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Convenient assembly of trimeric Le^x determinants using carbosilane scaffolds by means of Huisgen cycloaddition ☆

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ABSTRACT

The Le^X glycoside having an N_3 moiety at the ω position, which was prepared by using living cells from GlcNAcO$(CH_2)_{12}N_3$ as a starting material, was efficiently introduced into a trivalent-type carbosilane core scaffold by means of Huisgen cycloaddition reaction to yield the corresponding glycocluster having three Le^X moieties at each end. Structural elucidation of the product was performed by a combination of NMR and mass spectroscopic analyses, and the results of the analyses supported the structure of the glycocluster. Evaluation of the glycocluster was carried out using Lotus lectin as a model lectin. Environmental changes of tryptophan residues located at or near the binding sites of Lotus lectin caused fluorescence intensity change.

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Oligosaccharide chains in glycoconjugates, such as glycoproteins and glycolipids, play important roles in biological events. Among the various oligosaccharides, Lewis X determinant [Le^X; Galβ1 → 4(Fucα1 → 3)GlcNAc] is known as an extremely valuable core structure of glycoconjugates.[1] Recently, biocombinatorial synthesis of oligosaccharides by means of animal cells in culture has been developed, and oligosaccharide libraries of various biologically important sugars are now under investigation.[2] The Le^X derivative **1**[3] having an azide moiety at the ω-position of the aglycon was isolated from the residues of cell culture using HL-60 (Human promyelocytic leukemia cells) in the presence of an *N*-acetyl glucosaminyl primer (GlcNAcO$(CH_2)_{12}N_3$).[4] Since synthetic assembly of the Le^X unit was paid much attention, this approach to obtain the Le^X trisaccharidic component is of great interest for biochemists and medicinal scientists.[5] On the other hand, a cluster-type trisaccharide is also very attractive from the point of view of biochemical as well as biomedical applications.[6] In our previous study,[7] a convergent chemical synthesis of the polymerizable Le^x trisaccharidic glycomonomer via Gabriel amine synthesis and the chemical conversion into a highly clustered glycopolymer were accomplished. In addition to linear-type glycoclusters, we have introduced a series of glycodendrimers using carbosilanes as pivotal supporting tools for bioactive carbohydrate moieties.[8] In this Letter, we describe the efficient construction of a trivalent-type carbosilane having Le^X trisaccharidic determinants **2** as shown in Figure1 and the biochemical evaluation of the glycocluster for *Lotus tetragonolobus agglutinin* (LTA) by means of fluorospectroscopic analysis.

We have reported efficient coupling procedures in order to build up glycodendrimers using carbosilanes through sulfide linkages by means of a simple S_N2 reaction between an alkyl halide **4** and a thiolate **6** (Scheme 1).[9] Although the sulfide linkage in **7** is suitable and stable for biochemical and biomedical uses, an alternative procedure for effective coupling between a carbohydrate moiety and a multivalent-type compound was explored. Huisgen cycloaddition reaction[10] of an azido functionalized compound and an alkynylated compound reminded us that the reaction can be applicable for the formation of a cluster-type compound, because of the high yield and high specificity for the coupling reaction.[11] Thus, an alkynylated carbosilane compound was needed as a core scaffold. Scheme 1 summarizes an elongation reaction of a known triol **3**[12] compound of a carbosilane by means of the Williamson ether synthesis. It was noted that the reaction required 3 equiv molar excess of propargyl bromide against an alcoholic function since usual ether synthesis required slightly excess alkyl bromide. Therefore, triol **3** was treated with 9 equiv molar of

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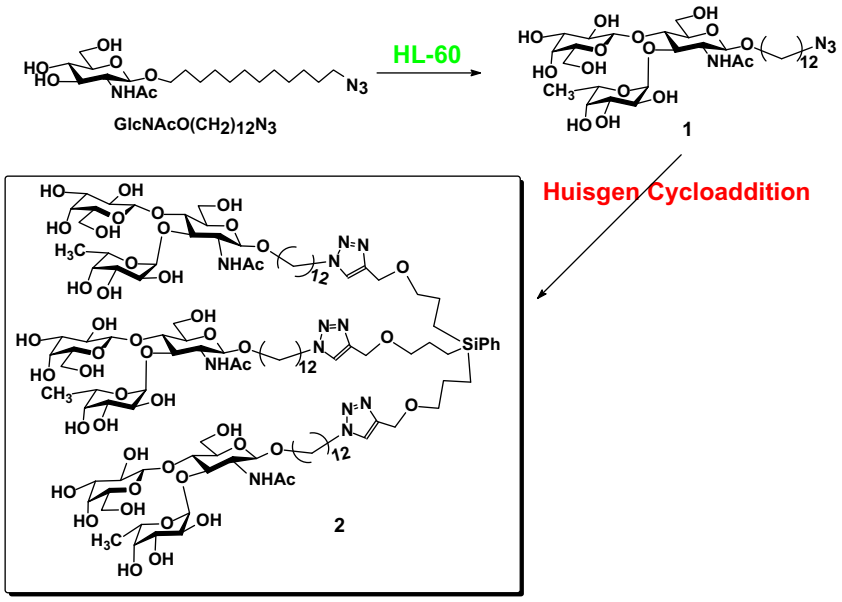
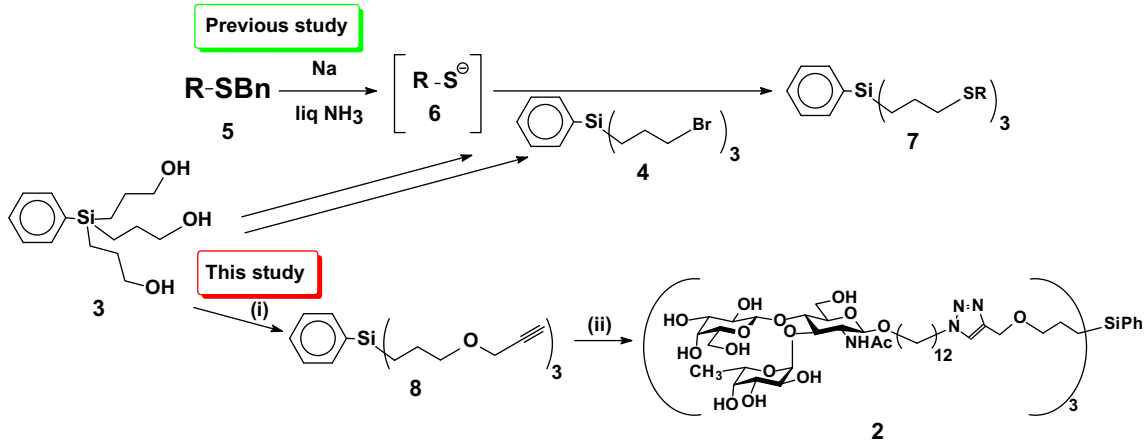


Figure 1. Synthetic assembly of trimeric Le^x derivatives.



Scheme 1. Reagents and conditions: (i) $BrCH_2C{\equiv}CH$ (9 equiv molar), NaH, DMF, 0 °C, 5 h, 66.9%, (ii) compound **1** (3.75 equiv molar), 0.1 M aq $CuSO_4$, 1 M aq Na ascorbate, MeOH, 50 °C, 1 d, 57.9%.

propargyl bromide in the presence of NaH in DMF and the reaction proceeded smoothly to afford trialkynylated carbosilane **8**[13] in 66.9% yield after chromatographic purification on silica gel with 10/1 (v/v; *n*-hexane–EtOAc).

Since the scaffold for supporting the carbohydrate moieties was prepared, chemical introduction of Le^x derivative **1** into the carbosilane **8** was attempted under slightly modified Huisgen cycloaddition conditions. Thus, a methanolic solution of an alkyne **8** and an azide **1** was treated with 0.1 M aq $CuSO_4$ and 1 M aq sodium ascorbate at 50 °C for 24 h. Silica gel chromatography of the reaction mixture followed by gel filtration using LH-20 gave the corresponding carbosilane **2** having three Le^x moieties at each end in 57.9% yield, R_f 0.47 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; ^{1}H NMR (CD_3OD) δ 7.94 [s, 3 H, 3 N–CH= (triazole)], 5.04 [d, 3 H, $J_{1'',2''}$ = 3.7 Hz, 3 H-1″ (Fuc)], 4.66 (s, 6H, 3=C–CH_2O), 4.45 [d, 3 H, $J_{1',2'}$ = 7.7 Hz, 3H-1′ (Gal)], 4.40 (t, 6H, J = 6.8 Hz, 3 CH_2N), 1.97 (s, 9H, 3 NAc), 1.19 (d, 9 H, $J_{5'',6''}$ = 6.3 Hz, 3 H-6″ (Fuc)], MALDI-TOF MS calcd for [M+Na$^+$]: 2635.374; Found *m/z* 2635.451.

Given the success of preparation of trimetric Le^x derivative **2**, our attention was turned toward the biological properties of the glycocluster. In our ongoing synthetic study of glycoclusters, preliminary investigations of the glycoclusters against lectins have been carried out by using fluorescence measurement.[7,14] The spectral change of the lectin due to tryptophan residues located around the binding site of target sugars was monitored when the titrimetric sugars were added to the measuring solution.[15] Thus, *Lotus tetragonolobus agglutinin* (LTA) was selected as a suitable lectin for binding to L-fucose residue.[16] The structure of LTA was recently estimated to be a homotetramer.[16c] Figure2 shows fluorescence emission of LTA and of its complexes with various concentrations of trimeric Le^x **2**. When the protein was saturated with the glycocluster **2**, the maximum fluorescence intensity was enhanced by 7.2% and the emission maximum was not downfield-shifted, when a monomeric Le^x glycoside **10** and L-fucose **9** slightly shifted (−2 nm). The results suggested that the environment of tryptophan residues located at or near the binding sites of LTA is altered from hydrophilic to relatively more hydrophobic upon interaction with the glycocluster **2**. In a plot of $\Delta F/F_0$ versus [S] based on sugar unit concentration followed by analyses using the Hill equation,[17] association constant K_a was estimated to be 1.2×10^6 (M^{-1}). The

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