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Systematic syntheses of influenza neuraminidase inhibitors: A series of carbosilane dendrimers uniformly functionalized with thioglycoside-type sialic acid moieties ☆

Jun-Ichi Sakamoto [a], Tetsuo Koyama [a], Daisei Miyamoto [b,c], Sangchai Yingsakmongkon [d], Kazuya I. P. J. Hidari [b,c], Wipawee Jampangern [e], Takashi Suzuki [b,c], Yasuo Suzuki [c,f], Yasuaki Esumi [g], Takemichi Nakamura [g], Ken Hatano [a], Daiyo Terunuma [a], Koji Matsuoka [a,*]

[a] Division of Material Science, Graduate School of Science and Engineering, Saitama University, Sakura, Saitama 338-8570, Japan
[b] Department of Biochemistry, University of Shizuoka, School of Pharmaceutical Sciences, and Global COE Program for Innovation in Human Health Sciences, Suruga, Shizuoka 422-8526, Japan
[c] Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan
[d] Department of Microbiology and Immunology, Faculty of Veterinary Medicine, Kasetsart University, Bangkok 10900, Thailand
[e] Department of Medical Sciences, National Institute of Health, Ministry of Public Health, Nonthaburi 11000, Thailand
[f] Department of Biomedical Sciences, College of Life and Health Sciences, Chubu University, Kasugai, Aichi 487-8501, Japan
[g] The Institute of Physical and Chemical Research (RIKEN), Wako, Saitama 351-0198, Japan

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ABSTRACT

In order to develop novel influenza sialidase inhibitors, we constructed a library of glycoclusters composed of twelve types of sialylated dendrimers with thioglycosidic linkage that are resistant to hydrolysis by the sialidases. These sialodendrimers were synthesized by condensation reaction between a thiosialoside modified on the aglycon terminal end by a thioacetyl group and twelve types of carbosilane dendrimers having brominated terminal ends under deacetylation conditions, and temporal re-protection was performed for purification. Removal of all protection of the glycodendrimers was accomplished by transesterification and subsequent saponification to provide corresponding water-soluble glycodendrimers in good yields. For investigation of the structure–activity relationship, dendrimer scaffolds having differences in number of the sugar moieties, such as 3-, 4-, 6- and 12-functionalized dendrimers, and in linkage patterns, such as normal aliphatic linkage, ether- and amide-linkages. Biological evaluations of these glycodendrimers showed that all of the ether- and amide-elongated compounds had inhibitory potencies for the influenza sialidases in the mM range, while compounds having normal aliphatic linkage did not have any activities except for a 12-functionalized compound.

1. Introduction

There has been much concern recently about the possibility of a worldwide influenza outbreak leading to pandemic flu. The most catastrophic pandemic was Spanish flu in 1918–1919, which claimed the lives of at least 20 million people.[1] If a new type of pandemic flu occurs, it is expected that the flu will kill about 62 million people worldwide.[2] Medicines that might be useful for a forthcoming pandemic are Tamiflu®[3] and Relenza®,[4] which are used as inhibitors against influenza viral glycosidases. Influenza A and B viruses have two types of sialic acid-recognizing glycoproteins on their surfaces.[5] One of them is hemagglutinin (HA), which is a kind of lectin and binds to sialyloligosaccharides as specific receptors on host cells with viral infection beginning.[6] Then in order to spread infection, replicated viruses are released from the infected cells by enzymatic cleavage of the sialic acid residues of the sialyloligosaccharides by the other surface glycoprotein, referred to as either sialidase or neuraminidase (NA).[7] Tamiflu® and Relenza® have potent inhibitory activities against infection spread because they plug the active sites of neuraminidases by interaction with the amino acids forming the active sites and thereby inhibit the viral particle release process and cut off the virus multiplication cycle. However, Tamiflu-resistant viruses, which have a hidden potential to cause an outbreak of infection, have already been isolated.[8] Therefore, treatment of influenza infection requires other novel anti-viral agents to prepare for an influenza outbreak.

Although molecular designs of Tamiflu® and Relenza® are based on the transition state analogue of sialic acid in enzymatic hydrolysis of sialoside by neuraminidases, substrates for neuraminidases

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* Corresponding author. Tel./fax: +81 48 858 3099.
E-mail address: koji@fms.saitama-u.ac.jp (K. Matsuoka).

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are absolutely natural sialic acids. Consequently, we focused on thioglycoside of sialic acid as a wild-type artificial substrate for neuraminidases because thioglycosidic linkage is generally resistant to hydrolysis by glycosidases, such as neuramindases.[9] The substrates plug active sites of neuraminidases and prevent infection spread. In addition, we planned to use the glyco-clustering effect[10] since monomeric sialoside does not have inhibitory potency for neuraminidases. Glycoclusters generally express greater affinity between glycosides and sugar-recognition proteins than those of corresponding monomeric glycosides. Influenza HAs and NAs also have trimeric[11] and tetrameric[12] structures, respectively, in order to enhance sialic acid-recognition activity. Therefore, the thioglycosidic sialocluster is expected to be a promising multivalent-type therapeutic agent for influenza disease. In fact, we have designed and synthesized a linear polymer expressing pendant-type thiosialoside moieties that showed inhibitory activity against influenza virus NAs.[13]

Recently, we have synthesized various carbosilane dendrimers having bioactive carbohydrate moieties on the terminal ends[14] and investigated their biological activities.[15] For example, it was found that sialyllactose-modified dendrimers[16a] have potent binding activities for influenza HAs.[16b] As a part of our studies on glycodendrimers, we previously reported six types of carbosilane dendrimers having thioglycoside-type sialic acid moieties and their inhibitory activities against human influenza NAs.[17] In this paper, we describe a systematic synthesis of a series of sialodendrimers based on carbosilane scaffolds and the preliminary results of their inhibition assays for human influenza NAs.

2. Results and discussion

We designed a series of oligomeric thiosialosides using carbosilane dendrimers as core scaffolds, since the carbosilanes showed the ability to support carbohydrate moieties in our ongoing synthetic studies on glycoclusters. For investigation of the structure–activity relationship (SAR) for human influenza NAs, we selected a series of carbosilane dendrimers that consist of Fan(0)3, Ball(0)4, Dumbbell(1)6 and Ball(1)12, named by their shapes, generation number and number of terminal ends (Fig. 1). In addition, on each framework, novel ether-linkage dendrimers[17] as well as known normal aliphatic dendrimers[14] and amide-linkage dendrimers[18] were used for clustering of thiosialosides. Therefore, we thought that a library of thiosialoside clusters could be constructed and that the most appropriate structure for a neuraminidase inhibitor would be determined.

2.1. Synthesis of sialoside having thioglycosidic linkage

Synthesis of thioglycosidic sialoside for clustering on carbosilane dendrimers is shown in Scheme 1. Known β-sialyl-chloride **17**[19] was converted into α-anomeric thioacetate **18** according to Hasegawa's method,[20] which was S_N2-type reaction in the presence of potassium thioacetate in CH_2Cl_2. In this method, produced thioacetate **18** was contaminated with glycal product **19** (5−10%) formed by elimination reaction of chloride **17**.[21] Chromatographic purification or re-crystallization for separation of thioacetate **18** from glycal **19** was unsuccessful at this stage. Therefore, a mixture of **18** and **19** was treated with potassium carbonate in methanol to generate potassium thiolate, which reacted with 5-bromo-1-pentene. After re-acetylation as temporal protection for purification, pure pentenyl thiosialoside **20** was obtained in 84.2% yield. The sialoside **20** has slightly better mobility on TLC than that of glycal **19** and could be isolated from the afforded mixture by flash column chromatography on silica gel. The ^{1}H NMR spectrum of **20** indicated that the newly produced thioglycosidic linkage of sialic acid is α-configuration based on the empirical rule[22]: $J_{7,8}$ = 8.2 Hz,

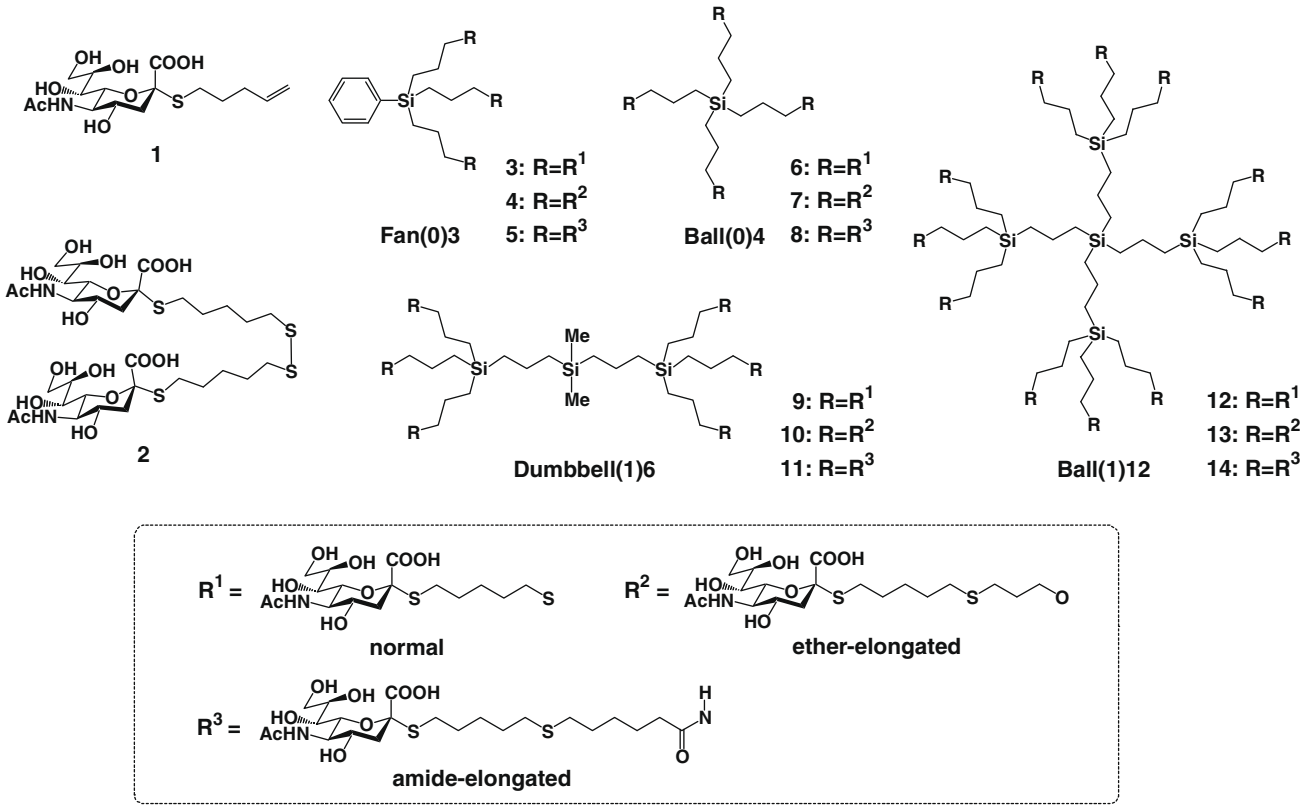
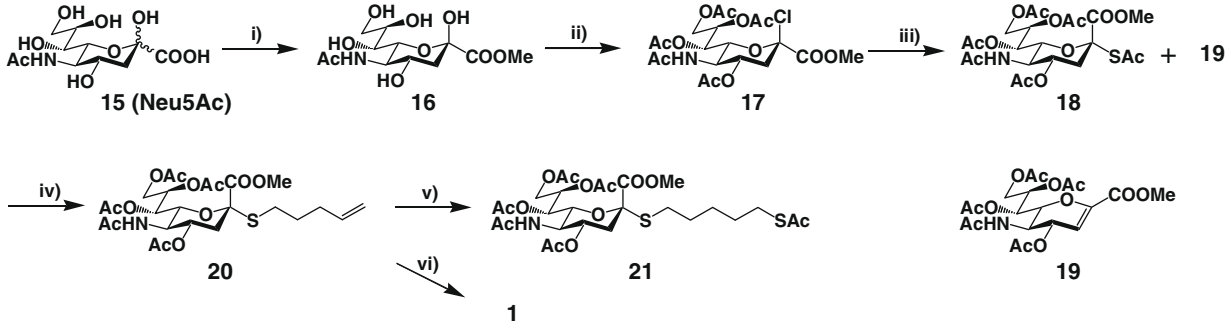


Figure 1. Synthetic substrate of thioglycoside-type sialic acid residue on terminal ends.



Scheme 1. Reagents and conditions: (i) MeOH, Dowex-50 (H^+), rt, overnight; (ii) AcCl, rt, 24 h; (iii) AcSK, CH_2Cl_2, rt, 24 h ; (iv) 5-bromo-1-pentene, K_2CO_3, MeOH, 0 °C→rt, 3 h, then Ac_2O, Pyr., rt, overnight; (v) AcSH, AIBN, 1,4-dioxane, 50 °C→80 °C, 3 h; (vi) NaOMe, MeOH, rt, 0.5 h, then 0.5 M aq NaOH, rt, overnight.

$\Delta\delta$ |H-9a–H9b| = 0.20 ppm. Finally, radical addition of thioacetic acid[16] into terminal olefin of pentenyl sialoside **20**, using AIBN as a radical initiator, gave corresponding primary thioacetate **21** in quantitative yield. Further transformation of **20** was performed by means of transesterification and subsequent saponification to afford water-soluble thiosialoside **1** in quantitative yield, which was used as a monomeric substrate for the biological assay.

2.2. Elongation of spacer-arm of carbosilane dendrimers by ether-linkage

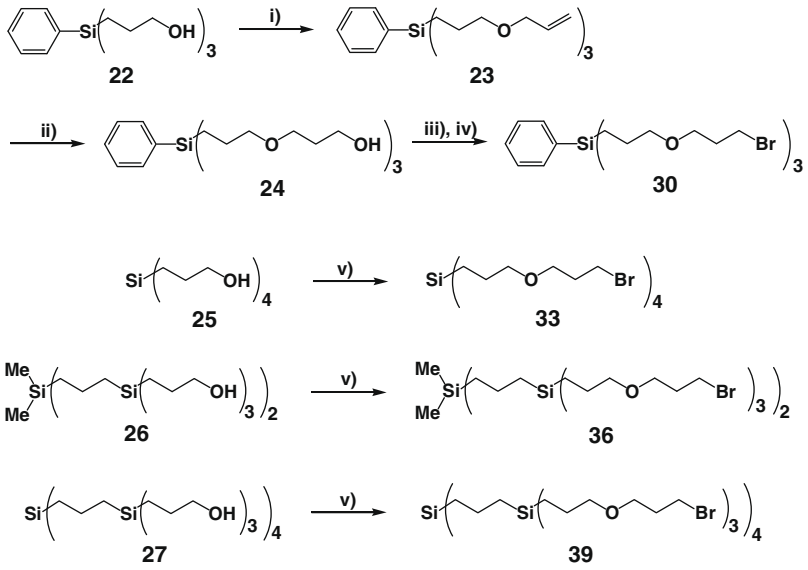
A synthetic scheme of ether-linked carbosilane dendrimers is shown in Scheme 2. Known triol **22**[14b] was reacted with allyl bromide in THF under sodium hydride-mediated Williamson's ether synthesis condition to afford allyl ether **23**. Sequential functionality conversion for preparation of carbosilane dendrimers having bromo atoms on the terminal ends was carried out. Thus, the terminal olefins were converted into a hydroxyl group by hydroboration using sterically-hindered dicyclohexylborane, which improved the terminal selectivity to afford ether-elongated triol **24** after oxidation under an alkali condition. Triol **24** was treated with methanesulfonyl chloride in pyridine to give mesylate, which underwent replacement reaction by sodium bromide in DMF to give corresponding tribrominated dendrimer **30**. The other three types of hydroxylated dendrimers **25**[18a], **26**[14c] and **27**[23] also underwent similar chemical conversion to give ether-elongated dendrimers **33**, **36**, and **39**, respectively.

2.3. Elongation of spacer-arm of carbosilane dendrimer by amide-linkage

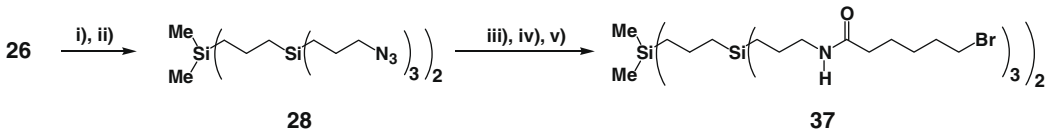
Amide-elongation was carried out by the method reported previously[18] (Scheme 3). Mesylate of Dumbbell(1)6 converted from known hexaol **26** was replaced by azide anion in DMF to give hexaazide **28** in good yield. Reduction of azide groups of **28** in Staudinger's condition followed by treatment with aqueous HCl solution quantitatively yielded a hexaamine hydrochloride salt, which was condensed with 6-bromohexanoyl chloride to afford the desired amide-elongated dendrimer **37**. Syntheses of twelve types of carbosilane dendrimers having differences in the number of bromo atoms on each terminal end, spacer lengths and linkage patterns, including normal aliphatic (**29**,[14b] **32**,[14c] **35**,[14c] **38**[14c]), ether- (**30**, **33**, **36**, **39**) and amide-linked (**31**,[18a] **34**,[18a] **37**, **40**[18b]) dendrimers, were efficiently accomplished and the structures of the carbosilanes are shown in Table 1.

2.4. Construction of carbosilane dendrimers having thiosialosides

Having prepared the thiosialoside and a series of carbosilane dendrimers, we carried out a reaction in which the sialoside was introduced into the dendrimers. The thioacetate **21** was condensed with known tribromodendrimer **29**[14b] under a deacetylation condition in the presence of sodium methoxide in DMF–methanol (Scheme 4). In this reaction, generated thiolates of the sialoside



Scheme 2. Reagents and conditions: (i) NaH, AllBr, THF, reflux temperature, 3 h; (ii) dicyclohexylborane, THF, rt, 3 h, then 3 M aq NaOH, 30% aq H_2O_2, 60 °C, 2 h; (iii) MsCl, Pyr., 0 °C, 3 h; (iv) NaBr, DMF, 60 °C, 3 h; (v) (i)–(iv).



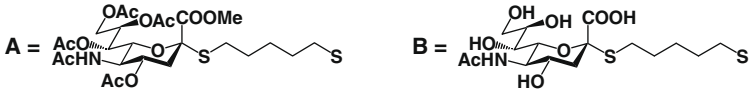
Scheme 3. Reagents and conditions: (i) MsCl, Pyr., 0 °C, 3 h; (ii) NaN_3, DMF, 60 °C, 3 h; (iii) PPh_3, H_2O, THF, rt, overnight, then 1 N HCl aq; (v) Et_3N, 6-bromohexanoyl chloride, MeOH, −20 °C, 1.5 h.

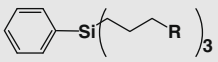
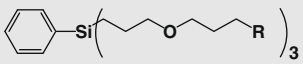
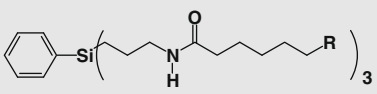
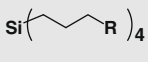
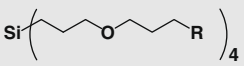
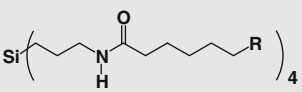
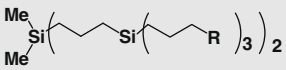
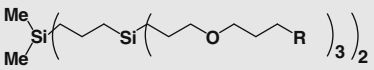
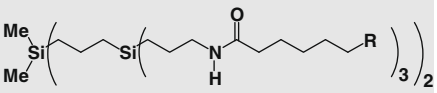
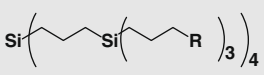
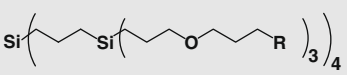
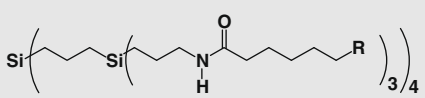
substituted bromine atoms on terminal ends of dendrimers to give fully protected three-functional sialodendrimer **41** in 80.2% yield after re-protection. At the same time, fully protected dimeric byproduct **53** having disulfide linkage was also obtained. In the ^{1}H NMR spectrum of **41**, the integral ratio due to corresponding protons elucidated that one dendrimer core scaffold had three sialoside moieties; $SiCH_2/CH_2SCH_2/Ph/H$-4(Neu) = 6:12:5:3. In addition to the NMR spectrum, a high-resolution ESI-MS spectrum of **41** proved construction of this compound; calcd for $[M+H]^+$: 2056.71535; found *m/z*: 2056.72008. In the final step, removal of all protections of sialodendrimer **41** was carried out by a combination of transesterification and subsequent saponification to give water-soluble sialodendrimer **3** in 87.2% yield after size exclusion chromatography using a Sephadex G-25 column followed by lyophilization. Production of **3** was supported by the results of the high-resolution ESI-MS spectroscopy; calcd for $[M+H]^+$: 1510.54162; found *m/z*: 1510.53494. Each of the other eleven types of sialodendrimers **4**–**14** was efficiently synthesized by similar condensation reaction and subsequent de-protection, and details are shown in Section 4. A library of thiosialodedrimers having twelve different types of core scaffolds was successfully constructed. Furthermore, removal of the protective groups in **53** was carried out by a method similar to that described for the sialodendrimer to afford water-soluble dimeric sialoside **2** in high yield (Scheme 4), which was also used as a comparative substrate for biological assays.

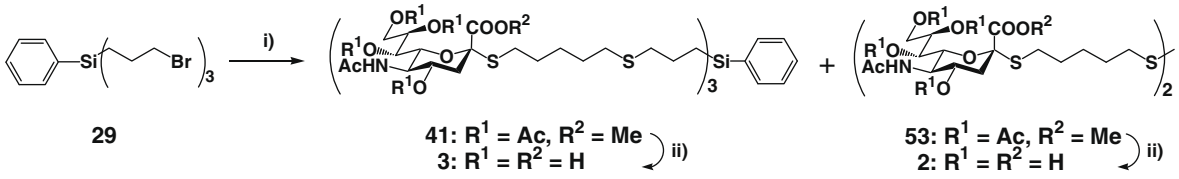
2.5. Inhibitory sialidase activity assay

Since a series of thiosialoside clusters **3**–**14** as well as thioglycosidic monomer **1** and dimer **2** had been prepared, biological evaluation of the thiosialosides for inhibitory activity against

Table 1
Brominated carbosilane dendrimers **29**–**40** and corresponding sialodendrimers (protected **41**–**52** and free **3**–**14**)



	Normal	Ether-elongated	Amide-elongated
Fan(0)3			
	29: R = Br **41**: R = A **3**: R = B	**30**: R = Br **42**: R = A **4**: R = B	**31**: R = Br **43**: R = A **5**: R = B
Ball(0)4			
	32: R = Br **44**: R = A **6**: R = B	**33**: R = Br **45**: R = A **7**: R = B	**34**: R = Br **46**: R = A **8**: R = B
Dumbbell(1)6			
	35: R = Br **47**: R = A **9**: R = B	**36**: R = Br **48**: R = A **10**: R = B	**37**: R = Br **49**: R = A **11**: R = B
Ball(1)12			
	38: R = Br, **50**: R = A, **12**: R = B	**39**: R = Br **51**: R = A **13**: R = B	**40**: R = Br **52**: R = A **14**: R = B



Scheme 4. Reagents and conditions: (i) **20**, MeONa, MeOH, DMF, rt, overnight, then Ac_2O, Pyr., rt, overnight; then CH_2N_2 in Et_2O, MeOH, 0 °C; (ii) MeONa, MeOH, rt, 3 h, then 0.5 M aq NaOH, rt, overnight.

neuraminidases of two subtypes of human influenza virus (H1N1 and H3N2) was performed The IC_{50} values measured by a previously reported method[24] are summarized in Table 2. Interestingly, all of the ether- and amide-elongated sialodendrimers and Ball(1)12-*S*-Neu5Ac$_{12}$ (**12)** showed inhibitory potencies not only for H3N2-type sialidase but also for H1N1-type sialidase in the mM range, although monomeric sialoside **1** and dimeric sialoside **2** as well as normal aliphatic-type dendrimers **3**, **6**, **9** did not show any inhibitory activities. The most potent inhibitory activities were observed when Dumbbell(1)6-ether-*S*-Neu5Ac$_6$ (**10**) for H3N2-type sialidase and Fan(0)3-amide-*S*-Neu$_3$ (**5**) as well as Dumbbell(1)6-amide-*S*-Neu$_6$ (**11**) for H1N1-type sialidase were used as substrates. Among the normal aliphatic-type dendrimers (**3**, **6**, **9**, **12**), only Ball(1)12-type dendrimer **12** showed inhibitory activity, indicating the glycocluster effect was effectively functioned with enhancing the binding affinity. However, among ether- and amide-elongated dendrimers, Ball(1)12-ether-Neu5Ac$_{12}$ (**13**) and Ball(1)12-amide-Neu5Ac$_{12}$ (**14**) interestingly showed the weakest inhibition potencies, respectively, indicating that the cluster effect functioned toward adverse direction. According to these results, elongation of the dendrimer may have a more favorable influence than increase in the number of sialic acid moieties for inhibitory activities against sialidases. Therefore, it is thought that the distance between the sialic acid moieties as well as the degree of freedom of the sialic acid moieties are important for effective binding to active sites on the tetrameric sialidases on virus surfaces.

Table 2
Preliminary results of inhibition assays of a series of glycodendrimers against human influenza virus sialidases

Compound	Inhibitory potency (mM)[a]	
	A/Memphis/1/71 (H3N2)	A/PR/8/34 (H1N1)
S-Neu5Ac (**1**)	N.D.[b]	N.D.[b]
S-Neu5Ac$_2$ (**2**)	N.D.[b]	N.D.[b]
Fan(0)3-*S*-Neu5Ac$_3$ (**3**)	N.D.[b]	N.D.[b]
Fan(0)3-ether-*S*-Neu5Ac$_3$ (**4**)	5.00	5.00
Fan(0)3-amide-*S*-Neu5Ac$_3$ (**5**)	7.1	2.7
Ball(0)4-*S*-Neu5Ac$_4$ (**6**)	N.D.[b]	N.D.[b]
Ball(0)4-ether-*S*-Neu5Ac$_4$ (**7**)	5.00	5.00
Ball(0)4-amide-*S*-Neu5Ac$_4$ (**8**)	8.8	4.8
Dumbbell(1)6-*S*-Neu5Ac$_6$ (**9**)	N.D.	N.D.
Dumbbell(1)6-ether-*S*-Neu5Ac$_6$ (**10**)	1.25	5.00
Dumbbell(1)6-amide-*S*-Neu5Ac$_6$ (**11**)	8.1	2.8
Ball(1)12-*S*-Neu5Ac$_{12}$ (**12**)	7.0	5.0
Ball(1)12-ether-*S*-Neu5Ac$_{12}$ (**13**)	6.5	6.4
Ball(1)12-amide-*S*-Neu5Ac$_{12}$ (**14**)	10.0<	7.2

[a] IC_{50} value are indicated in millimolar concentration (mM) based on a monomeric sugar unit concentration.
[b] N.D. means not determined due to weak inhibition.

3. Conclusion

Systematic construction of a library of a series of carbosilane dendrimers carrying thioglycosidic sialic acid moieties has been efficiently accomplished. These glycodendrimers were synthesized on the basis of introduction of thiosialoside functionalized on the aglycon terminal end with a thioacetyl group into twelve types of brominated carbosilane dendrimers having difference in the dendrimer frame and linkage pattern. Biological evaluation of these sialodendrimers against human influenza virus sialidases was carried out, and the results showed that all of the ether- and amide-elongated dendrimers have inhibitory activity against the sialidase. Dumbbell(1)6-ether-*S*-Neu$_6$ (**10**) for H3N2-type sialidase and Fan(0)3-amide-*S*-Neu$_3$ (**5**) as well as Dumbbell(1)6-amide-*S*-Neu$_6$ (**11**) for H1N1-type sialidase showed the most potent inhibition.

Further investigation of different types of thioglycosidic sialosides and the clustering of the sialosides using dendric core scaffolds is now in progress. Details of the syntheses and their biological evaluation will be reported elsewhere.

4. Experimental

4.1. General methods

All reactions were carried out in dried solvents under an argon atmosphere. Unless otherwise stated, all commercial solvents and reagents were used without further purification. Pyridine (Pyr.) and dimethylformamide (DMF) were stored over molecular sieves (4 Å MS), and methanol (MeOH) was stored over 3 Å MS prior to use. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl under argon atmosphere and distilled prior to use. 2′-(4-Methylumbelliferyl)-α-D-*N*-acetylneuraminic acid (4-MU-Neu5Ac) was purchased from Sigma. Reactions were monitored by TLC using Merck silica gel plates 60 F_{254} (0.25 mm in layer thickness). Detection was carried out by UV light when applicable and treatment with a solution of 85:10:5 (v/v/v) MeOH/*p*-anisaldehyde/concd sulfuric acid followed by charring or exposure to an iodide atmosphere for visualization. Purification by 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). The ratio between silica gel and crude product is 20–50:1 (w/w). IR spectra were recorded on a Shimadzu IR-Prestige 21 using KBr pellet (for solid) or as neat sample (for liquid). ^1H and ^{13}C NMR spectra were recorded using a Bruker AM 400 and a Buruker DRX 400 (at 400 MHz for ^1H and 100 MHz for ^{13}C) or a Varian Gemini 2000 (at 200 MHz for ^1H and 50 MHz for ^{13}C) in $CDCl_3$ or D_2O. Chemical shifts are expressed as parts per million (ppm, δ) and are relative to an internal tetrametylsilane (TMS) in $CDCl_3$ (δ 0.0) or HDO in D_2O (δ 4.78) for ^1H, and $CDCl_3$ (δ 77.0), MeOD (δ 49.0) or acetone (δ 215.0) for ^{13}C. FAB, ESI and MALDI-TOF mass spectra were obtained with a JEOL JMS-700AM spectrometer, a JEOL JMS-HX110A and a Buruker Autoflex spectrometer, respectively. Elemental analyses were performed with a Fisons EA1108 on samples extensively dried in vacuo at 40–50 °C over phosphorus pentoxide for 4–5 h.

4.1.1. Methyl (*n*-pentenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)-onate (20)

To a solution of anomeric thioacetate **18** (2.26 g, 4.11 mmol) and 5-bromo-1-pentene (974 μL, 8.22 mmol) in MeOH (22 mL) was added potassium carbonate (568 mg, 4.11 mmol) at 0 °C, and the mixture was stirred for 3 h at room temperature. After quenching of the reaction with acetic acid (50 μL), the reaction mixture was concentrated. The residue was treated with acetic anhydride (20 mL) in pyridine (20 mL) at room temperature overnight. After concentration (co-evaporation with toluene), the residual mixture was extracted with $CHCl_3$. The extraction solution was washed with 1 M aq H_2SO_4, satd aq $NaHCO_3$ and brine, dried over anhyd $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography [2:3 (v/v) toluene/EtOAc] to give *n*-pentenyl thiosialoside **20** (1.99 g, 84.2%) as a white foam: R_f 0.52 [5:4:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{27}$ +29.2 (*c* 1.13, $CHCl_3$); IR (KBr): 2940 (ν_{C-H}), 1742 ($\nu_{C=O}$), 1663 ($\nu_{C=O}$, amide I), 1549 (δ_{N-H}, amide II), 1227 (ν_{C-O}), 1038 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (m, 1H, C*H*=CH_2), 5.37 (ddd, 1H, $J_{7,8}$ = 8.2 Hz, $J_{8,9a}$ = 2.4 Hz, $J_{8,9b}$ = 4.9 Hz, H-8), 5.33 (dd, 1H, $J_{6,7}$ = 2.0 Hz, H-7), 5.24 (d, 1H, $J_{5,NH}$ = 10.4 Hz, NH), 5.03, 4.97 (2 × dd, 2H, J_{trans} = 17.1 Hz, J_{cis} = 10.2 Hz, J_{gem} = 1.7 Hz, CH=CH_2), 4.86 (ddd, 1H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.6 Hz, H-4), 4.32 (dd, 1H, $J_{9a,9b}$ = 12.4 Hz, H-9a), 4.12 (dd, 1H, H-9b), 4.05 (q, 1H, $J_{5,6}$ = 10.4 Hz, H-5), 3.84 (dd, 1H, H-6), 3.80 (s, 3H, OMe), 2.79–2.72 (m, 1H, SCH[a]), 2.72 (dd, 1H, $J_{3ax,3eq}$ = 12.3 Hz, H-3*eq*), 2.60–2.53 (m, 1H, SCH[b]), 2.21–2.08 (m, 2H, $SCH_2CH_2CH_2$), 2.16, 2.14, 2.04, 2.03 (4 × s, 12H, OAc), 1.99 (t, 1H, H-3*ax*), 1.88 (s, 3H, NAc), 1.71–1.53 (m, 2H, SCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.86, 170.54, 170.11, 170.08, 169.98, 168.59, 137.59, 111.14, 83.23, 74.20, 69.69, 68.90, 67.48, 62.19, 52.83, 49.50, 38.16, 32.65, 28.56, 28.34, 23.14, 21.08, 20.78, 20.69; MS (FAB): calcd for $[M+H]^+$: 576.2, found: *m*/*z* 576.0; calcd for $[M+Na]^+$: 598.2, found: *m*/*z* 597.9.

Anal. Calcd for $C_{25}H_{37}NO_{12}S$: C, 52.16; H, 6.48; N, 2.43. Found: C, 52.02; H, 6.48; N, 2.38.

4.1.2. Methyl (5-acetylthiopentyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (21)

AIBN (996 mg, 6.08 mmol) was added to a stirred solution of *n*-pentenyl sialoside **20** (1.75 g, 3.04 mmol) and thioacetic acid (7.4 mL, 103.53 mmol) in 1,4-dioxane (7.4 mL) at 50 °C. The mixture was stirred for 2 h at 80 °C. After addition of cyclohexene (20.9 mL, 206.32 mmol) at 0 °C, the mixture was stirred at room temperature for a few minutes and concentrated. The resulting mixture was purified by silica gel column chromatography [1:0 to 0:1 (v/v) toluene/EtOAc] to afford thioacetate **21** (1.98 g, quantitative) as a white foam: R_f 0.57 [5:4:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{28}$ +25.4 (*c* 1.11, $CHCl_3$); IR (KBr): 2938 (ν_{C-H}), 1744 ($\nu_{C=O}$), 1663 ($\nu_{C=O}$, amide I), 1541 (δ_{N-H}, amide II), 1227 (ν_{C-O}, ester), 1036 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.36 (ddd, 1H, $J_{7,8}$ = 8.6 Hz, $J_{8,9a}$ = 2.1 Hz, $J_{8,9b}$ = 4.3 Hz, H-8), 5.33 (dd, 1H, $J_{6,7}$ = 1.6 Hz, H-7), 5.26 (d, 1H, $J_{5,NH}$ = 10.7 Hz, NH), 4.86 (ddd, 1H, $J_{4,5}$ = 10.7 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.6 Hz, H-4), 4.31 (dd, 1H, $J_{9a,9b}$ = 12.9 Hz, H-9a), 4.11 (dd, 1H, H-9b), 4.05 (q, 1H, $J_{5,6}$ = 10.7 Hz, H-5), 3.83 (dd, 1H, H-6), 3.80 (s, 3H, OMe), 2.86 (t, 2H, *J* = 7.2 Hz, CH_2SAc), 2.77–2.69 (m, 1H, SCH[a]), 2.71 (dd, 1H, $J_{3ax,3eq}$ = 12.6 Hz, H-3*eq*), 2.57–2.50 (m, 1H, SCH[b]), 2.32 (s, 3H, SAc), 2.16, 2.14, 2.04, 2.03 (4 × s, 12H, OAc), 1.98 (t, 1H, H-3*ax*), 1.88 (s, 3H, NAc), 1.61–1.40 (m, 6H, $SCH_2CH_2CH_2CH_2CH_2SAc$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.66, 170.80, 170.48, 170.07, 170.04, 169.92, 168.54, 83.17, 74.16, 69.69, 68.82, 67.45, 62.21, 52.79, 49.44, 38.11, 30.50, 28.97, 28.85, 28.75, 28.63, 27.83, 23.08, 21.04, 20.73, 20.65.; MS (FAB): calcd for $[M+H]^+$: 651.2, found: *m*/*z* 652.0.

Anal. Calcd for $C_{27}H_{41}O_{13}NS_2$: C, 49.76; H, 6.34; N, 2.15. Found: C, 49.83; H, 6.33; N, 2.17.

4.1.3. *n*-Pentenyl 5-acetamido-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranoside sodium salt (1)

Fully protected *n*-pentenyl *S*-sialoside **20** (300 mg, 0.521 mmol) was dissolved in 1 M NaOMe in MeOH (1 mL), and the solution was stirred for 0.5 h at room temperature. Then 0.5 M aq solution of NaOH was added and the reaction mixture was stirred overnight at room temperature. The solution was treated with IR-120B (H^+) resin and adjusted to pH ~4, and then the suspension was filtered. The resin was washed with water, and the filtrate and washings were combined and concentrated. The resulting mixture was purified by size exclusion column chromatography on Sephadex G-15 with 5% aq AcOH as an eluent to give de-protected *n*-pentenyl *S*-sialoside **1** (199 mg, quantitative) as a white powder after lyophilization: R_f 0.47 [8:6:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{25}$ +21.3 (*c* 1.07, H_2O); IR (KBr): 3399 (ν_{O-H}), 2930 (ν_{C-H}), 1707 ($\nu_{C=O}$), 1638 ($\nu_{C=O}$, amide I), 1560 (δ_{N-H}, amide II), 1279 (ν_{C-O}), 1034 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 5.87 (m, 1H, C*H*=CH_2), 5.09, 5.03 (dd and d, 1H, J_{trans} = 17.3 Hz, J_{cis} = 10.2 Hz, J_{gem} = 1.6 Hz, CH=CH_2), 3.87–3.58 (m, 7H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 2.81 (dd, 1H, $J_{3eq,4}$ = 4.8 Hz, $J_{3ax,3eq}$ = 12.8 Hz, H-3*eq*), 2.83–2.73 (m, 1H, SCH[a]), 2.68–2.61 (m, 1H, SCH[b]), 2.21–2.09 (m, 2H, CH_2CH=CH_2), 2.04 (s, 3H, NAc), 1.78 (t, $J_{3ax,4}$ = 11.7 Hz, H-3*ax*), 1.74–1.63 (m, 2H, $SCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, D_2O): δ 174.68, 173.18, 138.08, 114.71, 84.95, 74.47, 71.30, 67.86, 67.72, 62.19, 51.33, 40.38, 31.80, 28.48, 27.94, 21.64; MS (MALDI-TOF): calcd for $[M+Na]^+$: 438.117, found: *m*/*z* 437.996; Calcd for $[M+K]^+$: 454.091, found: *m*/*z* 453.980.

Anal. Calcd for $C_{16}H_{26}NO_8SNa{\cdot}1.0H_2O$: C, 44.34; H, 6.51; N, 3.23. Found: C, 44.53; H, 6.62; N, 3.19.

4.1.4. Tris(4-oxa-6-heptenyl)phenylsilane (23, Fan(0)3-ether-All)

Fifty five percent of NaH dispersion in mineral oil (1.07 g, 24.52 mol) was washed with *n*-hexane and suspended in THF (10 mL). A solution of triol **22** (1.15 g, 4.07 mmol) in THF (15 mL) was dropwise added to the suspension at 0 °C, followed by addition of 3-bromopropene (2.11 mL, 24.38 mmol), and the mixture was stirred for 3 h at reflux temperature (ca. 70 °C). The reaction was quenched by dropwise addition of MeOH (~5 mL) at 0 °C. The concentrated mixture was dissolved in water and twice extracted with Et_2O. The combined extract was washed with brine, dried over anhyd $MgSO_4$, filtered, and concentrated. The syrupy residue was chromatographed on silica gel [15:1 (v/v) *n*-hexane–EtOAc] to afford allyl ether **23** (1.44 g, 87.9%) as a colorless liquid: R_f 0.49 [5:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2930 (ν_{C-H}), 2853 (ν_{C-H}), 1107 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.52–7.29 (m, 5H, SiPh), 5.99–5.80 (m, 3H, C*H*=CH_2), 5.30–5.11 (m, 6H, CH=CH_2), 3.95–3.90 (m, 6H, CH_2CH=CH_2), 3.37 (t, 6H, *J* = 6.9 Hz, $SiCH_2CH_2CH_2O$), 1.69–1.54 (m, 6H, $SiCH_2CH_2CH_2O$), 0.87–0.79 (m, 6H, $SiCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.58, 134.94, 133.97, 128.87, 127.69, 116.56, 73.06, 71.63, 23.90, 8.21; MS (FAB): calcd for $[M+Na]^+$: 425.2, found: *m*/*z* 425.1.

Anal. Calcd for $C_{25}H_{37}NO_{12}S$: C, 71.59; H, 9.51. Found: C, 71.64; H, 9.70.

4.1.5. Tris(7-hydroxy-4-oxaheptyl)phenylsilane (24, Fan(0)3-ether-OH)

To a 1 M solution of BH_3–THF complex in THF (2.24 mL) was added cyclohexene (453 μL, 4.47 mmol) at 0 °C, and the mixture was stirred for 2.5 h at 0 °C. A solution of allyl ether **23** (150 mg, 0.373 mmol) in THF (5 mL) was dropwise added at 0 °C, and the

reaction mixture was stirred for 3 h at room temperature. To the mixture were dropwise added MeOH (0.2 mL), 3 M aq NaOH solution (2 mL) and 30% aq H_2O_2 (1 mL) at 0 °C, successively, and then the heterogeneous mixture was stirred at 60 °C for 2 h. The organic layer was separated from the reaction mixture, and the aq layer was twice extracted with EtOAc. The organic layer and extract were combined, washed with brine, dried over anhyd $MgSO_4$, filtered, and concentrated. The residual syrup was purified by flash column chromatography on silica gel [50:1 (v/v) $CHCl_3$–MeOH] to afford triol **24** (143 mg, 84.1%) as a light yellow syrup: R_f 0.33 [10:1 (v/v) $CHCl_3$–MeOH]; IR (neat): 3395 (ν_{O-H}), 2930 (ν_{C-H}), 2866 (ν_{C-H}), 1111 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49–7.29 (m, 5H, SiPh), 3.74 (t, 6H, J = 5.6 Hz, CH_2OH), 3.56 (t, 6H, J = 5.8 Hz, OCH_2CH$_2$CH$_2$OH), 3.38 (t, 6H, J = 6.7 Hz, SiCH$_2$CH$_2$-CH_2O), 3.00 (br s, 3H, OH), 1.80 (quint, 6H, J = 5.7 Hz, OCH$_2$CH_2-CH$_2$OH), 1.66–1.51 (m, 6H, SiCH$_2$CH_2CH$_2$O), 0.86–0.77 (m, 6H, SiCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.32, 133.86, 128.97, 127.76, 73.76, 69.63, 61.54, 31.90, 23.77, 8.06; MS (FAB): calcd for $[M+H]^+$: 457.3, found: m/z 457.1; Calcd for $[M+Na]^+$: 479.3, found: m/z 479.0.

Anal. Calcd for $C_{24}H_{44}O_6Si{\cdot}0.5H_2O$: C, 61.90; H, 9.74. Found: C, 61.85; H, 10.03.

4.1.6. Tris(7-methylsulfonyloxy-4-oxaheptyl)phenylsilane (Fan(0)3-ether-OMs)

To a solution of triol **24** (67 mg, 0.147 mmol) in pyridine (0.7 mL) was added methanesulfonyl chloride (68 μL, 0.879 mmol) at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. The resulting mixture was diluted in $CHCl_3$, successively washed twice with 5% aq H_2SO_4, satd aq $NaHCO_3$ and brine, dried over anhyd $MgSO_4$, filtered, and concentrated to afford mesylate (107 mg, quantitative) as a yellow syrup. This compound was used for the next step without further purification.: R_f 0.66 [10:1 (v/v) $CHCl_3$–MeOH]; IR (neat): 2934 (ν_{C-H}), 2866 (ν_{C-H}), 1354 ($\nu_{O=S=O}$), 1175 ($\nu_{O=S=O}$), 1113 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.50–7.28 (m, 5H, SiPh), 4.32 (t, 6H, J = 6.3 Hz, CH_2OMs), 3.49 (t, 6H, J = 6.0 Hz, OCH_2CH$_2$CH$_2$OMs), 3.37 (t, 6H, J = 6.8 Hz, SiCH$_2$CH$_2$-CH_2O), 2.99 (s, 9H, OMs), 1.98 (quint, 6H, J = 6.1 Hz, OCH$_2$CH_2-CH$_2$OMs), 1.65–1.50 (m, 6H, SiCH$_2$CH_2CH$_2$O), 0.85–0.77 (m, 6H, SiCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.41, 133.90, 129.00, 127.75, 73.70, 67.39, 65.83, 37.06, 29.41, 23.83, 8.14.

4.1.7. Tris(7-bromo-4-oxaheptyl)phenylsilane (30, Fan(0)3-ether-Br)

NaBr (227 mg, 2.205 mmol) was added to a solution of mesylate (107 mg, 0.147 mmol) in DMF (1 mL), and the mixture was stirred for 3 h at 60 °C. The resulting mixture was diluted in $CHCl_3$, successively washed with water and brine, dried over anhyd $MgSO_4$, filtered, and concentrated. The syrupy residue was purified by flash column chromatography on silica gel [20:1 (v/v) *n*-hexane–EtOAc] to give bromide **30** (74 mg, 77.9%) as a colorless syrup: R_f 0.39 [5:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2930 (ν_{C-H}), 2862 (ν_{C-H}), 1110 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.51–7.33 (m, 5H, SiPh), 3.50 (t, 12H, J = 6.4 Hz, OCH_2CH$_2$CH_2Br), 3.37 (t, J = 6.8 Hz, 6H, SiCH$_2$CH$_2$CH_2O), 2.07 (quint, 6H, J = 6.1 Hz, OCH$_2$CH_2CH$_2$Br), 1.66–1.51 (m, 6H, SiCH$_2$CH_2), 0.86–0.77 (m, 6H, SiCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.54, 133.97, 128.97, 127.77, 73.75, 67.93, 32.84, 30.74, 23.85, 8.16; MS (FAB): calcd for $[M+H]^+$: 643.1, found: m/z 642.7.

Anal. Calcd for $C_{24}H_{41}O_3SiBr_3$: C, 44.67; H, 6.40. Found: C, 44.90; H, 6.45.

4.1.8. Tetrakis(4-oxa-6-heptenyl)silane (Ball(0)4-ether-All)

Ball(0)4-OH **25** (200 mg, 0.756 mmol) was subjected to allylation in the same manner as that described for **23** to give Ball(0)4-ether-All (263 mg, 81.9%) as a colorless liquid: R_f 0.46 [5:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2928 (ν_{C-H}), 2851 (ν_{C-H}), 1103 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.01–5.82 (m, 4H, CH=CH$_2$), 5.32–5.13 (m, 8H, CH=CH_2), 3.97–3.93 (m, 8H, CH_2CH=CH$_2$), 3.36 (t, 8H, J = 7.0 Hz, SiCH$_2$CH$_2$CH_2O), 1.66–1.50 (m, 8H, SiCH$_2$CH_2CH$_2$O), 0.58–0.50 (m, 8H, SiCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.94, 116.67, 73.29, 71.71, 23.99, 8.07; MS (FAB): calcd for $C_{24}H_{45}O_4Si$ $[M+H]^+$: 425.3, found: m/z 425.1.

Anal. Calcd for $C_{24}H_{44}O_4Si$: C, 67.88; H, 10.44. Found: C, 68.02; H, 10.73.

4.1.9. Tetrakis(7-hydroxy-4-oxaheptenyl)silane (Ball(0)4-ether-OH)

Ball(0)4-ether-All (250 mg, 0.756 mmol) was subjected to hydroxylation in the same manner as that described for **24** to give Ball(0)4-ether-OH (256 mg, 87.7%) as a white solid: R_f 0.71 [5:1 (v/v) $CHCl_3$–MeOH]; IR (KBr): 3339 (ν_{O-H}), 2926 (ν_{C-H}), 2872 (ν_{C-H}), 1111 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.75 (t, 8H, J = 5.6 Hz, CH_2OH), 3.60 (t, 8H, J = 5.8 Hz, OCH_2CH$_2$CH$_2$OH), 3.38 (t, 8H, J = 6.7 Hz, SiCH$_2$CH$_2$CH_2O), 3.01 ((br s, 4H, OH), 1.82 (quint, 8H, J = 5.7 Hz, OCH$_2$CH_2CH$_2$OH), 1.63–1.48 (m, 8H, SiCH$_2$CH_2-CH$_2$O), 0.58–0.49 (m, 8H, SiCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 73.93, 69.64, 61.55, 31.96, 23.88, 8.02; MS (FAB): calcd for $[M+H]^+$: 497.4, found: m/z 497.1; Calcd for $[M+Na]^+$: 519.3, found: m/z 519.1.

Anal. Calcd for $C_{24}H_{52}O_8Si$: C, 58.03; H, 10.55. Found: C, 58.16; H, 10.78.

4.1.10. Tetrakis(7-methylsulfonyloxy-4-oxaheptyl)silane (Ball(0)4-ether-OMs)

Ball(0)4-ether-OH (74 mg, 0.149 mmol) was subjected to mesylation in the same manner as that described for mesylate of **24** to give Ball(0)4-ether-OMs (121 mg, quantitative) as a yellow syrup: R_f 0.63 [10:1 (v/v) $CHCl_3$–MeOH]; IR (neat): 2932 (ν_{C-H}), 2866 (ν_{C-H}), 1350 ($\nu_{O=S=O}$), 1175 ($\nu_{O=S=O}$), 1115 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.34 (t, 8H, J = 6.3 Hz, CH_2OMs), 3.52 (t, 8H, J = 6.0 Hz, OCH_2CH$_2$CH$_2$OMs), 3.36 (t, 8H, J = 6.8 Hz, SiCH$_2$CH$_2$-CH_2O), 3.02 (s, 12H, OMs), 2.00 (quint, 8H, J = 6.1 Hz, OCH$_2$CH_2-CH$_2$OMs), 1.62–1.47 (m, 8H, SiCH$_2$CH_2CH$_2$O), 0.57–0.49 (m, 8H, SiCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 73.90, 67.39, 65.86, 37.09, 29.42, 23.88, 8.02.

4.1.11. Tetrakis(7-bromo-4-oxaheptyl)silane (33, Ball(0)4-ether-Br)

Ball(0)4-ether-OMs (121 mg, 0.149 mmol) was subjected to bromination in the same manner as that described for **30** to give Ball(0)4-ether-Br **33** (84 mg, 75.7%) as a colorless syrup: R_f 0.39 [4:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2930 (ν_{C-H}), 2860 (ν_{C-H}), 1113 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.53 (t, 8H, J = 5.9 Hz, OCH_2CH$_2$CH$_2$Br), 3.51 (t, 8H, J = 6.5 Hz, CH$_2$Br), 3.37 (t, 8H, J = 6.9 Hz, SiCH$_2$CH$_2$CH_2O), 2.09 (quint, 8H, J = 6.2 Hz, OCH$_2$CH_2CH$_2$Br), 1.64–1.48 (m, 8H, SiCH$_2$CH_2CH$_2$O), 0.58–0.50 (m, 8H, SiCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 73.94, 67.95, 32.83, 30.74, 23.91, 8.04; MS (FAB): calcd for $[M+H]^+$ 749, found: m/z 748.5.

Anal. Calcd for $C_{24}H_{48}O_4SiBr_4$: C, 38.52; H, 6.47. Found: C, 38.90; H, 6.50.

4.1.12. Bis[tris(4-oxa-6-heptenyl)silylpropyl]dimethylsilane (Dumbbell(1)6-ether-All)

Dumbbell(1)6-OH **26** (1.46 g, 2.60 mmol) was subjected to allylation in the same manner as that described for **23** to afford Dumbbell(1)6-ether-All (1.87 g, 89.3%) as a colorless liquid: R_f 0.41 [5:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2913 (ν_{C-H}), 2866 (ν_{C-H}), 1103 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.02–5.82 (m, 6H, CH=CH$_2$), 5.32–5.13 (m, 12H, CH=CH_2), 3.98–3.94 (m, 12H, CH_2CH=CH$_2$), 3.37 (t, 12H, J = 7.1 Hz, SiCH$_2$CH$_2$CH_2O), 1.65–1.50

(m, 12H, $SiCH_2CH_2CH_2O$), 1.38–1.22 (m, 4H, $SiCH_2CH_2CH_2Si$), 0.63–0.48 (m, 20H, $SiCH_2$), −0.07 (s, 6H, $SiCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.35, 116.61, 73.34, 71.66, 24.02, 20.29, 18.24, 16.99, 8.14, −3.30; MS (FAB): calcd for $[M+H]^+$: 793.1, found: *m/z* 793.1.

Anal. Calcd for $C_{44}H_{84}O_6Si_3$: C, 66.61; H, 10.67. Found: C, 66.44; H, 10.95.

4.1.13. Bis[tris(7-hydroxy-4-oxaheptyl)silylpropyl]dimethylsilane (Dumbbell(1)6-ether-OH)

Dumbbell(1)6-ether-All (200 mg, 0.271 mmol) was subjected to hydroxylation in the same manner as that described for **24** to give Dumbbell(1)6-ether-OH (185 mg, 80.8%) as a yellow syrup: R_f 0.58 [5:1 (v/v) $CHCl_3$–MeOH]; IR (neat): 3381 (ν_{O-H}), 2926 (ν_{C-H}), 2868 (ν_{C-H}), 1115 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.74 (t, *J* = 5.8 Hz, 12H, CH_2OH), 3.59 (t, 12H, *J* = 5.9 Hz, $OCH_2CH_2CH_2OH$), 3.38 (t, 12H, *J* = 6.8 Hz, $SiCH_2CH_2CH_2O$), 3.07 ((br s, 6H, OH), 1.82 (quint, 12H, *J* = 5.8 Hz, $OCH_2CH_2CH_2OH$), 1.63–1.47 (m, 12H, $SiCH_2CH_2CH_2O$), 1.38–1.22 (m, 4H, $SiCH_2CH_2CH_2Si$), 0.63–0.47 (m, 20H, $SiCH_2$), −0.06 (s, 6H, $SiCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 74.00, 69.43, 61.30, 31.94, 23.87, 20.16, 18.20, 16.85, 8.02, −3.32; MS (FAB): calcd for $[M+H]^+$: 901.6, found: 901.3; calcd for $[M+Na]^+$: 923.6, found: *m/z* 923.3.

Anal. Calcd for $C_{44}H_{96}O_{12}Si_3 \cdot 1.5H_2O$: C, 56.92; H, 10.75. Found: C, 57.02; H, 10.95.

4.1.14. Bis[tris(7-methylsulfonyloxy-4-oxaheptyl)silylpropyl]-dimethylsilane (Dumbbell(1)6-ether-OMs)

Dumbbell(1)6-ether-OH (224 mg, 0.265 mmol) was subjected to mesylation in the same manner as that described for mesylate of **24** to give Dumbbell(1)6-ether-OMs (363 mg, quantitative) as a yellow syrup: R_f 0.63 [10:1 (v/v) $CHCl_3$–MeOH]; IR (neat): 2928 (ν_{C-H}), 2868 (ν_{C-H}), 1354 ($\nu_{O=S=O}$), 1175 ($\nu_{O=S=O}$), 1116 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.33 (t, 12H, *J* = 6.2 Hz, CH_2OMs), 3.52 (t, 12H, *J* = 6.0 Hz, $OCH_2CH_2CH_2OMs$), 3.37 (t, 12H, *J* = 6.8 Hz, $SiCH_2CH_2CH_2O$), 3.01 (s, 18H, OMs), 2.00 (quint, 12H, *J* = 6.1 Hz, $OCH_2CH_2CH_2OMs$), 1.62–1.46 (m, 6H, $SiCH_2CH_2CH_2O$), 1.38–1.26 (m, 4H, $SiCH_2CH_2CH_2Si$). 0.64–0.47 (m, 20H, $SiCH_2$), −0.05 (s, 6H, $SiCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 73.83, 67.35, 65.72, 36.91, 29.28, 23.81, 20.13, 18.09, 16.80, 7.97, −3.44.

4.1.15. Bis[tris(7-bromo-4-oxaheptyl)silylpropyl]dimethylsilane (36, Dumbbell(1)6-ether-Br)

Dumbbell(1)6-ether-OMs (363 mg, 0.265 mmol) was subjected to bromination in the same manner as that described for **30** to afford Dumbbell(1)6-ether-Br (197 mg, 58.1%) as a colorless syrup: R_f 0.43 [4:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2910 (ν_{C-H}), 2862 (ν_{C-H}), 1113 (ν_{C-O-C}) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.54 (t, 12H, *J* = 5.9 Hz, $OCH_2CH_2CH_2Br$), 3.51 (t, 12H, *J* = 6.6 Hz, CH_2Br), 3.38 (t, 12H, *J* = 6.9 Hz, $SiCH_2CH_2CH_2O$), 2.10 (quint, 12H, *J* = 6.2 Hz, $OCH_2CH_2CH_2Br$), 1.63–1.48 (m, 12H, $SiCH_2CH_2CH_2O$), 1.39–1.22 (m, 4H, $SiCH_2CH_2CH_2Si$), 0.64–0.47 (m, 20H, $SiCH_2$), −0.06 (s, 6H, $SiCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 74.07, 67.97, 32.89, 30.72, 24.00, 20.34, 18.30, 17.03, 8.19 , −3.25; MS (MALDI-TOF) Calcd for $[M+Na]^+$: 1301.099, found: *m/z* 1301.119; Calcd for $[M+K]^+$: 1315.074, found: *m/z* 1315.092.

Anal. Calcd for $C_{44}H_{90}O_6Si_3Br_6$: C, 41.32; H, 7.09. Found: C, 41.69; H, 7.16.

4.1.16. Tetrakis[tris(4-oxa-6-heptenyl)silylpropyl]silane (Ball(1)12-ether-All)

Ball(1)12-OH **27** (500 mg, 0.492 mmol) was subjected to allylation in the same manner as that described for **23** to give Ball(1)12-ether-All (429 mg, 58.3%) as a colorless liquid: R_f 0.58 [3:1 (v/v) *n*-hexane–EtOAc]. IR (neat): 2916 (ν_{C-H}), 2855 (ν_{C-H}), 1103 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.96–5.86 (m, 12H, $CH{=}CH_2$), 5.29–5.15 (m, 24H, $CH{=}CH_2$), 3.96 (d, 24H, *J* = 5.6 Hz, $CH_2CH{=}CH_2$), 3.37 (t, 24H, *J* = 6.9 Hz, $SiCH_2CH_2CH_2O$), 1.61–1.50 (m, 8H, $SiCH_2CH_2CH_2O$), 1.30–1.21 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.66–0.50 (m, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.903, 116.61, 73.40, 71.72, 24.10, 18.43, 17.64, 17.47, 8.22 (SiC_4); HRMS (ESI): calcd for $[M+2Na]^{2+}/2$: 771.51138, found: *m/z* 771.5130.

Anal. Calcd for $C_{84}H_{156}O_{12}Si_5$: C, 67.33; H, 10.49. Found: C, 67.25; H, 10.57.

4.1.17. Tetrakis[tris(7-hydroxy-4-oxaheptyl)silylpropyl]silane (Ball(1)12-ether-OH)

Ball(1)12-ether-All (280 mg, 0.187 mmol) was subjected to hydroxylation in the same manner as that described for **24** to give Ball(1)12-ether-OH (210 mg, 65.6%) as a yellow solid: R_f 0.34 [5:1 (v/v) $CHCl_3$–MeOH]; IR (KBr): 3389 (ν_{O-H}), 2926 (ν_{C-H}), 2868 (ν_{C-H}), 1115 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (t, 24H, *J* = 5.7 Hz, CH_2OH), 3.59 (t, 24H, *J* = 5.9 Hz, $OCH_2CH_2CH_2OH$), 3.39 (t, 24H, *J* = 6.8 Hz, $SiCH_2CH_2CH_2O$), 3.17 ((br s, 12H, OH), 1.82 (quint, 24H, *J* = 5.8 Hz, $OCH_2CH_2CH_2OH$), 1.59–1.52 (m, 24H, $SiCH_2CH_2CH_2O$), 1.32–1.23 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.62–0.50 (m, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.07, 69.49, 61.31, 32.09, 24.03, 18.47, 17.60, 17.34, 8.19; HRMS (ESI): calcd for $[M+2Na]^{2+}/2$: 879.57477, found: *m/z* 879.5757.

Anal. Calcd for $C_{84}H_{180}O_{24}Si_5 \cdot 2H_2O$: C, 57.63; H, 10.59. Found: C, 57.48; H, 10.45.

4.1.18. Tetrakis[tris(7-methylsulfonyloxy-4-oxaheptyl)silylpropyl]silane (Ball(1)12-ether-OMs)

Ball(1)12-ether-OH (150 mg, 0.087 mmol) was subjected to mesylation in the same manner as that described for mesylate of **24** to give Ball(1)12-ether-OMs (225 mg, 97.0%) as a yellow syrup: R_f 0.48 [10:1 (v/v) $CHCl_3$–MeOH]; IR (neat): 2928 (ν_{C-H}), 2868 (ν_{C-H}), 1356 ($\nu_{O=S=O}$), 1177 ($\nu_{O=S=O}$), 1117 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.33 (t, 24H, *J* = 6.3 Hz, CH_2OMs), 3.52 (t, 24H, *J* = 6.0 Hz, $OCH_2CH_2CH_2Ms$), 3.37 (t, 24H, *J* = 6.9 Hz, $SiCH_2CH_2CH_2O$), 3.02 (s, 36H, OMs), 2.00 (quint, 24H, *J* = 6.1 Hz, $OCH_2CH_2CH_2OMs$), 1.58–1.50 (m, 24H, $SiCH_2CH_2CH_2O$), 1.29–1.21 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.61–0.49 (m, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.07, 67.46, 66.02, 37.17, 29.53, 24.05, 18.43, 17.66, 17.51, 8.15; HRMS (ESI): calcd for $[M+2Na]^{2+}/2$: 1347.44007, found: *m/z* 1347.4434.

4.1.19. Tetrakis[tris(7-bromo-4-oxaheptyl)silylpropyl]silane (39, Ball(1)12-ether-Br)

Ball(1)12-ether-OMs (225 mg, 0.085 mmol) was subjected to bromination in the same manner as that described for **30** to give Ball(1)12-ether-Br (129 mg, 61.4%) as a colorless syrup: R_f 0.63 [2:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2916 (ν_{C-H}), 2862 (ν_{C-H}), 1111 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.54 (t, 24H, *J* = 5.9 Hz, $OCH_2CH_2CH_2Br$), 3.51 (t, 24H, *J* = 6.5 Hz, CH_2Br), 3.38 (t, 24H, *J* = 6.9 Hz, $SiCH_2CH_2CH_2O$), 2.10 (quint, 24H, *J* = 6.2 Hz, $OCH_2CH_2CH_2Br$), 1.60–1.52 (m, 24H, $SiCH_2CH_2CH_2O$), 1.31–1.23 (m, 24H, $SiCH_2CH_2CH_2Si$), 0.62–0.50 (m, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.08, 68.03, 32.92, 30.75, 24.08, 18.47, 17.66, 17.53, 8.22; HRMS (ESI): calcd for $[M+2Na]^{2+}/2$: 1258.0630, found: *m/z* 1258.0664.

Anal. Calcd for $C_{84}H_{168}Br_{12}O_{12}Si_5$: C, 40.85; H, 6.86. Found: C, 41.16; H, 6.83.

4.1.20. Bis[tris(3-azidepropyl)silylpropyl]dimethylsilane (28, Dumbbell(1)6-N_3)

NaN_3 (706 mg, 10.862 mmol) was added to a solution of Dumbbell(1)6-ether-OMs (311 mg, 0.361 mmol) in DMF (5 mL), and the mixture was stirred for 1 h at 80 °C. The resulting mixture was

poured into ice water and extracted with $CHCl_3$. The extract was successively washed with water and brine, dried over anhyd $MgSO_4$, filtered, and concentrated. The syrupy residue was purified by flash column chromatography on silica gel [15:1 (v/v) *n*-hexane–EtOAc] to give hexaazide **28** (211 mg, 83.1%) as a colorless syrup: R_f 0.39 [10:1 (v/v) *n*-hexane–EtOAc]; IR (neat): 2922 (ν_{C-H}), 2874 (ν_{C-H}), 2097 cm^{-1} ($\nu_{N=N=N}$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.26 (t, 12H, J = 6.8 Hz, CH_2N_3), 1.62–1.54 (m, 12H, $SiCH_2CH_2$-CH_2N_3), 1.36–1.28 (m, 4H, $SiCH_2CH_2CH_2Si$), 0.67–0.55 (m, 20H, $SiCH_2$), −0.03 (s, 6H, $SiCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.44, 23.57, 20.25, 18.28, 16.74, 9.38, −3.30.

Anal. Calcd for $C_{26}H_{54}N_{18}Si_3$: C, 44.42; H, 7.74; N, 35.86. Found: C, 44.70; H, 7.88; N, 35.96.

4.1.21. Bis{tris[3-(6-bromohexanoylamino)propyl]silylpropyl}-dimethylsilane (37, Dumbbell(1)6-amide-Br)

To a solution of Dumbbell(1)6-N_3 **28** (276 mg, 0.393 mmol) in 6:1(v/v) THF–water (7 mL) was added triphenylphosphine (680 mg, 2.593 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature and was concentrated in vacuo. The residue was suspended in $CHCl_3$ and extracted with 1 M aq HCl. Concentration of the aqueous extract gave white foamy amine hydrochloride (300 mg).

The amine hydrochloride (300 mg) was dissolved in MeOH (6 mL) with Et_3N (723 μL), and 6-bromohexanoyl choloride was added dropwise to the mixture at −20 °C. The reaction mixture was stirred at −20 °C for 1 h and then diluted with $CHCl_3$ and poured into ice water. The organic layer was separated and washed with satd aq $NaHCO_3$ and brine, dried over anhyd $MgSO_4$, filtered, and concentrated. The residual syrup was purified by flash column chromatography on silica gel [15:4:1 (v/v/v) $CHCl_3$–EtOAc–MeOH] to give bromide **37** (627 mg, 99.2%) as a colorless syrup: R_f 0.53 [5:4:1 (v/v) $CHCl_3$–EtOAc–MeOH]; ^1H NMR (400 MHz, $CDCl_3$): δ 6.45 (t, 12H, J = 5.6 Hz, NH), 3.42 (t, 24H, CH_2Br), 3.19 (br q, 12H, J = 6.6 Hz, CH_2N), 2.22 (t, 12H, J = 7.5 Hz, CH_2CO), 1.88 (quint, 12H, J = 7.1 Hz, CH_2CH_2Br), 1.67 (quint, 12H, J = 7.6 Hz, CH_2CH_2CO), 1.48 (m, 24H, $CH_2CH_2CH_2Br$, CH_2CH_2N), 1.32–1.22 (m, 4H, $SiCH_2CH_2$), 0.59–0.48 (m, 20H, $SiCH_2$), −0.06 (s, 6H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.05, 42.64, 36.34, 33.70, 32.40, 27.76, 24.86, 24.05, 20.17, 18.43, 16.96, 9.39, −3.00; MS (MALDI-TOF): calcd for $[M+Na]^+$: 1633.351, found: *m/z* 1633.398; Calcd for $[M+K]^+$: 1649.325, found: *m/z* 1649.370.

Anal. Calcd for $C_{62}H_{120}N_6O_6Br_6Si_3$: C, 46.27; H, 7.52; N, 5.22. Found: C, 45.89; H, 7.47; N, 4.89.

4.1.22. Fan(0)3-*S*-Neu5Ac$_3$(OAc, OMe) (41)

NaOMe (17.5 mg, 0.325 mmol) was added to a solution of thiosialoside **21** (192 mg, 0.295 mmol) and Fan(0)3-Br dendrimer **29** (23 mg, 0.049 mmol) in 1:1 (v/v) DMF–MeOH (0.8 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, and then the reaction was quenched by addition of acetic acid (50 μL). After removal of MeOH by evaporation, the residual mixture was treated with acetic anhydride (1.5 mL) in pyridine (2 mL) at room temperature overnight. After co-evaporation with toluene in vacuo to dryness, the residue was treated with ethereal CH_2N_2. Purification of the concentrated crude product by column chromatography on silica gel [40:1 (v/v) $CHCl_3$–MeOH] afforded **41** (81 mg, 80.2%) as a white foam: R_f 0.28 [5:4:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{33}$ +26.2 (*c* 1.10, $CHCl_3$); IR (KBr): 2932 (ν_{C-H}), 1740 ($\nu_{C=O}$), 1663 ($\nu_{C=O}$, amide I), 1545 (δ_{N-H}, amide II), 1229 (ν_{C-O}), 1038 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.33 (2 × m, 5H, SiPh), 5.36 (ddd, 3H, $J_{7,8}$ = 8.4 Hz, $J_{8,9a}$ = 2.3 Hz, $J_{8,9b}$ = 4.6 Hz, H-8), 5.33 (dd, 3H, $J_{6,7}$ = 1.8 Hz, H-7), 5.25 (d, 3H, $J_{5,NH}$ = 10.4 Hz, NH), 4.86 (ddd, 3H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.2 Hz, $J_{3eq,4}$ = 4.8 Hz, H-4), 4.31 (dd, 3H, $J_{9a,9b}$ = 12.5 Hz, H-9a), 4.11 (dd, 3H, H-9b), 4.05 (m, 3H, $J_{5,6}$ = 10.4 Hz, H-5), 3.83 (dd, 3H, H-6), 3.80 (s, 9H, OMe), 2.77–2.71 (m, 3H, SCH[a]), 2.72 (dd, 3H, $J_{3ax,3eq}$ = 12.7 Hz, H-3*eq*), 2.57–2.50 (m, 3H, SCH[b]), 2.50 (t, 6H, J = 7.2 Hz, CH_2SCH_2), 2.44 (t, 6H, J = 7.2 Hz, CH_2SCH_2), 2.16, 2.14, 2.04, 2.03 (4 × s, 36H, OAc), 1.98 (t, 3H, H-3*ax*), 1.87 (s, 9H, NAc), 1.61–1.41 (2 × m, 24H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.93–0.88 (m, 6H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.89, 170.57, 170.13, 170.07, 169.97, 168.44, 136.28, 133.98, 129.10, 127.86, 83.12, 74.08, 69.66, 68.62, 67.28, 62.12, 52.89, 49.35, 38.05, 35.86, 31.89, 29.24, 28.82, 28.69, 28.03, 24.03, 23.15, 21.15, 20.82, 20.75, 11.89; HRMS (ESI): calcd for $[M+H]^+$: 2056.71535, found: *m/z* 2056.72008.

Anal. Calcd for $C_{90}H_{137}N_3O_{36}S_6Si$: C, 52.54; H, 6.71; N, 2.04. Found: C, 52.33; H, 6.75; N, 2.00.

A disulfide dimer **53** (35 mg) as a white foam was obtained as a byproduct; R_f 0.39 [5:4:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{28}$ +28.1 (*c* 1.13, $CHCl_3$); IR (KBr): 2936 (ν_{C-H}), 1740 ($\nu_{C=O}$), 1665 ($\nu_{C=O}$, amide I), 1541 (δ_{N-H}, amide II), 1227 (ν_{C-O}), 1038 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (ddd, 2H, $J_{7,8}$ = 8.6 Hz, $J_{8,9a}$ = 2.1 Hz, $J_{8,9b}$ = 4.6 Hz, H-8), 5.33 (dd, 2H, $J_{6,7}$ = 2.1 Hz, H-7), 5.18 (d, 2H, $J_{5,NH}$ = 10.4 Hz, NH), 4.86 (ddd, 2H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.6 Hz, H-4), 4.31 (dd, 2H, $J_{9a,9b}$ = 12.6 Hz, H-9a), 4.11 (dd, 2H, H-9b), 4.05 (q, 2H, $J_{5,6}$ = 10.4 Hz, H-5), 3.83 (dd, 2H, H-6), 3.81 (s, 6H, OMe), 2.78–2.71 (m, 2H, SCH[a]), 2.72 (dd, 2H, $J_{3ax,3eq}$ = 12.6 Hz, H-3*eq*), 2.67 (t, 4H, J = 7.2 Hz, $CH_2S_2CH_2$), 2.58–2.51 (m, 2H, SCH[b]), 2.17, 2.14, 2.04, 2.03 (4 × s, 24H, OAc), 1.98 (t, 2H, H-3*ax*), 1.88 (s, 6H, NAc), 1.69–1.59 (m, 8H, $SCH_2CH_2CH_2CH_2CH_2S$), 1.51–1.43 (m, 4H, $SCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.88, 170.57, 170.13, 170.07, 169.99, 168.45, 83.11, 74.08, 69.66, 68.63, 67.29, 62.14, 52.89, 49.33, 38.66, 38.04, 28.82, 28.67, 27.58, 23.14, 21.14, 20.81, 20.74; MS (FAB): calcd for $[M+H]^+$ 1217.4, found: *m/z* 1218.0.

Anal. Calcd for $C_{50}H_{76}N_2O_{24}S_4$: C, 49.33; H, 6.29; N, 2.30. Found: C, 49.01; H, 6.27; N, 2.24.

4.1.23. Fan(0)3-*s*-neu5ac$_3$ (3)

Solution of NaOMe (0.5 M) in MeOH was added to a solution of fully protected Fan(0)3-*S*-Neu5Ac$_3$(OAc, OMe) **41** (36.6 mg, 17.79 μmol) in MeOH (1 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, and then 0.5 M aq solution of NaOH was added and reaction mixture was stirred overnight at room temperature. The solution was treated with IR-120B (H^+) and adjusted to pH ~4, and then the suspension was filtered. The resin was washed with water, and the filtrate and washings were combined and concentrated. The resulting mixture was purified by size exclusion column chromatography on Sephadex G-25 with 5% aq AcOH as an eluent to give de-protected Fan(0)3-Neu5Ac **3** (23.5 mg, 87.4%) as a white powder after lyophilization: R_f 0.63 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{29}$ +27.7 (*c* 1.03, H_2O); IR (KBr): 3420 (ν_{O-H}), 2924 (ν_{C-H}), 1697 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1557 (δ_{N-H}, amide II), 1271 (ν_{C-O}), 1032 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.38, 7.17 (2 × br s, 5H, SiPh), 3.90–3.62 (m, 21H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 2.82 (br s, 6H, SCH[a] and H-3*eq*), 2.66 (br s, 3H, SCH[b]), 2.41 (br s, 12H, CH_2SCH_2), 2.04 (s, 9H, NAc), 1.88 (br s, 3H, H-3*ax*), 1.51, 1.41 (2 × br s, 24H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.84 (br s, 6H, $SiCH_2$); ^{13}C NMR (100 MHz, D_2O): δ 174.66, 172.03, 133.70, 127.61, 83.44, 74.68, 71.00, 67.76, 62.25, 51.45, 40.42, 35.29, 31.35, 29.06, 28.87, 28.45, 28.14, 27.81, 23.67, 21.82, 11.33; HRMS (ESI): calcd for $[M+H]^+$: 1510.54162, found: *m/z* 1510.53494.

4.1.24. Bis[*n*-pentenyl 5-acetamido-3,5-dideoxy-2-thio-α-D-*glycero*-D-*galacto*-2-nonulopyranosidyl]disulfide (2)

The de-protection of disulfide dimer (OAc, OMe) **53** (21.1 mg, 4.90 μmol) was carried out by a similar method similar to that described for the preparation of **1** to give de-protected disulfide dimer **2** (16.2 mg, quantitative) as a white powder after lyophiliza-

tion: R_f 0.34 [8:6:1 (v/v/v) $CHCl_3$−MeOH−H_2O]; $[\alpha]_D^{30}$ +25.2 (*c* 1.03, H_2O); IR (KBr): 3420 (ν_{O-H}), 2930 (ν_{C-H}), 1705 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1558 (δ_{N-H}, amide II), 1273 (ν_{C-O}), 1034 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.90−3.59 (m, 14H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 2.81 (dd, 2H, $J_{3eq,4}$ = 4.8 Hz, $J_{3ax,3eq}$ = 12.9 Hz, H-3*eq*), 2.83−2.78 (m, 2H, SCH[a]), 2.73−2.66 (m, 2H, SCH[b]), 2.02 (s, 6H, NAc), 1.86 (t, 2H, $J_{3ax,4}$ = 11.8 Hz, H-3*ax*), 1.69−1.59 (m, 8H, $SCH_2CH_2CH_2CH_2CH_2S$), 1.51–1.43 (m, 4H, $SCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, D_2O): δ 174.74, 171.98, 83.53, 74.75, 71.10, 67.97, 67.65, 62.43, 51.53, 40.27, 38.23, 28.85, 28.37, 28.09, 26.99, 21.82; MS (FAB): calcd for $[M+H]^+$: 853.3, found: 853.0; Calcd for $[M+Na]^+$: 875.2, found: *m/z* 874.9.

Anal. Calcd for $C_{32}H_{56}O_{16}N_2S_4{\cdot}1.4H_2O$: C, 43.76; H, 6.75; N, 3.19. Found: C, 43.65; H, 6.64; N, 3.10.

4.1.25. Fan(0)3-ether-*S*-Neu5Ac$_3$(OAc, OMe) (42)

The condensation reaction between thiosialoside **21** (327 mg, 0.502 mmol) and Fan(0)3-ether-Br **30** (44 mg, 0.068 mmol) was carried out by a method similar to that described for the preparation of **41** to give Fan(0)3-ether-*S*-Neu5Ac$_3$(OAc, OMe) **42** (85 mg, 55.9%) as a white foam: R_f 0.38 [5:4:1 (v/v/v) $CHCl_3$−EtOAc−MeOH]; $[\alpha]_D^{27}$ +23.1 (*c* 1.11, $CHCl_3$); IR (KBr): 2934 (ν_{C-H}), 2859 (ν_{C-H}), 1742 ($\nu_{C=O}$), 1663 ($\nu_{C=O}$, amide I), 1545 (δ_{N-H}, amide II), 1227 (ν_{C-O}), 1109 (ν_{C-O-C}), 1036 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48−7.30 (m, 5H, SiPh), 5.36 (ddd, 3H, $J_{7,8}$ = 8.4 Hz, $J_{8,9a}$ = 2.1 Hz, $J_{8,9b}$ = 4.6 Hz, H-8), 5.33 (dd, 3H, $J_{6,7}$ = 1.9 Hz, H-7), 5.29 (d, 3H, $J_{5,NH}$ = 10.4 Hz, NH), 4.86 (ddd, 3H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.4 Hz, $J_{3eq,4}$ = 4.4 Hz, H-4), 4.31 (dd, 3H, $J_{9a,9b}$ = 12.3 Hz, H-9a), 4.11 (dd, 3H, H-9b), 4.05 (q, 3H, $J_{5,6}$ = 10.4 Hz, H-5), 3.83 (dd, 3H, H-6), 3.80 (s, 9H, OMe), 3.45 (t, 6H, *J* = 6.3 Hz, $OCH_2CH_2CH_2S$), 3.35 (t, 6H, *J* = 6.9 Hz, $SiCH_2CH_2CH_2O$), 2.77−2.71 (m, 3H, SCH[a]), 2.71 (dd, 3H, $J_{3ax,3eq}$ = 12.7 Hz, H-3*eq*), 2.57−2.50 (m, 3H, SCH[b]), 2.56 (t, 6H, *J* = 7.3 Hz, CH_2SCH_2), 2.49 (t, 6H, *J* = 7.3 Hz, CH_2SCH_2), 2.16, 2.14, 2.04, 2.03 (4 × s, 36H, OAc), 1.98 (t, 3H, H-3*ax*), 1.88 (s, 9H, NAc), 1.83 (quint, 6H, $OCH_2CH_2CH_2S$), 1.61−1.42 (m, 24H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.82−0.77 (m, 6H, Si CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.87, 170.55, 170.14, 170.07, 169.97, 168.46, 136.65, 134.01, 128.94, 127.75, 83.13, 74.10, 73.75, 69.66, 69.25, 68.70, 67.34, 62.14, 52.86, 49.37, 38.06, 35.86, 31.88, 29.79, 29.13, 28.82, 28.69, 28.01, 23.92, 23.13, 21.12, 20.79, 20.72, 8.24; HRMS (ESI): calcd for $[M+Na]^+$ 2252.82289, found: *m/z* 2252.82345.

4.1.26. Fan(0)3-ether-*S*-Neu5Ac$_3$ (4)

The de-protection of Fan(0)3-ether-*S*-Neu5Ac$_3$(OAc, OMe) **42** (32.6 mg, 14.61 μmol) was carried out by a method similar to that described for the preparation of **3** to give Fan(0)3-ether-*S*-Neu5Ac$_3$ **4** (24.6 mg, quantitative) as a white powder after lyophilization: R_f 0.52 [3:3:1 (v/v/v) $CHCl_3$−MeOH−H_2O]; $[\alpha]_D^{24}$ +25.4 (*c* 1.07, H_2O); IR (KBr): 3414 (ν_{O-H}), 2930 (ν_{C-H}), 2857 (ν_{C-H}), 1700 ($\nu_{C=O}$), 1634 ($\nu_{C=O}$, amide I), 1558 (δ_{N-H}, amide II), 1275 (ν_{C-O}), 1110 (ν_{C-O-C}), 1032 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.37, 7.18 (2 × br s, 5H, SiPh), 3.82−3.58 (m, 21H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 3.35 (t, 6H, $OCH_2CH_2CH_2S$), 3.25 (t, 6H, $SiCH_2CH_2CH_2O$), 2.77 (br s, 6H, SCH[a] and H-3*eq*), 2.62 (br s, 3H, SCH[b]), 2.45, 2.43 (2 × br s, 12H, CH_2SCH_2), 2.00 (s, 9H, NAc), 1.83 (br s, 3H, H-3*ax*), 1.71 (br s, 6H, $OCH_2CH_2CH_2S$), 1.50, 1.39 (2 × br s, 24H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.73 (br s, 6H, $SiCH_2$); ^{13}C NMR (100 MHz, D_2O): δ 174.78, 172.09, 136.48, 133.64, 127.58, 83.66, 74.78, 72.98, 71.12, 68.71, 67.93, 67.77, 62.38, 51.61, 40.49, 31.42, 29.39, 28.84, 28.48, 28.27, 27.69, 23.54, 21.88, 8.11; HRMS (ESI): calcd for $[M+Na]^+$: 1706.64916, found: *m/z* 1706.65283.

4.1.27. Fan(0)3-amide-*S*-Neu5Ac$_3$(OAc, OMe) (43)

The condensation reaction between thiosialoside **20** (145 mg, 0.222 mmol) and Fan(0)3-amide-Br **31** (40 mg, 0.049 mmol) was carried out by a method similar to that described for the preparation of **41** to give Fan(0)3-amide-*S*-Neu5Ac$_3$(OAc, OMe) **43** (95 mg, 80.5%) as a white foam: R_f 0.33 [5:4:1 (v/v/v) $CHCl_3$−EtOAc−MeOH]; $[\alpha]_D^{30}$ +21.5 (*c* 1.11, $CHCl_3$); IR (KBr): 3292 (ν_{N-H}), 2934 (ν_{C-H}), 2859 (ν_{C-H}), 1744 ($\nu_{C=O}$), 1651 ($\nu_{C=O}$, amide I), 1549 (δ_{N-H}, amide II), 1261 (ν_{C-N}), 1227 (ν_{C-O}), 1036 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44−7.32 (m, 5H, SiPh), 5.91(t, 3H, *J* = 5.7 Hz, $NHCH_2$), 5.37−5.32 (m, 9H, $J_{8,9a}$ = 2.1 Hz, $J_{8,9b}$ = 4.4 Hz, $J_{6,7}$ = 1.8 Hz, $J_{5,NH}$ = 10.4 Hz, H-8, H-7 and NH), 4.86 (ddd, 3H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.7 Hz, H-4), 4.31 (dd, 3H, $J_{9a,9b}$ = 12.5 Hz, H-9a), 4.11 (dd, 3H, H-9b), 4.05 (q, 3H, $J_{5,6}$ = 10.4 Hz, H-5), 3.83 (dd, 3H, H-6), 3.80 (s, 9H, OMe), 3.20 (q, 6H, *J* = 6.6 Hz, CH_2N)), 2.77−2.70 (m, 3H, SCH[a]), 2.72 (dd, 3H, $J_{3ax,3eq}$ = 12.3 Hz, H-3*eq*), 2.57−2.50 (m, 3H, SCH[b]), 2.484 (t, 6H, *J* = 7.3 Hz, CH_2SCH_2), 2.478 (t, 6H, *J* = 7.3 Hz, CH_2SCH_2), 2.18 (t, 6H, *J* = 7.5 Hz, CH_2CO), 2.16, 2.14, 2.04, 2.03 (4 × s, 36H, OAc), 1.98 (t, 3H, H-3*ax*), 1.88 (s, 9H, NAc), 1.67−1.36 (m, 42H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$), 0.82−0.78 (m, 6H, CH_2Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.05, 170.87, 170.64, 170.19, 170.07, 170.01, 168.44, 136.04, 133.85, 129.27, 127.98, 83.10, 74.04, 69.66, 68.59, 67.27, 62.10, 52.88, 49.29, 42.36, 38.04, 36.54, 31.87, 29.29, 29.13, 28.80, 28.66, 28.49, 27.98, 25.32, 23.81, 23.14, 21.15, 20.82, 20.76, 9.13; HRMS (ESI): calcd for $[M+3Na]^{3+}$/3: 821.30913, found: *m/z* 821.3100.

4.1.28. Fan(0)3-amide-*S*-Neu5Ac$_3$ (5)

The de-protection of Fan(0)3-amide-*S*-Neu5Ac$_3$(OAc, OMe) **43** (32.5 mg, 13.56 μmol) was carried out by a method similar to that described for the preparation of **3** to give Fan(0)3-amide-*S*-Neu5Ac$_3$ **5** (25.1 mg, quantitative) as a white powder after lyophilization: R_f 0.61 [3:3:1 (v/v/v) $CHCl_3$−MeOH−H_2O]; $[\alpha]_D^{25}$ +23.0 (*c* 1.09, H_2O); IR (KBr): 3420 (ν_{O-H}), 2924 (ν_{C-H}), 1697 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1557 (δ_{N-H}, amide II), 1271 (ν_{C-O}), 1032 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.40, 7.30 (2 × br s, 5H, SiPh), 3.84−3.61 (m, 21H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 3.12 (br s, 6H, CH_2N), 2.78 (br s, 6H, SCH[a] and H-3*eq*), 2.63 (br s, 3H, SCH[b]), 2.41 (br s, 12H, CH_2SCH_2), 2.13 (br s, 6H, CH_2CO), 2.03 (s, 9H, NAc), 1.84 (br s, 3H, H-3*ax*), 1.49, 1.39 (2 × br s, 42H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$), 0.83 (br s, 6H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.11 (2 × C,), 172.36, 133.93, 128.18, 83.68, 75.17, 71.56, 68.16, 52.84, 52.07, 42.12, 40.80, 36.11, 31.79, 29.29, 28.87, 28.14, 25.81, 23.50, 22.32, 9.68; HRMS (ESI): calcd for $[M+2Na]^{2+}$/2: 947.38222, found: *m/z* 947.3817.

4.1.29. Ball(0)4-*S*-Neu5Ac$_4$(OAc, OMe) (44)

The condensation reaction between thiosialoside **21** (273 mg, 0.419 mmol) and Ball(0)4-Br **32** (27 mg, 0.052 mmol) was carried out by a method similar to that described for the preparation of **41** to give Ball(0)4-*S*-Neu5Ac$_4$(OAc, OMe) **44** (103 mg, 75.2%) as a white foam: R_f 0.13 [5:4:1 (v/v/v) $CHCl_3$−EtOAc−MeOH]; $[\alpha]_D^{24}$ +26.5 (*c* 1.19, $CHCl_3$); IR (KBr): 2932 (ν_{C-H}), 1742 ($\nu_{C=O}$), 1667 ($\nu_{C=O}$, amide I), 1549 (δ_{N-H}, amide II), 1229 (ν_{C-O}), 1038 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.36 (ddd, 3H, $J_{7,8}$ = 8.4 Hz, $J_{8,9a}$ = 2.1 Hz, $J_{8,9b}$ = 4.6 Hz, H-8), 5.33 (dd, 3H, $J_{6,7}$ = 1.6 Hz, H-7), 5.25 (d, 4H, $J_{5,NH}$ = 10.3 Hz, NH), 4.86 (ddd, 4H, $J_{4,5}$ = 10.3 Hz, $J_{3ax,4}$ = 12.1 Hz, $J_{3eq,4}$ 4.5 = Hz, H-4), 4.31 (dd, 4H, $J_{9a,9b}$ = 12.5 Hz, H-9a), 4.11 (dd, 4H, H-9b), 4.05 (q, 4H, $J_{5,6}$ = 10.3 Hz, H-5), 3.84 (dd, 4H, H-6), 3.81 (s, 12H, OMe), 2.78−2.71 (m, 4H, SCH[a]), 2.72 (dd, 4H, $J_{3ax,3eq}$ = 12.7 Hz, H-3*eq*), 2.58−2.53 (m, 4H, SCH[b]), 2.495 (t, 8H, *J* = 7.1 Hz, CH_2SCH_2), 2.487 (t, 8H, *J* = 7.2 Hz, CH_2SCH_2), 2.17, 2.14, 2.04, 2.03 (4 × s, 48H, OAc), 1.98 (t, 4H, H-3*ax*), 1.87 (s, 12H, NAc), 1.61−1.42 (m, 32H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.62 (m, 8H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.89, 170.60, 170.15, 170.08, 169.98, 168.46, 83.14, 74.09, 69.67, 68.62, 67.28, 62.12, 52.91, 49.37, 38.06, 36.03, 32.03, 29.28, 28.86,

28.71, 28.07, 24.23, 23.16, 21.17, 20.83, 20.77, 12.00; HRMS (ESI): calcd for $[M+Na]^+$: 2651.88866, found: *m/z* 2651.87993.

4.1.30. Ball(0)4-*s*-neu5ac$_4$ (6)

The de-protection of Ball(0)4-*S*-Neu5Ac$_4$(OAc, OMe) **44** (30.0 mg, 11.04 μmol) was carried out by a method similar to that described for the preparation of **3** to give Ball(0)4-*S*-Neu5Ac$_4$ **6** (21.6 mg, 99.5%) as a white powder after lyophilization: R_f 0.52 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{31}$ +23.2 (*c* 1.06, H_2O); IR (KBr): 3424 (ν_{O-H}), 2927 (ν_{C-H}), 1701 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1560 (δ_{N-H}, amide II), 1279 (ν_{C-O}), 1034 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.86–3.62 (m, 28H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 2.82 (br s, 8H, SCH^a and H-3*eq*), 2.71 (br s, 4H, SCH^b), 2.54 (br s, 16H, CH_2SCH_2), 2.03 (s, 12H, NAc), 1.87 (br s, 4H, H-3*ax*), 1.60, 1.49 (2 × br s, 32H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.69 (br s, 6H, $SiCH_2$); ^{13}C NMR (100 MHz, D_2O): δ 174.86, 172.13, 83.59, 74.70, 71.04, 67.87, 67.75, 62.34, 51.50, 40.41, 35.50, 31.45, 29.11, 28.86, 28.51, 27.80, 23.97, 21.83, 11.62; HRMS (ESI): calcd for $[M+H]^+$: 1901.67508, found: *m/z* 1901.66668.

4.1.31. Ball(0)4-ether-*S*-Neu5Ac$_4$(OAc, OMe) (45)

The condensation reaction between thiosialoside **21** (321 mg, 0.493 mmol) and Ball(0)4-ether-Br **33** (64 mg, 0.069 mmol) was carried out by a method similar to that described for the preparation of **41** to give Ball(0)4-ether-*S*-Neu5Ac$_4$(OAc, OMe) **45** (113 mg, 59.2%) as a white foam: R_f 0.23 [5:4:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{25}$+23.3 (*c* 1.06, $CHCl_3$); IR (KBr): 2932 (ν_{C-H}), 2857 (ν_{C-H}), 1742 ($\nu_{C=O}$), 1667 ($\nu_{C=O}$, amide I), 1549 (δ_{N-H}, amide II), 1227 (ν_{C-O}), 1109 (ν_{C-O-C}), 1036 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.39 (d, 4H, $J_{5,NH}$ = 10.4 Hz, NH), 5.36–5.31 (m, 8H, $J_{8,9a}$ = 2.1 Hz, $J_{8,9b}$ = 4.6 Hz, $J_{6,7}$ = 1.9 Hz, H-8 and H-7), 4.86 (ddd, 4H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ 4.6 = Hz, H-4), 4.32 (dd, 4H, $J_{9a,9b}$ = 12.3 Hz, H-9a), 4.11 (dd, 4H, H-9b), 4.04 (q, 4H, $J_{5,6}$ = 10.4 Hz, H-5), 3.84 (dd, 4H, H-6), 3.80 (s, 12H, OMe), 3.47 (t, 8H, *J* = 6.3 Hz, $OCH_2CH_2CH_2S$), 3.34 (t, 8H, *J* = 7.0 Hz, $SiCH_2CH_2CH_2O$), 2.78–2.70 (m, 4H, SCH^a), 2.72 (dd, 4H, $J_{3ax,3eq}$ = 12.7 Hz, H-3*eq*), 2.59–2.48 (m, 4H, SCH^b), 2.57 (t, 8H, *J* = 7.3 Hz, CH_2SCH_2), 2.50 (t, 8H, *J* = 7.3 Hz, CH_2SCH_2), 2.16, 2.14, 2.04, 2.03 (4 × s, 48H, OAc), 1.98 (m, 4H, H-3*ax*), 1.87 (s, 12H, NAc), 1.83 (quint, 8H, $OCH_2CH_2CH_2S$), 1.62–1.41 (m, 32H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.53–0.49 (m, 8H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.80, 170.49, 170.10, 170.03, 169.95, 168.49, 83.13, 74.14, 73.94, 69.67, 69.29, 68.82, 67.41, 62.16, 52.80, 49.37, 38.07, 31.88, 29.81, 29.12, 28.85, 28.82, 28.96, 27.99, 23.98, 23.07, 21.06, 20.74, 20.66, 8.15; HRMS (ESI): calcd for $[M+2Na]^{2+}$/2: 1453.52295, found: *m/z* 1453.51809.

4.1.32. Ball(0)4-ether-*S*-Neu5Ac$_4$ (7)

The de-protection of Ball(0)4-ether-*S*-Neu5Ac$_4$(OAc, OMe) **45** (33.2 mg, 11.59 μmol) was carried out by a method similar to that described for the preparation of **3** to give Ball(0)4-ether-*S*-Neu5Ac$_4$ **7** (24.8 mg, quantitative) as a white powder after lyophilization: R_f 0.59 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{25}$ +28.6 (*c* 1.12, H_2O); IR (KBr): 3420 (ν_{O-H}), 2928 (ν_{C-H}), 2857 (ν_{C-H}), 1699 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1558 (δ_{N-H}, amide II), 1273 (ν_{C-O}), 1113 (ν_{C-O-C}), 1032 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.84–3.63 (m, 28H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 3.51 (t, 8H, $OCH_2CH_2CH_2S$), 3.40 (t, 8H, $SiCH_2CH_2CH_2O$), 2.82 (br s, 8H, SCH^a and H-3*eq*), 2.70 (br s, 4H, SCH^b), 2.59, 2.54 (2 × br s, 16H, CH_2SCH_2), 2.04 (s, 12H, NAc), 1.84 (br s, 12H, H-3*ax*, $OCH_2CH_2CH_2S$), 1.60, 1.50 (2 × br s, 32H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 0.58 (br s, 6H, $SiCH_2$); ^{13}C NMR (100 MHz, D_2O): δ 174.68, 171.82, 83.19, 74.72, 73.25, 70.99, 68.71, 67.69, 62.30, 61.48, 40.24, 31.36, 29.35, 28.89, 28.76, 28.44, 28.19, 27.76, 23.61, 21.80, 20.05, 7.98; HRMS (ESI): calcd for $[M+Na]^+$: 2155.82448, found: *m/z* 2155.81847.

4.1.33. Ball(0)4-amide-*S*-Neu5Ac$_4$(OAc, OMe) (46)

The condensation reaction between thiosialoside **21** (203 mg, 0.311 mmol) and Ball(0)4-amide-Br **34** (42 mg, 0.043 mmol) was carried out by a method similar to that described for the preparation of **41** to give Ball(0)4-amide-*S*-Neu5Ac$_4$(OAc, OMe) **46** (106 mg, 80.9%) as a white foam: R_f: 0.37 [7:2:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{27}$ +24.0 (*c* 1.15, $CHCl_3$); IR (KBr): 3289 (ν_{N-H}), 2932 (ν_{C-H}), 2859 (ν_{C-H}), 1740 ($\nu_{C=O}$), 1651 ($\nu_{C=O}$, amide I), 1549 (δ_{N-H}, amide II), 1261 (ν_{C-N}), 1227 (ν_{C-O}), 1036 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.12 (t, 4H, *J* = 5.7 Hz, $NHCH_2$), 5.43 (d, 4H, $J_{5,NH}$ = 10.5 Hz, NH), 5.38–5.32 (m, 8H, $J_{8,9a}$ = 2.1 Hz, $J_{8,9b}$ = 4.4 Hz, $J_{6,7}$ = 1.7 Hz, H-8 and H-7), 4.86 (ddd, 4H, $J_{4,5}$ = 10.5 Hz, $J_{3ax,4}$ = 12.2 Hz, $J_{3eq,4}$ 4.6 = Hz, H-4), 4.31 (dd, 4H, $J_{9a,9b}$ = 12.4 Hz, H-9a), 4.11 (dd, 4H, H-9b), 4.05 (q, 4H, $J_{5,6}$ = 10.5 Hz, H-5), 3.83 (dd, 4H, H-6), 3.80 (s, 12H, OMe), 3.18 (q, 8H, *J* = 6.6 Hz, CH_2N)), 2.78–2.70 (m, 4H, SCH^a), 2.72 (dd, 4H, $J_{3ax,3eq}$ = 12.2 Hz, H-3*eq*), 2.57–2.50 (m, 4H, SCH^b), 2.50 (t, 8H, *J* = 7.3 Hz, CH_2SCH_2), 2.49 (t, 8H, *J* = 7.2 Hz, CH_2SCH_2), 2.18 (t, 8H, *J* = 7.5 Hz, CH_2CO), 2.17, 2.14, 2.05, 2.03 (4 × s, 48H, OAc), 1.98 (t, 4H, H-3*ax*), 1.88 (s, 12H, NAc), 1.68–1.41 (m, 56H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$), 0.53–0.49 (m, 8H, Si CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.12, 170.87, 170.65, 170.18, 170.07, 169.99, 168.44, 83.10, 74.05, 69.67, 68.56, 67.27, 62.11, 52.90, 49.30, 42.46, 40.71, 38.05, 36.55, 31.90, 29.33, 29.15, 28.83, 28.67, 28.53, 28.00, 25.36, 23.89, 23.16, 21.17, 20.84, 20.78, 9.15; HRMS (ESI): calcd for $[M+3Na]^{3+}$/3: 1050.06760, found: *m/z* 1050.0695.

4.1.34. Ball(0)4-amide-*S*-Neu5Ac$_4$ (8)

The de-protection of Ball(0)4-amide-*S*-Neu5Ac$_4$(OAc, OMe) **46** (30.7 mg, 9.96 μmol) was carried out by a method similar to that described for the preparation of **3** to give Ball(0)4-amide-*S*-Neu5Ac$_4$ **8** (23.4 mg, quantitative) as a white powder after lyophilization: R_f 0.54 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{26}$ +22.4 (*c* 1.41, H_2O); IR (KBr): 3399 (ν_{O-H}), 2930 (ν_{C-H}), 2857 (ν_{C-H}), 1701 ($\nu_{C=O}$), 1638 ($\nu_{C=O}$, amide I), 1555 (δ_{N-H}, amide II), 1273 (ν_{C-O}), 1036 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.84–3.61 (m, 28H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 3.15 (br s, 8H, CH_2N), 2.80 (br s, 8H, SCH^a and H-3*eq*), 2.68 (br s, 4H, SCH^b), 2.52 (br s, 16H, CH_2SCH_2), 2.24 (br s, 8H, CH_2CO), 2.04 (s, 12H, NAc), 1.84 (br s, 4H, H-3*ax*), 1.58, 1.45 (2 × br s, 56H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$), 0.53 (br s, 8H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.14 (2 × C), 172.52, 83.89, 75.21, 71.54, 68.13, 62.81, 52.03, 42.78, 40.83, 36.19, 31.85, 29.29, 28.91, 28.40, 28.13, 25.69, 23.74, 22.29, 9.23; HRMS (ESI): calcd for $[M+2Na]^{2+}$/2: 1199.49098, found: *m/z* 1199.4899.

4.1.35. Dumbbell(1)6-*S*-Neu5Ac$_6$(OAc, OMe) (47)

The condensation reaction between thiosialoside **21** (457 mg, 0.701 mmol) and Dumbbell(1)6-Br **35** (64 mg, 0.069 mmol) was carried out by a method similar to that described for the preparation of **41** to give Dumbbell(1)6-*S*-Neu5Ac$_6$(OAc, OMe) **47** (151 mg, 53.5%) as a white foam: R_f 0.27 [7:2:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{24}$ +23.6 (*c* 0.66, $CHCl_3$); IR (KBr): 2931 (ν_{C-H}), 1736 ($\nu_{C=O}$), 1665 ($\nu_{C=O}$, amide I), 1545 (δ_{N-H}, amide II), 1221 (ν_{C-O}), 1036 (ν_{C-O-C}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (ddd, 6H, $J_{7,8}$ = 8.5 Hz, $J_{8,9a}$ = 2.2 Hz, $J_{8,9b}$ = 4.6 Hz, H-8), 5.33 (dd, 6H, $J_{6,7}$ = 1.7 Hz, H-7), 5.28 (d, 6H, $J_{5,NH}$ = 10.4 Hz, NH), 4.86 (ddd, 6H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.1 Hz, $J_{3eq,4}$ = 4.5 Hz, H-4), 4.31 (dd, 6H, $J_{9a,9b}$ = 12.3 Hz, H-9a), 4.11 (dd, 6H, H-9b), 4.05 (q, 6H, $J_{5,6}$ = 10.4 Hz, H-5), 3.83 (dd, 6H, H-6), 3.81 (s, 18H, OMe), 2.78–2.71 (m, 6H, SCH^a), 2.72 (dd, 6H, $J_{3ax,3eq}$ = 12.7 Hz, H-3*eq*), 2.58–2.47 (m, 8H, SCH^b), 2.50 (t, 12H, *J* = 7.1 Hz, CH_2SCH_2), 2.49 (t, 12H, *J* = 7.3 Hz, CH_2SCH_2), 2.17, 2.14, 2.05, 2.03 (4 × s, 72H, OAc), 1.98 (t, 6H, H-3*ax*), 1.87 (s, 18H, NAc), 1.62–1.43 (m, 48H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 1.32–1.23 (m, 4H, $SiCH_2CH_2CH_2Si$),

0.63–0.51 (m, 20H, SiCH_2), −0.06 (s, 6H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.86, 170.58, 170.17, 170.05, 170.00, 168.44, 83.11, 74.07, 69.66, 68.67, 67.26, 62.10, 52.88, 49.27, 38.02, 36.03, 31.97, 29.25, 28.82, 28.67, 28.04, 24.27, 23.11, 21.14, 20.80, 20.74, 20.37, 18.29, 17.06, 12.08, −3.27; HRMS (ESI): calcd for $[M+2H]^{2+}$/2: 2072.71705, found: *m/z* 2072.71684.

4.1.36. Dumbbell(1)6-*s*-neu5ac$_6$ (9)

The de-protection of Dumbbell(1)6-*S*-Neu5Ac$_6$(OAc, OMe) **47** (21.1 mg, 4.90 μmol) was carried out by a method similar to that described for the preparation of **3** to give Dumbbell(1)6-*S*-Neu5Ac$_6$ **9** (16.2 mg, quantitative) as a white powder after lyophilization: R_f 0.42 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{27}$ +23.2 (*c* 0.99, H_2O); IR (KBr): 3418 (ν_{O-H}), 2924 (ν_{C-H}), 1701 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1560 (δ_{N-H}, amide II), 1261 (ν_{C-O}), 1032 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 3.88–3.63 (m, 42H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 2.83 (br s, 12H, SCH^a and H-3*eq*), 2.72 (br s, 6H, SCH^b), 2.54 (br s, 24H, CH_2SCH_2), 2.04 (s, 18H, NAc), 1.88 (br s, 6H, H-3*ax*), 1.61, 1.50 (2 × br s, 48H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 1.34 (m, 4H, $SiCH_2CH_2CH_2Si$), 0.68 (br s, 20H, $SiCH_2$), −0.07 (s, 6H, $SiCH_3$); ^{13}C NMR (100 MHz, D_2O): δ 174.73, 172.07, 83.50, 74.72, 71.03, 67.83, 62.32, 51.52, 40.40, 35.59, 31.55, 29.19, 28.91, 28.59, 27.94, 24.04, 21.86, 20.01, 18.35, 17.19, 11.69, −2.68; HRMS (ESI): calcd for $[M+2H]^{2+}$/2: 1504.5614, found: *m/z* 1504.5558.

4.1.37. Dumbbell(1)6-ether-*S*-Neu5Ac$_6$(OAc, OMe) (48)

The condensation reaction between thiosialoside **21** (306 mg, 0.470 mmol) and Dumbbell(1)6-ether-Br **36** (50 mg, 0.039 mmol) was carried out by a method similar to that described for the preparation of **41** to give Dumbbell(1)6-ether-*S*-Neu5Ac$_6$(OAc, OMe) **48** (55 mg, 31.6%) as a white foam: R_f 0.33 [7:2:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{21}$ +24.7 (*c* 1.29, $CHCl_3$); IR (KBr): 2930 (ν_{C-H}), 2857 (ν_{C-H}), 1744 ($\nu_{C=O}$), 1663 ($\nu_{C=O}$, amide I), 1541 (δ_{N-H}, amide II), 1227 (ν_{C-O}), 1111 (ν_{C-O-C}), 1036 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (ddd, 6H, $J_{7,8}$ = 8.4 Hz, $J_{8,9a}$ = 2.2 Hz, $J_{8,9b}$ = 4.6 Hz, H-8), 5.33 (dd, 6H, $J_{6,7}$ = 2.0 Hz, H-7), 5.27 (d, 6H, $J_{5,NH}$ = 10.4 Hz, NH), 4.86 (ddd, 6H, $J_{4,5}$ = 10.4 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.6 Hz, H-4), 4.31 (dd, 6H, $J_{9a,9b}$ = 12.4 Hz, H-9a), 4.11 (dd, 6H, H-9b), 4.05 (q, 6H, $J_{5,6}$ = 10.4 Hz, H-5), 3.83 (dd, 6H, H-6), 3.80 (s, 18H, OMe), 3.48 (t, 12H, *J* = 6.3 Hz, OC$H_2CH_2CH_2S$), 3.34 (t, 12H, *J* = 7.0 Hz, $SiCH_2CH_2CH_2O$), 2.78–2.70 (m, 6H, SCH^a), 2.72 (dd, 6H, $J_{3ax,3eq}$ = 12.7 Hz, H-3*eq*), 2.59–2.48 (m, 6H, SCH^b), 2.57 (t, 12H, *J* = 7.2 Hz, CH_2SCH_2), 2.50 (t, 12H, *J* = 7.3 Hz, CH_2SCH_2), 2.17, 2.14, 2.04, 2.03 (4 × s, 72H, OAc), 1.98 (m, 6H, H-3*ax*), 1.87 (s, 18H, NAc), 1.83 (quint, 12H, $OCH_2CH_2CH_2S$), 1.62–1.41 (m, 48H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 1.32–1.24 (m, 4H, $SiCH_2CH_2CH_2Si$), 0.60–0.47 (m, 20H, $SiCH_2$), −0.07 (s, 6H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.88, 170.58, 170.14, 170.07, 169.96, 168.44, 83.11, 74.07, 69.66, 69.31, 68.59, 67.26, 62.11, 52.89, 49.34, 38.04, 31.86, 29.78, 29.13, 28.83, 28.69, 28.04, 24.04, 23.16, 21.16, 20.83, 20.76, 20.41, 18.28, 17.06, 8.15, −3.27; HRMS (ESI): calcd for $[M+3Na]^{3+}$/3: 1505.55837, found: *m/z* 1505.55195.

4.1.38. Dumbbell(1)6-ether-*S*-Neu5Ac$_6$ (10)

The de-protection of Dumbbell(1)6-ether-*S*-Neu5Ac$_6$(OAc, OMe) **48** (26.2 mg, 5.89 μmol) was carried out by a method similar to that described for the preparation of **3** to give Dumbbell(1)6-ether-*S*-Neu5Ac$_6$ **10** (20.0 mg, quantitative) as a white powder after lyophilization: R_f 0.58 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{25}$ +20.0 (*c* 1.05, H_2O); IR (KBr): 3408 (ν_{O-H}), 2928 (ν_{C-H}), 2855 (ν_{C-H}), 1699 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1558 (δ_{N-H}, amide II), 1273 (ν_{C-O}), 1113 (ν_{C-O-C}), 1032 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 3.84–3.40 (m, 66H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4, OC$H_2CH_2CH_2S$, $SiCH_2CH_2CH_2O$), 2.82 (br s, 12H, SCH^a and H-3*eq*), 2.70 (br s, 6H, SCH^b), 2.54 (br s, 24H, CH_2SCH_2), 2.04 (s, 18H, NAc), 1.84 (br s, 18H, H-3*ax*, $OCH_2CH_2CH_2S$), 1.61, 1.51 (2 × br s, 52H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$ and $SiCH_2CH_2CH_2Si$), 0.58 (br s, 20H, $SiCH_2$), −0.02 (s, 6H, $SiCH_3$); ^{13}C NMR (100 MHz, D_2O): δ 174.72, 171.79, 83.32, 74.81, 73.23, 71.06, 68.75, 67.89, 67.63, 66.45, 62.90, 62.41, 61.56, 40.34, 31.44, 29.47, 28.90, 28.76, 28.47, 28.30, 27.72, 23.69, 21.86, 2.78, 8.17, −3.01; HRMS (ESI): calcd for $[M-2H]^{2-}$/2: 1676.67135, found: *m/z* 1676.67301.

4.1.39. Dumbbell(1)6-amide-*S*-Neu5Ac$_6$(OAc, OMe) (49)

The condensation reaction between thiosialoside **21** (219 mg, 0.336 mmol) and Dumbbell(1)6-amide-Br **37** (50 mg, 0.031 mmol) was carried out by a method similar to that described for the preparation of **41** to give Dumbbell(1)6-amide-*S*-Neu5Ac$_6$(OAc, OMe) **49** (104 mg, 70.0%) as a white foam: R_f 0.30 [7:2:1 (v/v/v) $CHCl_3$–EtOAc–MeOH]; $[\alpha]_D^{27}$ +23.3 (*c* 1.04, $CHCl_3$); IR (KBr): 3291 (ν_{N-H}), 2930 (ν_{C-H}), 2859 (ν_{C-H}), 1744 ($\nu_{C=O}$), 1651 ($\nu_{C=O}$, amide I), 1549 (δ_{N-H}, amide II), 1261 (ν_{C-N}), 1227 (ν_{C-O}), 1036 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22 (t, 6H, *J* = 5.3 Hz, N*H*CH_2), 5.42 (d, 6H, $J_{5,NH}$ = 10.3 Hz, NH), 5.38–5.32 (m, 12H, $J_{8,9a}$ = 2.0 Hz, $J_{8,9b}$ = 4.4 Hz, $J_{6,7}$ = 1.6 Hz, H-8 and H-7), 4.86 (ddd, 6H, $J_{4,5}$ = 10.3 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.6 Hz, H-4), 4.32 (dd, 6H, $J_{9a,9b}$ = 12.4 Hz, H-9a), 4.11 (dd, 6H, H-9b), 4.05 (q, 6H, $J_{5,6}$ = 10.3 Hz, H-5), 3.84 (dd, 6H, H-6), 3.80 (s, 18H, OMe), 3.18 (q, 12H, *J* = 6.4 Hz, CH_2N), 2.78–2.70 (m, 6H, SCH^a), 2.72 (dd, 6H, $J_{3ax,3eq}$ = 12.3 Hz, H-3*eq*), 2.57–2.50 (m, 6H, SCH^b), 2.50 (t, 12H, *J* = 7.2 Hz, CH_2SCH_2), 2.49 (t, 12H, *J* = 7.3 Hz, CH_2SCH_2), 2.18 (t, 12H, *J* = 7.6 Hz, CH_2CO), 2.16, 2.14, 2.04, 2.03 (4 × s, 72H, OAc), 1.97 (t, 6H, H-3*ax*), 1.88 (s, 18H, NAc), 1.68–1.41 (m, 84H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$), 1.28–1.26 (m, 4H, $SiCH_2CH_2CH_2Si$), 0.59–0.48 (m, 20H, $SiCH_2$), −0.07 (s, 6H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.17, 170.87, 170.66, 170.24, 170.09, 170.03, 168.48, 83.13, 74.04, 69.69, 68.64, 67.31, 62.13, 52.90, 49.31, 43.83, 42.61, 38.07, 36.53, 31.93, 29.36, 29.17, 28.84, 28.69, 28.57, 28.01, 25.40, 23.98, 23.15, 21.17, 20.83, 20.78, 20.16, 18.43, 16.99, 9.29, −3.02; HRMS (ESI): calcd for $[M+4Na]^{4+}$/4: 1217.47896, found: *m/z* 1217.4819.

4.1.40. Dumbbell(1)6-amide-*S*-Neu5Ac$_6$ (11)

The de-protection of Dumbbell(1)6-amide-*S*-Neu5Ac$_6$(OAc, OMe) **49** (32.7 mg, 6.84 μmol) was carried out by a method similar to that described for the preparation of **3** to give Dumbbell(1)6-amide-*S*-Neu5Ac$_6$ **11** (24.9 mg, 98.8%) as a white powder after lyophilization: R_f 0.53 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{26}$ +18.4 (*c* 1.01, H_2O); IR (KBr): 3383 (ν_{O-H}), 2930 (ν_{C-H}), 2859 (ν_{C-H}), 1701 ($\nu_{C=O}$), 1639 ($\nu_{C=O}$, amide I), 1557 (δ_{N-H}, amide II), 1271 (ν_{C-O}), 1034 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 3.85–3.62 (m, 42H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4), 2.82 (br s, 12H, SCH^a and H-3*eq*), 2.68 (br s, 6H, SCH^b), 2.53 (br s, 24H, CH_2SCH_2), 2.04 (s, 18H, NAc), 1.85 (br s, 6H, H-3*ax*), 1.59, 1.47 (2 × br s, 88H, $SCH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$ and $SiCH_2CH_2CH_2Si$), 0.58 (br s, 20H, $SiCH_2$), −0.02 (s, 6H, SiMe); ^{13}C NMR (100 MHz, D_2O): δ 175.16 (2 × C), 172.36, 83.67, 75.25, 71.60 68.16, 62.82, 52.23, 41.05, 40.70, 31.90, 29.37, 28.91, 28.19, 25.89, 22.30, 9.23, −2.65; HRMS (ESI): calcd for $[M+3Na]^{3+}$/3: 1251.52639, found: *m/z* 1251.5248.

4.1.41. Ball(1)12-*S*-Neu5Ac$_{12}$(OAc, OMe) (50)

The condensation reaction between thiosialoside **21** (250 mg, 0.384 mmol) and Ball(1)12-Br **38** (40 mg, 0.023 mmol) was carried out by a method similar to that described for the preparation of **41** to give Ball(1)12-*S*-Neu5Ac$_{12}$(OAc, OMe) **50** (108 mg, 59.0%) as a white foam: R_f 0.45 [7:1 (v/v) $CHCl_3$–MeOH]; $[\alpha]_D^{26}$ +27.4 (*c* 1.05, $CHCl_3$); IR (KBr): 2924 (ν_{C-H}), 1740 ($\nu_{C=O}$), 1663 ($\nu_{C=O}$, amide I), 1549 (δ_{N-H}, amide II), 1229 (ν_{C-O}), 1038 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (d, 12H, $J_{5,NH}$ = 10.3 Hz, NH), 5.38–5.32 (m, 12H, $J_{8,9b}$ = 4.5 Hz, H-8 and H-7), 4.86 (ddd, 12H, $J_{4,5}$ = 10.3 Hz, $J_{3ax,4}$ = 12.4 Hz, $J_{3eq,4}$ = 4.6 Hz, H-4), 4.31 (d, 12H,

$J_{9a,9b}$ = 11.6 Hz, H-9a), 4.12 (dd, 12H, H-9b), 4.05 (q, 12H, $J_{5,6}$ = 10.3 Hz, H-5), 3.84 (d, 12H, H-6), 3.81 (s, 36H, OMe), 2.76–2.70 (m, 12H, SCH[a]), 2.72 (dd, 12H, $J_{3ax,3eq}$ = 12.4 Hz, H-3*eq*), 2.57–2.50 (m, 12H, SCH[b]), 2.50 (t, 24H, *J* = 7.2 Hz, CH_2SCH_2), 2.49 (t, 24H, *J* = 7.3 Hz, CH_2SCH_2), 2.17, 2.14, 2.05, 2.03 (4 × s, 144H, OAc), 1.99 (t, 12H, H-3*ax*), 1.87 (s, 36H, NAc), 1.61–1.41 (m, 96H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2Si$), 1.28–1.26 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.64–0.51 (m, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.86, 170.65, 170.24, 170.06, 169.99, 168.48, 83.14, 74.07, 69.69, 68.61, 67.23, 62.09, 52.93, 49.28, 38.03, 36.13, 32.08, 29.64, 29.33, 28.87, 28.70, 28.13, 24.31, 23.12, 21.19, 20.84, 20.79, 18.41, 17.59, 12.09; HRMS (ESI): calcd for $[M+5Na]^{5+}$/5: 1646.3587, found: *m/z* 1646.3777.

4.1.42. Ball(1)12-*s*-neu5ac$_{12}$ (12)

The de-protection of Ball(1)12-*S*-Neu5Ac$_{12}$(OAc, OMe) **50** (39.7 mg, 4.89 μmol) was carried out by a method similar to that described for the preparation of **3** to give Ball(1)12-*S*-Neu5Ac$_{12}$ **12** (27.2 mg, 93.8%) as a white powder after lyophilization: R_f 0.17 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{24}$ +30.7 (*c* 1.13, H_2O); IR (KBr): 3379 (ν_{O-H}), 2920 (ν_{C-H}), 1717 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1558 (δ_{N-H}, amide II), 1279 (ν_{C-O}), 1034 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 3.92–3.60 (m, 84H, H-9a, H-9b, H-8, H-7, H-6, H-5 and H-4), 2.81 (br s, 24H, SCH[a] and H-3*eq*), 2.69 (br s, 12H, SCH[b]), 2.56 (br s, 48H, CH_2SCH_2), 2.03 (s, 36H, NAc), 1.80 (br s, 12H, H-3*ax*), 1.62, 1.50 (2 × br s, 96H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2Si$), 1.48 (br s, 8H, $SiCH_2CH_2CH_2Si$), 0.70 (br s, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.15, 172.28, 83.67, 75.16, 71.43, 68.18, 62.78, 51.90, 49.00, 40.70, 36.08, 32.01, 29.63, 29.29, 28.97, 28.34, 24.47, 22.27, 20.52, 18.97, 12.18; HRMS(MALDI-TOF): calcd for $[M+Na]^+$: 5954.138, found: *m/z* 5954.212.

4.1.43. Ball(1)12-ether-*S*-Neu5Ac$_{12}$(OAc, OMe) (51)

The condensation reaction between thiosialoside **21** (180 mg, 0.276 mmol) and Ball(1)12-ether-Br **39** (40 mg, 0.016 mmol) was carried out by a method similar to that described for the preparation of **41** to give Ball(1)12-ether-*S*-Neu5Ac$_{12}$(OAc, OMe) **51** (93 mg, 65.0%) as a white foam: R_f 0.43 [8:1 (v/v) $CHCl_3$–MeOH]; $[\alpha]_D^{27}$ +22.7 (*c* 1.09, $CHCl_3$); IR (KBr): 2932 (ν_{C-H}), 2859 (ν_{C-H}), 1742 ($\nu_{C=O}$), 1665 ($\nu_{C=O}$, amide I), 1545 (δ_{N-H}, amide II), 1227 (ν_{C-O}), 1111 (ν_{C-O-C}), 1036 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (d, 12H, $J_{5,NH}$ = 10.3 Hz, NH), 5.38–5.32 (m, 24H, $J_{8,9a}$ = 1.7 Hz, $J_{8,9b}$ = 4.4 Hz, H-8 and H-7), 4.86 (ddd, 12H, $J_{4,5}$ = 10.3 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.7 Hz, H-4), 4.31 (dd, 12H, $J_{9a,9b}$ = 12.4 Hz, H-9a), 4.12 (dd, 12H, H-9b), 4.05 (q, 12H, $J_{5,6}$ = 10.4 Hz, H-5), 3.83 (d, 12H, H-6), 3.81 (s, 36H, OMe), 3.47 (t, 24H, *J* = 6.3 Hz, $OCH_2CH_2CH_2S$), 3.34 (t, 24H, *J* = 7.0 Hz, $SiCH_2CH_2CH_2O$), 2.78–2.70 (m, 12H, SCH[a]), 2.72 (dd, 12H, $J_{3ax,3eq}$ = 12.3 Hz, H-3*eq*), 2.59–2.48 (m, 12H, SCH[b]), 2.57 (t, 24H, *J* = 7.2 Hz, CH_2SCH_2), 2.50 (t, 24H, *J* = 7.3 Hz, CH_2SCH_2), 2.17, 2.14, 2.05, 2.03 (4 × s, 144H, OAc), 1.98 (t, 12H, H-3*ax*), 1.87 (s, 36H, NAc), 1.83 (quint, 24H, $OCH_2CH_2CH_2S$), 1.62–1.43 (m, 96H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 1.28–1.21 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.58–0.46 (m, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.87, 170.62, 170.19, 170.07, 169.98, 168.47, 83.11, 74.11, 74.08, 69.67, 69.39, 68.60, 67.26, 62.11, 52.91, 49.31, 38.04, 31.85, 29.78, 29.15, 28.84, 28.69, 28.07, 24.07, 23.14, 21.17, 20.83, 20.78, 18.39, 17.66, 17.53, 8.12; HRMS (ESI): calcd for $[M+5Na]^{5+}$/5: 1785.6593, found: *m/z* 1785.6934.

4.1.44. Ball(1)12-ether-*S*-Neu5Ac$_{12}$ (13)

The de-protection of Ball(1)12-ether-*S*-Neu5Ac$_{12}$(OAc, OMe) **51** (32.3 mg, 3.66 μmol) was carried out by a method similar to that described for the preparation of **3** to give Ball(1)12-ether-*S*-Neu5Ac$_{12}$ **13** (24.3 mg, quantitative) as a white powder after lyophilization: R_f 0.17 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{21}$ +30.7 (*c* 1.12, H_2O); IR (KBr): 3401 (ν_{O-H}), 2928 (ν_{C-H}), 2857 (ν_{C-H}), 1701 ($\nu_{C=O}$), 1638 ($\nu_{C=O}$, amide I), 1560 (δ_{N-H}, amide II), 1275 (ν_{C-O}), 1112 (ν_{C-O-C}), 1032 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 3.86–3.38 (m, 132H, H-9a, H-9b, H-8, H-7, H-6, H-5, H-4, CH_2OCH_2), 2.83 (br s, 24H, SCH[a] and H-3*eq*), 2.70 (br s, 12H, SCH[b]), 2.58 (br s, 48H, CH_2SCH_2), 2.04 (s, 36H, NAc), 1.85 (br s, 36H, H-3*ax* and $OCH_2CH_2CH_2S$), 1.61, 1.50 (2 × br s, 96H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2$), 1.39 (br s, 8H, $SiCH_2CH_2CH_2Si$), 0.58 (br s, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, D_2O): δ 175.14, 172.28, 83.66, 75.22, 74.67, 73.77, 71.47, 69.26, 68.19, 62.79, 51.94, 49.00 (MeOD), 40.80, 31.83, 30.28, 29.84, 29.38, 28.94, 28.70, 28.25, 24.25, 22.29, 24.25, 22.29, 18.00, 8.54; HRMS (ESI): calcd for $[M-6H]^{6-}$/6: 1103.7681, found: *m/z* 1103.7648.

4.1.45. Ball(1)12-amide-*S*-Neu5Ac$_{12}$(OAc, OMe) (52)

The condensation reaction between thiosialoside **21** (175 mg, 0.269 mmol) and Ball(1)12-amide-Br **40** (46 mg, 0.015 mmol) was carried out by a method similar to that described for the preparation of **41** to give Ball(1)12-amide-*S*-Neu5Ac$_{12}$(OAc, OMe) **52** (88 mg, 63.3%) as a white foam: $[\alpha]_D^{26}$ +20.5 (*c* 0.83, $CHCl_3$); R_f 0.47 [7:1 (v/v) $CHCl_3$–MeOH]; IR (KBr): 3275 (ν_{N-H}), 2932 (ν_{C-H}), 2860 (ν_{C-H}), 1742 ($\nu_{C=O}$), 1647 ($\nu_{C=O}$, amide I), 1545 (δ_{N-H}, amide II), 1261 (ν_{C-N}), 1227 (ν_{C-O}), 1036 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (br s, 12H, $NHCH_2$), 5.54 (d, 12H, $J_{5,NH}$ = 10.3 Hz, NH), 5.38–5.32 (m, 24H, $J_{8,9a}$ = 1.9 Hz, $J_{8,9b}$ = 4.1 Hz, H-8 and H-7), 4.86 (ddd, 12H, $J_{4,5}$ = 10.3 Hz, $J_{3ax,4}$ = 12.3 Hz, $J_{3eq,4}$ = 4.4 Hz, H-4), 4.31 (dd, 12H, $J_{9a,9b}$ = 12.4 Hz, H-9a), 4.11 (dd, 12H, H-9b), 4.05 (q, 12H, $J_{5,6}$ = 10.3 Hz, H-5), 3.84 (d, 12H, H-6), 3.81 (s, 36H, OMe), 3.16 (br d, 24H, *J* = 5.1 Hz, CH_2N), 2.77–2.70 (m, 12H, SCH[a]), 2.72 (dd, 12H, $J_{3ax,3eq}$ = 12.3 Hz, H-3*eq*), 2.58–2.50 (m, 12H, SCH[b]), 2.50 (t, 24H, *J* = 7.2 Hz, CH_2SCH_2), 2.49 (t, 24H, *J* = 7.2 Hz, CH_2SCH_2), 2.19 (t, 24H, *J* = 7.5 Hz, CH_2CO), 2.17, 2.14, 2.05, 2.03 (4 × s, 144H, OAc), 1.97 (t, 12H, H-3*ax*), 1.88 (s, 18H, NAc), 1.67–1.37 (m, 168H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$), 1.29–1.24 (m, 8H, $SiCH_2CH_2CH_2Si$), 0.50 (br d, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.37, 170.84, 170.66, 170.24, 170.07, 170.02, 168.46, 83.10, 74.04, 69.69, 68.59, 67.27, 62.11, 52.89, 49.24, 42.68, 38.03, 36.42, 31.91, 29.38, 29.15, 28.82, 28.65, 28.62, 28.01, 25.45, 23.92, 23.12, 21.17, 20.82, 20.78, 18.54, 17.49, 17.13, 9.38; HRMS (ESI): calcd for $[M+5Na]^{5+}$/5: 1918.0024, found: *m/z* 1918.1611.

4.1.46. Ball(1)12-amide-*S*-Neu5Ac$_{12}$ (14)

The de-protection of Ball(1)12-amide-*S*-Neu5Ac$_{12}$(OAc, OMe) **52** (34.0 mg, 3.59 μmol) was carried out by a method similar to that described for the preparation of **3** to give Ball(1)12-amide-*S*-Neu5Ac$_{12}$ **14** (26.0 mg, 99.2%) as a white powder after lyophilization: R_f 0.14 [3:3:1 (v/v/v) $CHCl_3$–MeOH–H_2O]; $[\alpha]_D^{25}$ +12.6 (*c* 1.06, H_2O); IR (KBr): 3318 (ν_{O-H}), 2928 (ν_{C-H}), 2859 (ν_{C-H}), 1699 ($\nu_{C=O}$), 1636 ($\nu_{C=O}$, amide I), 1558 (δ_{N-H}, amide II), 1273 (ν_{C-O}), 1032 (ν_{C-O-C}) cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 4.78 (s, HDO, internal standard), 3.83–3.57 (m, 84H, H-9a, H-9b, H-8, H-7, H-6, H-5 and H-4), 3.17 (br s, 24H, CH_2N), 2.79 (br s, 24H, SCH[a] and H-3*eq*), 2.66 (br s, 12H, SCH[b]), 2.53 (br s, 48H, CH_2SCH_2), 2.25 (br s, 24H, CH_2CO), 2.03 (s, 36H, NAc), 1.79 (br s, 12s H, H-3*ax*), 1.59, 1.45 (2 × br s, 168H, $SCH_2CH_2CH_2CH_2CH_2SCH_2CH_2CH_2CH_2CONHCH_2CH_2$), 1.25 (br s, 8H, $SiCH_2CH_2CH_2Si$), 0.55 (br s, 40H, $SiCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.14 (2 × C), 172.23, 84.81, 75.10, 71.73, 68.35, 68.27, 62.69, 51.98, 42.75, 41.09, 36.17, 31.77, 29.37, 29.21, 29.06, 28.30, 28.07, 25.71, 23.80, 22.24, 18.80, 17.44, 9.49; HRMS (ESI): calcd for $[M-7H]^{7-}$/7: 1040.3013, found: *m/z* 1040.2980.

4.2. Viruses and sialidases

Influenza virus A/PR/8/34 (H1N1) and A/Memphis/1/71 (H3N2) were cultured in 11-day-old embryonic cheken eggs, purified, and

concentrated as described previously.[24] The virus suspensions in saline were used as the source of sialidase.

4.3. Sialidase inhibition assay

Influenza A virus suspension (HAU = 2^6), suitable amounts of glycodendrimers and 4-MU-Neu5Ac were mixed in 20 mM acetate buffer (pH 5.2), and the mixture was adjusted to 0.4 mM of final concentration of 4-MU-Neu5Ac and total volume 20 μL. The reaction mixture was incubated at 37 °C for 30 min. The reaction was stopped by the addition of 1 mL of 100 mM carbonate buffer (pH 10.7). The fuorescence of released 4-methylumbelliferone (4-MU) was measured using a fuorescence spectrophotometer (Hitachi F-4010) with excitation at 355 nm and emission at 460 nm. The concentration causing 50% inhibition (IC_{50}) of sialidase activity using 4-MU-Neu5Ac was calculated graphically by plotting percent inhibition versus inhibitor concentration.

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