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Note

Synthesis of a series of novel heteroglycoclusters and homoglycoclusters and the study of their anti-adhesion activities

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ABSTRACT

A new series of mixed-type heteroglycoclusters containing mannose and lactose were synthesized. In the synthesis of rigid scaffold of heteroglycocluster, we found that trans-isomer could be prepared stereoselectively by means of Grubbs olefin cross-metathesis reactions. Moreover, sequential acylation using cyclic anhydride as scaffold could give cis-isomer. These two methods may provide complementarity of stereochemistry in heteroglycocluster assembling. The anti-adhesion activities of these compounds were assessed by Surface Plasmon Resonance (SPR) and static state cell-based adhesion assay. These results indicated that the rigid scaffold might not affect the anti-adhesion activities.

1. Experimental

Adhesion of leukocytes to endothelium plays an important role in inflammatory diseases.[1] The biological process involving carbohydrate–protein interactions, which employs various acceptors and relevant carbohydrate ligands. Many cell adhesion molecules (CAMs) are involved in leukocyte–endothelium interactions.[2] For example, the selectin family of CAMs mainly mediates the initial capture and rolling of leukocytes, and firm adhesion through integrins is followed.[3] In our previous research, we have demonstrated some synthesized multivalent lactosides can inhibit the adhesion of leukocytes to endothelial cells effectively.[4] Mechanism research revealed that the target of these multivalent lactosides is integrin $\alpha_M\beta_2$ (CD11b/CD18), which plays an important role in the immune-inflammatory responses.[3,5] It has been found that CD11b interacts specifically with certain sugars, including some polysaccharides containing glucose, N-acetyl-D-glucosamine, mannose, and lactose.[4b,6]

Many factors can influence the bioactivities of glycoclusters. In addition to the composition, the geometry of glycocluster is a very important factor.[7] In order to investigate the effects of valency and geometry of heteroglycocluster systematically especially the fine geometry of glycoclusters on bioactivity, we synthesized a new series of mixed-type containing mannose and lactose heteroglycoclusters with homo-structural unit. In order to evaluate their binding properties to lectins, the binding affinities (represented as K_D value) of all synthesized glycoclusters with recombinant human integrin $\alpha_M\beta_2$ were determined via SPR assay and the potential anti-adhesion activities were assessed by a static state cell-based adhesion assay (Fig. 1).

We used divalent mannoside **2a**, divalent lactosides **1** and **2b** as assembling units[4] (Fig. 2).

Acylation using glutaric anhydride followed by acylation of the generated carboxylic acid was employed to prepare (2+2) heteroglycocluster **10** (Scheme 1). Divalent lactoside **2b** was reacted with glutaric anhydride in CH_2Cl_2, which affords compound **8**. Compound **8** was reacted with **2a** in the presence of EDC·HCl, HOBt, and NMM to give compound **9** in 54% yield for two steps. Compound **10** was then obtained in 92% yield after deprotection by CH_3ONa/CH_3OH.

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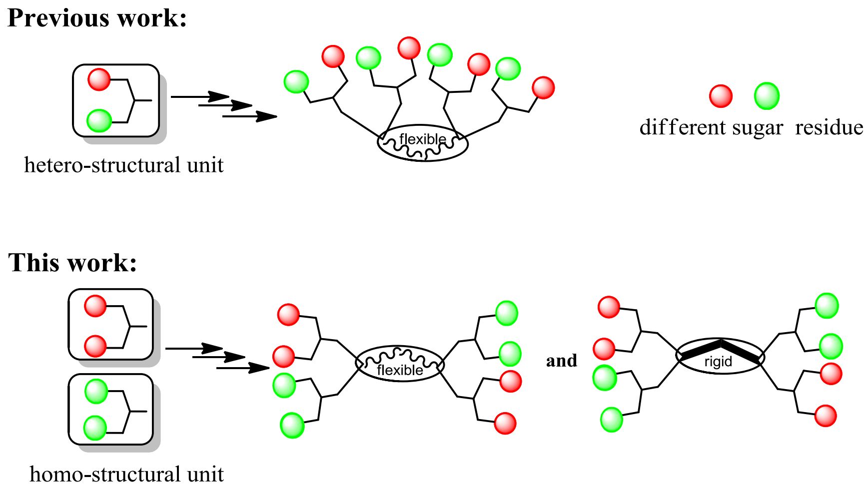


Fig. 1. Assembling of heteroglycocluster.

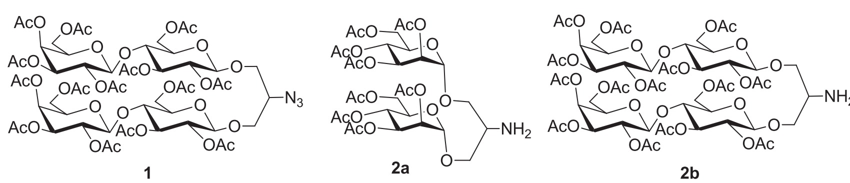
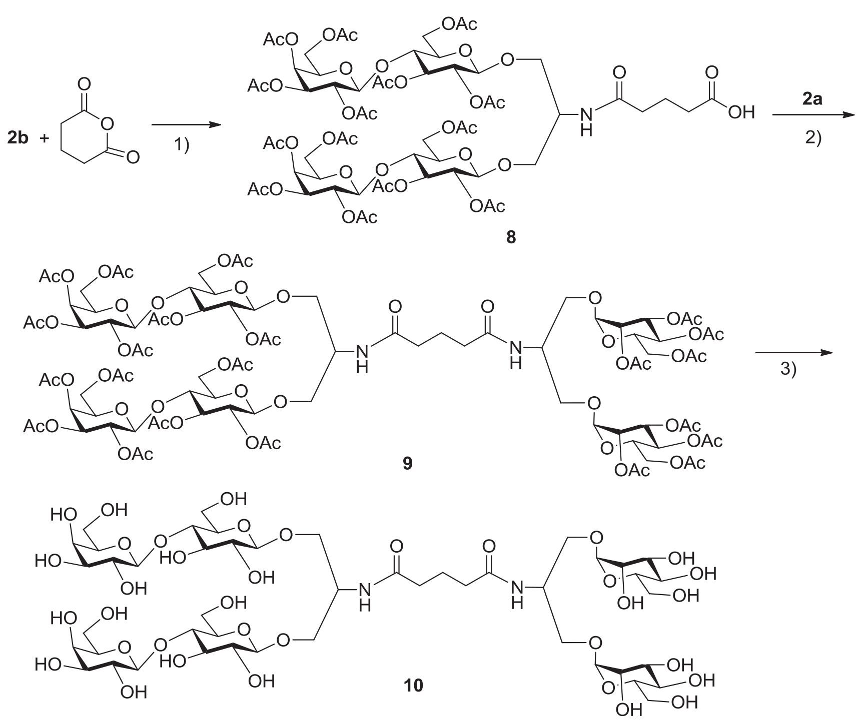


Fig. 2. Divalent glycoside unit **1**, **2a**, and **2b**.



Scheme 1. Synthesis of (2+2) heteroglycocluster **10**. Conditions: (1) CH_2Cl_2, rt, overnight; (2) EDC, HOBt, NMM, dry THF, rt, 12 h, 54% for two steps; (2) CH_3ONa, CH_3OH, rt, 12 h, 92%.

Using the same amide-formation condition, compounds **3a** and **3b** were afforded in 76–79% yield, which utilized divalent glycosides **2a** and **2b** as the substrates, respectively, and N-Boc-L-glutamic acid benzyl ester as the linker. After cleavage of the benzyl ester, amide condensation was carried out again using **2a** and **2b**, which gave protected-tetravalent lactosides **5a** and **5b** in 84% and 80% yields, respectively. After global deprotection, **7a** and **7b** were produced in 85% and 90% yields, respectively (Scheme 2).