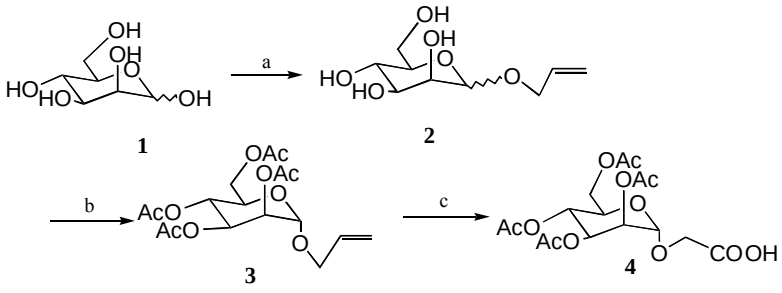
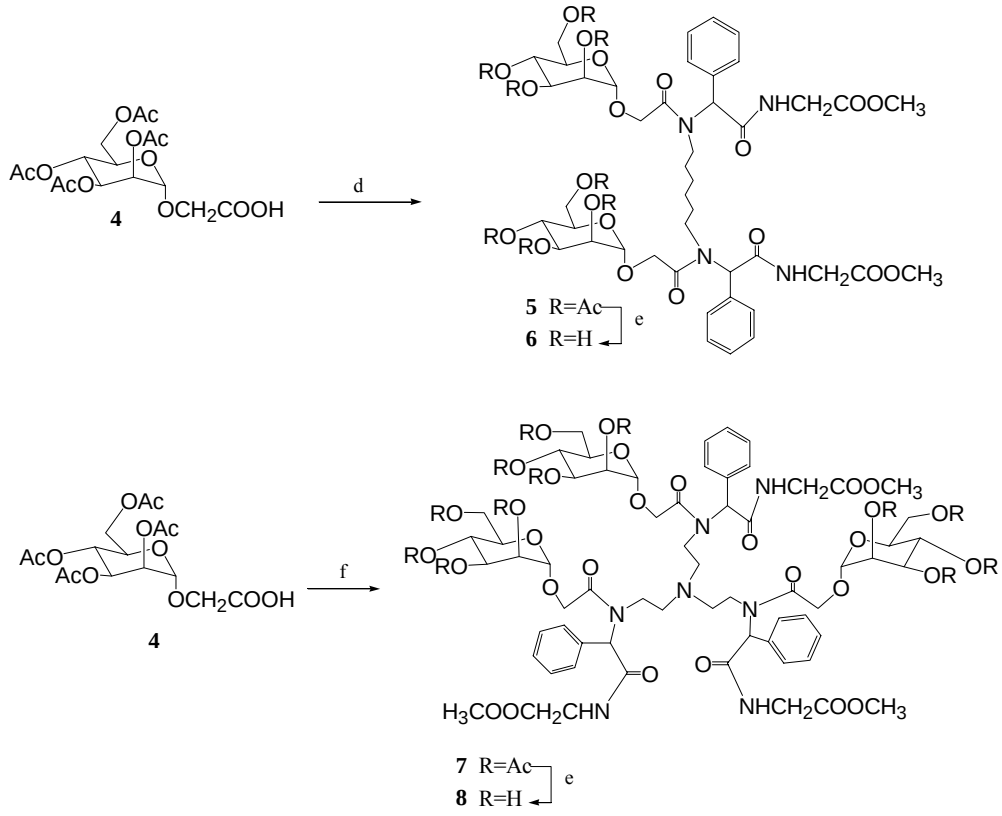
Scheme 2



Reagents and conditions: (a) CH_2=CH_2CH_2OH, Dow-50-X-8(H)$^+$, reflux, 90 min; (b) Ac_2O, Py/ DMAP 45.6%; (c) $NaIO_4/RuCl_3$.

Scheme 3



Reagents and condition: (d) benzaldehyde,methyl isocyanoacetate, 1,6-hexanediamine, MeOH, rt, 48 hr, 46.0%; (e) NaOMe/ MeOH, 20 min, rt, 98%. (f) benzaldehyde, methyl isocyanoacetate, tris(2-aminoethyl) amine, MeOH, rt, 48 hr, 40.5% .

Divalent and trivalent cluster mannosides have demonstrated the improved biological activity[4]. In this communication we attempt to investigate a synthetic route

using the Ugi four-component reaction to prepare divalent, trivalent and higher order multivalent cluster mannosides.

The synthetic route is outlined in **Scheme 2**. The key intermediate allyl-D-mannopyranoside **2** was obtained by Fischer's glycosidation method[5]. After acetylation and purification on silica gel column, the main product **3** was obtained in yield of 45.6% (from **1)**. Oxidation of **3** with $NaIO_4$/ $RuCl_3$[6] afforded carboxymethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **4** quantitatively.

The Ugi four-component reaction of **4** with freshly distilled benzaldehyde, methyl isocyanoacetate (2.2 equiv of each reagent), and 1,6-hexanediamine (1.0 equiv) gave divalent mannoside **5**. The acetate **5** was hydrolyzed using NaOMe/MeOH to give the target compound **6**.

Similarly, reaction of **4** with freshly distilled benzaldehyde, methyl isocyanoacetate (3.3 equiv of each reagent), and tris(2-aminoethyl)amine (1.0 equiv) gave trivalent mannoside **7**. **8** was obtained from **7** after hydrolysis with NaOMe/MeOH (**Scheme 3**).

The structures of all compounds were identified by NMR (^1H, ^{13}C, COSY, HMQC) and HRMS spectra.

In summary, the Ugi four-component reactions have been used for the synthesis of divalent and trivalent carbohydrate derivatives in one pot. High generation of cluster mannosides and diverse structures can be easily obtained using this method. These diverse multivalent carbohydrate derivatives will be useful for further research on the mechanism of multivalent ligands action and for the development of carbohydrate-based phamaceutics.

References and Note

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