

# An Alternative Route for Construction of Carbosilane Dendrimers Uniformly Functionalized with Lactose or Sialyllactose Moieties<sup>†</sup>

Koji Matsuoka<sup>a,\*</sup>, Hiroyuki Oka<sup>a</sup>, Tetsuo Koyama<sup>a</sup>, Yasuaki Esumi<sup>b</sup>, and Daiyo Terunuma<sup>a</sup>

<sup>a</sup>*Department of Functional Materials Science, Faculty of Engineering, Saitama University, Urawa, Saitama 338-8570, Japan*

<sup>b</sup>*The 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 (Neu5Ac $\alpha$ 2 $\rightarrow$ 3/6Gal $\beta$ 1 $\rightarrow$ 4Glc $\beta$ 1 $\rightarrow$ ) is known as a receptor of hemagglutinin on the surface of the influenza virus.<sup>1</sup> Hitherto, several groups have reported polymeric inhibitors against such interaction between the receptors on a cell surface and the hemagglutinin of the virus.<sup>2</sup> In the course of our recent work on Glyco-Silicon Functional Materials, carbosilane dendrimers having globotriaose moieties

<sup>†</sup>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.<sup>3</sup> 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  $\beta$ -cyclodextrin,<sup>4</sup> globotriaose,<sup>5</sup> and functional monosaccharides.<sup>6</sup> 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.<sup>6</sup> 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.*,<sup>7</sup> and this reaction has been widely used.<sup>8</sup> A similar strategy for introduction of a thioacetic residue into the acrylamide portion by a Michael reaction has also been reported.<sup>9</sup> Since the radical addition of thioacetic acid,<sup>10</sup> 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**)<sup>11</sup> and *n*-pentenyl (**2**)<sup>12</sup> 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**,<sup>†</sup>  $[\alpha]_D^{21} -15.1^\circ$  (*c* 1.77, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 2.85 (t, 2 H, *J* 7.2 Hz, CH<sub>2</sub>SAc), 2.32 (s, 3 H, SAc). Thus, the *n*-pentenyl group proved to be an effective acceptor for the radical addition of thioacetic acid.

<sup>†</sup> 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**<sup>5</sup> 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) S<sub>N</sub>2-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<sup>+</sup>]: 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, [α]<sub>D</sub><sup>21</sup> -14.2° (*c* 1.40, CHCl<sub>3</sub>), integral ratio of the H atoms by <sup>1</sup>H NMR: SiCH<sub>2</sub>:SCH<sub>2</sub>:Ph:H-1 and -1' = 6:12:5:6, FABMS calcd for [M+H<sup>+</sup>]: 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**<sup>5</sup> 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, [α]<sub>D</sub><sup>21</sup> -15.3° (*c* 0.80, CHCl<sub>3</sub>), integral ratio of the H atoms by <sup>1</sup>H NMR: SiCH<sub>3</sub>:SiCH<sub>2</sub>:SCH<sub>2</sub>: H-1 and -1' = 6:20:24:12, FABMS calcd for [M+H<sup>+</sup>]: 4877.8; Found *m/z*: 4877.6. Transesterification of **9** and **6**, followed by saponification gave water-soluble glycodendrimers **10**, [α]<sub>D</sub><sup>20</sup> -4.4° (*c* 0.76, H<sub>2</sub>O), MALDI-TOF MS calcd for [M+Na<sup>+</sup>]: 3134.30; Found *m/z*: 3138.09, and **11**, [α]<sub>D</sub><sup>19</sup> -5.0° (*c* 0.16, H<sub>2</sub>O), FABMS calcd for [M+H<sup>+</sup>]: 1561.6; Found *m/z*: 1561.9 in good yields, respectively.

### Scheme 3

An *n*-pentenyl sialyllactoside **13**, [α]<sub>D</sub><sup>18</sup> -6.9° (*c* 2.02, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 4.67 (d, 1 H, *J*<sub>1,2'</sub> 10.0 Hz, H-1'), 4.52 (dd, 1 H, *J*<sub>2',3'</sub> 10.2 Hz & *J*<sub>3',4'</sub> 3.3 Hz, H-3'), 4.45 (d, 1 H, *J*<sub>1,2</sub> 8.0 Hz, H-1), was prepared from a known imidate **12**<sup>13</sup> 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, [α]<sub>D</sub><sup>29</sup> -6.3° (*c* 1.29, CHCl<sub>3</sub>), <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.85 (t, 2 H, *J* 7.2 Hz, CH<sub>2</sub>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  $^1\text{H}$  NMR: SiCH<sub>2</sub>:SCH<sub>2</sub>:Ph:H-1 and -1' = 6:12:5:6, FABMS calcd for [M+Na<sup>+</sup>]: 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  $^1\text{H}$  NMR: SiCH<sub>3</sub>:SiCH<sub>2</sub>:SCH<sub>2</sub>:H-1 and -1' = 6:20:24:12, FABMS calcd for [M+Na<sup>+</sup>]: 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 sialyl $\alpha$ 2 $\rightarrow$ 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

This work was partly supported by a Grant-in-Aid for Encouragement of Young Scientists (12750754) from the Ministry of Education, Science, and Culture of Japan (K. M) and by a grant from NEDO [New Energy and Industrial Technology Development Organization (Glycocluster project)]. We are grateful to Snow Brand Milk Products Co., Ltd. for providing the sialic acid used in this study.

## References

1. For example, (a) Webster, R.G.; Bean, W.J.; Gorman, O.T.; Chambers, T.M.; Kawaoka, Y. *Microbiol. Reviews* **1992**, *56*, 152-179. (b) Wiely, D.C.; Skehel, J.J. *Ann. Rev. Biochem.* **1987**, *56*, 365-394, and references cited therein.
2. For example, (a) Kingery-Wood, J.E.; Williams, K.W.; Sigal, G.B.; Whiteside, G.M. *J. Am. Chem. Soc.* **1992**, *114*, 7303-7305. (b) Zazani, D.; Roy, R. *J. Org. Chem.* **1998**, *63*, 3486-3491. (c) Kamitakahara, H.; Kanie, O.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1524-1528. (d) Abo, S.; Ciccotosto, S.;

- Alafaci, A.; von Itzstein, M. *Carbohydr. Res.* **1999**, 322, 201-208. (e) Furuike, T.; Aiba, S.; Suzuki, T.; Takahashi, T.; Suzuki, Y.; Yamada, K.; Nishimura, S.-I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3000-3005.
- (f) Wu, W.-Y.; Jin, B.J.; Krippner, G.Y.; Watson, K. G. *Bioorg. Med. Chem. Lett.* **2000**, 10, 341-343, and references cited therein.
3. (a) Nishikawa, K.; Natori, Y. 4th Int. Symp. on VTEC2000, Abstract p. 61. (b) Nishikawa, K.; Matsuoka, K.; Okabe, N.; Mizuguchi, M.; Aoki, J.; Yamasaki, C.; Yamakawa, Y.; Nishijima, M.; Arai, H.; Terunuma, D.; Kuzuhara, H.; Natori, Y. 4th Int. Symp. on VTEC2000, Abstract p. 180.
4. (a) Matsuoka, K.; Terabatake, M.; Saito, Y.; Hagihara, C.; Esumi, Y.; Terunuma, D.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1998**, 71, 2709-2713. (b) Matsuoka, K.; Saito, Y.; Terunuma, D.; Kuzuhara, H. *Kobunshironbunshyu* **2000**, 57, 691-695.
5. Matsuoka, K.; Terabatake, M.; Esumi, Y.; Terunuma, D.; Kuzuhara, H. *Tetrahedron Lett.* **1999**, 40, 7839-7842.
6. Matsuoka, K.; Kurosawa, H.; Esumi, Y.; Terunuma, D.; Kuzuhara, H. *Carbohydr. Res.* **2000**, 329, 765-772.
7. Lee, R.T.; Lee, Y.C. *Carbohydr. Res.* **1974**, 37, 193-201.
8. Roy, R.; Tropper, F.D. *J. Chem. Soc., Chem. Commun.* **1988**, 1058-1060. (b) van Seeventer P.B.; van Dorst J.A.L.M.; Siemerink J.F.; Kamerling J.P.; Vliegthart J.F.G. *Carbohydr. Res.* **1997**, 300, 369-373.
9. (a) Park, W.K.C.; Meunier, S.J.; Zanini, D.; Roy, R. *Carbohydr. Lett.* **1995**, 1, 179-184. (b) Furuike, T.; Aiba, S.; *Chem. Lett.* **1999**, 69-70. (c) Furuike, T. Aiba, S.; Nishimura, S.-I. *Tetrahedron* **2000**, 56, 9909-9915.
10. (a) Brown, R.; Jones, W.E.; Pinder, A.R. *J. Chem. Soc.* **1951**, 2123-2125. (b) Salo, H.; Guzaev, A.; Lönnberg, H. *Bioconjugate Chem.* **1998**, 9, 365-371.
11. Bernstein, M.A.; Hall, L.D. *J. Am. Chem. Soc.* **1982**, 104, 5553-5555.
12. Matsuoka, K.; Nishimura, S.-I. *Macromolecules* **1995**, 28, 2961-2968.
13. Tietze, L.F.; Gretzke, D. *Eur. J. Org. Chem.* **1998**, 1895-1899.

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

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

<sup>a</sup>Isolated Yield. <sup>b</sup>Due to unseparable mixture of the starting material and the product. <sup>c</sup>Starting materials were also recovered in 31% yields.

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

Charged ratio <b>4:5</b>	First step Conditions	Second step Conditions	Yield <sup>a</sup> (%)
6:1	NaOMe (6 mol. equiv.), MeOH, -30~-15 °C, then concentrated	<b>5</b> , K <sub>2</sub> CO <sub>3</sub> (6 mol. equiv.), DMF, 50 °C	19
6:1	<b>5</b> , Et <sub>2</sub> NH (120 mol. equiv.), DMF, 0 °C	K <sub>2</sub> CO <sub>3</sub> (6 mol. equiv.), DMF, 60 °C	0
6:1	NaOMe (6 mol. equiv.), MeOH, rt, then concentrated	<b>5</b> , NaOMe (6 mol. equiv.), THF, 50 °C	0
6:1	NaOMe (7 mol. equiv.), MeOH, rt, then concentrated	<b>5</b> , NaOMe (7 mol. equiv.), DMF, -30 °C ~rt	33
6:1	<b>5</b> , NaOMe (6 mol. equiv.), MeOH-DMF, -30 °C, then concentrated	None	19
6:1	<b>5</b> , NaOMe (6 mol. equiv.), MeOH-DMF, rt, then concentrated	None	84

<sup>a</sup>Isolated 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, Ac<sub>2</sub>O, Pyr., r.t., iii) NaOMe, MeOH, r.t..

**Scheme 3.** *Reagents and conditions:* i) 4-penten-1-ol, BF<sub>3</sub>·Et<sub>2</sub>O, MS4Å, CH<sub>2</sub>Cl<sub>2</sub>, -25 °C→-5 °C, ii) AcSH, AIBN, 1,4-dioxane, 50 °C→80 °C, iii) NaOMe, MeOH—DMF, r.t., then, Ac<sub>2</sub>O, Pyr., then, CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, iv) NaOMe, MeOH, r.t., then, 0.05 M aq. NaOH, r.t..