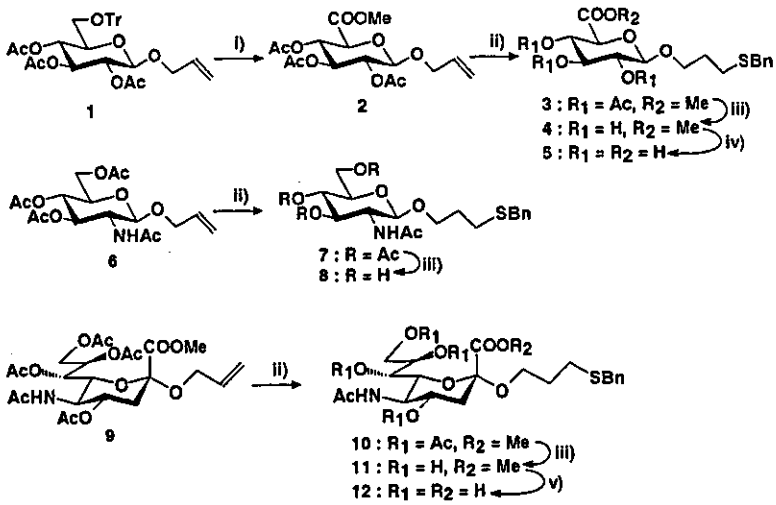


Scheme 1. Reagents and conditions: (i) Jones oxidation, then CH_2N_2, Et_2O; (ii) α-toluenethiol, AIBN, 1,4-dioxane, 50→80 °C; (iii) NaOMe, MeOH, rt; (iv) 1 M aq NaOH; (v) 0.05 M aq NaOH.

carrying a bromine atom at its ω-positions to provide crude products. Purification by gel filtration for removal of the by-products, including incompletely reacted compounds, gave the carbosilane dendrimer **14** having six D-glucuronic acid moieties in 64% yield based on **13**, and which had the expected molecular-ion peak (*m/z* 2076). The benzyl sulfide **8** was also treated with dendrimer **13** by the method described for the preparation of **14** to afford a coupled product. Unfortunately, the crude product was found to be a mixture, including *N*-de-acetylated moieties that gave a positive ninhydrin test for the amino function. Therefore, an *N*-selective acetylation of the amino function of the product was carried out in MeOH, followed by gel filtration to give the corresponding *O*-de-acetylated glycodendrimer, accompanied by some impurities. Next, the crude *O*-de-acetylated **15** was acetylated completely to provide the corresponding dendrimer **15** having six per-*O*-acetylated *N*-acetyl-D-glucosamine moieties in 46% yield, based on **13**; it showed the expected molecular ion peak at *m/z* 2973.

An initial trial coupling of **12** with **13**, using the same conditions as those described for **15**, was carried out. Unfortunately, pure **16** was not obtained because of difficulties in removal of impurities. As the impurity seemed to consist of incompletely coupled products, the stoichiometric ratio of **12**:**13** was raised to 18:1 in order to enhance the efficiency of the SN2 coupling reaction. In a second trial, the coupled product **16** was obtained as acetate showing a molecular ion peak by FABMS at *m/z* 3838 (Scheme 2).

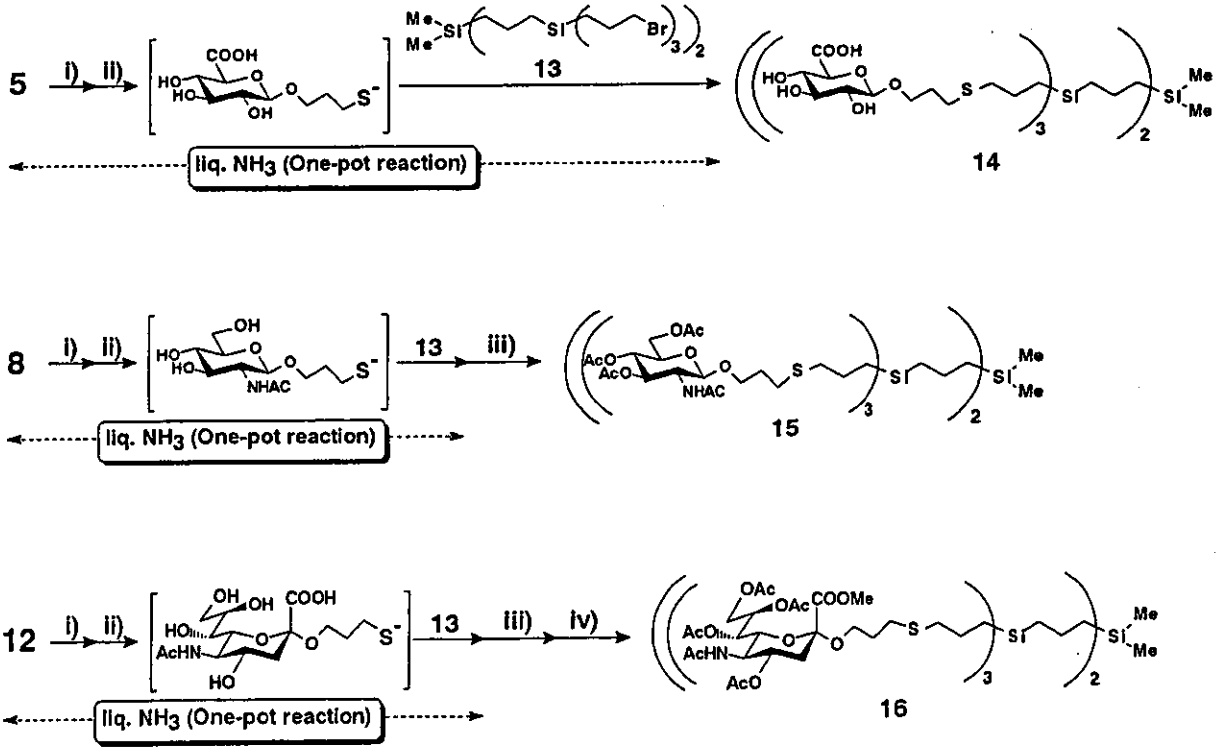
In conclusion, we have demonstrated the feasibility of a one-pot reaction in liquid NH_3 for Birch reduction and the subsequent SN2 replacement to construct carbosilane dendrimers bearing three kinds of monosaccharide derivatives containing carboxylic acid and amide functional groups. Further applications of this procedure for assembling complex oligosaccharides, using a series of carbosilane dendrimers as the core frame, are now under way.

3. Experimental

Materials and methods.—Unless otherwise stated, all commercially available solvents and reagents were used without further purification. Pyridine, 1,4-dioxane, and tetrahydrofuran (THF) were stored over molecular sieves (4 Å MS), and methanol (MeOH) was stored over 3 Å MS before use. Melting points were measured with a Laboratory Devices Meltemp II apparatus and were uncorrected. The optical rotations were determined with a Jasco DIP-1000 digital polarimeter. The IR spectra were obtained using a Jasco FT/IR-300E spectrophotometer. The ^1H NMR spectra were recorded at 400 MHz with a Bruker

AM-400 or at 200 MHz with a Varian Gemini-2000 spectrometer in chloroform-*d* or D_2O. Tetramethylsilane (Me_4Si) and MeOH (3.3 ppm) were used as internal standards. Ring-proton assignments in NMR were made by first-order analysis of the spectra and were supported by the results of homonuclear decoupling experiments. Elemental analyses were performed with a Fisons EA1108 instrument on samples extensively dried at 50–60 °C over P_2O_5 for 4–5 h. Fast atom bombardment mass (FABMS) spectra were recorded with a Joel JMS-HX110 spectrometer. Reactions were monitored by thin-layer chromatography (TLC) on precoated plates of Silica Gel $60F_{254}$ (layer thickness, 0.25 mm; E. Merck, Darmmstadt, Germany). For detection of the intermediates, TLC sheets were sprayed with (a) a solution of 85:10:5 (v/v/v) MeOH–*p*-anisaldehyde–H_2SO_4, and heated for a few minutes (for carbohydrate) or (b) an aqueous solution of 5 wt% $KMnO_4$ and heated similarly (for C=C double bond). Column chromatography was performed on silica gel (Silica Gel 60; 63–200 μm, E. Merck). Flash column chromatography was performed on silica gel (Silica Gel 60, spherical neutral; 40–100 μm, E. Merck). All extractions were conducted below 45 °C under diminished pressure.

Methyl (allyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (**2**) *[9].*—To a solution of the known allyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside (**1**, 5.00 g, 8.49 mmol) [6] in acetone (100 mL) was added a solution of CrO_3 (17.0 g, 170 mmol) in 3.5 M aq H_2SO_4 (23 mL) at 0 °C, and the mixture was kept warm at rt for 50 min. When TLC indicated the complete conversion of **1**, the resultant mixture was poured into ice–water and extracted with $CHCl_3$. The organic solution was washed with brine, dried ($NaSO_4$), and evaporated. The residual syrup was dissolved in CH_2Cl_2 (100 mL), and the solution was treated with ethereal CH_2N_2. Conventional work-up gave **2** (1.65 g, 51.9%) after crystallization from 2-propanol; mp 136–137 °C; IR (KBr) 2952 (ν_{C-H}), 1758 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 6 H, 2 Ac), 2.05 (s, 3 H, Ac), 3.76 (s, 3 H, Me), 4.04 (m, 1 H, H-5), 4.24 (m, 2 H, OCH_2), 4.61 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 5.04 (m, 1 H, H-2), 5.45



Scheme 2. The one-pot reaction, reagents and conditions: (i) Na; (ii) NH_4Cl; (iii) acetylation; (vi) CH_2N_2, ether.

(m, 4 H, H-3, H-4, $=CH_2$), 5.84 (m, 1 H, CH=).

Methyl (3-benzylthiopropyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (**3**).—To a stirred solution of **2** (102 mg, 0.272 mmol) and α-toluenethiol (479 μL, 4.08 mmol) in 1,4-dioxane (0.5 mL) was added 2,2′-azobisisobutyronitrile (AIBN; 22.3 mg, 0.136 mmol) at 50 °C under an Ar atmosphere. The mixture was stirred for 1.5 h at 80 °C at which time cyclohexene (413 μL, 40.8 mmol) was added, and the mixture was stirred at rt for 15 min. After evaporation, silica gel chromatography of the residual syrup (8:1 (v/v) toluene–EtOAc) yielded sulfide **3** (134 mg, 98.5%) as crystals: mp 75–77 °C, $[\alpha]_D^{28}$ −16.6° (*c* 0.44, $CHCl_3$); IR (neat) 2951 (ν_{C-H}), 1755 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (m, 2 H, CH_2), 2.00, 2.02, 2.02 (each s, 9 H, 3 Ac), 2.46 (t, 2 H, *J* 7.1 Hz, SCH_2), 3.68 (s, 3 H, Me), 3.74 (s, 2 H, CH_2Ph), 3.76 (m, 2 H, OCH_2), 4.02 (d, 1 H, $J_{4,5}$ 9.4 Hz, H-5), 4.51 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.98 (dd, 1 H, $J_{2,3}$ 9.2 Hz, H-2), 5.21 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-4), 5.24 (t, 1 H, H-3), 7.22–7.33 (m, 5 H, Ph). Anal. Calcd for $C_{23}H_{30}O_{10}S$: C, 55.41; H, 6.07. Found: C, 55.67; H, 6.06.

Methyl (3-benzylthiopropyl β-D-glucopyranosid)uronate (**4**).—A solution of acetate **3** (1.60 g, 3.21 mmol) in MeOH was treated with NaOMe (52.0 mg, 0.962 mmol) at rt under an Ar atmosphere for 2 h, and then additional NaOMe (17.3 mg, 0.322 mmol) was added. After 1 h of stirring at rt, when TLC indicated the complete conversion of **3**, the reaction mixture was neutralized with IR-120B (H^+) resin until pH 7 and then filtered. The filtrate was concentrated and the residue was subjected to column chromatography on silica gel with 10:1 (v/v) $CHCl_3$–MeOH to afford pure **4** (824 mg, 69.0%) as a colorless syrup, $[\alpha]_D^{28}$ −30.0° (*c* 0.43, MeOH); IR (neat) 3399 (ν_{O-H}), 2917 (ν_{C-H}), 1746 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (400 MHz, Me_2SO-d_6 with D_2O) δ 1.71 (m, 2 H, CH_2), 2.42 (t, 2 H, *J* 7.2 Hz, SCH_2), 2.99 (t, 1 H, H-2), 3.21 (t, 1 H, $J_{2,3}$ 9.0 Hz, H-3), 3.31 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-4), 3.58 (m, 2 H, OCH_2), 3.62 (s, 3 H, Me), 3.65 (s, 2 H, CH_2Ph), 3.74 (d, 1 H, $J_{4,5}$ 9.7 Hz, H-5), 4.22 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 7.18–7.30 (m, 5 H, Ph). Anal. Calcd for $C_{17}H_{24}O_7S{\cdot}0.5\ H_2O$: C, 53.53; H, 6.61. Found: C, 53.70; H, 6.58.

3-Benzylthiopropyl β-D-glucopyranosyluronic acid (**5**).—A solution of methyl ester **4** (389 mg, 1.04 mmol) in 1 M aq NaOH (5 mL) was stirred for 15 min at rt. To the solution was added an IR-120B (H^+) resin to remove Na^+, and the suspension was filtered and concentrated to give **5** (354 mg, 94.7%) as an amorphous solid, $[\alpha]_D^{27}$ −33.4° (*c* 1.13, MeOH); IR (KBr) 3304 (ν_{O-H}), 2923 (ν_{C-H}), 1741 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (400 MHz, Me_2SO-d_6 with D_2O) δ 1.74 (m, 2 H, CH_2), 2.46 (t, 2 H, *J* 7.2 Hz, SCH_2), 2.95 (t, 1 H, $J_{2,3}$ 8.6 Hz, H-2), 3.15 (t, 1 H, H-3), 3.26 (t, 1 H, $J_{3,4}$ 9.3, $J_{4,5}$ 9.4 Hz, H-4), 3.70 (s, 2 H, CH_2Ph), 4.18 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 7.22–7.30 (m, 5 H, Ph). Anal. Calcd for $C_{16}H_{22}O_7S{\cdot}0.2\ H_2O$: C, 53.08; H, 6.24. Found: C, 53.09; H, 6.17.

3-Benzylthiopropyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside (**7**).—Allyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**6**) (1.30 g, 3.36 mmol) [7a] was treated with α-toluenethiol (5.91 mL, 50.3 mmol) in the same way as that previously described for the preparation of **3** to afford white crystalline **7** (1.68 g, 97.8%), mp 136–137 °C, $[\alpha]_D^{28}$ −1.77° (*c* 0.55, $CHCl_3$); IR (KBr) 2922 (ν_{C-H}), 1742 ($\nu_{C=O}$), 1663 ($\nu_{C=O}$; amide I), 1538 (δ_{N-H}; amide II) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.83 (m, 2 H, CH_2), 1.90 (s, 3 H, NAc), 2.03, 2.03, 2.08 (each s, 9 H, 3 Ac), 2.48 (t, 2 H, *J* 7.4 Hz, SCH_2), 3.69 (s, 2 H, CH_2Ph), 4.12 (dd, 1 H, $J_{5,6a}$ 2.6, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.23 (dd, 1 H, $J_{5,6b}$ 4.8 Hz, H-6b), 4.58 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 5.06 (t, 1 H, $J_{3,4}$ 9.4, $J_{4,5}$ 9.6 Hz, H-4), 5.24 (t, 1 H, $J_{2,3}$ 10.6 Hz, H-3), 5.41 (d, 1 H, $J_{2,NH}$ 8.8 Hz, NH), 7.22–7.34 (m, 5 H, Ph). Anal. Calcd for $C_{24}H_{33}O_9NS$: C, 56.35; H, 6.50; N, 2.74. Found: C, 56.60; H, 6.50; N, 2.74.

3-Benzylthiopropyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**8**).—A solution of acetate **7** (1.50 g, 2.93 mmol) in MeOH (30 mL) was treated with NaOMe (47.5 mg, 0.88 mmol) at rt for 1.5 h under an Ar atmosphere. To the resulting mixture was added IR-120B (H^+) resin for neutralization, and then the mixture was filtered. The filtrate was evaporated in vacuo to give **8** (1.12 g, 99.0%) as white crystals, mp 160–162 °C, $[\alpha]_D^{27}$ −23.8° (*c* 0.99,

Me_2SO); IR (KBr) 3277 (ν_{O-H}), 2921 (ν_{C-H}), 1653 ($\nu_{C=O}$; amide I), 1550 (δ_{N-H}; amide II) cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 1.76 (m, 2 H, CH_2), 1.94 (s, 3 H, NAc), 2.47 (t, 2 H, J 7.2 Hz, SCH_2), 3.70 (s, 2 H, CH_2Ph), 4.36 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 7.24–7.30 (m, 5 H, Ph). Anal. Calcd for $C_{18}H_{27}O_6NS{\cdot}0.5\ H_2O$: C, 54.80; H, 7.15; N, 3.55. Found: C, 55.05; H, 7.17; N, 3.51.

3-Benzylthiopropyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-β-D-glycero-D-galacto-2-nonulopyranosonic acid methyl ester (**10**).—Allyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-glycero-D-galacto-2-nonulopyranosonic acid methyl ester (**9**) (1.30 g, 2.45 mmol) [8] was allowed to react with α-toluenethiol (4.31 mL, 36.7 mmol) in the same way as described for the preparation of **3** to afford amorphous **10** (1.54 g, 96.2%), $[\alpha]_D^{27}$ −20.6° (*c* 1.56, $CHCl_3$); IR (KBr) 2959 (ν_{C-H}), 1748 ($\nu_{C=O}$), 1660 ($\nu_{C=O}$; amide I), 1549 (δ_{N-H}; amide II) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (m, 2 H, OCH_2CH_2), 1.88 (s, 3 H, NAc), 1.93 (dd, 1 H, $J_{3ax,3eq}$ 12.8, $J_{3ax,4}$ 12.4 Hz, H-3ax), 2.03, 2.04, 2.12, 2.15 (each s, 12 H, 4 Ac), 2.48 (t, 2 H, J 7.2 Hz, SCH_2), 2.56 (dd, 1 H, $J_{3eq,4}$ 4.6 Hz, H-3eq), 3.56 (m, 2 H, OCH_2), 3.70 (s, 2 H, CH_2Ph), 3.77 (s, 3 H, Me), 4.06 (q, 1 H, H-5), 4.09 (dd, 1 H, $J_{8,9b}$ 5.5, $J_{9a,9b}$ 12.5 Hz, H-9b), 4.11 (dd, 1 H, $J_{5,6}$ 10.6, $J_{6,7}$ 2.2 Hz, H-6), 4.30 (dd, 1 H, $J_{8,9a}$ 2.7 Hz, H-9a), 4.84 (ddd, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 5.17 (d, 1 H, $J_{5,NH}$ 9.6 Hz, NH), 5.32 (dd, 1 H, $J_{7,8}$ 8.4 Hz, H-7), 5.40 (ddd, 1 H, H-8), 7.15–7.33 (m, 5 H, Ph). Anal. Calcd for $C_{30}H_{41}O_{13}NS$: C, 54.95; H, 6.30; N, 2.14. Found: C, 54.91; H, 6.29; N, 2.14.

3-Benzylthiopropyl 5-acetamido-3,5-dideoxy-β-D-glycero-D-galacto-2-nonulopyranosonic acid methyl ester (**11**).—A solution of acetate **10** (1.30 g, 1.98 mmol) in MeOH (15 mL) was stirred in the presence of NaOMe (43.0 mg, 0.793 mmol) at rt for 2 h under an Ar atmosphere. The resulting mixture was treated with IR-120B (H^+) resin, filtered, and concentrated. The residual syrup was chromatographed on silica gel with 5:1 (v/v) $CHCl_3$–MeOH to give pure **11** (755 mg, 78.1%) as white crystals: mp 148–150 °C, $[\alpha]_D^{27}$ −27.4° (*c* 1.77, Me_2SO); IR (KBr) 3352 (ν_{O-H}), 2935 (ν_{C-H}), 1724 ($\nu_{C=O}$), 1625 ($\nu_{C=O}$; amide I), 1561 (δ_{N-H}; amide II) cm^{-1}; ^1H NMR (200 MHz, Me_2SO-d_6 with D_2O) δ 1.52 (t, 1 H, $J_{3ax,3eq} = J_{3ax,4}$ 11.8 Hz, H-3ax), 1.64 (m, 2 H, OCH_2CH_2), 1.84 (s, 3 H, NAc), 2.34 (t, 2 H, J 7.1 Hz, SCH_2), 2.46 (dd, 1 H, $J_{3eq,4}$ 1 > Hz, H-3eq), 3.63 (s, 2 H, CH_2Ph), 3.68 (s, 3 H, Me), 7.19–7.28 (m, 5 H, Ph). Anal. Calcd for $C_{22}H_{33}O_9NS$: C, 54.20; H, 6.82; N, 2.87. Found: C, 54.24; H, 6.86; N, 2.80.

3-Benzylthiopropyl 5-acetamido-3,5-dideoxy-α-D-glycero-D-galacto-2-nonulopyranosonic acid (**12**).—A solution of methyl ester **11** (796 mg, 1.63 mmol) in 0.05 M aq NaOH (80 mL) was stirred at rt for 1 h, at which time an IR-120B (H^+) resin was added to the mixture. After filtration, the filtrate was concentrated in vacuo to give amorphous **12** in quantitative yield, $[\alpha]_D^{23}$ −18.6° (*c* 1.12, Me_2SO); IR (KBr) 3415 (ν_{O-H}), 2933 (ν_{C-H}), 1635 ($\nu_{C=O}$; amide I), 1562 (δ_{N-H}; amide II) cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.60 (t, 1 H, $J_{3ax,3eq} = J_{3ax,4}$ 12 Hz, H-3ax), 1.79 (m, 2 H, OCH_2CH_2), 2.00 (s, 3 H, NAc), 2.50 (t, 2 H, J 7.3 Hz, SCH_2), 2.69 (dd, 1 H, $J_{3eq,4}$ 4.7 Hz, H-3eq), 3.74 (s, 2 H, CH_2Ph), 7.28–7.39 (m, 5 H, Ph). Anal. Calcd for $C_{21}H_{31}O_9NS{\cdot}0.7\ H_2O$: C, 51.88; H, 6.72; N, 2.88. Found: C, 51.84; H, 6.64; N, 2.89.

Carbosilane dendrimer carrying six D-glucuronic acid moieties (**14**).—To a stirred solution of **5** (229 mg, 0.639 mmol) in liquid NH_3 (~30 mL) was added Na (147 mg, 6.39 mmol) at −30 °C, and the mixture was stirred for 1 h. The stirred mixture was treated with NH_4Cl (273 mg, 5.11 mmol) for 10 min, and then a solution of bis[(3-bromopropylsilyl)propyl]dimethylsilane (**13**) (53 mg, 57 μmol) [5] in THF (2 mL) was added dropwise. The mixture was stirred overnight and then evaporated to dryness. The residue was purified by Sephadex G-25 with 5% aq AcOH as an eluent to give **14** (80 mg, 64.0%) as an amorphous solid. An analytical sample was treated with IR-120B (H^+) resin for 20 min at rt. After filtration, the filtrate was lyophilized to give pure **14** as white powder, $[\alpha]_D^{22}$ −36.4° (*c* 0.98, water); IR (KBr) 3377 (ν_{O-H}), 2913 (ν_{C-H}), 1732 ($\nu_{C=O}$) cm^{-1}; ^1H NMR (400 MHz, D_2O) δ −0.05 (s, 6 H, 2 Me), 0.65 (m, 20 H, 10 $SiCH_2$), 1.37 (m, 4 H, 2 CH_2), 1.61 (m, 12 H, 6 CH_2), 1.93 (m, 12 H, 6 CH_2), 2.61 (m, 24 H, 12 SCH_2), 3.39 (t, 6 H, $J_{2,3}$ 8.5 Hz, H-2),

3.56 (t, 6 H, $J_{3,4}$ 9.1 Hz, H-3), 3.62 (t, 6 H, $J_{4,5}$ 9.2 Hz, H-4), 3.85 (m, 12 H, 6 OCH_2), 3.99 (d, 6 H, H-5), 4.50 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR (100.6 MHz, D_2O) δ −2.19 (Me), 12.02 [SiC (G1)], 17.52 [CH_2 (G0)], 18.70 [CH_2 (G0)], 20.34 [CH_2 (G0)], 24.28, 28.32, 29.56, 35.79, 69.29 (C-4), 71.49 (C-2), 72.92, 74.90, 75.43, 102.65 (C-1), 172.27 (C-6); FABMS Calcd for [M^+]: 2076.7. Found: *m/z* 2076.5. Anal. Calcd for $C_{80}H_{144}O_{42}S_6Si_3 \cdot 2\ H_2O$: C, 45.96; H, 7.14. Found: C, 46.05; H, 7.07.

Carbosilane dendrimer carrying six N-*acetyl*-D-*glucosamine moieties* (**15**).—A mixture of **8** (254 mg, 0.658 mmol), Na (151 mg, 6.58 mmol) in liquid NH_3 (~30 mL) was stirred for 1 h at −30 °C. After adding NH_4Cl (317 mg portionwise, 5.92 mmol), the dendrimer **13** (51 mg, 57 μmol) in THF (1 mL) was injected dropwise to the stirred mixture and the stirring was continued for 19 h. When the TLC of the reaction mixture indicated *N*-de-acetylation of products, as judged by the results of a ninhydrin test, the reaction mixture was acetylated in the conventional way in MeOH after removal of NH_3. Chromatographic purification by Sephadex G-25 eluting with 5% aq AcOH gave crude products. Further manipulation of the products into the complete acetates was accomplished by Ac_2O with pyridine. Chromatography of the resulting acetates on silica gel with 10:1 (v/v) $CHCl_3$–MeOH afforded pure **15** (75 mg, 46.0%) as an amorphous solid, $[\alpha]_D^{25}$ −3.0° (*c* 0.63, $CHCl_3$); IR (KBr) 2920 (ν_{C-H}), 1748 ($\nu_{C=O}$), 1661 ($\nu_{C=O}$; amide I), 1557 (δ_{N-H}; amide II) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.10 (s, 6 H, 2 CH_3), 0.53 (m, 20 H, 10 $SiCH_2$), 1.23 (m, 4 H, 2 CH_2), 1.50 (m, 12 H, 6 CH_2), 1.80 (m, 12 H, 6 CH_2), 1.92 (s, 18 H, 6 NAc), 1.98, 2.00, 2.04 (each s, 54 H, 18 Ac), 2.45 (t, 12 H, *J* 7.1 Hz, 6 SCH_2), 2.51 (t, 12 H, *J* 7.0 Hz, 6 SCH_2), 3.72 (ddd, 6 H, $J_{4,5}$ 9.7, $J_{5,6a}$ 2.4, $J_{5,6b}$ 4.7 Hz, H-5), 3.74 (m, 12 H, 6 OCH_2), 3.88 (q, 6 H, H-2), 4.09 (dd, 6 H, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.23 (dd, 6 H, H-6b), 4.66 (d, 6 H, $J_{1,2}$ 8.3 Hz, H-1), 5.03 (t, 6 H, $J_{3,4}$ 9.6 Hz, H-4), 5.26 (t, 6 H, $J_{2,3}$ 9.9 Hz, H-3), 6.44 (d, 6 H, $J_{2,NH}$ 8.9 Hz, NH); FABMS Calcd for [M^+]: 2973.15. Found: *m/z* 2973.07. Anal. Calcd for $C_{128}H_{210}O_{54}N_6S_6Si_3$: C, 51.70; H, 7.12; N, 2.83. Found: C, 52.20; H, 7.19; N, 2.62.

Carbosilane dendrimer carrying six N-*acetylneuraminic acid moieties* (**16**).—Sodium (148 mg, 6.45 mmol) was added to a solution of **12** (305 mg, 0.645 mmol) in liquid NH_3 (~30 mL) at −55 °C, and the dark blue mixture was stirred for 1 h. The mixture was treated with NH_4Cl (276 mg, 5.16 mmol) for 5 min, and then a solution of dendrimer **13** (25 mg, 27 μmol) in THF (2 mL) was added dropwise to the mixture at −30 °C. The mixture was stirred overnight and evaporated. The white residue was allowed to react with Ac_2O (5 mL) in pyridine (15 mL) at rt overnight. After evaporation in vacuo, the residue was treated with CH_2N_2 in diethyl ether. A combination of a gel filtration with Sephadex LH-20 eluted with MeOH and silica gel chromatography of the concentrated reactant mixture gave **16** as a colorless solid (42 mg, 40.8%): ^1H NMR (400 MHz, $CDCl_3$) δ −0.68 (s, 6 H, 2 CH_3), 0.56 (m, 20 H, 10 $SiCH_2$), 1.25 (m, 4 H, 2 CH_2), 1.52 (m, 12 H, 6 CH_2), 1.80 (m, 12 H, 6 CH_2), 1.86 (s, 18 H, 6 NAc), 1.92 (t, 6 H, $J_{3ax,4}$ 12.6 Hz, H-3ax), 2.00, 2.03, 2.12, 2.13 (each s, 72 H, 24 Ac), 2.48 (t, 12 H, *J* 7.3 Hz, 6 SCH_2), 2.53 (t, 12 H, *J* 7.2 Hz, 6 SCH_2), 2.56 (dd, 6 H, $J_{3ax,3eq}$ 13.2, $J_{3eq,4}$ 4.6 Hz, H-3eq), 3.56 (m, 12 H, 6 OCH_2), 3.78 (s, 18 H, Me), 4.05 (q, 6 H, H-5), 4.10 (m, 6 H, H-6), 4.12 (dd, 6 H, H-9b), 4.29 (dd, 6 H, $J_{8,9a}$ 2.3, $J_{9a,9b}$ 12.4 Hz, H-9a), 4.83 (ddd, 6 H, $J_{4,5}$ 9.5 Hz, H-4), 5.30 (d, 6 H, $J_{5,NH}$ 8.9 Hz, NH), 5.32 (dd, 6 H, $J_{6,7}$ 1.9, $J_{7,8}$ 8.4 Hz, H-7), 5.38 (ddd, 6 H, $J_{8,9b}$ 5.7 Hz, H-8); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −3.30 (SiMe), 12.11 [SiC (G1)], 20.76 [CH_2 (G0)], 20.82 [CH_2 (G0)], 20.86 [CH_2 (G0)], 21.08, 23.13, 24.23, 28.43, 29.67, 35.88, 38.02, 49.36 (OMe), 52.70, 62.28, 63.36, 67.25, 68.54, 69.10, 72.43, 77.20, 98.76 (C-2), 168.43 (C=O), 169.96 (C=O), 170.06 (C=O), 170.21 (C=O), 170.62 (C=O), 170.94 (C=O); FABMS Calcd for [$M + H^+$]: 3838.42. Found: *m/z* 3838.20.

Acknowledgements

This work was partly supported by a grant in aid from NEDO [New Energy and Industrial Technology Development Organization (Glycocluster project)].

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高分子論文集 (Kobunshi Ronbunshu), Vol. 57, No. 10, pp. 691—695 (Oct., 2000)

〔ノ ー ト〕

カルボシランデンドリマーをコア骨格として用いた β-シクロデキストリン残基の合成的アッセンブリー

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(受付 2000 年 5 月 18 日・審査終了 2000 年 6 月 19 日)

要 旨 末端に 12 個の臭素原子を含むカルボシランデンドリマーを合成した．得られたデンドリマーと，β-シクロデキストリン (β-CD) のベンジルスルフィド誘導体からバーチ還元により生成するチオレートアニオンとの置換反応を液体アンモニア中，ワンポットで行ったところ，12 個の β-CD 残基を含有する目的物とともに 11, 10, 9 個の β-CD 残基を含有する化合物の混合物として得られることがわかった．得られた化合物の包接能を，2-*p*-トルイジニルナスタレン-6-スルホン酸 (TNS) をゲスト分子として評価したところ，β-CD 残基：TNS が 2：1 の包接錯体を形成していると推定した．

1 緒 言

D-グルコースが α 1→4 結合により環状に連なったシクロデキストリン (CD) は，そのD-グルコース残基数により α，β，γ-CD と呼ばれ，水溶液中でその内孔に適した疎水性ゲスト分子を包接する能力を備えている．CD の内孔より大きなゲスト分子を CD 分子の協同作用により効率よく包接することが期待できる数多くの CD 2 量体[1]，4 量体[2]，さらに側鎖に CD を含む直鎖状高分子[3] がこれまでに合成されてきた．最近，筆者らは，生体に対する毒性が極めて低いと期待できるカルボシラン化合物に注目し，3 官能性あるいは，4 官能性カルボシランの末端に CD を硫黄分子を介して結合させた新規な CD 含有化合物の合成に成功した[4]．その際，CD 誘導体とカルボシラン化合物との結合反応において，液体アンモニア中でのバーチ還元と S_N2 反応をワンポットで効率よく行う反応を開発した．今回は，この手法をさらに Fig. 1 に示すカルボシランデンドリマー 1 へ展開したので報告する．

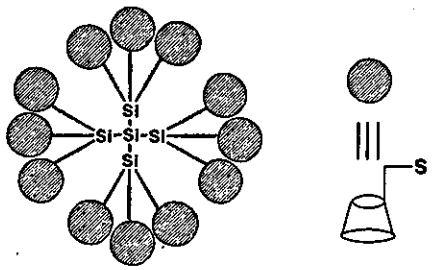

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Fig. 1. Carbosilane dendrimer carrying 12 β-CD moieties.

2 実 験

【試薬・機器】

本研究に用いた反応溶媒は，指定していないものはすべて以下の市販の特級品に活性化した合成ゼオライトを加え，乾燥後，上澄みを使用した．メタノールは合成ゼオライト A-3，ピリジン，*N*,*N*-ジメチルホルムアミド (DMF) は合成ゼオライト A-4 にて行った．^{1}H NMR スペクトルは，Bruker 製 AM-400 (400 MHz) 型核磁気共鳴分光計を使用した．標準は，重クロロホルムにはテトラメチルシラン (0 ppm) を用い，重水にはメタノール (3.3 ppm) あるいは残存プロトン (HDO；4.78 ppm) を基準とした．^{13}C NMR スペクトルは，100.6 MHz で同上の装置を用いて測定し，標準には重クロロホルム (77.0 ppm) あるいは，メタノール (49.0 ppm) を用いた．IR スペクトルは，日本分光(株)製 FT/IR-300 E 型分光光度計を使用した．MALDI-TOF-MS の測定には，サーモクエスト製レーザーマット 2000 型分光計を使用した．薄層クロマトグラフ (TLC) は，MERCK 製 TLC plates silicagel 60 F_{254} を，0.25 mm を 50×10 mm に切って使用した．蛍光測定は(株)島津製作所製 RF-530 PC 型分光光度

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計に蛍光用4方向透過セル（1 cm×1 cm）を用いた．

2.1 テトラキス{トリス[3-(メチルスルホニルオキシ)プロピル]シリルプロピル}シラン(3)

アルコール2[5]（133 mg, 0.131 mmol）を窒素ガス雰囲気下，ピリジン（3 mL）に溶解後，−30℃に冷却した．その冷溶液に，塩化メタンスルホン酸(541 mL, 4.72 mL）を滴下し，−30℃で1時間かくはんした．反応溶液に水を滴下，ついでクロロホルムで希釈した．有機層を5%硫酸水溶液，飽和炭酸水素ナトリウム水溶液，飽和食塩水で順次洗浄し，無水硫酸ナトリウムで乾燥後，濃縮することにより無色透明，シラップ状の3(248 mg, 96.9%）を得た．得られた3はこのまま次の反応に用いた．R_f0.42（10：1(v/v)クロロホルム-メタノール）；IR (neat) 2916 (ν_{C-H}), 1416(ν_{Si-C}), 1337($\nu_{O=S=O}$), 1173 ($\nu_{O=S=O}$), 812(ν_{Si-C})cm^{-1}；^{1}H NMR δ(CDCl$_3$)0.57–0.70 (m, 40 H, 20 SiCH$_2$), 1.30(m, 8 H, 4 CH$_2$), 1.74(m, 24 H, 12 C*H*$_2$CH$_2$O), 3.02(s, 36 H, 12 CH$_3$), 4.18(t, 24 H, J＝6.5 Hz, 12 CH$_2$O)；^{13}C NMR δ(CDCl$_3$) 7.51 (SiCH$_2$), 16.76(CH$_2$), 17.34(CH$_2$), 18.28(CH$_2$), 23.73 (Me), 37.20(CH$_2$CH$_2$O), 72.48(CH$_2$O).

2.2 テトラキス[トリス(3-アジドプロピル)シリルプロピル]シラン(4)

メシレート3(159 mg, 0.813 mmol）とアジ化ナトリウム(317 mg, 4.88 mmol)をアルゴンガス雰囲気下，DMF (5 mL）に懸濁後，80℃，1時間かくはんした．反応液を水とジエチルエーテルで希釈後，分液し，エーテル層を無水硫酸ナトリウムで乾燥，濃縮した．得られた残渣をシリカゲルクロマトグラフ（展開溶媒：5：1(v/v) n-ヘキサン-酢酸エチル）にて精製し，4(62 mg, 57.9%）を無色透明のシラップとして得た．R_f0.33(4：1(v/v) n-ヘキサン-酢酸エチル)；IR(neat) 2921(ν_{C-H}), 2094 ($\nu_{N=N=N}$), 1414(ν_{Si-C}), 829(ν_{Si-C}) cm^{-1}；^{1}H NMR δ (CDCl$_3$) 0.58–0.67(m, 40 H, 20 SiCH$_2$), 1.31(m, 8 H, 4 CH$_2$), 1.58(m, 24 H, 12 C*H*$_2$CH$_2$N$_3$), 3.26(t, 24 H, J ＝6.8 Hz, 12 CH$_2$N$_3$)；^{13}C NMR δ(CDCl$_3$)9.38(SiCH$_2$), 17.10(CH$_2$), 17.49(CH$_2$), 18.40(CH$_2$), 23.59(*C*H$_2$CH$_2$N$_3$), 54.43(CH$_2$N$_3$). Anal. Calcd for C$_{48}$H$_{96}$N$_{36}$Si$_5$：C, 43.74；H, 7.34；N, 38.26%.

Found：C, 44.20；H, 7.39；N, 38.18%.

2.3 テトラキス[トリス(3-アミノープロピル)シリルプロピル]シラン(5)

アジド4(280 mg, 0.121 mmol）をピリジン-トリエチルアミン[7 mL, 7：3(v/v)]に溶解させ，硫化水素ガスを1時間吹き込み，密栓をした後，室温中2日間放置した．反応混合物を濃縮後，1 M塩酸水溶液とクロロホルムで希釈した．水層を濃縮後，残渣をイオン交換クロマトグラフ（アンバーライトIRA-400, OH$^-$型）で精製することによりアミン5を褐色シラップとして定量的に得た．得られた5はこれ以上精製を行わずに次の反応に用いた．IR(neat)3292(ν_{N-H}), 2918(ν_{C-H}), 1574(δ_{N-H}), 1415(ν_{Si-C}) cm^{-1}；^{1}H NMR δ(D$_2$O) 0.61(brs, 40 H, 20 SiCH$_2$), 1.50(brs, 32 H, 16 CH$_2$), 2.64(brs, 24 H, 12 CH$_2$ND$_2$)；^{13}C NMR δ(D$_2$O) 9.35(G 0, SiCH$_2$), 17.77 (CH$_2$), 18.02(CH$_2$), 19.00(CH$_2$), 26.77(*C*H$_2$CH$_2$N$_3$), 44.46 (CH$_2$N).

2.4 テトラキス{トリス[3-(6-ブロモヘキサノイルアミノ)プロピル]シリルプロピル}シラン(6)

得られたアミン5とトリエチルアミン（533 μL, 3.83 mmol）のメタノール溶液（7 mL）に，氷冷下，塩化6-ブロモヘキサン酸（585 μL, 3.82 mmol）を滴下し，室温で4時間かくはんした．濃縮後，クロロホルム溶液とし，飽和食塩水で洗浄，無水硫酸ナトリウムで乾燥，濃縮，シリカゲルクロマトグラフ（展開溶媒：10：8：1〜5：4：1(v/v)クロロホルム-酢酸エチル-メタノール）にて精製し，6(602 mg, 2段階で90.5%）を無色透明のシラップとして得た．R_f0.37（5：4：1(v/v)クロロホルム-酢酸エチル-メタノール）；IR(neat) 3298(ν_{N-H}), 2928(ν_{C-H}), 1644($\nu_{C=O}$), 1555(δ_{N-H}), cm^{-1}；^{1}H NMR δ(CDCl$_3$)0.44–0.50(m, 40 H, 20 SiCH$_2$), 1.26(m, 8 H, 4 CH$_2$), 1.48(m, 24 H, 12 CH$_2$), 1.50(m, 24 H, 12 CH$_2$), 1.67(m, 24 H, 12 CH$_2$), 2.22(t, 24 H, J＝7.5 Hz, 12 CH$_2$CO), 3.18(q, 24 H, J＝6.4 Hz, 12 CH$_2$N), 3.42(t, 24 H, J＝6.7 Hz, 12 CH$_2$Br), 6.71(brs, 12 H, 12 NH)；^{13}C NMR δ(CDCl$_3$)9.35(G 0, SiCH$_2$), 17.06, 17.45, 18.52, 23.87, 24.82, 27.69, 32.33, 33.69, 36.18, 42.61, 173.15 (C＝O)；Anal.Calcd for C$_{120}$H$_{228}$N$_{12}$Si$_5$Br$_{12}$：C, 46.04；H, 7.34；N, 5.37%. Found：C, 45.83；H, 7.48；N, 5.19%.

2.5 コアとしてカルボシランデンドリマー(6)を用いたβ-CD残基のアッセンブリー

モノ-6-デオキシ-6-ベンジルメルカプト-β-CD 7[4]（500 mg, 0.403 mmol）を液体アンモニア（40 mL）中，還流温度においてナトリウム（91 mg, 3.96 mmol）と30分間反応させた．塩化アンモニウム(190 mg, 3.56 mmol)にて過剰のナトリウムを中和後，ハロゲン化アルキル6 (53 mg, 16.8 mmol）のメタノール溶液を滴下し，一晩反応させた．アンモニアを留去後，SepahdexG-50（展開溶媒：5%酢酸水溶液）にて精製，凍結乾燥することにより1を含む白色粉末（196 mg）を得た．IR (neat) 3367 ($\nu_{N-H\&O-H}$), 2931(ν_{C-H}), 1638($\nu_{C=O}$), 1557(δ_{N-H}), cm^{-1}；^{1}H NMR δ(D$_2$O) 0.60(brs, SiCH$_2$), 5.10(brs, H−1)；^{13}C NMR δ(D$_2$O)9.43(G 0, SiCH$_2$), 17.12, 18.73, 23.61, 25.41, 27.88, 28.89, 30.41, 32.67, 33.25, 36.01, 42.66, 60.45(C−6), 72.00, 72.17, 73.20, 81.23(C−4), 102.00(C−1), 175.90(C=O). MALDI-TOF-MS Calcd for [M+H$^+$]:15973. Found:m/z 15973. Anal. Calcd for C$_{624}$

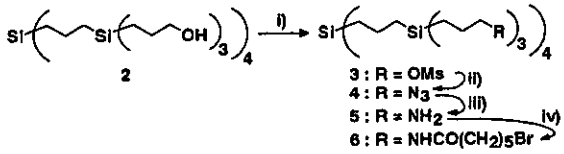
$_{356}O_{420}N_{12}S_{12}Si_5 \cdot 72\ H_2O$：C, 43.40；H, 7.00；N, 0.97%. und：C, 43.59；H, 6.79；N, 1.01%.

2.6 蛍光測定

2-*p*-トルイジニルナフタレン-6-スルホン酸（TNS）を いた蛍光測定は，0.1 M リン酸緩衝液（pH 5.9）中，温で行った．TNS の励起は 366 nm で行い，445 nm の光強度を測定値として用いた．

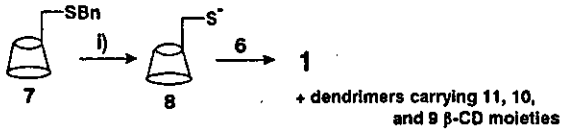
3 結果と考察

これまで筆者らは，β-CD を集積化させる際，かさ高いβ-CD 分子の立体障害を低減させるために，ヘキサノイル基をスペーサーとして用いてきた．本研究においても，Scheme 1 に示すように，デンドリマーの末端をアミノ基に変換後，このスペーサーを用いることとした．すなわち，既知のアルコール性カルボシランデンドリマー 2[5] を −30℃ の低温でメシル化を行った．この際，0℃以上の反応温度では，メシル化された後の副反応が進行するため，目的物を効率よく単離できなかった．得られたメシレート 3 を，常法に従いアジド化合物へと変換後，2100 cm^{-1} 付近のアジド基由来の赤外吸収が消失するまで硫化水素ガスによる還元を行うことにより，アミン 5 へと誘導した．スペーサーの導入には，アミン 5 のメタノール溶液中低温下，6-ブロモヘキサン酸塩化物を滴下することで行い，目的とする 12 個の臭素原子を末端に均一に担持したカルボシランデンドリマー 6 を 91%の高収率で得た．



Scheme 1. Reagents and conditions : i) Ms-Cl, Pyr, −30 ℃, 1 h, 97% ; ii) NaN_3, DMF, 80℃, 1 h, 58% ; iii) H_2S, Pyr−Et_3N (7 : 3, *v/v*), rt, 2 d, q.y. ; iv) Br $(CH_2)_5COCl$, Et_3N, MeOH, 0℃→rt, 4 h, 91%.

得られたデンドリマー 6 と β-CD 由来のベンジルスルフィド体 7[4] との結合には，筆者らの開発した液体アンモニア中でのワンポット結合法[4] を用いた（Scheme 1）．すなわち，まず，液体アンモニア中，−33℃ においてベンジルスルフィド 7 のベンジル基をバーチ還元により除去し，過剰のナトリウムを塩化アンモニウムによって中和することで，チオアニオン 8 を生成させた．ついで，単離することなく，系中に臭素化デンドリマー 6（臭素原子当たり 2 倍量の β-CD 誘導体となる仕込み



Scheme 2. Reagents and conditions : i) Na, liquid NH_3, −33℃, 30 min, then, NH_4Cl, −33℃, 61%.

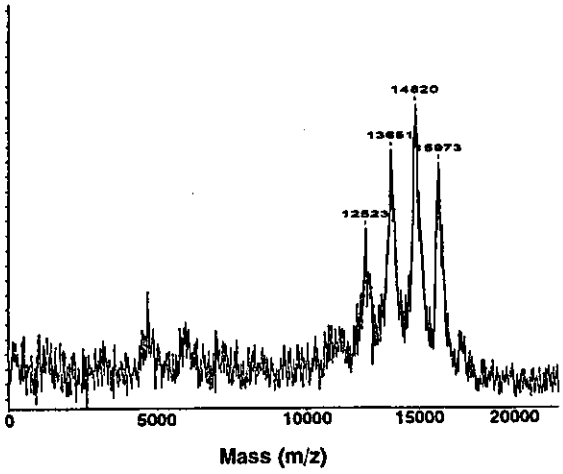


Fig. 2. MALDI-TOF-MS spectrum of carbosilane dendrimers carrying 12, 11, 10, and 9 β-CD moieties.

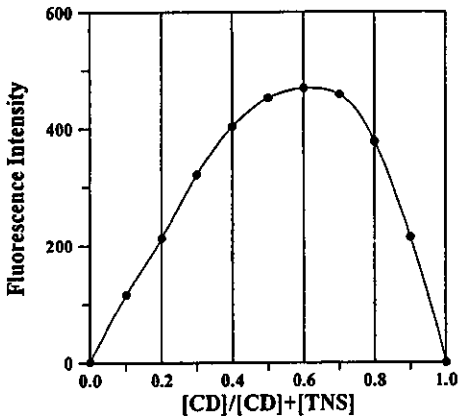


Fig. 3. Continuous variation plot of carbosilane dendrimers carrying β-CD moieties−TNS system ; [CD]+[TNS]= 10^{-4} M.

比）を滴下することにより結合反応を行った．液体アンモニアを除去後，ゲル沪過による精製を行い，凍結乾燥することにより白色粉状のデンドリマーを61％の収率で得た．得られたデンドリマーの分子量を測定するためにMALDI-TOF-MS測定を行ったところ，目的とする**1**のほかにβ-CD残基を11，10，9個含有する化合物との混合物であることが判明した．混合物のMALDI-TOF-MSスペクトルをFig. 2に示す．それらの面積比から推定した混合比は，12個のβ-CD残基を含有する化合物から順におよそ3：3：3：2であった．この結果より，求核剤の不足と置換反応の際の−33℃に起因する低温が反応効率を低下させていると考え，仕込み比を臭素原子：チオアニオン＝1：3とし，バーチ還元後の溶媒をDMFに置換後，50℃で一晩反応を行った．しかしながら，得られた化合物のMALDI-TOF-MS測定の結果からは，条件を変更する前のスペクトルとの違いが確認できなかった．以上の結果から，従来より用いているスペーサーでは，多数のβ-CD残基から誘発される立体障害を完全には克服することができないことが示唆された．

一方，得られた最大12個のβ-CD残基を有するデンドリマー混合物の包接能の評価をTNSをゲスト分子として行った．化合物中のβ-CD残基とTNSとの結合比を求めるため，連続変化法（Job法）[1)-h)]による測定を行った．Fig. 3のグラフより，β-CD残基：TNSの比は，2：1であることが推定された．

4 結　論

末端に12個の臭素原子を含むカルボシランデンドリマーを合成し，β-CD由来の硫黄アニオンとのS_N2反応を行ったところ，最大12個のβ-CD残基を含むデンドリマーに加え，11から9個のβ-CD残基を有するデンドリマーとの混合物となることが判明した．このことからかさ高いβ-CD残基の立体障害を回避するためには，より長鎖のスペーサー分子が必要であることが示唆された．また，TNSをゲスト分子として得られたデンドリマーの包接挙動の評価を行ったところ，β-CD残基：TNSは2：1で包接複合体を形成していると推定された．

謝　辞　MALDI-TOF-MSの測定をしていただきました北海道大学大学院理学研究科西村紳一郎教授とグループの皆様に感謝の意を表します．

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カルボシランデンドリマーをコア骨格として用いたβ-CD残基の合成的アッセンブリー

[Notes]

Synthetic Assembly of β-CD Moieties Using Carbosilane Dendrimer as the Core Frame

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In order to assemble β-CD moieties using a carbosilane dendrimer as the core frame, a carbosilane dendrimer having 12 bromine atoms at the terminal positions has been synthesized from tetrakis[tris[3-(hydroxyl)propyl]silylpropyl]silane as starting material. One-pot coupling reaction between the carbosilane dendrimer and mono-6-deoxy-benzylmercapto-β-CD in liquid ammonia for Birch reduction and the subsequent SN2 reaction gave the carbosilane dendrimer carrying 12 β-CD moieties as a mixture with three compounds carrying 11, 10, or 9 β-CD moieties. The mixture formed an inclusion complex with 2-*p*-toluidinyl-naphthalene-6-sulfonate (TNS) in water having a ratio of [CD] : [TNS]=2 : 1.

KEY WORDS Dendrimer / Cyclodextrin / Carbosilane / Inclusion Complex / Sulfide / Liquid Ammonia /

(Received May 18, 2000 : Accepted June 19, 2000) [*Kobunshi Ronbunshu*, **57** (10), 691—695 (2000)]

Pergamon

Tetrahedron Letters 40 (1999) 7839–7842

TETRAHEDRON LETTERS

Synthetic assembly of trisaccharide moieties of globotriaosyl ceramide using carbosilane dendrimers as cores. A new type of functional glyco-material

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Received 30 July 1999; accepted 12 August 1999

Abstract

As a novel type of artificial receptor for Vero toxins, three pairs of carbosilane dendrimers uniformly carrying 12, 6, and 3 units of trisaccharide moieties of globotriaosyl ceramide were prepared through formation of the sulfide linkages in liquid NH_3, which revealed unexpected differences among their biological responses.

Keywords: carbohydrates; biologically active compounds; dendrimers; sulfides.

Globotriaosyl ceramide (Gb_3; Galα1-4Galβ1-4Glcβ1-Cer) is a major glycolipid located on the surface of the kidney glomerular endothelial cell and is known as the host receptor for Verotoxins (VTs; VT1 and VT2),[1] which are produced by pathogenic *Escherichia coli* O157.[2] Since the extremely selective and potent affinity of Gb_3 for VTs is mainly attributable to its trisaccharide component, clustering the trisaccharide (globotriose) moieties of Gb_3 as an artificial receptor for VTs might give potential glyco-materials of medicinal use. Thus, Nishida et al. co-polymerized an acrylamide derivative carrying the globotriosyl moiety with acrylamide, obtaining a linear co-polymer holding the trisaccharides like pendants.[3] Although this polymer showed some inhibitory effect against cytotoxicity of VT1, it did not reveal any activity against VT2.

This communication describes a novel type of assembly of the globotriosyl moieties using carbosilane dendrimers as polymers supporting them. Carbosilane dendrimers have recently been developed and found to have several unique characteristics: (1) simplicity of the synthetic process to extend the generation;[4] (2) accessibility to the polymer with definite molecular weight and a definite number of terminal functions, which depend on the polymer generation; (3) neutral nature in contrast to the usual

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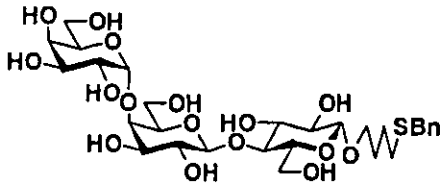

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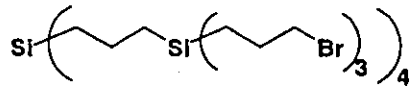


A

polyamine-type dendrimers;[5] and (4) biological inertness, and so on. Hitherto, most modifications of such dendrimers have been conducted by coupling with various functional molecules through condensation reactions; i.e., esterification or amide formation, etc. In contrast, our strategy to uniformly modify carbosilane dendrimers with globotriosyl moieties employed the coupling of both components through S_N2 reaction to form more stable sulfide linkages.[6] Thus, we designed compounds **1** as a precursor of the globotriosyl reactant and **A** as a generation 1 (G1) of the carbosilane dendrimer, since our initial target was the preparation of the G1 carrying 12 globotriosyl moieties.

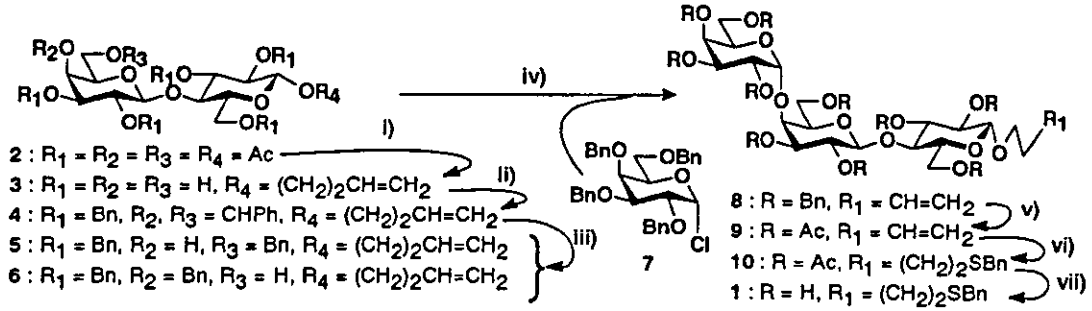
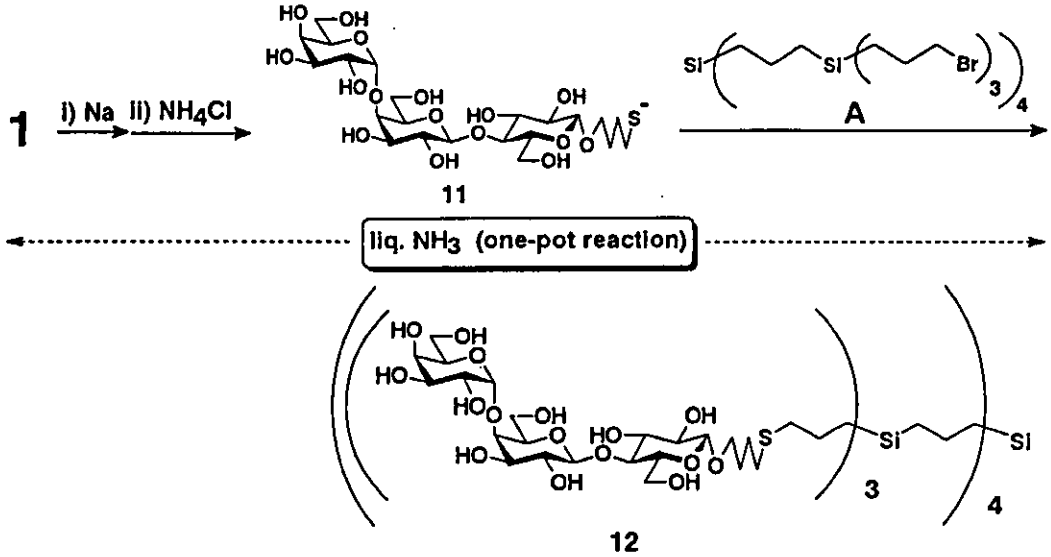


Figure 1. *Reagents and conditions*: (i) 3-Buten-1-ol, $BF_3 \cdot Et_2O$, $ClCH_2CH_2Cl$, 0°C, then NaOMe, MeOH, rt; (ii) α,α-dimethoxytoluene, CSA, DMF, 60°C, then BnBr, NaH, DMF, 0°C; (iii) $BH_3 \cdot NMe_3$, $AlCl_3$, MS4 Å, THF, rt; (iv) AgOTf, MS4 Å, Et_2O; (v) Na, liq. NH_3, −78°C, then Ac_2O, Pyr., rt; (vi) BnSH, AIBN, Dioxane, 50−80°C; (vii) NaOMe, MeOH, rt

For the synthesis of **1** (Fig. 1), the starting peracetyl-β-lactose **2** underwent glycosidation with 3-buten-1-ol in the presence of Lewis acid[7] and subsequent deacetylation, giving **3** in ca. 60% overall yield, $[\alpha]_D^{28}$ −12 (MeOH), ^{1}H NMR (D_2O) δ: 4.5 (d, 1H, $J_{1,2}$=8.0 Hz, H-1), 4.4 (d, 1H, $J_{1',2'}$=7.8 Hz, H-1′). After 4′,6′-*O*-benzylidenation of **3**, the remaining OH groups were all benzylated to give **4**, which was subjected to reductive cleavage by treatment with $BH_3 \cdot NMe_3$ in the presence of $AlCl_3$, giving **5** with the 4-OH in 82% yield, mp 101°C, $[\alpha]_D^{24}$ +20 ($CHCl_3$) and the 6-OH isomer **6** in 13% yield. Glycosidation of **5** with 2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl chloride **7**[8] in the presence of AgOTf in ether at −20°C proceeded steroselectively to give syrupy **8** in 80% yield, ^{13}C NMR ($CDCl_3$) δ: 104 (β; C-1′), 103 (β; C-1), 101 (α; C-1″). Debenzylation of **8** without affecting the terminal double bond was conducted through Birch reduction. Thus, **8** was treated with Na in liq. NH_3 at −78°C and then acetylated to give fully acetylated *n*-butenyl glycoside **9** in 54% overall yield, $[\alpha]_D^{25}$ +38 ($CHCl_3$), ^{1}H NMR ($CDCl_3$) δ: 5.0 (d, 1H, $J_{1'',2''}$=3.6 Hz, H-1″), 4.5 (d, 1H, $J_{1',2'}$=7.7 Hz, H-1′), 4.5 (d, 1H, $J_{1,2}$=7.9 Hz, H-1). When **9** was treated with α-toluenethiol in 1,4-dioxane in the presence of AIBN, radical addition of the thiol to the double bond of **9** proceeded smoothly,[9] giving the sulfide **10** in quantitative yield, $[\alpha]_D^{26}$ +35 ($CHCl_3$), ^{1}H NMR ($CDCl_3$) δ: 5.0 (d, 1H, $J_{1'',2''}$=3.5 Hz, H-1″), 4.5 (d, 1H, $J_{1',2'}$=7.7 Hz, H-1′), 4.4 (d, 1H, $J_{1,2}$=8.0 Hz, H-1). Deacetylation of **10** gave **1** quantitatively as an amorphous solid, $[\alpha]_D^{27}$ +39 (MeOH), ^{1}H NMR (D_2O) δ: 4.9 (br s, 1H, H-1″), 4.5 (d, 1H, $J_{1',2'}$=6.7 Hz, H-1′), 4.3 (d, 1H, $J_{1,2}$=6.1 Hz, H-1), ^{13}C NMR (D_2O) δ: 103, 102 (C-1 and -1′), 100 (C-1″).

For the synthesis of **A**, the known polyhydroxyl dendrimer having the same G1 skeleton[10] was used as the precursor and was fully *O*-mesylated. The resulting compound was treated with NaBr in DMF, giving **A** in 60% overall yield, ^{1}H NMR ($CDCl_3$) δ: 3.4 (t, 24H, *J*=6.8 Hz, 12CH_2Br), 1.8 (m, 24H, 12CH_2CH$_2$Br), 1.3 (m, 8H, 4SiCH$_2$CH_2CH$_2$Si), 0.7–0.6 (m, 40H, 20SiCH_2).

Before coupling of **1** with **A**, the *S*-benzyl group of **1** should be removed. We developed methodology to perform the removal of the benzyl group and the coupling reaction in a one-pot manner, using liq. NH_3 as the solvent. Thus, Birch reduction of **1** was accomplished in the presence of Na in liq. NH_3 at −33°C giving a thiolate anion **11**, which was successively treated with the brominated dendrimer **A** after neutralization of the excess Na with NH_4Cl. The resulting raw product was purified with Sephadex G-25 to give **12** carrying 12 globotriosyl moieties as a white powder in 36% yield based on **A**, MALDI MS calcd for [M+Na$^+$]: 7935.0; found *m/z*: 7935.5, integral ratio of the H atoms by ^{1}H NMR: SiCH$_2$:SCH$_2$:H-1 and 1′=40:48:24, ^{13}C NMR (D_2O) δ: 103, 103 (C-1 and -1′), 101 (C-1″).



Examination of the relationship between the number of the globotriaosyl moieties assembled and their biological responses has also attracted much attention. Therefore, we further prepared **B**, a dumbell-type of G1 dendrimer carrying six bromine atoms, and **C**, a G0 dendrimer with three bromine atoms, for coupling with **1**. The synthetic scheme for **B** is shown in Fig. 2. The starting dichlorodimethylsilane **13** was subjected to a series of reactions such as Grignard, hydrosilation, and the second Grignard reaction to give the hexaallyl compound **14**, which further underwent successively hydroboration, *O*-mesylation, and replacement with bromo anions, giving **B** in 26% overall yield, ^{1}H NMR ($CDCl_3$) δ: 3.4 (t, 12H, *J*=6.9 Hz, 6CH_2Br), 1.8 (m, 12H, 6CH_2CH$_2$Br), 1.3 (m, 4H, 2SiCH$_2$CH_2CH$_2$Si), 0.7–0.5 (m, 20H, 10SiCH_2). The synthesis of **C**, ^{1}H NMR ($CDCl_3$) δ: 7.5–7.4 (m, 5H, Ph), 3.4 (t, 6H, *J*=6.8 Hz, 3CH_2Br), 1.9 (m, 6H, 3CH_2CH$_2$Br), 1.0 (m, 6H, 3SiCH_2), was accomplished from the corresponding triol **15**[6] via the sulfonates like the synthesis of **A** and **B** (Fig. 2).

Coupling of **1** with **B** and **C** was performed in liq. NH_3 in the same way as for the preparation of **12**, giving dendrimers **16** (50% yield) and **17** (88% yield), which carry six and three globotriaosyl moieties, respectively. Compound **16**: FABMS calcd for [M+H$^+$]: 4000.5; found *m/z*: 4001.0, ^{1}H NMR (D_2O) δ: 4.9 (d, 6H, $J_{1'',2''}$=3.1 Hz, H-1″), 4.5 (d, 6H, $J_{1',2'}$=6.9 Hz, H-1′), 4.4 (d, 6H, $J_{1,2}$=6.7 Hz, H-1), −0.04 (br s, 6H, CH$_3$×2). Compound **17**: FABMS calcd for [M+H$^+$]: 2005.75; found *m/z*: 2005.64, ^{1}H NMR

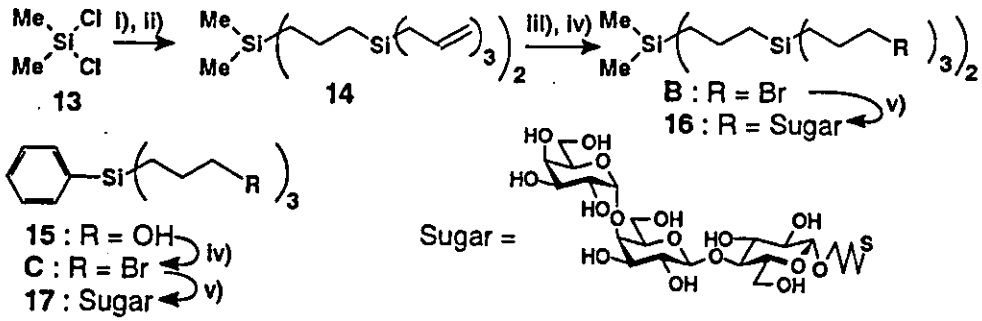


Figure 2. *Reagents and conditions*: (i) CH_2=$CHCH_2MgBr$, Ether; (ii) $HSiCl_3$, H_2PtCl_6, THF,[4] then CH_2=$CHCH_2MgBr$, Ether–THF; (iii) BH_3–THF, THF, then 3 M NaOH aq., H_2O_2; (iv) MsCl, Pyr., then NaBr, DMF; (v) **1**, Na, liq. NH_3, then NH_4Cl, liq. NH_3

(D_2O) δ: 7.3 (m, 5H, ph), 4.9 (d, 3H, $J_{1'',2''}$=3.3 Hz, H-1″), 4.5 (d, 3H, $J_{1',2'}$=7.1 Hz, H-1′), 4.4 (d, 3H, $J_{1,2}$=7.1 Hz, H-1).

Inhibitory activities of **12**, **16**, and **17** against cytotoxicity of VT1 and VT2 were examined, using cell culture assay. Unexpectedly, **12** and **16** showed a similar degree of potent activities against both VTs, while **17** did not show any activity. The detailed results of the biological assay will be reported elsewhere in due course.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, and Culture of Japan.

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Advantages of Carbosilane Dendrimer as a Carbohydrate Scaffold – Application to Artificial Receptor of *E. Coli*, Influenza and Dengue Virus –

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The surface of eukaryotic cells is covered in an array of glycoconjugate such as glycoproteins and glycolipids. Carbohydrates in part of their glycoconjugates play a key role in cell adhesion process with protein of bacteria, viruses and toxins. We will report the successful syntheses of carbosilane dendrimer periphery functionalized such carbohydrates as globotriose, sialyllactose, lacto-*N*-tetraose, and results of its biological assays as artificial receptor against to Vero toxins producing *Escherichia Coli* O157:H7, hemagglutinin of influenza virus, and dengue virus.

Syntheses and Biological Assay of a Series of Lacto-*N*-neotetraose Cluster using Carbosilane Dendrimer Scaffolds

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In recent years, dengue fever has become a major infection disease. The prevalence of dengue has increased scenically in decades. We have recently found that paragloboside and lacto-*N*-neotetraose blocked the uptake of dengue virus. Therefore lacto-*N*-neotetraose cluster compounds are expected as a candidate of artificial dengue virus inhibitor. Fundamental core structures of carbosilane dendrimers (Fan, Ball and Dumbbell shapes) were used as scaffolds for syntheses of glycoclusters (Fig. 1). The synthesis and biological assay of carbosilane dendrimers periphery functionalized lacto-*N*-neotetraose will be also described.

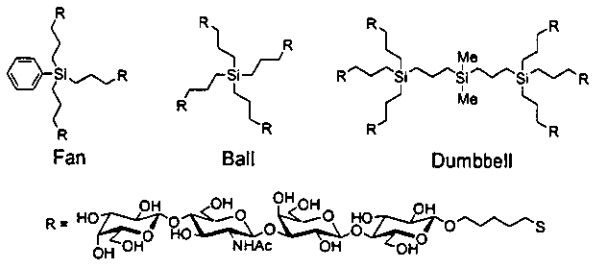

Fig. 1. A Series of Carbosilane Dendrimer periphery functionalized lacto-*N*-neotetraose

チオグリコシド型グロボ３糖誘導体の合成研究（２）

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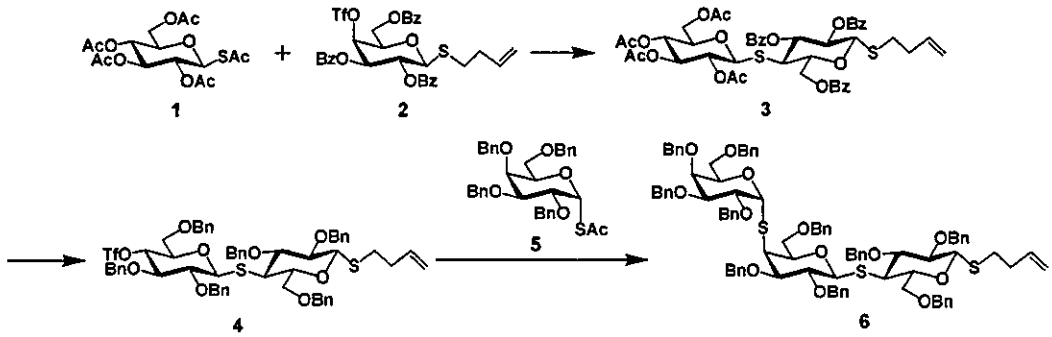
Synthetic studies of globotriaose analogues having interthioglycosidic bonds (2) (Fac. of Engineering, Saitama Univ., The Inst. of Phys. and Chem. Res. (RIKEN)) KUROSAWA, Sunao; KOYAMA, Tetsuo; ESUMI, Yasuaki; HATANO, Ken; TERUNUMA, Daiyo; MATSUOKA, Koji

病原性大腸菌O157:H7が産生するベロ毒素は腸管細胞表層上に存在する糖脂質の１つであるグロボトリオシルセラミドの糖鎖部分（グロボ３糖）を特異的に認識し、接着する。その後、毒性を発揮するユニットが細胞内へ取り込まれ、発病する事が知られている。このグロボ３糖はベロ毒素のレセプターであり中和剤としての活用が期待され、その誘導体が利用されているが、*O*-グリコシド結合が生体内の加水分解酵素によって切断されてしまう可能性があるため、中和後の代謝系をつき止めるには至っていない。そこで本研究では、生体内においてグリコシダーゼ阻害剤として期待できる*S*-グリコシド結合型新規グロボ３糖誘導体の合成を目的とした。

グルコースのβ-チオアセチル体 **1** と１位にブテニル基を導入したチオグリコシドのトリフレート **2** とをチオグリコシル化することによりβ-*S*-グリコシド結合を有するセロビオース類似体 **3** を構築した。次いで **3** の4'位のみを遊離とした後、トリフレート化を行い **4** へと変換した。現在、目的化合物 **6** を構築するために、**4** とガラクトースのα-チオアセチル体 **5** とのチオグリコシル化反応を検討中である。



糖鎖含有カルボシランデンドリマーの合成研究(Ⅷ)
ーデンドリマー中心元素の変化によるベロ毒素阻害活性への効果ー

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Synthetic Studies of Carbosilane Dendrimers Functionalized with Sugar Moieties (Ⅷ) -Element Effect on Biological Assay of Dendrimers bearing Globotriaoses as Vero Toxin Neutralizer-

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病原性大腸菌 O157;H7 は、溶血性尿毒症症候群など深刻な被害を引き起こすベロ毒素を産生することが知られている。このベロ毒素が細胞表層に存在している糖脂質グロボトリオシルセラミドの糖鎖部分グロボ3糖を認識し接着することが感染の第1歩となる。

我々はこれまでに様々な形状・サイズのカルボシランデンドリマーを用いてグロボ3糖の集積化およびそのクラスター化合物群のベロ毒素への阻害活性評価を行ってきた。その結果、第1世代6分岐化合物 Dumbbell(1)6 (Fig. 1 El=Si)が *in vitro* および *in vivo* においても高い阻害活性を示すことを見出している[1]。

今回、この Dumbbell(1)6 の中心ケイ素を炭素およびゲルマニウムで置換した新規グロボ3糖クラスター化合物(Fig. 1 El=C, Ge)の合成および評価を行うこととした。これらクラスター化合物の合成および中心元素によるベロ毒素阻害活性への効果について報告する予定である。

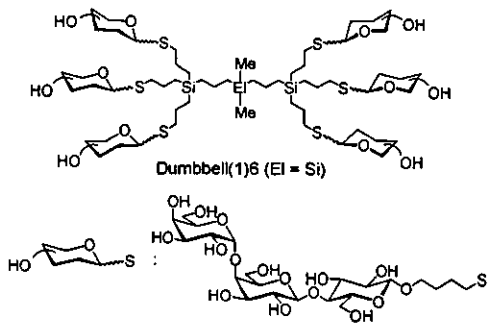

Fig. 1 Dendrimers bearing Globotriaoses

1) NISHIKAWA, K.; MATSUOKA, K. and TERUNUMA, D. *et al.*, *Proc. Natl. Acad. Sci.U. S. A.*, **99**, 7669 (2002).

N-結合型糖ペプチドの基礎的な合成研究

(埼玉大工) ○松山恭子・鈴木美穂・小山哲夫・幡野健・照沼大陽・松岡浩司

Primary synthetic studies of *N*-linked glycopeptide

(Faculty of engineering, Saitama university) MATSUYAMA, Kyoko; SUZUKI, Miho; KOYAMA, Tetsuo; HATANO, Ken; TERUNUMA, Daiyo; MATSUOKA, Koji

糖タンパク質は、生体内において酵素、輸送タンパク、受容体、ホルモン、構造タンパクなどとして存在し、さまざまな生命現象をつかさどっていることから、近年、糖タンパク質を医薬分野へ応用させる研究がさかんに行われている。このような背景から、どの糖鎖が、どのように機能しているのかを詳細に解明していくことが極めて重要である。

一方、一連の糖タンパク質の生合成経路において、糖鎖のタンパク質への結合位置や結合糖鎖の長さ、シークエンスは遺伝子支配を受けないため、その構造は不均一である。故に、特定の構造を持つ糖タンパク質の精製や構造決定は、しばしば困難であった。そのため、糖タンパク質の糖鎖構造の機能については、他の生体高分子と比較して研究のスピードが極めて遅いのが現状である。この問題の一つの解決方法として、有機合成の手法を用い特定の構造を持つ糖ペプチドを合成する手法が考えられる。本研究では、この合成研究の基盤となる、光分解反応によって脱保護が可能な2-Nitrobenzyl 基(NBn 基)及び4,5- Dimethoxy-2-nitrobenzyl 基(NVOC 基)を持つ新規糖ペプチドを合成することを目的とした。

L-Asp を出発物として、N 端を Fmoc 保護し、C 端カルボキシル基のみをベンジルエステル化したカルボン酸と、GlcNAc を出発物として、3,4,6 位を NBn 保護し、アノメリック位にアミノ基を導入したグリコシルアミンをそれぞれ合成し、2 つの化合物をカップリングさせることにより、糖アミノ酸を合成した。さらにアスパラギンの N 端 Fmoc 基を NVOC 基に変換し、最後に C 端ベンジルエステルを脱保護することにより、C 端が遊離となったグルコサミニルアスパラギンを得ることに成功した。構造決定は IR、NMR、元素分析により行った。現在、合成したグルコサミニルアスパラギンを用いたタンパク質合成について検討中である。