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Syntheses of glycodendrimers having *scyllo*-inositol as the scaffold

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Abstract—Synthetic glycoconjugated dendrimers have emerged as important functional glycomimetics for studying multivalency effects in the cell–cell communications. We report herein, a synthetic route to functionalized glycodendrimers with *scyllo*-inositol as the scaffold, which have a directed geometry; one side of the dendrimers is designed for ready attachment to the AFM probe/solid matrix, and the other to have a varying number of a sugar.

Glycobiology is undergoing a kind of renaissance in the post-genomic era, since there are a number of important biological and physiological phenomena that depend on the carbohydrate–protein interactions.[1] One of the major topics in the current glycobiology research is understanding the precise nature of the carbohydrate–protein interactions, which play crucial roles in cell–cell communications. The binding affinity of the glycan-binding proteins (GBP) for individual monosaccharide units is generally very weak. However, the binding affinity increases synergistically with an increasing number of sugar residues ('glycoside cluster effect').[2] A strong glycocluster effect, a result of multivalent interactions, obviously requires a sugar-cluster structure that can present the sugars with proper orientation and spacing. In order to mimic this synergy effect and their biological functions a variety of glycodendrimers have been developed.[3]

In order to assess the carbohydrate–protein interactions more precisely, it would be highly desirable to be able to control the carbohydrate density and the size of glycoclusters. Furthermore, a direct measurement of the binding interactions at the individual molecular level would provide more accurate information needed for the fundamental insights and potential applications. The atomic force microscopy (AFM) is in principle capable of measuring such interactions in the pico-Newton range under pseudo-physiological conditions, and it has emerged as a useful tool for probing the interaction force between individual ligand–receptor complexes.[4] With such a goal in mind (e.g., measuring the unbinding force between concanavalin A and α-mannosyl sugar residues), we have developed synthetic routes to various glycodendrimers in which the 3D-geometry is well defined and better controlled. As the first example of such glycodendrimers, we wish to report herein a synthetic route to functionalized glycodendrimers based on the *scyllo*-inositol scaffold, in which the directionality as well as the number and density of the terminal carbohydrate may be controlled for their appropriate applications.

It is envisioned that the overall linear directionality of the desired glycodendrimer structure can be introduced by tying up the alternating hydroxyl groups of readily available *myo*-inositol in the form of orthoformate[5] and the following stereo-inversion of the equatorial hydroxyl group as shown in Scheme 1. Thus, after protecting the equatorial hydroxyl group in the *myo*-inositol orthoformate **1** as *tert*-butyldimethylsilyl ether (**2**),[5a] allylation of the two remaining hydroxyl groups and subsequent removal of the TBDMS protecting group gave compound **4**.[5e] Now the equatorial hydroxyl group of **4** was efficiently inverted to the axial orientation by oxidation with PCC in dichloromethane and subsequent reduction with $NaBH_4$ in methanol/THF. Additional allylation of compound **6** followed by the hydrolysis of the orthoformate in compound **7**[5f] provided the tri-hydroxy compound (**8**). Reaction between **8** and trimethyl 4-bromoorthobutyrate in

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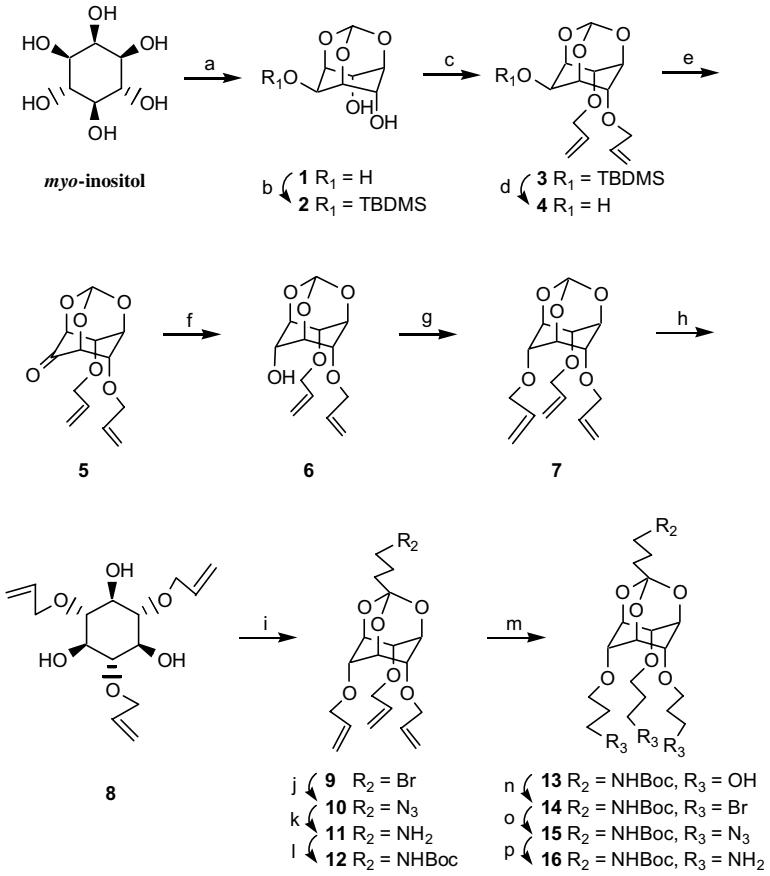


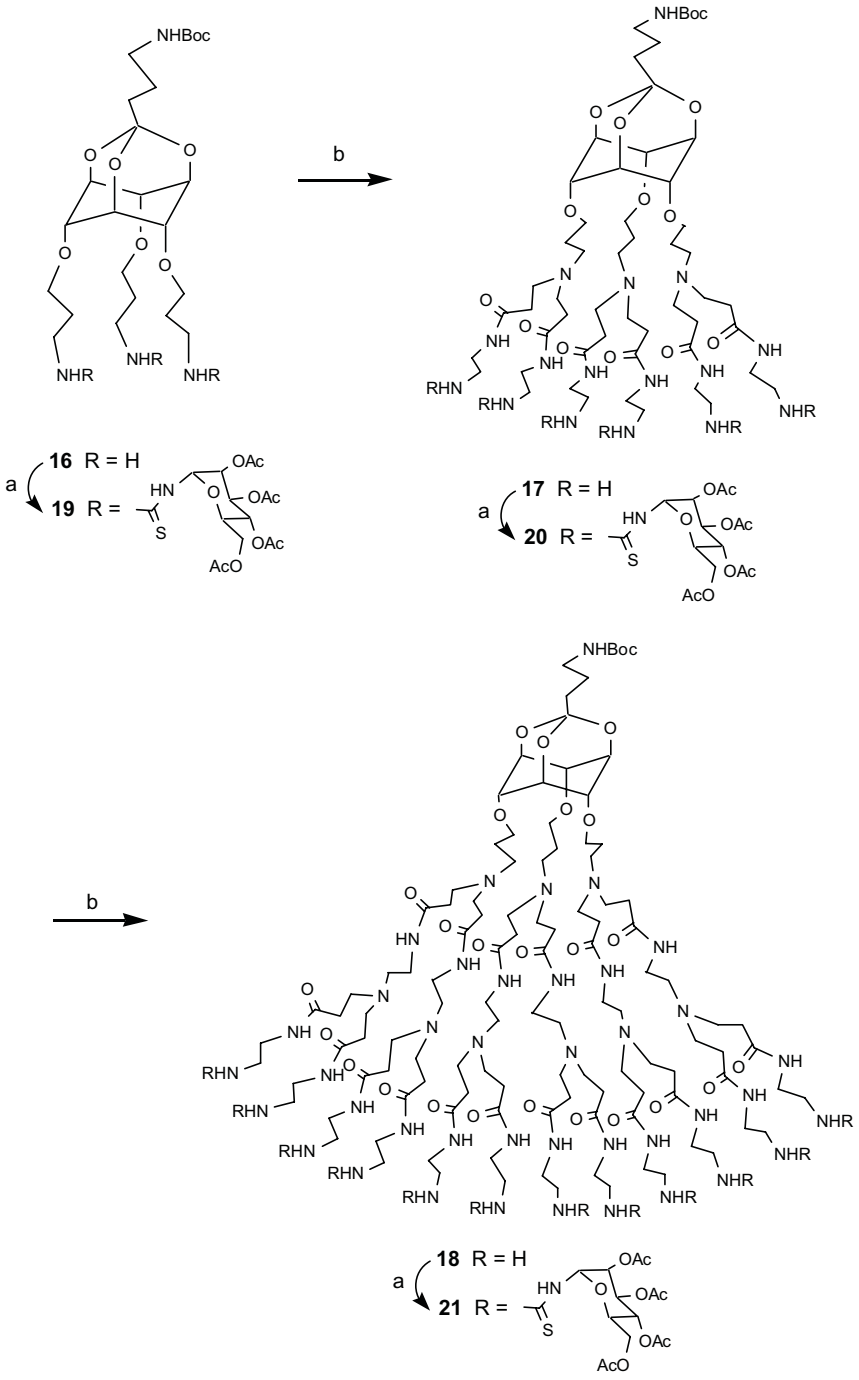
Scheme 1. Reagents and conditions: (a) $(MeO)_3CH$, TSA, DMF, 110 °C, 72%; (b) TBDMSCl, imidazole, DMF, 0 °C → rt, 75%; (c) allyl bromide, NaH, DMF, 81%; (d) TBAI, THF, quant.; (e) PCC, CH_2Cl_2, reflux, 79%; (f) $NaBH_4$, MeOH/THF, quant.; (g) allyl bromide, NaH, DMF, 94%; (h) TSA, MeOH/EtOAc, quant.; (i) trimethyl 4-bromoorthobutyrate, TSA, toluene, 100 °C, 78%; (j) NaN_3, DMF, 93%; (k) PPh_3, H_2O, THF, 93%; (l) $(Boc)_2O$, TEA, THF, 87%; (m) 9-BBN, THF, 3 N NaOH, H_2O_2, 82%; (n) PPh_3, CBr_4, THF, 87%; (o) NaN_3, DMF, quant.; (p) H_2, Pd–C, THF.

toluene containing a catalytic amount of *p*-toluene sulfonic acid with removal of azeotropic water[5b] gave the bidirectional key intermediate (**9**),[6] in which the two functional groups could now be independently and orthogonally manipulated.

First, the conversion of bromide **9** to azide **10** was effected by treatment with sodium azide in DMF, and the azide (**10**) was reduced with triphenylphosphine in THF in the presence of water to give the primary amine **11**.[7] After the amino group protection of **11** with Boc_2O and triethylamine, the product (**12**) was hydroborated with 9-BBN and oxidatively worked up to generate compound **13**. The alcohol functionality of **13** was conveniently converted to the amino functionality (**16**)[8] by successive Appel procedure[9] to a bromide (**14**), conversion to an azide (**15**), and its hydrogenolysis over Pd–C in THF. The scaffold molecule (**16**) is now ready for glycosylation as well as chain elongation and multiplication to the desired dendrimeric structures (Scheme 2). First, exhaustive Michael addition of the amine functionality with methyl acrylate in methanol in dark and the subsequent amidation of the resulting esters with ethylenediamine[10] afforded amidoamine dendrimer **17** (g_1) in 80% yield. Reiteration of this two-step reaction sequence successfully resulted in the doubling of peripheral amino functionalities in g_2-dendrimer **18**; thus doubling of branched chain numbers could be accomplished with each increasing generation.

Secondly, the thiourea coupling method has been successfully utilized for the preparation of glycoconjugated dendrimers.[11] Thus, each of the amino-functionalized dendrimers (**16**–**18**) was reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl isothiocyanate[11] to produce the thiourea-linked α-mannosylated dendrimers **19**, **20**, and **21** in 54%, 55%, and 26% yields, respectively. After removal of the Boc protecting group from the amino functionality in the glycodendrimers (**19**–**21**),[12] the resulting products should be suitable for the attachment to the AFM probe or other solid matrix.

In summary, we have successfully utilized the *scyllo*-inositol scaffold in developing a synthetic methodology for functional glycodendrimers having a linear bi-directionality as well as a varying number of terminal sugars, which are suitable for the glycobiology application studies such as multivalent glycomimetics and construction of carbohydrate microarrays after suitable functional group modifications and structural elaborations.



Scheme 2. Reagents and conditions: (a) 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl isothiocyanate, CH_2Cl_2, reflux, 54% (**19**), 55% (**20**), 26% (**21**); (b) (i) methyl acrylate, MeOH, in dark, (ii) ethylene diamine, MeOH, 80% (**17**), 47% (**18**).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.001.

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6. Compound (**9**): ^{1}H NMR ($CDCl_3$): δ 1.80 (dd, $J = 8.4$, 6.5 Hz, 2H), 2.0 (m, 2H), 3.41 (t, $J = 6.7$ Hz, 2H), 4.11 (dt, $J = 5.5$, 1.4 Hz, 6H, $3\times$—OCH_2CH=CH$_2$), 4.16 (dd, $J = 4.5$, 2.8 Hz, 3H), 4.39 (dd, $J = 4.4$, 2.9 Hz, 3H), 5.18 (ddt, $J = 10.3$, 1.6, 1.2 Hz, 3H, $3\times$—OCH$_2$CH=CH_{cis}H$_{trans}$), 5.31 (ddt, $J = 17.2$, 1.7, 1.6 Hz, 3H, $3\times$—OCH$_2$CH=CH$_{cis}H_{trans}$), 5.91 (ddt, $J = 17.2$, 10.5, 5.5 Hz, 3H, $3\times$—OCH$_2$CH=CH$_{cis}$H$_{trans}$); ^{13}C NMR ($CDCl_3$): δ 27.3, 34.1, 35.8, 69.3, 71.1, 72.6, 110.0, 117.8, 135.2; MS (FAB) m/z 453 $[M+Na]^+$; HRMS (FAB) m/z calcd for $C_{19}H_{28}BrO_6$: 431.1069. Found: 431.1068 $[M+1]^+$.
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8. Compound (**16**): ^{1}H NMR (CD_3OD): δ 1.43 (s, 9H), 1.57–1.85 (m, 4H), 1.77 (p, $J = 6.25$ Hz, 6H), 2.81 (t, $J = 6.46$ Hz, 6H), 2.98 (m, 2H), 3.71 (t, $J = 6.0$ Hz, 3H), 4.1 (s, 3H), 4.43 (s, 3H); ^{13}C NMR (CD_3OD): δ 24.9, 28.9, 32.0, 35.3, 40.2, 41.5, 69.6, 70.4, 75.1, 79.9, 111.1, 158.6; MS (FAB) m/z 519 $[M+1]^+$; HRMS (FAB) m/z calcd for $C_{24}H_{47}N_4O_8$: 519.3394. Found: 519.3389 $[M+1]^+$.
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12. The Boc protecting group could be selectively removed. For example, treatment of compound **19** with TMSCl, NaI, MeOH, and TEA in CH_3CN gave the Boc deprotected compound in 88% yield without causing hydrolysis of the orthoester which is labile to usual acidic Boc deprotection conditions. It is envisioned that the glycodendrimer after removal of the acetate groups in sugar, can be reacted to a SAM on AFM tip containing *N*-hydroxysuccinimide-activated carboxy terminal groups, which is expected to preferentially react with NH_2 group over OH groups.