An Alternative Route for Construction of Carbosilane Dendrimers Uniformly Functionalized with Lactose or Sialyllactose Moieties†

Koji Matsuokaa,*, Hiroyuki Okaa, Tetsuo Koyamaa, Yasuaki Esumib, and Daiyo Terunumaa

aDepartment of Functional Materials Science, Faculty of Engineering, Saitama University, Urawa, Saitama 338-8570, Japan
bThe Institute of Physical and Chemical Research (RIKEN), Wako, Saitama 351-0198, Japan

Abstract

A new approach for the formation of an acetylthio linkage on aglycon by means of a radical addition of thioacetic acid into the C=C double bond of the aglycon was examined. An introduction of a carbohydrate moiety into carbosilane dendrimers was demonstrated using a one-pot coupling reaction in MeOH—DMF in the presence of NaOMe via removal of an acetyl group of the acetylthio linkage in the saccharide moieties, producing a thiolate anion and a nucleophilic replacement of the thiolate to dendric alkyl bromide to form carbosilane dendrimers uniformly bearing lactose or sialyllactose moieties through thioether linkages in high yields.

Keywords: radical additions; thioacetate; carbosilane dendrimers; sulfide; glycodendrimers

The sialyllactose sequence (Neu5Acα2→3/6Galβ1→4Glcβ1→) is known as a receptor of hemagglutinin on the surface of the influenza virus.1 Hitherto, several groups have reported polymeric inhibitors against such interaction between the receptors on a cell surface and the hemagglutinin of the virus.2 In the course of our recent work on Glyco-Silicon Functional Materials, carbosilane dendrimers having globotriaose moieties

†Glyco-Silicon Functional Materials. Part 5. For Part 4, see Ref. 6.
*Corresponding author. Tel/Fax: +81-48-858-3099, E-mail: koji@fms.saitama-u.ac.jp
showed neutralization potency against verotoxin. Therefore, we set about to synthesize carbosilane dendrimers functionalized with sialyllactose moieties as a new type of inhibitor for hemagglutinin of the influenza virus.

In our ongoing synthetic study of glycoclusters, synthetic assembly of carbohydrate moieties using carbosilane dendrimers was achieved using β-cyclodextrin, globotriaose, and functional monosaccharides. In our previous investigation, the efficiency of a coupling reaction between a sialic acid derivative and a carbosilane dendrimer by means of our one-pot procedure in liquid ammonia was moderate, even when a further amount of the sialic acid derivative was used for the reaction. Therefore, an alternative and highly efficient procedure for introducing sialic acid residues on the dendrimers is required. In this communication, we describe a convenient radical addition of thioacetic acid into the C=C double bond at the terminus of sugar aglycon and a new approach for construction of carbosilane dendrimers uniformly functionalized with carbohydrate moieties, such as lactose or sialyllactose, as potential receptors of hemagglutinin of the influenza virus.

The radical addition of mercaptan in carbohydrate chemistry was first demonstrated by Lee et al., and this reaction has been widely used. A similar strategy for introduction of a thioacetic residue into the acrylamide portion by a Michael reaction has also been reported. Since the radical addition of thioacetic acid, however, has not been applied to an olefinic C=C double bond on sugar aglycon, we initially optimized the radical addition of thioacetic acid using the known allyl (1) and n-pentenyl (2) lactosides as model candidates. The results of the reaction are summarized in Table 1.

Scheme 1 & Table 1

An allyl glycoside 1 was used as a candidate for the radical addition of thioacetic acid; however, the reaction was not completed due to the low reactivity of the allyl group in the glycoside even when large excess of thioacetic acid was used. Consequently, another known n-pentenyl glycoside 3 was used under the same reaction conditions, and the radical addition proceeded smoothly to afford a nearly quantitative yield of thioacetate 4, \( [\alpha]_D^{21} -15.1^\circ \) (c 1.77, CHCl₃), \(^1\)H NMR (CDCl₃) \( \delta: 2.85 \) (t, 2 H, \( J 7.2 \) Hz, CH₃SAc), 2.32 (s, 3 H, SAc). Thus, the n-pentenyl group proved to be an effective acceptor for the radical addition of thioacetic acid.

\(^1\) All new compounds with specific rotation data gave satisfactory elemental analyses.
Given the success of the introduction of a thioacetate residue into aglycon, we next turned our attention to the coupling reaction of thioacetate 4 with a dendrimer 5 to produce a sulfide linkage. Scheme 2 shows the coupling reaction, and the conditions used are summarized in Table 2. The reaction includes 1) O- and S-deacetylation, 2) SN2-type displacement, and 3) usual acetylation for purification by silica gel chromatography. Although a two-step procedure, i.e., deacetylation followed by addition of dendrimer 5, gave incomplete reaction products together with the starting materials and disulfide compound 7, FABMS calcd for [M+H\(^+\)]: 1475; Found m/z: 1475, the direct coupling procedure in the presence of dendrimer 5 was found to be the most effective coupling reaction to form 6 in 84% yield after removal of byproducts by chromatography on silica gel, [\(\alpha\)\(_{D}\)]\(_{21}\) -14.2° (c 1.40, CHCl\(_3\)), integral ratio of the H atoms by \(^1\)H NMR: SiCH\(_2\):SCH\(_2\):Ph:H-1 and -1’ = 6:12:5:6, FABMS calcd for [M+H\(^+\)]: 2444.9; Found m/z: 2444.6.

Scheme 2 & Table 2

As an extension of this new coupling reaction, we examined a combination of a dendrimer 8 and an even more complex oligosaccharide, sialyllactose. The synthetic routes for construction of glycodendrimers are shown in Scheme 3. The coupling reaction of 4 with dumbbell-type dendrimer 8 under the same conditions as those described for the preparation of 6 proceeded efficiently to provide homogeneous 9 having six lactose moieties in 62% yield, [\(\alpha\)\(_{D}\)]\(_{21}\) -15.3° (c 0.80, CHCl\(_3\)), integral ratio of the H atoms by \(^1\)H NMR: SiCH\(_3\):SiCH\(_2\):SCH\(_2\): H-1 and -1’ = 6:20:24:12, FABMS calcd for [M+H\(^+\)]: 4877.8; Found m/z: 4877.6. Transesterification of 9 and 6, followed by saponification gave water-soluble glycodendrimers 10, [\(\alpha\)\(_{D}\)]\(_{20}\) -4.4° (c 0.76, H\(_2\)O), MALDI-TOF MS calcd for [M+Na\(^+\)]: 3134.30; Found m/z: 3138.09, and 11, [\(\alpha\)\(_{D}\)]\(_{19}\) -5.0° (c 0.16, H\(_2\)O), FABMS calcd for [M+H\(^+\)]: 1561.6; Found m/z: 1561.9 in good yields, respectively.

Scheme 3

An n-pentenyl sialyllactoside 13, [\(\alpha\)\(_{D}\)]\(_{18}\) -6.9° (c 2.02, CHCl\(_3\)), \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 4.67 (d, 1 H, \(J_{1',2'}\) 10.0 Hz, H-1’), 4.52 (dd, 1 H, \(J_{2',3'}\) 10.2 Hz & \(J_{3',4'}\) 3.3 Hz, H-3’), 4.45 (d, 1 H, \(J_{1,2}\) 8.0 Hz, H-1), was prepared from a known imidate 12 coupled with 4-penten-1-ol under Tietze’s conditions in 84% yield. The glycoside 13 was derivatized to thioacetate 14 by the radical addition of thioacetic acid in 99% yield, [\(\alpha\)\(_{D}\)]\(_{29}\) -6.3° (c 1.29, CHCl\(_3\)), \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 2.85 (t, 2 H, \(J\) 7.2 Hz, CH\(_2\)SAC), 2.32 (s, 3 H, SAC). The acetylthio derivative of
sialyllactose 14 was then coupled with dendrimer 5 under the same condition as that described for 6 to give glycodendrimer 15 in 80% yield, integral ratio of the H atoms by $^1$H NMR: SiCH$_2$:SCH$_2$:Ph:H-1 and -1' = 6:12:5:6, FABMS calcd for [M+Na$^+$]: 3761.28; Found $m/z$: 3760.84, which was then deprotected in the usual manner to afford 16 in quantitative yield, FABMS calcd for [M-H$^-$]: 2433.9; Found $m/z$: 2434.1. Sialyllactose derivative 14 was also allowed to react with dendrimer 8 to give 17 in 77% yield, integral ratio of the H atoms by $^1$H NMR: SiCH$_3$:SiCH$_2$:SCH$_2$:H-1 and -1' = 6:20:24:12, FABMS calcd for [M+Na$^+$]: 7488.61; Found $m/z$: 7488.30. Deprotection of 17 gave 18 having six sialyllactose units in quantitative yield, FABMS calcd for [M-H$^-$]: 4857.9; Found $m/z$: 4859.2.

In conclusion, we have succeeded in introduction of an acetylthio moiety into aglycon of lactose and a sialylα2→3lactose sequence and incorporation of those carbohydrate chains into a couple of carbosilane dendrimers through a sulfide linkage. Biological evaluation of these novel glycodendrimers is now in progress, and the results will be reported in the near future.

Acknowledgments

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References


### Table 1. Results of radical addition of thioacetic acid into C=C double bond of aglycon.

<table>
<thead>
<tr>
<th>Sugar</th>
<th>AcSH eq</th>
<th>AIBN Eq</th>
<th>Solvent</th>
<th>Temp. °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>0.2</td>
<td>—</td>
<td>50 → 80</td>
<td>ND b</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>0.5</td>
<td>Dioxane</td>
<td>50 → 80</td>
<td>67c</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>0.5</td>
<td>Dioxane</td>
<td>50 → 80</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>1</td>
<td>Dioxane</td>
<td>50 → 80</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>1</td>
<td>—</td>
<td>50 → 80</td>
<td>93</td>
</tr>
</tbody>
</table>

*aIsolated Yield. *bDue to unseparable mixture of the starting material and the product. *cStarting materials were also recovered in 31% yields.

### Table 2. Results of one-pot coupling reaction between lactosyl thioacetate and tris(3-bromopropyl)phenylsilane.

<table>
<thead>
<tr>
<th>Charged ratio</th>
<th>First step Conditions</th>
<th>Second step Conditions</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:1</td>
<td>NaOMe (6 mol. equiv.), MeOH, -30~15 °C, then concentrated</td>
<td>5, K₂CO₃ (6 mol. equiv.), DMF, 50 °C</td>
<td>19</td>
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<tr>
<td>6:1</td>
<td>5, Et₂NH (120 mol. equiv.), DMF, 0 °C</td>
<td>K₂CO₃ (6 mol. equiv.), DMF, 60 °C</td>
<td>0</td>
</tr>
<tr>
<td>6:1</td>
<td>NaOMe (6 mol. equiv.), MeOH, rt, then concentrated</td>
<td>5, NaOMe (6 mol. equiv.), THF, 50 °C</td>
<td>0</td>
</tr>
<tr>
<td>6:1</td>
<td>NaOMe (7 mol. equiv.), MeOH, rt, then concentrated</td>
<td>5, NaOMe (7 mol. equiv.), DMF, -30 °C ~rt</td>
<td>33</td>
</tr>
<tr>
<td>6:1</td>
<td>5, NaOMe (6 mol. equiv.), MeOH-DMF, -30 °C, then concentrated</td>
<td>None</td>
<td>19</td>
</tr>
<tr>
<td>6:1</td>
<td>5, NaOMe (6 mol. equiv.), MeOH-DMF, rt, then concentrated</td>
<td>None</td>
<td>84</td>
</tr>
</tbody>
</table>

*aIsolated yield of 6 based on 5 after acetylation.
Legend to Figure and Schemes

**Scheme 1.** Reagents and conditions: i) summarized in Table 1.

**Scheme 2.** Reagents and conditions: i) summarized in Table 2, ii) 8, NaOMe, MeOH—DMF, r.t., then, Ac₂O, Pyr., r.t., iii) NaOMe, MeOH, r.t..

**Scheme 3.** Reagents and conditions: i) 4-penten-1-ol, BF₃·Et₂O, MS₄Å, CH₂Cl₂, -25 °C→-5 °C, ii) AcSH, AIBN, 1,4-dioxane, 50 °C→80 °C, iii) NaOMe, MeOH—DMF, r.t., then, Ac₂O, Pyr., then, CH₂N₂, Et₂O, iv) NaOMe, MeOH, r.t., then, 0.05 M aq. NaOH, r.t.