Synthesis of New α-Thiosialodendrimers and Their Binding Properties to the Sialic Acid Specific Lectin from *Limax flavus*

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Abstract: Carbohydrate−protein binding interactions can be greatly amplified using the cluster or multivalent effect. In previous studies, sialylated multibranched L-lysine dendrimers were found to be potent inhibitors of the hemagglutination of human erythrocytes by *Influenza* viruses. In order to further the understanding of multivalency and its role in carbohydrate−protein interactions, glycoconjugates with differing carbohydrate densities, conformations, and interglycosidic spacings must be prepared. The synthesis and biological testing of structurally similar divergent and tethered α-sialodendrimers are presented herein. α-Thiosialoside-containing dendrimers scaffolded on an orthogonally protected 3,3′-iminobis(propylamine) core were efficiently prepared *via* Cbz-protecting group and HOBt/DIC coupling strategies. The potential of these sialodendrimers to cross-link and precipitate *Limax flavus* lectin (LFA) was confirmed by turbidimetric analysis. When tested in enzyme-linked lectin inhibition assays using human α_1-acid glycoprotein (orosomucoid) as coating antigen and horseradish peroxidase-labeled LFA for detection di- (**31**), tetra- (**32**), octa- (**33**), and hexadecavalent (**34**) divergent dendrimers showed IC_{50} values of 176, 11.8, 206, and 425 nM while the tethered structures with valencies of four (**14**), six (**20**), eight (**25**), and twelve (**30**) exhibited IC_{50} values of 58.7, 16.9, 17.5, and 8.22 nM, respectively. These data represent 3.5 (**34**) to 182 (**30**) fold increases in inhibitory potential over monovalent 5-acetamido-5-deoxy-D-glycero-α-D-galacto-2-nonulopyranosyl azide used as a standard (IC_{50} 1500 nM). The tethered α-sialodendrimers appeared to have structural organizations more suitable than the divergent dendrimers for the solid phase inhibition of the binding of human α_1-acid glycoprotein to LFA. All α-sialodendrimers are currently being evaluated as inhibitors of human erythrocyte hemagglutination by *Influenza* viruses.

Introduction

Sialic acid-containing polymers[1] have been shown to be potent inhibitors of the hemagglutination of human erythrocytes by *Influenza* viruses.[1−3] The increased inhibitory capacity of these sialopolymers, over their monosaccharide counterparts, was attributed to their increase in valency. This phenomenon is based on synergistic cluster or multivalent effects and is known to compensate for the usually low dissociation constants (K_D's)[4] of natural oligosaccharides by the cooperative combination of multiple carbohydrate−protein interactions.

Glycopolymers, however, by their very nature, have ill-defined chemical structures. They are polydisperse, varying in size and containing carbohydrate contents that are randomly distributed. As such, while they can effectively show that multivalency plays a role in carbohydrate−protein recognition processes, they fail to allow precise biophysical analyses of multivalent effects in these interactions.

Dendrimers, on the other hand, are monodisperse high molecular weight macromolecules. They represent chemically well-defined polymers and may be prepared by divergent or convergent methods.[5] Much scientific effort has gone into the design and synthesis of dendrimers over the last 10 years. The reasons for this are numerous. Potential applications for dendrimers include those in medicinal engineering, photocopier toners, imaging, radiation and gene therapy, catalysis, and charge separation and as carriers of bioactive molecules with both agrochemical and pharmaceutical applications.[5] It was recently demonstrated that sialylated dendrimers scaffolded onto multibranched L-lysine dendrimers were as potent as sialopolymers in the inhibition of the hemagglutination of human erythrocytes by *Influenza* viruses.[6]

Furthermore, cell surface carbohydrates have critical roles in a wide variety of biological functions such as cell growth, regulation, and differentiation, cellular trafficking, cancer metastasis, inflammation, and infection processes.[7] Thus, chemically well-defined glycodendrimers such as those described above and herein represent potentially useful therapeutic agents in the prevention of bacterial and viral infections.

Divergent glycodendrimers based on L-lysine[6,8−10] and gallic acid[10,11] cores have been previously described.[12−14] These hyperbranched dendritic cores have been conjugated to α-thio-

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(6) (a) Roy, R.; Zanini, D.; Meunier, S. J.; Romanowska, A. *ACS Symp. Ser.* **1994**, *560*, 104−119. (b) Roy, R.; Zanini, D.; Meunier, S. J.; Romanowska, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1869−1872.

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(8) Zanini, D.; Park, W. K. C.; Roy, R. *Tetrahedron Lett.* **1995**, *36*, 7383−7386.

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sialosides,[6] β-D-lactosides,[8,11] *N*-acetyllactosaminides,[8] *N*-acetylglucosaminides,[8] α-D-mannosides,[9] and a 3′-sulfo-Lewis^X-(Glc) analog.[10]

Spherical Starburst PAMAM dendrimers[5a,15] made of poly(amidoamine) are commercially available and have been used to attach various carbohydrate derivatives. Disaccharide lactones of lactose and maltose have been directly conjugated to the amine-terminated dendrimers.[16] An isothiocyanate[17,18] coupling strategy has also been employed to conjugate poly(amidoamine) dendrimers to α-[17,18] and β-D-mannose,[17] β-D-glucose,[17] β-D-galactose,[17] β-cellobiose,[17] and β-lactose[17] isothiocyanate derivatives.

Still, no study has involved the preparation and biological property evaluation of structurally similar divergent and spherical glycodendrimers. Since a systematic analysis of multivalency and its role in carbohydrate−protein interactions must consider structural organization of the carbohydrate residues, this comparison seems to be necessary.

We present herein the design, synthesis, and biological properties of a new family of symmetrically tethered sialodendrimers with even valencies between four and twelve based on a 3,3′-iminobis(propylamine) core (**1**). For comparison purposes, the relative binding properties of previously reported symmetrical dendrons of sialic acid **31**−**34**[19] based on the same 3,3′-iminobis(propylamine) core will be presented.

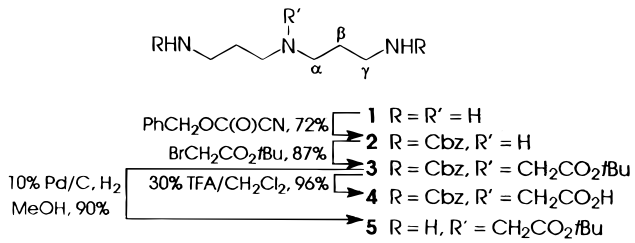
N-Acetylneuraminic acid (sialic acid, NeuAc) is the most ubiquitous member of the sialic acid family of derivatives present on cell surface glycolipids and glycoproteins and is the key epitope recognized as being essential for a number of virus infections.[20] α-Sialodendrimers, in addition to furthering the understanding of the multivalent effect, represent potent inhibitors of human erythrocyte hemagglutination by *Influenza* viruses.[6]

Also of importance is that the syntheses of the divergent and tethered dendritic cores presented here eliminate the need for large excesses of reagents used to ensure complete conversion and are not susceptible to base-catalyzed retro-Michael degradations. They, therefore, represent a viable alternative to PAMAM dendrimers, previously used as core structures.

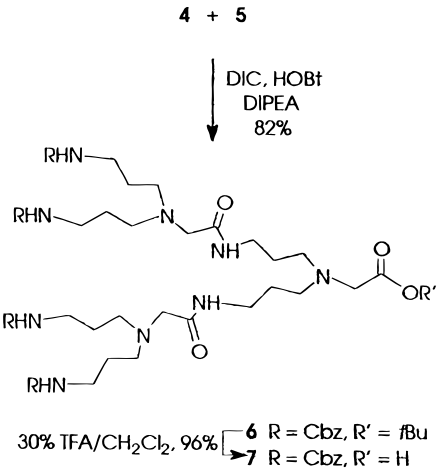
Results and Discussion

Synthesis of Tethered α-Sialodendrimers. First and second generation carbobenzyloxy-protected dendrimers **4** and **7** with valencies of two and four were efficiently and conveniently synthesized using carbodiimide−hydroxybenzotriazole (DIC/HOBt) coupling chemistry. They were prepared in the following manner.

Scheme 1



Scheme 2



The primary amines of 3,3′-iminobis(propylamine) (**1**) were regioselectively protected using the method of Murahashi *et al.*[21] to give diamine **2** (benzyl cyanoformate, CH_2Cl_2, 72% yield). Diamine **2** was then alkylated with *tert*-butyl bromoacetate in good yield (CH_3CN, 87%) to provide divalent core structure **3** with Cbz-protected amines and *tert*-butyl-protected acid functionalities. Trifluoroacetolysis of **3** gave acid **4** (30% TFA/CH_2Cl_2, 96% yield), and hydrogenolysis of the Cbz groups of **3** afforded diamine **5** (90%) (Scheme 1). Cbz-protected acid **4** was used to generate tetra- and hexavalent dendrimers **9** and **16** (see below).

Acid **4** and amine **5** were then coupled using diisopropylcarbodiimide (DIC) and HOBt to provide tetravalent Cbz-protected dendrimer **6**. The crude mixture was treated with anion exchange resin (HO^-, Amberlite IRA-400) in order to eliminate HOBt and the slight excess acid used in the reaction. The residue was then concentrated, and diisopropylcarbodiimide urea and **6** were separated by standard silica gel chromatography. Dendrimer **6** was isolated in 82% yield. Deprotection of tetravalent ester **6** with trifluoroacetic acid, as above, afforded acid **7** in excellent yield (96%) (Scheme 2).

The approach followed for the syntheses of the spherical dendrimers was based on the tethering of Cbz-protected dimer **4** and tetramer **7** with both hexamethylenediamine and tris(2-aminoethyl)amine to give dendrimers with valencies of between four and twelve. These tethered dendrimers were functionalized with *N*-chloroacetylated end groups to which thiolated carbohydrates were added in the last step. This strategy allows the incorporation of different carbohydrate haptens onto prebuilt dendritic structures. A slight excess of divalent acid **4** was coupled to hexamethylenediamine (**8**) to give Cbz-protected tetravalent spherical dendrimer **9** (DIC, HOBt, DIPEA, 86%) which upon hydrogenolysis afforded amine **10** (10% Pd/C, H_2, 95%). *N*-Chloroacetylated dendrimer **11** was obtained by treatment of amine **9** with chloroacetic anhydride in DMSO

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(20) Karlsson, K.-A. *Curr. Opin. Struct. Biol.* **1995**, *5*, 622−635.
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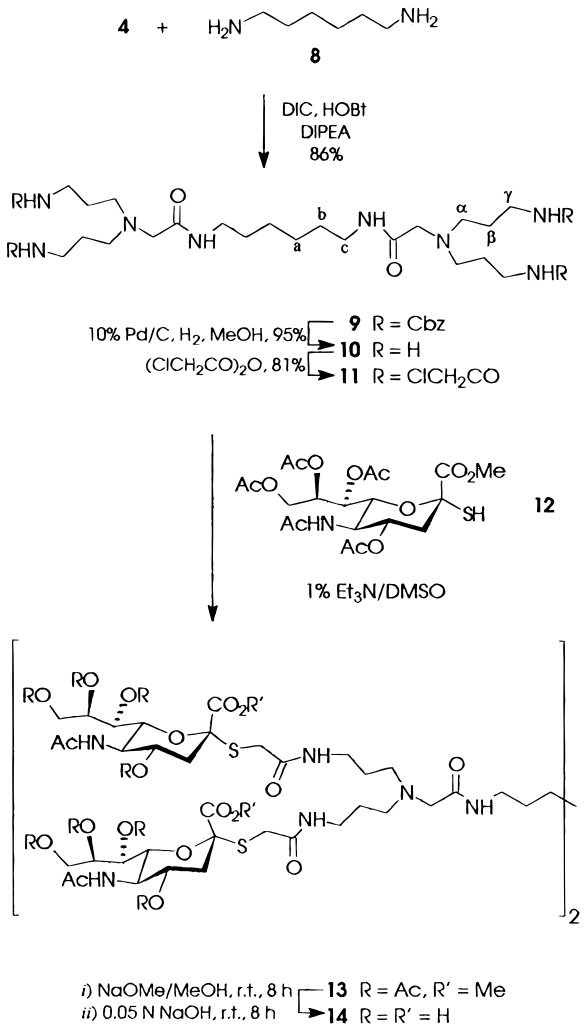
Scheme 3



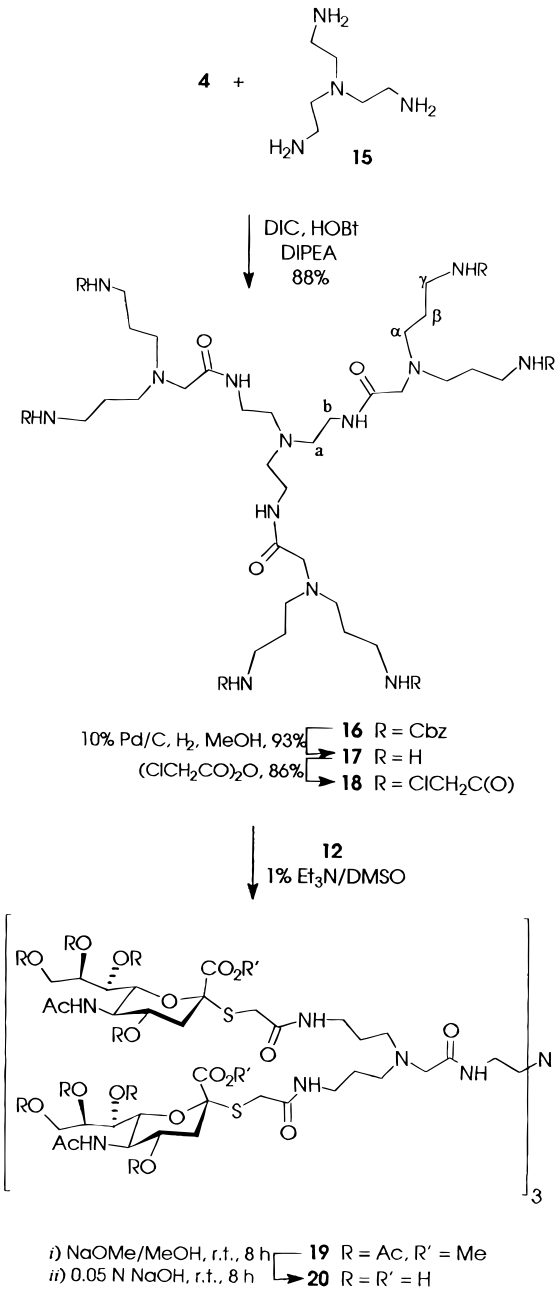
(81%). Multivalent *N*-chloroacetylated derivative **11** was too polar to allow easy isolation *via* standard chromatographic techniques. Instead, the crude mixture containing **11** was subjected to basic alumina column chromatography (20% H_2O/CH_3CN) to remove the chloroacetate anions generated (Scheme 3).

The corresponding *N*-chloroacetylated tethered hexa- (**18**), octa- (**23**), and dodeca- (**28**) valent dendrimers were generated in a similar manner. Tetravalent acid **7** was coupled to both hexamethylenediamine (**8**) and tris(2-aminoethyl)amine (**15**), and divalent acid **4** was conjugated to tris(2-aminoethyl)amine to give Cbz-protected octa- (**21**), dodeca- (**26**), and hexa- (**16**) valent dendrimers, respectively (72−88%, Schemes 4−6). Hydrogenolysis of **16**, **21**, and **26** afforded hexa- (**17**), octa- (**22**), and dodeca- (**27**) amines (Pd/C, H_2, 61−99%). Amines **17**, **22**, and **27** were treated with chloroacetic anhydride in DMSO to generate *N*-chloroacetylated dendrimers **18**, **23**, and **28** (64−86%) (Schemes 4−6).

Each *N*-chloroacetylated dendrimer (**11**, **18**, **23**, and **28**) was then treated with a slight excess of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galactononulopyranosonate (**12**)[6,22] to provide completely protected tethered α-sialodendrimers **13**, **19**, **24**, and **29** in good yields (83−87%). Dendrimers **13**, **19**, **24**, and **29** were isolated by precipitation from ethyl acetate. Ethyl acetate was used as the precipitating solvent as α-thiosialoside derivative **12** remained soluble in EtOAc.

(22) Park, W. K. C.; Meunier, S. J.; Zanini, D.; Roy, R. *Carbohydr. Lett.* **1994**, *1*, 179−182.

Scheme 4

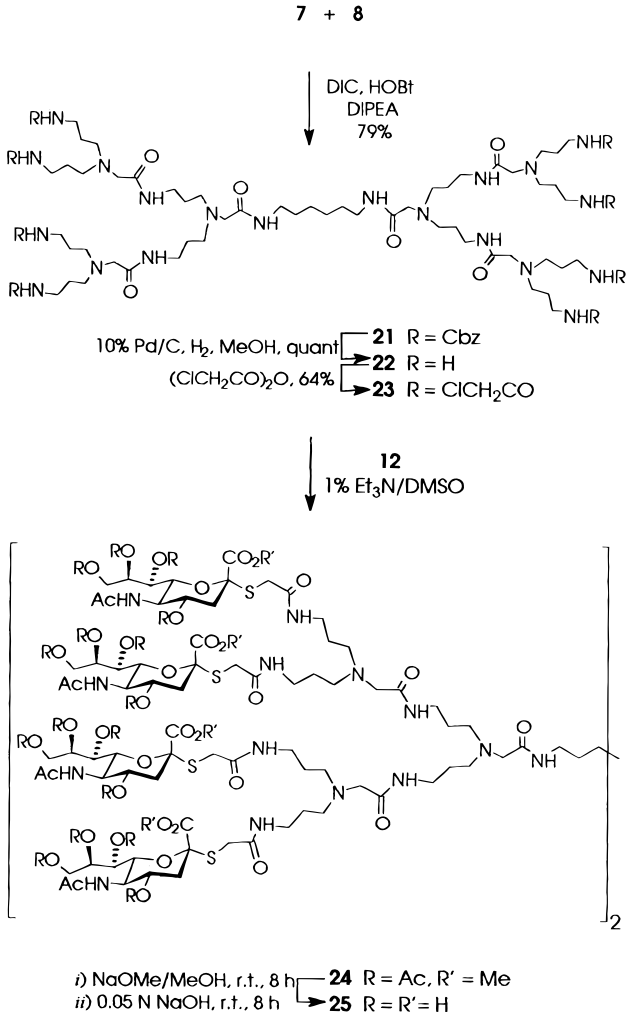


Complete coupling between the dendritic core and the α-thiosialoside was evident from the ^{1}H-NMR spectra of compounds **13**, **19**, **24**, and **29**. The disappearance of the *N*-chloroacetyl signals at 4.03 ppm (DMSO-d_6) and the emergence of new signals corresponding to the NeuAc residues (H-4 at 4.83 ppm, H-3 equatorial at 2.70 ppm, and *N*-Ac at 1.83 ppm, DMSO-d_6) integrating for the desired valency clearly established the extent of sialoside incorporation.

Deprotection of sialodendrimers **13**, **19**, **24**, and **29** by sequential ester hydrolysis ((i) NaOMe/MeOH; (ii) 0.05 N NaOH) followed by gel permeation chromatography (GPC, Biogel-P2, H_2O as eluent) afforded fully deprotected tethered dendrimers **14**, **20**, **25**, and **30** with four, six, eight, and twelve NeuAc residues, respectively (56−73%) (Schemes 4−6).

The strategy described for the syntheses of these glycodendrimers is convenient and efficient. The convergent assembly of multibranched dendrimers having *N*-chloroacetylated end groups allows the conjugation of other thiolated carbohydrate derivatives at the last stage.

Scheme 5



Due to their symmetrical structures, dendrimer characterization is facile. Characteristic ^{1}H-NMR signals were observed at δ 2.50−2.55, 1.50−1.60, 3.00−3.20, and 4.03 for α-, β-, and γ-CH_2, and $ClCH_2$ residues, respectively (DMSO-d_6). Furthermore, the well-resolved singlet at 4.03 ppm, corresponding to the chloromethylene groups, may be precisely integrated (±3%) relative to other signals. Following carbohydrate attachment, the signal was shifted upfield (3.40−3.80 ppm) due to the sulfur atom.

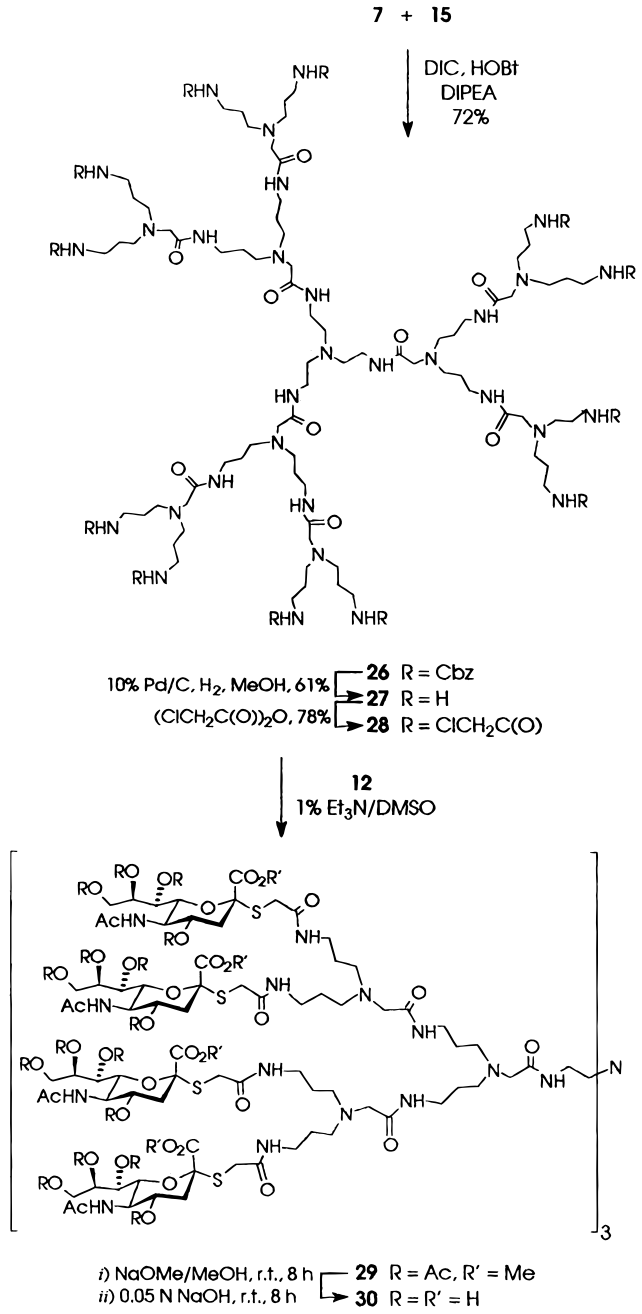
Hypervalent *N*-chloroacetylated and protected NeuAc dendrimers are extremely polar molecules, and consequently isolation by standard chromatographic techniques (silica gel chromatography) was cumbersome. Alternative carbohydrate conjugation methods are therefore currently being investigated. In addition, this approach is amenable to solid phase syntheses as described for previously reported L-lysine dendrimers.[6,8−10] Work is in progress to assess the efficiency of the solid phase strategy and will be reported in due course.[23]

Synthesis of Divergent α-Sialodendrimers. Using the same Cbz-protecting group strategy, DIC/HOBt coupling techniques, and the (chloroacetyl)thiosialoside conjugation method, first through fourth generation α-sialodendrimers **31**−**34** (Chart 1) with valencies of two to sixteen were synthesized. Their preparation has been described in a recent paper.[19]

Turbidimetric Analysis of α-Sialodendrimers. *Limax flavus* (LFA), consisting of two equal sized, noncovalently

(23) Llinares, M.; Roy, R. *Proceedings of the XVIIIth International Carbohydrate Symposium*, Milan, July 21−26, 1996; p 427.

Scheme 6



associated subunits (M_r = 22 000), is a sialic acid (NeuAc) specific binding animal lectin and has been previously used as a model for the study of a large number of NeuAc−protein binding interactions. It is specific for *N*-acetylneuraminic acid (Neu5Ac) and *N*-glycolylneuraminic acid (Neu5Gc) residues, with the binding affinity being much greater for Neu5Ac than for Neu5Gc.[24] To demonstrate the ability of these α-sialodendrimers to bind to LFA, turbidimetric analysis was performed. The time course formation of insoluble precipitin complexes between LFA and dendrimer **32** is illustrated in Figure 1. Maximum turbidity was reached after only 30 min. These microquantitative precipitation experiments confirmed the direct binding and cross-linking properties of all α-sialodendrimers with LFA.

Enzyme-Linked Lectin Inhibition Assays (ELLA). The efficiency of each dendrimer to inhibit the binding of horseradish

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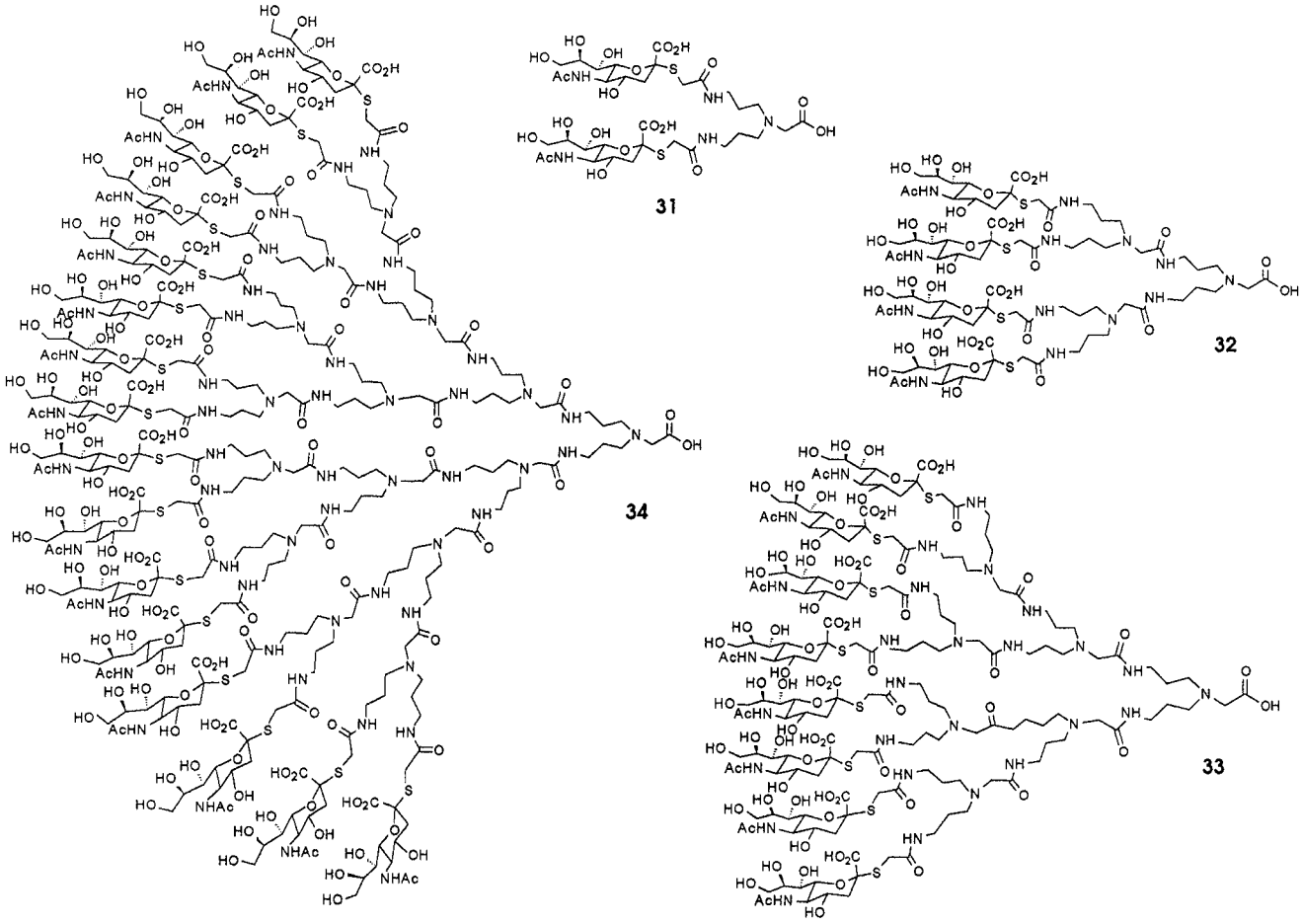
Chart 1



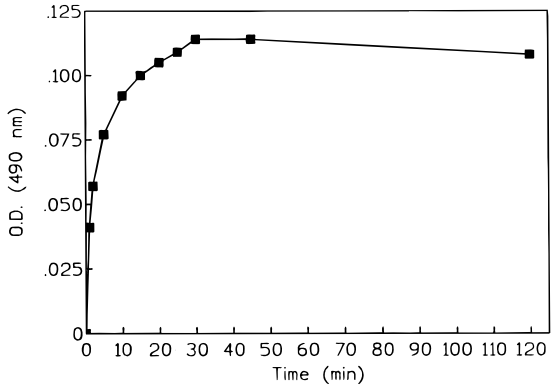


Figure 1. Turbidimetric analysis (microquantitative precipitation) of LFA (0.50 mg/mL) with divergent tetrameric **32** (0.25 mg/mL). The measurements were done in PBS at 25 °C, $\lambda = 490$ nm.

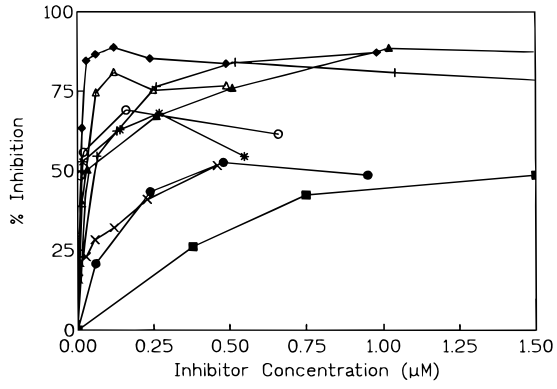


Figure 2. Inhibition of binding of LFA to human α_1-acid glycoprotein by NeuAcαN$_3$ (■), and glycodendrimers **31** (▲), **32** (◆), **33** (●), **34** (×), **14** (+), **20** (*), **25** (△), and **30** (○).

peroxidase-labeled LFA to human α_1-acid glycoprotein (orosomucoid) was determined by ELLA. Human α_1-acid glycoprotein, which contains a large number of α-linked sialoside residues (10−12.5% by weight)[25] was used as a coating antigen, and horseradish peroxidase-labeled LFA was used for quantitative detection. The results for the inhibition of binding of LFA to human α_1-acid glycoprotein are shown in Figure 2. 2-Acetamido-5-deoxy-D-glycero-α-D-galacto-2-nonulopyranosonyl azide (NeuAcαN$_3$)[26] was used as a standard.

In the divergent α-sialodendrimer series, the best results were obtained with tetravalent dendrimer **32**. An IC_{50} of 11.8 nM was measured, representing a 127-fold increase over that of NeuAcαN$_3$ (IC_{50} 1500 nM) used as a standard (Table 1). On a per sialoside basis, each residue was 32 times more potent than the corresponding monomer. Interestingly, no further increase in inhibitory potency was observed for third and fourth generations (**33** and **34**).

In the tethered α-sialodendrimer series, an increase in multivalency resulted in a steady increase in inhibitory potential. Tetra- (**14**), hexa- (**20**), octa- (**25**), and dodeca- (**30**) valent dendrimers exhibited IC_{50} values of 58.7, 16.9, 17.5, and 8.22 nM, respectively. This represents a 26−182-fold (6.4−15-fold/sialoside) jump in inhibitory potential. These data confirm previous findings that multivalency may be responsible for an increase in the binding of carbohydrate−protein interactions.

(25) Jeanloz, R. W. *Glycoproteins*; Elsevier Publishing Co.: New York, 1972; Vol. 5, pp 565−611.

(26) Tropper, F.; Andersson, F. O.; Braun, S.; Roy, R. *Synthesis* **1992**, *7*, 618−620.

Table 1. Inhibition of Binding of Human α_1-Acid Glycoprotein (Orosomucoid) to *L. flavus* by Sialodendrimers

series	compound	IC_{50}[a] (nM)	relative potency[a]
	NeuAcαN_3	1500	1
divergent	**31** (dimer)	176 (352)	8.5 (4.2)
	32 (tetramer)	11.8 (47.2)	127 (32)
	33 (octamer)	206 (1650)	7.3 (0.91)
	34 (hexadecamer)	425 (6800)	3.5 (0.22)
tethered	**14** (tetramer)	58.7 (235)	26 (6.4)
	20 (hexamer)	16.9 (101)	89 (15)
	25 (octamer)	17.5 (140)	86 (11)
	30 (dodecamer)	8.22 (98.6)	182 (15)

[a] Values in parentheses are based on per sialoside residue.

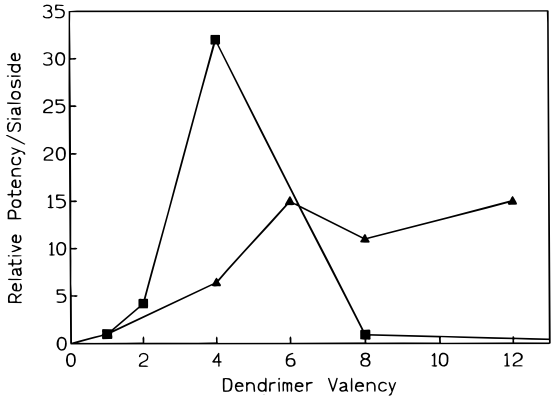


Figure 3. Relative potency per sialoside as a function of dendrimer valency for the divergent series **31**−**34** (■) and for the tethered series **14**, **20**, **25**, and **30** (▲).

For the inhibition of the binding of LFA to human α_1-acid glycoprotein, the tethered dendrimers appear to be more effective than the divergent dendrimers. These results indicate that the increased inhibitory capacity cannot be solely attributed to an increase in multivalency. In fact, divergent hexadecamer **34** showed the poorest inhibition. It may be argued that glycoside conformation and position may be inappropriate in the higher homologues of the divergent dendrimer series to allow for effective inhibition. It is realistic to assume that not all sialic acid residues are involved in tight associations. In fact, when comparing relative potency on a per sialoside basis to dendrimer valency (Figure 3), values fell below one sialoside residue for divergent octamer **33** and hexadecamer **34**. This infers that some sialic acid residues are not involved in binding and negate the effect of some of the tight NeuAc−α_1-acid glycoprotein binding associations, thereby reducing some of the observed relative potency values. This phenomenon has been observed with some previously reported polymeric sialosides.[1−3]

Conclusions

The methods described herein were used for the convenient and efficient synthesis of symmetrical divergent (dendrons) and tethered dendrimers bearing up to sixteen sialic acid residues. All yields were fair to excellent. The sialodendrimers were generated as metabolically stable α-thioglycosides using stereospecific phase transfer catalyzed glycosylation. Turbidimetric analysis confirmed the direct binding properties of α-sialodendrimers **14**, **20**, **25**, and **30**−**34** with the lectin from *L. flavus*. Solid phase inhibition assays (ELLA) revealed that the inhibitory potency increased with a corresponding increase in valency.

This strategy enables the syntheses of hypervalent glycoconjugates with varying carbohydrate densities, conformations, and interglycosidic distances. It is presented as a means by which to generate families of multivalent glycoconjugates in which all of the above considerations, including carbohydrate residue, may be varied. In this manner, the multivalent effect in carbohydrate−protein interactions may come to be understood. Moreover, the divergent series, containing an acid moiety, is amenable to further functionalization and represents key precursors in the search for hypervalent compounds with possible therapeutic uses in areas such as drug targeting. The fact that (di)sialosides are known to bind to sialoadhesin receptors found predominantly in the immunoglobulin (Ig) superfamily of resting B cells[27] makes these novel sialodendrimers particularly interesting.

In summary, the above α-sialodendrimers are multivalent, monodispersed biopolymers. They are complementary to sialopolymers, but surpass them in accuracy for biophysical measurements. They also augment the arsenal of existing multivalent sialosides.[13]

Experimental Methods

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded on a Brüker 500 MHz AMX NMR spectrometer. Proton chemical shifts (δ) are given relative to internal $CHCl_3$ (7.24 ppm) for $CDCl_3$ solutions, to internal dimethyl sulfoxide (2.49 ppm) for DMSO-d_6 solutions, and to internal HOD (4.76 ppm) for D_2O solutions. Carbon chemical shifts are given relative to deuteriochloroform (77.0 ppm) and DMSO-d_6 (39.4 ppm). Assignments were based on COSY, HMQC, and DEPT experiments. Mass spectra were obtained either on a VG 7070-E spectrometer (CI, ether) or on a Kratos Concept IIH spectrometer (FAB-MS, glycerol matrix). Human α_1-acid glycoprotein (orosomucoid) was purchased from Sigma, and the lectins *L. flavus* (LFA) and LFA−peroxidase labeled were obtained from E-Y Laboratories (CA). Thiosialic acid derivative **12**,[6,22] bidirectional dendrimers **31**−**34**,[19] and 2-acetamido-5-deoxy-D-glycero-α-D-galacto-2-nonulopyranosonyl azide (NeuAcαN_3)[26] were synthesized as previously described. Thin layer chromatography was performed on silica gel 60 F-254, and column chromatography was carried out on silica gel 60. Gel permeation chromatography (GPC) was performed using Biogel P-2.

Preparation of 3,3′-Bis(carbobenzyloxy)-3,3′-iminobis(propylamine) (2). To a solution of 3,3′-iminobis(propylamine) (**1**) (2.00 g, 0.015 mol) in dry CH_2Cl_2 (50 mL) was added dropwise a solution of benzyl cyanoformate (4.91 g, 0.030 mol) in dry CH_2Cl_2 (25 mL) over a period of 2 h at 25 °C. Hydrogen cyanide generated during the reaction was carefully introduced into a solution of sodium hydroxide in water. After removal of the organic solvent, the residue was subjected to column chromatography and eluted with $CHCl_3$ and MeOH (2:1) to give compound **2** as a white solid in 72% yield (4.36 g, 0.11 mol): ^{1}H-NMR ($CDCl_3$) δ 1.31 (br s, 1H, NH amine), 1.63 (t, 4H, β-CH_2), 2.61 (t, 4H, $J_{\alpha,\beta}$ = 7.4 Hz, α-CH_2), 3.24 (m, 4H, γ-CH_2), 5.06 (s, 4H, Cbz-CH_2), 5.49 (s, 2H, Cbz-NH), 7.24−7.31 (m, 10H, Cbz-Ph); ^{13}C-NMR ($CDCl_3$) δ 29.6 (β-C), 39.5 (γ-C), 47.4 (α-C), 66.5 (Cbz-CH_2), 128.0 (2×), 128.3, and 128.5 (Cbz-Ph, ortho, meta, para), 136.7 (Cbz-Ph, C-1), 156.5 (C═O); FAB-MS (pos) calcd for $C_{22}H_{29}N_3O_4$ 399.22, found 400.3 ($M^+ + 1$, 83.7% base peak).

Preparation of Monomer 3. To a solution of **2** (4.00 g, 0.010 mol) in acetonitrile (25 mL) was added *tert*-butyl bromoacetate (1.94 g, 0.010 mol). One equivalent of diisopropylethylamine (DIPEA, 1.28 g, 0.010 mol) was added and the solution stirred for 30 min at 25 °C. After solvent evaporation, the residue was subjected to column chromatography and eluted with a gradient of hexane/ethyl acetate to give yellow resin **3** in 87% yield (4.42 g, 0.009 mol): ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 9H, *t*Bu), 1.62 (t, 4H, β-CH_2), 2.51 (t, 4H, $J_{\alpha,\beta}$ = 6.3 Hz, α-CH_2), 3.10 (s, 2H, $NCH_2C(O)$), 3.24 (m, 4H, γ-CH_2), 5.05 (s, 4H, Cbz-CH_2), 5.72 (br s, 2H, Cbz-NH), 7.24−7.31 (m, 10H, Cbz-Ph); ^{13}C-NMR ($CDCl_3$) δ 27.0 (β-C), 28.1 (CH_3's), 39.4 (γ-C), 52.2 (α-C), 56.1 ($NCH_2C(O)$), 66.3 (Cbz-CH_2), 81.4 ($OCMe_3$), 2 × 127.9 and 128.4 (Cbz-Ph, ortho, meta, para), 136.9 (Cbz-Ph, C-1), 156.6 (C═O); FAB-MS (pos) calcd for $C_{28}H_{39}N_3O_6$ 513.28, found 514.3 ($M^+ + 1$, 29.1% base peak).

Synthesis of Acids 4 and 7. Typical Procedure. A solution of **3** (2.00 g, 3.90 mmol) in 50 mL of 30% trifluoroacetic acid in CH_2Cl_2

(27) Powell, L. D.; Jain, R. K.; Matta, K. L.; Sabesan, S.; Varki, A. *J. Biol. Chem.* **1995**, *270*, 7523.

was stirred vigorously for 3 h at 25 °C. The solution was concentrated and dried under vacuum overnight. The trifluoroacetate salt of **4** was recovered as a yellow resin in 96% yield (2.14 g, 3.75 mmol) and used without further purification.

The trifluoroacetate salt of **7** was isolated as above from ester **6** to provide **7** as a yellow resin in quantitative yield.

Data for **4:** ^{1}H-NMR ($CDCl_3$) δ 1.78 (m, 4H, β-CH_2), 3.11 (m, 8H, α-CH_2, γ-CH_2), 3.79 (s, 2H, $NCH_2C(O)$), 4.99 (s, 4H, Cbz-CH_2), 5.81 (br s, 2H, Cbz-NH), 7.24−7.28 (m, 10H, Cbz-Ph), 10.6−11.2 (br s, CO_2H); ^{13}C-NMR ($CDCl_3$) δ 27.8 (β-C), 37.6 (γ-C), 53.0 (α-C), 53.4 ($NCH_2C(O)$), 66.9 (Cbz-CH_2), 114.9 and 117.2 (trifluoroacetate salt), 127.9, 128.2, and 128.4 (Cbz-Ph, ortho, meta, para), 136.3 (Cbz-Ph, C-1), 157.4 (acid C═O), 161.0 and 161.3 (Cbz C═O's), 167.9 (trifluoroacetate salt C═O); FAB-MS (pos) calcd for $C_{24}H_{31}N_3O_6$ 457.22, found 458.2 ($M^+ + 1$, 17.2% base peak).

Data for **7:** ^{1}H-NMR ($CDCl_3$) δ 1.83 (m, 12H, β-CH_2), 3.15 (m, 24H, α-CH_2, γ-CH_2), 3.92 (m, 6H, $NCH_2C(O)$), 5.15 (br s, 8H, Cbz-CH_2), 5.81 (br s, 4H, Cbz-NH), 7.21−7.40 (m, 20H, Cbz-Ph).

Preparation of Di- (5), Tetra- (10), Hexa- (17), Octa- (22), and Dodeca- (27) Amines. Typical Procedure. To compound **3** (400 mg, 0.78 mmol) was added MeOH (10 mL) containing 10% Pd/C (40 mg). H_2 was bubbled through the solution and the mixture stirred for 30 min at 25 °C. The mixture was then filtered and the Pd/C washed twice with MeOH. All filtrates were combined and dried down, giving compound **5** in 90% yield (264 mg, 0.70 mmol). Yellow resin **5** was used as is.

Amines **10**, **17**, **22**, and **27** were obtained in a similar manner as white solids in yields of 95, 93, 100, and 61%, respectively. Reaction times were 20 h.

Data for **5:** ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 9H, *t*Bu), 1.49 (m, 4H, β-CH_2), 1.75 (br s, 4H, NH_2), 2.49 (t, 4H, $J_{\alpha,\beta} = 7.0$ Hz, α-CH_2), 2.64 (t, 4H, $J_{\beta,\gamma} = 6.7$ Hz, γ-CH_2), 3.07 (s, 2H, $NCH_2C(O)$); ^{13}C-NMR ($CDCl_3$) δ 28.1 (CH_3's), 30.9 (β-C), 40.3 (γ-C), 52.0 (α-C), 56.0 ($NCH_2C(O)$), 170.9 (C═O); mass spectrum (CI) (rel intens) *m/z* 246.1 (M^+, 51.6%).

Data for **10:** ^{1}H-NMR ($CDCl_3$) δ 1.23 (m, 4H, a-CH_2), 1.48 (m, 12H, b-CH_2, NH_2), 1.59 (m, 8H, β-CH_2), 2.49 (m, 8H, α-CH_2), 2.72 (m, 8H, γ-CH_2), 3.02 (s, 4H, $NCH_2C(O)$), 3.21 (m, 4H, c-CH_2), 7.56 (s, 2H, NH amide); ^{13}C-NMR ($CDCl_3$) δ 26.6 (a-C), 29.7 (b-C), 30.9 (β-C), 38.8 (c-C), 40.3 (γ-C), 51.9 (α-C), 58.7 ($NCH_2C(O)$), 171.5 (C═O); mass spectrum (CI) (rel intens) *m/z* 458.9 (M^+, base peak).

Data for **17:** ^{1}H-NMR ($CDCl_3$) δ 1.52−1.75 (m, 24H, β-CH_2, NH_2), 2.47−2.92 (m, 30H, α-CH_2, γ-CH_2, a-CH_2), 3.02 (s, 6H, $NCH_2C(O)$), 3.43 (m, 6H, b-CH_2); ^{13}C-NMR ($CDCl_3$) δ 30.5, 30.6 (β-C), 36.9 (b-C), 38.7 (γ-C), 52.7 (α-C), 53.7 (a-C), 58.8 ($NCH_2C(O)$), 170.9 (C═O); FAB-MS (pos) calcd for $C_{30}H_{69}N_{13}O_3$ 659.56, found 660.5 ($M^+ + 1$, 3.1% base peak).

Data for **22:** ^{1}H-NMR (DMSO-d_6) δ 1.22 (m, 4H, a-CH_2), 1.52 (m, 4H, b-CH_2), 1.65 (m, 24H, β-CH_2), 2.36−2.49 (2m, 24H, α-CH_2), 2.75 (m, 12H, $NCH_2C(O)$), 2.99−3.26 (m, 28H, γ-CH_2, c-CH_2), 4.91 (br s, NH_2); ^{13}C-NMR (DMSO-d_6) δ 25.5 (β-C), 26.6 (a-C), 29.1 (b-C), 37.8 (c-C), 38.4 (γ-C), 51.7, 52.0 (α-C), 57.0 ($NCH_2C(O)$), 170.4−173.6 (C═O).

Data for **24:** ^{1}H-NMR (DMSO-d_6) δ 1.53−1.65 (m, 24H, β-CH_2), 2.39−2.51 (m, 24H, α-CH_2), 2.74 (m, 12H, $NCH_2C(O)$), 2.93−3.27 (m, 36H, γ-CH_2, a-CH_2, b-CH_2), 5.00 (br s, NH_2); ^{13}C-NMR (DMSO-d_6) δ 25.3, 26.6 (β-C), 36.7 (b-C), 37.6, 37.8 (γ-C), 51.7, 52.0 (α-C), 57.0, 57.5 ($NCH_2C(O)$), 170.8−173.3 (C═O).

Synthesis of Cbz-Protected Dendrimers 9, 16, 21, and 26. Typical Procedure. To a solution of amine **5** (170 mg, 0.45 mmol) in CH_3CN (15 mL) was added acid **4** (1.2 equiv per amine group, 617 mg, 1.08 mmol) already dissolved in CH_2Cl_2 (2 mL) and neutralized with DIPEA. To the stirred solution were added diisopropylcarbodiimide (DIC, 136 mg, 1.08 mmol) and hydroxybenzotriazole (HOBt, 146 mg, 1.08 mmol), and the mixture was stirred at 25 °C. The pH was kept at 9 by the addition of DIPEA. Completion of the reaction was monitored by the ninhydrin test. After 3 h, the solution was treated with HO^- resin for 15 min in order to remove excess acid and HOBt. The solution was concentrated and the residue subjected to column chromatography using a slow gradient of CH_3CN to 20% water in CH_3CN. Tetravalent **6** was isolated as a yellow resin in 82% yield (448 mg, 0.40 mmol).

Compounds **9**, **16**, **21**, and **26** were prepared in a similar fashion from hexamethylenediamine (**8**) or tris(2-(aminoethyl)amine **15** and from di- or tetravalent acids **4** and **7**. Reaction times required for complete coupling as measured *via* ninhydrin testing were each 20 h. After chromatography, isolated yields were 86% for **9**, 88% for **16**, 79% for **21**, and 72% for **26**.

Data for **6:** ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 9H, *t*Bu), 1.52−1.59 (m, 12H, β-CH_2), 2.47−2.57 (m, 12H, α-CH_2), 3.02−3.27 (m, 18H, γ-CH_2, $NCH_2C(O)$), 5.04 (s, 8H, Cbz-CH_2), 5.52 (br s, 4H, Cbz-NH), 7.24−7.36 (m, 20H, Cbz-Ph), 7.58 (br s, 2H, amide NH); ^{13}C-NMR ($CDCl_3$) δ 27.2 (β-C), 28.1 (CH_3), 37.3 and 38.9 (γ-C), 52.0 and 52.4 (α-C), 55.8 and 57.8 ($NCH_2C(O)$), 57.8 (Cbz-CH_2), 81.4 ($OCMe_3$), 128.0 and 128.5 (Cbz-Ph, ortho, meta, para), 136.7 (Cbz-Ph, C-1), 165.8−171.0 (C═O); FAB-MS (pos) calcd for $C_{60}H_{85}N_9O_{12}$ 1123.63, found 1125.1 ($M^+ + 1$, 14.5% base peak).

Data for **9:** ^{1}H-NMR ($CDCl_3$) δ 1.24 (m, 4H, a-CH_2), 1.43 (m, 4H, b-CH_2), 1.55 (m, 8H, β-CH_2), 1.89 (m, 8H, α-CH_2), 2.94 (br s, 4H, $NCH_2C(O)$), 3.14 (m, 12H, γ-CH_2, c-CH_2), 5.02 (s, 8H, Cbz-CH_2), 5.52 (br s, 4H, Cbz-NH), 7.23−7.30 (m, 20H, Cbz-Ph), 7.58 (br s, 2H, NH amide); ^{13}C-NMR ($CDCl_3$) δ 26.1 (a-C), 27.4 (β-C), 29.3 (b-C), 38.6 (c-C), 38.9 (γ-C), 52.5 (α-C), 58.4 ($NCH_2C(O)$), 66.5 (Cbz-CH_2), 127.8, 128.0, 128.3 (Cbz-Ph, ortho, meta, para), 136.7 (Cbz-Ph, C-1), 156.6−171.2 (C═O); FAB-MS (pos) calcd for $C_{54}H_{74}N_8O_{10}$ 994.55, found 995.5 ($M^+ + 1$, 75.6% base peak).

Data for **16:** ^{1}H-NMR ($CDCl_3$) δ 1.55 (m, 12H, β-CH_2), 2.41 (m, 12H, α-CH_2), 2.53 (m, 6H, a-CH_2), 3.12−3.23 (m, 24H, γ-CH_2, b-CH_2, $NCH_2C(O)$), 5.02 (s, 12H, Cbz-CH_2), 5.65 (br s, 6H, Cbz-NH), 7.23−7.30 (m, 30H, Cbz-Ph), 7.54 (br s, 3H, NH amide); ^{13}C-NMR ($CDCl_3$) δ 27.3 (β-C), 37.4 (b-C), 38.9 (γ-C), 52.5 (α-C), 54.1 (a-C), 58.0 ($NCH_2C(O)$), 66.5 (Cbz-CH_2), 127.8, 128.0, 128.5 (Cbz-Ph, ortho, meta, para), 136.7 (Cbz-Ph, C-1), 156.7−171.6 (C═O); FAB-MS (pos) calcd for $C_{78}H_{105}N_{13}O_{15}$ 1464.77, found 1466.4 ($M^+ + 1$, base peak).

Data for **21:** ^{1}H-NMR ($CDCl_3$) δ 1.21−1.25 (m, 4H, a-CH_2), 1.38−1.44 (m, 4H, b-CH_2), 1.54 (m, 24H, β-CH_2), 2.38 (m, 24H, α-CH_2), 2.90−3.34 (2m, 50H, γ-CH_2, c-CH_2, $NCH_2C(O)$), 5.01 (s, 16H, Cbz-CH_2), 5.64, 5.74 (2br s, 4H, NH amide), 5.84, 5.94 (2br s, 8H, Cbz-NH), 7.23−7.29 (m, 40H, Cbz-Ph), 7.39−7.41 (br s, 2H, NH amide); ^{13}C-NMR ($CDCl_3$) δ 26.4 (a-C), 27.3 (β-C), 29.3 (b-C), 36.6 (c-C), 38.8 (γ-C), 52.3 (α-C), 58.3 ($NCH_2C(O)$), 66.4 (Cbz-CH_2), 127.9, 128.0, 128.4 (Cbz-Ph, ortho, meta, para), 136.6 (Cbz-Ph, C-1), 156.6−172.9 (C═O); FAB-MS (pos) calcd for $C_{118}H_{166}N_{20}O_{22}$ 2216.74, found 2218 ($M^+ + 1$, 3.2% base peak).

Data for **26:** ^{1}H-NMR ($CDCl_3$) δ 1.56 (m, 36H, β-CH_2), 2.39 (m, 42H, α-CH_2, a-CH_2), 2.89−3.35 (2m, 60H, γ-CH_2, b-CH_2, $NCH_2C(O)$), 5.01 (s, 24H, Cbz-CH_2), 5.68−5.82 (m, 12H, Cbz-NH), 7.24−7.30 (m, 60H, Cbz-Ph); ^{13}C-NMR ($CDCl_3$) δ 27.4 (β-C), 37.4 (b-C), 38.9 (γ-C), 52.4 (α-C), 58.3 ($NCH_2C(O)$), 66.4 (Cbz-CH_2), 127.8, 128.0, 128.4 (Cbz-Ph, ortho, meta, para), 136.7 (Cbz-Ph, C-1), 156.7−172.9 (C═O).

Preparation of *N*-Chloroacetylated Dendrimers 11, 18, 23, and 28. Typical Procedure. To a solution of amine **10** (38 mg, 0.086 mmol) in DMSO (2 mL) was added chloroacetic anhydride (1.2 equiv per amine functionality, 70 mg, 0.41 mmol). The solution was stirred for 2 h at 25 °C. The reaction was judged to be complete by the ninhydrin test. The solvent was removed *in vacuo* and the residue was subjected to basic alumina chromatography using 20% H_2O in CH_3CN as eluent in order to remove the chloroacetate anion of **11**. Compound **11** was isolated in 81% yield as a yellow resin (52 mg, 0.069 mmol).

N-Chloroacetylated dendrimers **18**, **23**, and **29** were isolated in 86, 64, and 78% yields, respectively.

Data for **11:** ^{1}H-NMR ($CDCl_3$) δ 1.33 (m, 4H, a-CH_2), 1.51 (m, 4H, b-CH_2), 1.69 (m, 8H, β-CH_2), 2.50 (m, 8H, α-CH_2), 3.02 (br s, 4H, $NCH_2C(O)$), 3.24 (m, 4H, c-CH_2), 3.34 (m, 8H, γ-CH_2), 4.02 (s, 8H, $ClCH_2$); ^{13}C-NMR ($CDCl_3$) δ 26.1 (a-C), 26.9 (β-C), 29.3 (b-C), 38.1 (γ-C), 38.7 (c-C), 42.7 ($ClCH_2$), 52.5 (α-C), 58.4 ($NCH_2C(O)$), 166.3, 171.1 (C═O); FAB-MS (pos) calcd for $C_{30}H_{54}N_8O_6Cl_4$ 762.29, found 763.3 ($M^+ + 1$, 61.9% base peak).

Data for **18:** ^{1}H-NMR (DMSO-d_6) δ 1.75 (m, 12H, β-CH_2), 2.47−2.50 (m, 12H, α-CH_2), 3.12 (m, 30H, γ-CH_2, a-CH_2, b-CH_2, $NCH_2C(O)$), 4.03 (s, 12H, $ClCH_2$); ^{13}C-NMR (DMSO-d_6) δ 26.1 (β-C), 36.7 (b-C), 37.0 (γ-C), 42.6 ($ClCH_2$), 51.9 (α-C), 53.1 (a-C), 60.2 (NCH_2C-

(O)), 165.9−171.4 (C═O); FAB-MS (pos) calcd for $C_{42}H_{75}N_{13}O_9Cl_6$ 1115.39, found 1118.2 ($M^+ + 3$, 0.1% base peak).

Data for **23:** ^{1}H-NMR (DMSO-d_6) δ 1.22 (m, 4H, a-CH_2), 1.35 (m, 4H, b-CH_2), 1.54 (m, 24H, β-CH_2), 2.47−2.50 (m, 24H, α-CH_2), 2.85−3.30 (3m, 42H, γ-CH_2, c-CH_2, $NCH_2C(O)$), 4.03 (s, 16H, $ClCH_2$); ^{13}C-NMR (DMSO-d_6) δ 26.2 (a-C), 26.7 (β-C), 29.1 (b-C), 36.4 (c-C), 37.2 (γ-C), 42.7 ($ClCH_2$), 51.9 (α-C), 57.5 ($NCH_2C(O)$), 165.8, 170.4 (C═O).

Data for **29:** ^{1}H-NMR (DMSO-d_6) δ 1.54 (m, 36H, β-CH_2), 2.40 (m, 36H, α-CH_2), 2.48 (m, 6H, a-CH_2), 2.90−3.42 (3m, 60H, γ-CH_2, b-CH_2, $NCH_2C(O)$), 4.03 (s, 24H, $ClCH_2$); ^{13}C-NMR (DMSO-d_6) δ 26.2, 26.5, 26.6 (β-C), 36.5 (b-C), 36.6, 36.8, 37.0 (γ-C), 42.7 ($ClCH_2$), 51.9 (α-C), 57.5 ($NCH_2C(O)$), 165.8, 170.5 (C═O).

Synthesis of Peracetylated Dendritic α-Thiosialosides 13, 19, 24, and 29. Typical Procedure. *N*-Chloroacetylated dendrimer **11** (20 mg, 0.026 mmol) was dissolved in 1% Et_3N/DMSO (5 mL) and N_2 bubbled through the solution. To this was added thiol **12** (1.1 equiv per *N*-chloroacetyl functionality, 61 mg, 0.12 mmol) and the solution left stirring, under N_2, overnight at 25 °C. The solution was concentrated by lyophilization and then isolated by redissolution in the minimum amount of DMSO (typically 300 μL) and precipitated with ethyl acetate. NMR spectral data shows the incorporation of ethyl acetate in the dendrimer core. Off-white solid **13** was prepared in 87% yield (60 mg, 0.023 mmol).

Peracetylated NeuAc dendrimers **19**, **24**, and **29** were isolated in a similar manner in yields of 87, 83, and 85%, respectively.

Data for **13:** ^{1}H-NMR (DMSO-d_6) δ 1.26 (m, 4H, a-CH_2), 1.41 (m, 4H, b-CH_2), 1.65 (s, 12H, NAc), 1.66−2.10 (m, 12H, β-CH_2, H-3ax), 1.91, 1.96, 2.00, 2.01 (4s, 48H, OAc), 2.48 (m, 8H, α-CH_2), 2.67 (dd, 4H, H-3eq), 2.98−3.15 (m, 24H, γ-CH_2, c-CH_2, SCH_2, $NCH_2C(O)$), 3.74 (s, 12H, CO_2CH_3), 3.75−4.02 (m, 12H, H-5, H-6, H-9), 4.18 (dd, 4H, H-9′), 4.70 (ddd, 4H, H-4), 5.11−5.26 (m, 8H, H-7, H-8), 7.71 (d, 4H, N*H*Ac), 8.16 (br s, 4H, NH amide), 8.76 (br s, 2H, NH amide).

Data for **19:** ^{1}H-NMR (DMSO-d_6) δ 1.65 (s, 18H, NAc), 1.66−2.11 (m, 18H, β-CH_2, H-3ax), 1.91, 1.96, 1.99, 2.08 (4s, 72H, OAc), 2.46 (m, 12H, α-CH_2), 2.55−2.60 (m, 6H, H-3eq), 3.00−3.30 (m, 42H, γ-CH_2, SCH_2, a-CH_2, b-CH_2, $NCH_2C(O)$), 3.74 (s, 18H, CO_2CH_3), 3.74−4.05 (m, 18H, H-5, H-6, H-9), 4.19 (dd, 6H, H-9′), 4.70 (ddd, 6H, H-4), 5.11−5.29 (m, 12H, H-7, H-8).

Data for **24:** ^{1}H-NMR (DMSO-d_6) δ 1.28−146 (2m, 8H, a-CH_2, b-CH_2), 1.65 (s, 24H, NAc), 1.66−2.10 (m, 32H, β-CH_2, H-3ax), 1.92, 1.97, 2.00, 2.08 (4s, 96H, OAc), 2.48 (m, 24H, α-CH_2), 2.66 (m, 8H, H-3eq), 2.90−3.30 (m, 56H, γ-CH_2, c-CH_2, SCH_2, $NCH_2C(O)$), 3.74 (s, 24H, CO_2CH_3), 3.75−4.05 (m, 24H, H-5, H-6, H-9), 4.10−4.20 (m, 8H, H-9′), 4.71 (m, 8H, H-4), 5.12−5.31 (m, 16H, H-7, H-8).

Data for **29:** ^{1}H-NMR (DMSO-d_6) δ 1.65 (s, 36H, NAc), 1.66−2.11 (m, 48H, β-CH_2, H-3ax), 1.91, 1.96, 1.99, 2.08 (4s, 144H, OAc), 2.48 (m, 36H, α-CH_2), 2.70 (m, 12H, H-3eq), 3.00−3.38 (m, 90H, γ-CH_2, SCH_2, a-CH_2, b-CH_2, $NCH_2C(O)$), 3.74 (s, 36H, CO_2CH_3), 3.74−4.08 (m, 36H, H-5, H-6, H-9), 4.17 (m, 12H, H-9′), 4.70 (m, 12H, H-4), 5.11−5.28 (m, 24H, H-7, H-8).

Preparation of Fully Deprotected Dendritic α-Thiosialosides 14, 20, 25, and 30. Typical Procedure. To peracetylated glycodendrimer **13** (60 mg, 0.023 mmol) dissolved in DMSO (0.5 mL), was added 1 N NaOMe in MeOH (5 mL) and the solution was stirred at 25 °C. After 8 h, MeOH was removed *in vacuo* and 0.05 N NaOH added (5 mL). Again the mixture was stirred for 8 h at 25 °C. Solvent was removed by lyophilization, and the residue was purified by gel permeation chromatography on a Biogel-P2 column. Title compound **14** was isolated, after freeze-drying, as a white, spongy solid in 71% yield (31 mg, 0.016 mmol).

Glycodendrimers **20**, **25**, and **30** were synthesized as above in 63, 73, and 56% yields after GPC from compounds **19**, **24**, and **29**, respectively.

Data for **14:** ^{1}H-NMR (D_2O) δ 1.41 (m, 4H, a-CH_2), 1.61 (m, 4H, b-CH_2), 1.90−2.09 (m, 12H, β-CH_2, H-3ax), 2.11 (s, 12H, NAc), 2.93 (dd, 4H, H-3eq), 3.04−4.00 (m, 60H, α-CH_2, γ-CH_2, c-CH_2, SCH_2, $NCH_2C(O)$ and NeuAc residues those excluding above); ^{13}C-NMR (D_2O) (from HMQC) δ 21.6 (NAc), 23.1 (β-C), 26.1 (a-C), 29.3 (b-C), 38.6 (C-3).

Data for **20:** ^{1}H-NMR (D_2O) δ 2.00−2.10 (m, 18H, β-CH_2, H-3ax), 2.10 (s, 18H, NAc), 2.80−4.10 (m, 102H, α-CH_2, γ-CH_2, a-CH_2, b-CH_2, SCH_2, $NCH_2C(O)$ and NeuAc residues excluding those above); ^{13}C-NMR (D_2O) (from HMQC) δ 21.6 (NAc), 23.7 (β-C), 38.2 (C-3).

Data for **25:** ^{1}H-NMR (D_2O) δ 1.40 (m, 4H, a-CH_2), 1.62 (m, 4H, b-CH_2), 2.00−2.10 (m, 56H, β-CH_2, H-3ax, NAc), 2.93 (dd, 8H, H-3eq), 3.20−4.10 (4m, 136H, α-CH_2, γ-CH_2, c-CH_2, SCH_2, $NCH_2C(O)$ and NeuAc residues excluding those above); ^{13}C-NMR (D_2O) (from HMQC) δ 21.6 (NAc), 23.1 (β-C), 25.0 (a-C), 27.6 (b-C), 38.2 (C-3).

Data for **30:** ^{1}H-NMR (D_2O) δ 2.00−2.10 (m, 48H, β-CH_2, H-3ax), 2.10 (s, 36H, NAc), 2.97 (m, 12H, H-3eq), 3.38−4.10 (m, 210H, α-CH_2, γ-CH_2, a-CH_2, b-CH_2, SCH_2, $NCH_2C(O)$ and NeuAc residues excluding those above); ^{13}C-NMR (D_2O) δ 21.7 (NAc), 23.2 (β-C), 38.7 (C-3), 84.2 (C-2).

Turbidimetric Analysis. Turbidimetry experiments were performed in Linbro (Titertek) microtitration plates where 50 μL/well of stock lectin solutions prepared from *L. flavus* (1 mg/mL of PBS) were mixed with 50 μL of glycodendrimer solutions (0.5 mg/mL of PBS) and incubated at room temperature for up to 3 h. The turbidity of the solutions was monitored by reading the optical density (OD) at 490 nm at regular time intervals until no noticeable changes could be observed. Each test was performed in triplicate.

Enzyme-Linked Lectin Assays (ELLA). Linbro (Titertek) microtitration plates were coated with human α_1-acid glycoprotein (orosomucoid) at 100 μL/well of a stock solution of 5 μg/mL in 0.01 M phosphate buffer (pH 7.3) overnight. The wells were then washed three times with 300 μL/well of 0.01 M phosphate buffer (pH 7.3) containing 0.05% (v/v) Tween 20 (PBST). Similar washings with PBST were repeated after each incubation period. Wells were then blocked with 150 μL/well of 1% BSA/PBS for 1 h at 37 °C. After washing, the wells were filled with 100 μL/well of inhibitor solutions and incubated again at 37 °C for 1 h. Inhibitors used include 5-acetamido-5-deoxy-D-glycero-α-D-galacto-2-nonulopyranosonyl azide (NeuAcαN_3) as a reference monovalent compound, spherical glycodendrimers **14**, **20**, **25**, and **30**, and bidirectional glycodendrimers **31**−**34**. Each inhibitor was added in serial 2-fold dilutions (60 μL/well) in PBS with the appropriate lectin−enzyme conjugate concentration (60 μL/well of 100-fold dilution of a 1 mg/mL stock solution of *L. flavus* in PBS) on Nunclon (Delta) microtiter plates and incubated at 37 °C for 1 h. These inhibitor solutions (100 μL) were transferred to the antigen-coated plates and incubated for a second hour. The plates were washed, and 50 μL/well of 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) (1 mg/mL) in citrate−phosphate buffer (0.2 M, pH 4.0 with 0.015% H_2O_2) was added. The reaction was stopped after 20 min by adding 50 μL/well of 1 M H_2SO_4 and the optical density measured at 410 nm relative to 570 nm. The percent inhibition was calculated as follows:

$$\% \text{ inhibition} = (A_{\text{no inhibitor}} - A_{\text{with inhibitor}})/A_{\text{no inhibitor}} \times 100$$

IC_{50} values were reported as the concentration required for 50% inhibition of the coating antigen. Each test was performed in triplicate.

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Supporting Information Available: ^{1}H- and ^{13}C-NMR data of chromatographically isolated compounds **2**−**6**, **9**, **14**, **16**, **20**, **21**, **25**, **26**, and **30** (26 pages). See any current masthead page for ordering and Internet access instructions.

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