Synthesis and Anti-influenza Evaluation of Polyvalent Sialidase Inhibitors Bearing 4-Guanidino-Neu5Ac2en Derivatives

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Polyvalent sialidase inhibitors bearing 4-guanidino-Neu5Ac2en derivatives on a poly-L-glutamine backbone are described. Aiming for a longer retention time of 4-guanidino-Neu5Ac2en (zanamivir) in bronchi and lungs, we focused on supermolecules bearing 4-guanidino-Neu5Ac2en derivatives bound at their C-7 position through noncleavable alkyl ether linkages. We first found that alkylation of the 7-hydroxyl group of sialic acid derivative 8 proceeded smoothly, and produced 7-*O*-alkyl-4-guanidino-Neu5Ac2en derivatives 13, which exhibited equipotent inhibitory activity against not only influenza A virus sialidase but also influenza A virus in the cell culture. Next, we synthesized poly-L-glutamine bearing 7-*O*-alkyl-4-guanidino-Neu5Ac2en derivatives linked by amide bonds, 26, which showed enhanced antiviral activity against influenza A virus and more potent efficacy *in vivo* relative to a monomeric sialidase inhibitor.

Key words anti-influenza drug; sialidase inhibitor; sialic acid; zanamivir; poly-L-glutamine

Influenza virus infection is known to cause substantial fatigue and sometimes death worldwide. Treatments were limited before the development of influenza sialidase (neuraminidase) inhibitors, which has lead to a major breakthrough in the control of influenza.[1—3] The influenza sialidase is one of two viral coat glycoproteins critical for viral replication. It is an attractive target for antiviral intervention because its active site is antigenically conserved among all clinically relevant strains.[4—6]

Zanamivir (4-guanidino-Neu5Ac2en)[7—10] and Oseltamivir phosphate[11,12] are two influenza sialidase inhibitors that have been approved for human use for the treatment of influenza infection (Fig. 1). They are transition state analogs of sialyl glycoside linkage hydrolysis. Oseltamivir phosphate, an ethyl ester prodrug of GS 4071, is administered orally, whereas Zanamivir is delivered by oral inhalation due to its poor oral bioavailability. They have been widely used as they are safe, and effective against both A and B strains, as well as emerging resistant strains.[3]

In developing our sialidase inhibitor, administration by inhalation was preferred because direct delivery of the medicine to the site of viral replication in the respiratory tract assured the use of a much smaller dose and avoidance of systemic effects. However, zanamivir would require frequent administrations because it is rapidly eliminated in the unchanged form in the urine, and completely eliminated within 24 h, after a single dose.[13] Therefore, a new class of sialidase inhibitors to be inhaled at lower and less frequent doses was sought. To circumvent the short retention time of zanamivir, we modifed zanamivir so that it would not be released into the systemic circulation from the respiratory tract. We constructed a polymer carrying zanamivir equivalents on its sides attached by noncleavable linkages (Fig. 2).

In designing a polymer that carries zanamivir equivalents, the important point to consider was how to connect 4-guanidino-Neu5Ac2en molecules to the polymer backbone without a loss of inhibitory activity. From X-ray studies of the complex with sialidase and zanamivir reported by Varghese's

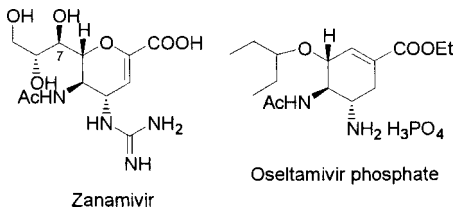

Fig. 1

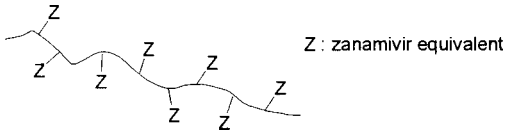

Fig. 2

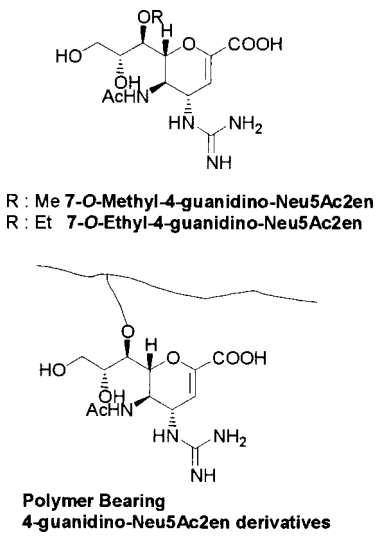

Fig. 3

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group, the 7-hydroxyl group of zanamivir was shown to form no direct hydrogen bonds with sialidase.[14] Moreover, as it was oriented outward of the enzyme active site, it was considered suitable for further elongatation (Fig. 4).[14] Based on this knowledge, we anticipated that the 7-hydroxyl group would help form a suitable link to the polymer.

In the course of our previous studies, we have investigated the synthesis and biological evaluation of analogues related to zanamivir modified at position-7 by using chemoenzymatic reactions.[15] Although the replacement of the 7-OH moiety with *N*-amide groups showed a decrease in virus growth inhibitory activity, replacement with methoxy and ethoxy groups retained or improved the inhibitory activity against both influenza A virus sialidase and influenza A virus growth in cell culture (Fig. 3). Therefore, we were interested in polymers with 4-guanidino-7-*O*-alkyl-Neu5Ac2en analogues attached as multivalent influenza sialidase inhibitors.

Here, we describe the detailed synthesis, characterization, and biological evaluation of 7-*O*-alkyl ether analogues related to zanamivir and polymer-type sialidase inhibitors.

Chemistry

Synthesis of 7-*O*-Alkyl Ether Derivatives Related to Zanamivir In fact, there were no reports on the direct chemical modification of the 7-hydroxyl group of sialic acid except by acylation.[16,17]

We first tried methylating the 7-hydroxyl group of dihydropyranyl intermediates **2**, **4**, and **6**, which were derived from intermediate **1**.[18—20] Despite many attempts, including under basic and acidic conditions, we could not obtain 7-methoxy compounds **3**, **5**, and **7** (Chart 1). We thought the steric hindrance of the 7-hydroxyl group of the glycerol moiety might have been the cause.

Instead of using dihydropyranyl compounds as substrates, we chose tetrahydropyranyl derivative **9**, which was reported to have been 7-*O*-acylated.[16] We found that the alkylation reaction proceeded smoothly with sodium hydrogen and an alkyl halide in DMF solution. Instead of sodium hydrogen and alkyl halide, activation with potassium hydroxide or potassium *tert*-butoxide followed by addition of various dialkylsulfates also afforded 7-*O*-alkylated sialic acid derivatives **9**. Successive methanolysis of **9** gave methyl ester **10**.

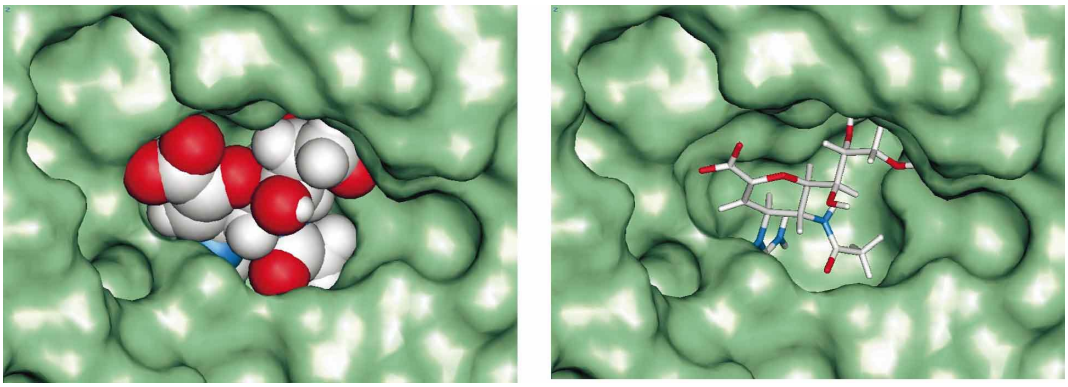


Fig. 4. Perspective View into the Active Site of the N9 Sialidase (Neuraminidase) Complexed with Zanamivir[14]
Left: CPA Model, right: Tube Model.

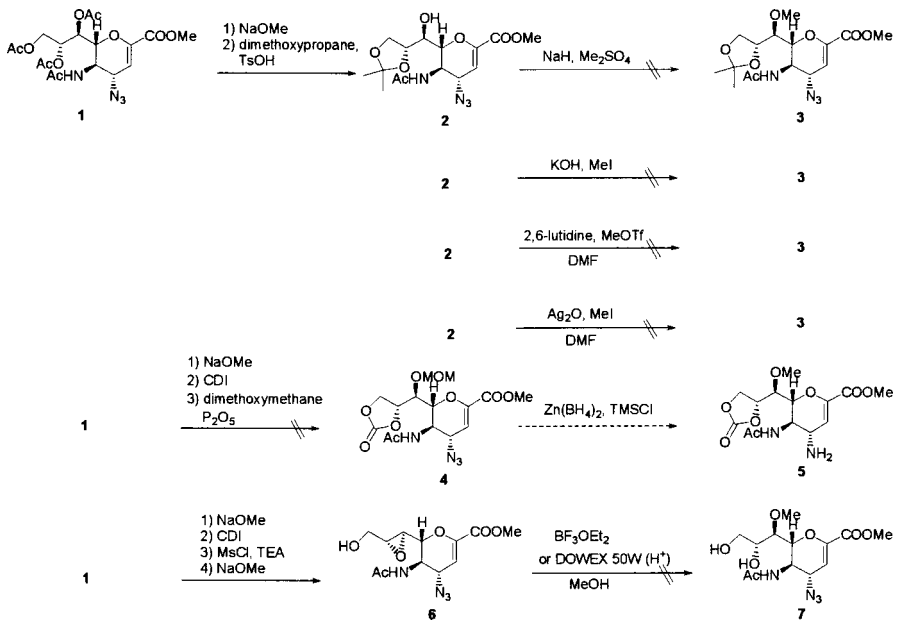


Chart 1. 7-Modification of Neu5Ac2en Intermediates

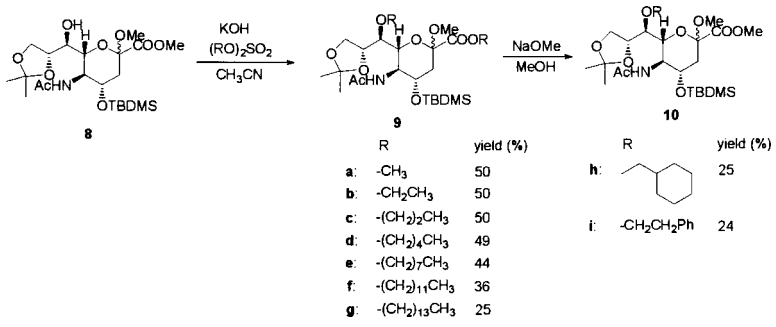


Chart 2. 7-*O*-Alkylation of Sialic Acid Derivative **8**

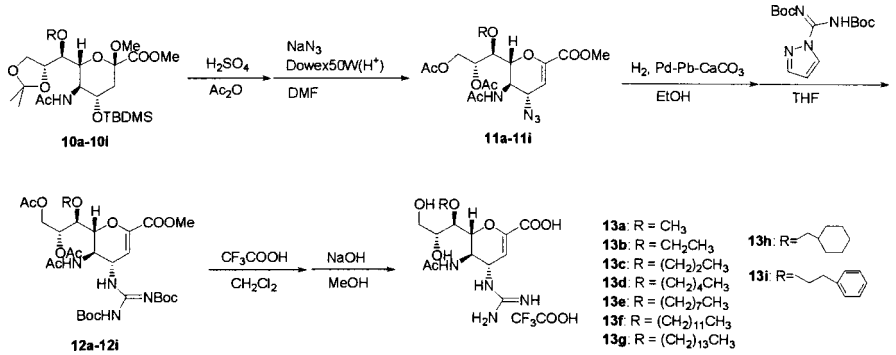


Chart 3. Synthetic Scheme of 7-*O*-Alkylether Derivatives Related to Zanamivir **13**

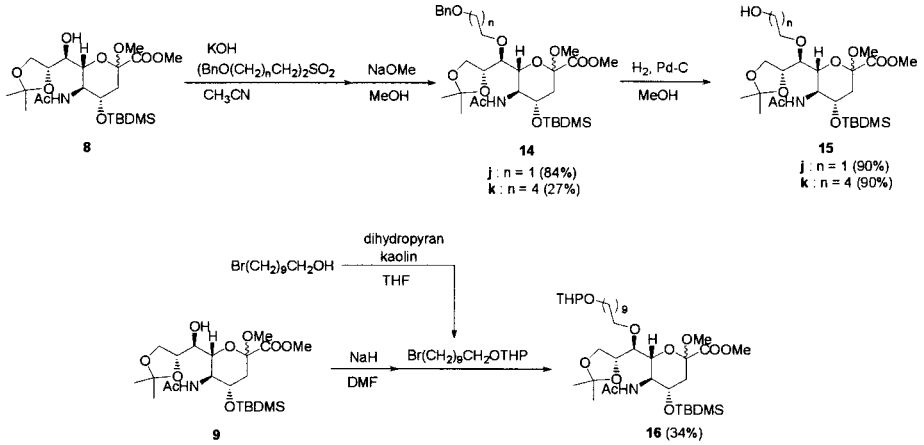


Chart 4. Synthetic Scheme of 7-*O*-Hydroxyalkyl Ether Sialic Acid Derivatives **15** and **16**

Dialkylsulfate was readily prepared by Ru-oxidation of dialkylsulfite, which was obtained by reacting thionyl chloride and alcohol with triethylamine.[30] **10** was converted to 7-*O*-alkylated zanamivir derivatives **13** using conventional methods *via* intermediates 4-azide compounds **11**, and 4-guanidino compounds **12** (Chart 3).[18—22]

To further develop compounds **13**, we modified the terminal position of the alkyl groups to allow coupling with the polymer backbone (Chart 4). Treatment of **8** with potassium hydroxide followed by di(benzyloxyethyl)- or di(benzyloxypentyl)-sulfate gave **14j** and **14k**, respectively. An ensuing reduction with Pd–C gave 7-*O*-hydroxyethyl ether **15j** and 7-*O*-hydroxypentyl ether **15k**, respectively. Treatment of **8** with sodium hydride followed by di[10-(tetrahydro-pyran-2-yloxy)-decyl]sulfate gave **16**. **15j**, **15k**, and **16** were converted to 4-protected guanidine compounds **18** using conventional methods followed by deprotection which gave hydroxyalkyl ether **13j**, **13k**, and **13l**, respectively (Chart 5). Methanolysis of **18** followed by acetonization gave 8,9-*O*-acetonide-7-*O*-hydroxyalkyl ether **19**. The primary alcohol of **19** was tosylated and successive treatment of the resulting compound with sodium azide gave azide compounds **20**. Deprotection of **20** gave azidealkyl ether derivatives **21** (Chart 6). Reaction of **20** with Lindlar catalyst gave amine compounds **22**, and further deprotection of **22** gave aminoalkyl ether derivatives **23**. Acetylation of the primary amine of **22** followed by deprotection gave acetylaminoalkyl ether derivatives **24** and **25** (Chart 7).

Treatment of 7-*O*-aminoethyl-4-guanidino-Neu5Ac2en **23j** with excess 1-(acetoxy)benzotriazole[23] and pyridine in water at room temperature for 2 h exclusively afforded acetylamino derivative **25j** without any *N*-acylguanidine (Chart 8). We

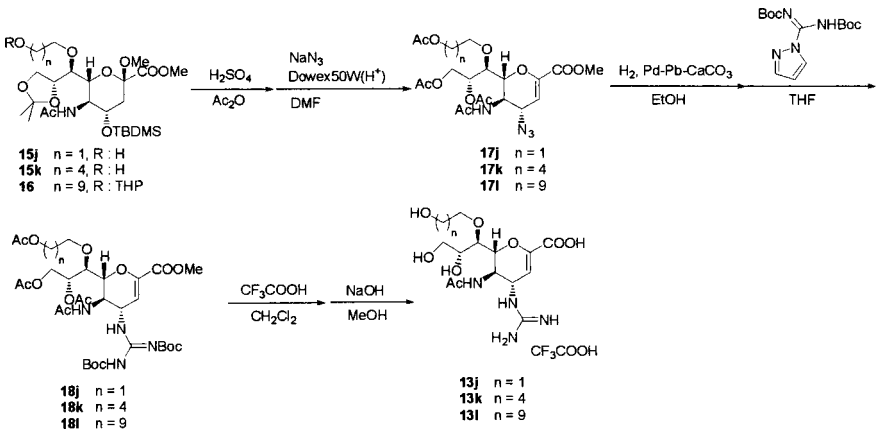


Chart 5. Synthetic Scheme of 7-*O*-Hydroxyalkyl Ether Derivatives **13**

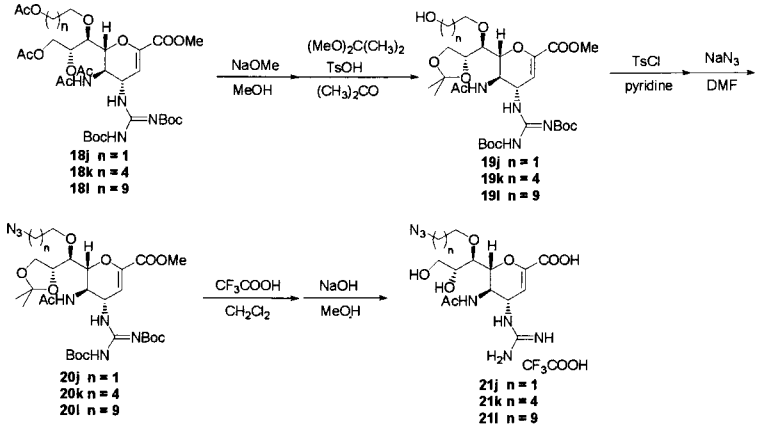


Chart 6. Synthetic Scheme of 7-*O*-Azidealkyl Ether Derivatives **21**

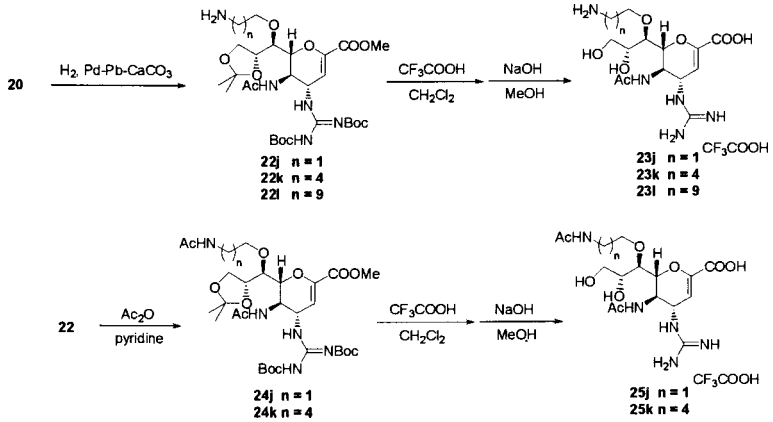


Chart 7. Synthetic Scheme of 7-Aminoalkyl Ether **23** and 7-*O*-Acetylaminoalkyl Ether Derivatives **26**

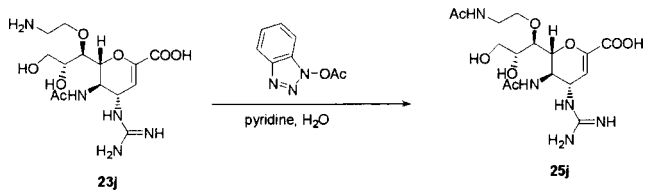


Chart 8. Treatment of **23j** with 1-(Acetoxy)benzotriazole and Pyridine in Water

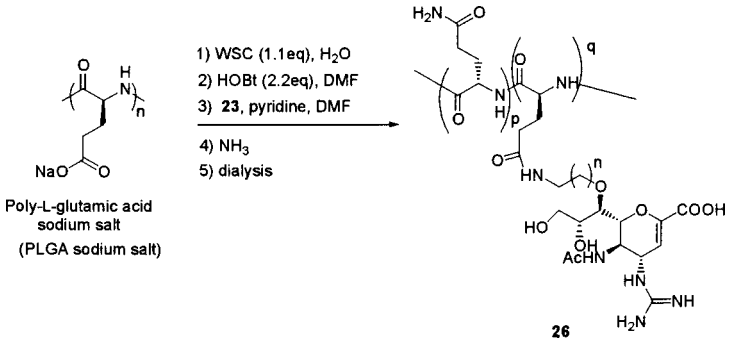


Chart 9. Synthesis of Polymer Bearng 4-Guanidino-Neu5Ac2en Derivatives as Side Chain **26**

found that selective acetylation of the aminoalkyl ether group was achieved. This result suggests that the primary amino group reacted readily perhaps due to its high flexibility. However, the guanidino group was slow to react probably due to intra- or intermolecular salt formation with carboxylic acid and steric hindrance. This selectivity is desirable for the condensation of **23** to form the polymer.

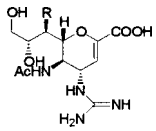
Synthesis of a Poly-L-glutamine Polymer Bearing Zanamivir Molecules As we were able to obtain 7-*O*-alkylamino-4-guanidino-Neu5Ac2en and subject it to selective acylation, we next focused on the synthesis of supermolecules bearing 4-guanidino-Neu5Ac2en derivatives.

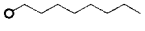
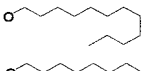
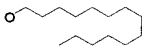
We selected poly-L-glutamic acid as a polymer backbone precursor because poly-L-glutamic acid possesses some advantages as a drug carrier such as good biodegradability, high water solubility, the presence of multiple carboxyl groups that are easily modified chemically, low toxicity, and low immunogenicity.[24)]

Reaction of poly-L-glutamic acid (MW: 50000—100000, average MW: 71400, average extent of polymerization=470) with benzotriazole ester and 0.1 or 0.3 eq of the 7-*O*-aminoalkyl-4-guanidino-Neu5Ac2en **23j**, **23k**, or **23l** for 1 h followed by quenching with aqueous ammonia to convert unreacted activated esters to carbamoyl groups and purification by dialysis afforded poly-L-glutamine conjugate **26**. The ^{1}H-NMR spectrum of conjugate **26** showed the incorporation of approximately 10 or 25% ligand **23** onto the polymer backbone confirming that a complete reaction had occurred.

Biological Evaluation. Structure–Activity Relationship of 7-*O*-Alkylated Derivatives Related to Zanamivir The neuraminidase inhibitory activity and the 50% effective inhibitory concentration (IC_{50}) against influenza A are shown in Table 1.[15)] **13a** (7-*O*-methyl ether), **13b** (7-*O*-ethyl ether), **13c** (7-*O*-*n*-propyl ether), **13d** (7-*O*-*n*-propyl ether), **13e** (7-*O*-*n*-octyl ether), and **13f** (7-*O*-*n*-dodecyl ether), whose linear alkyl ether linkages was less than 12 carbons in length exhibited similar inhibitory activity to zanamivir against influenza A virus sialidase. These compounds showed pronounced improvement in inhibitory activity against influenza A virus infection of MDCK cell compared to zanamivir. However, **13g** (7-*O*-*n*-tetradecyl ether) which has a linear linkage greater than 12 carbons in length showed a slight decrease in inhibitory activity against sialidase and virus infection, probably due to unfavorable steric and electrostatic interaction within the enzyme binding site. Substituting a cyclic aliphatic moiety, aromatic moiety, and hetero atom for the hydroxyl, azide, amino, and acetylamino group did not significantly affect the binding of compounds **13j**, **21j**, **23j**, and **25j**.

Table 1. Sialidase Inhibition and Plaque Reduction Activities of Compounds **13**, **21**, **23**, and **25** (IC_{50} (ng/ml))



	R	Sialidase inhibition assay	Plaque reduction assay
		A/PR/8/34	A/Yamagata/32/89
Zanamivir	OH	5.1—10.2 (1.0)[a)]	1.9—20 (1.0)[a)]
13a		6.1 (1.2)	3.0 (0.15)
13b		26.4 (2.6)	0.7 (0.14)
13c		30.6 (3.0)	1.5 (0.35)
13d		14.3 (2.6)	2.0 (0.23)
13e		20.2 (2.0)	1.8 (0.42)
13f		49.6 (4.9)	2.2 (0.51)
13g		262 (26)	11.0 (5.8)
13h		36.6 (3.6)	3.0 (1.6)
13i		26.3 (2.6)	1.9 (1.0)
13j		10.3 (1.4)	1.8 (0.21)
21j		14.8 (2.0)	1.5 (0.13)
23j		47.7 (6.5)	7.5 (0.63)
25j		9.8 (1.4)	2.4 (0.2)

a) Since IC_{50} values varied depending on the experiment, the relative potencies of the compounds to zanamivir are shown in parentheses based on the IC_{50} values. The IC_{50} values of zanamivir in enzyme inhibition and plaque reduction were 5.1—10.2 ng/ml and 1.9—20 ng/ml, respectively.

Structure–Activity Relationship of Poly-L-glutamine Bearing 4-Guanidino-Neu5Ac2en Derivatives The IC_{50} against influenza neuraminidase and influenza A of the synthesized polymers **26** are shown in Table 2.[25)] The IC_{50} values of each polymer relative to monomeric zanamivir were calculated. The inhibitory activity of all polymers **26** against influenza A virus sialidase was less potent than that of zanamivir. However, the evaluation of the inhibitory activity against influenza A virus infection of MDCK cells demon-

Table 2. Sialidase Inhibitory and Plaque Reduction Activities of Compounds **26** (IC_{50} (nM))[a]

	n	p : q[b]	Sialidase inhibitory assay	Plaque reduction assay
			A/PR/8/34	A/Yamagata/32/89
Zanamivir			11—29 (1.0)[c]	1.3—27 (1.0)[c]
25j	1		9.8 (1.4)	2.4 (0.2)
25k	4		90 (6.0)	5.9 (1.3)
26a	1	10 : 1	114 (5.2)	0.066 (0.0077)
26b	1	3 : 1	364 (22.8)	0.17 (0.020)
26c	4	10 : 1	161 (7.3)	0.072 (0.0085)
26d	9	10 : 1	62 (2.1)	0.076 (0.023)

a) Relative to the monomeric sialidase inhibitor content. *b*) The ratios were determined by ^{1}H-NMR. *c*) Since IC_{50} values varied depending on the experiment, the relative potencies of the compounds to zanamivir are shown in parentheses based on the IC_{50} values. The IC_{50} values of zanamivir in enzyme inhibition and plaque reduction were 11—29 nM and 1.3—27 nM, respectively.

Table 3. Survival Rates of Infected Mice[a] Administered Compound **26c**[b] and Zanamivir[b]

	No. of survivors/Total No. of mice	
	10 d after infection	20 d after infection
Zanamivir	1/8	0/8
26c[c]	7/7	7/7

a) Mice were infected with influenza A/PR/8/34 (H1N1) virus. *b*) Compound **26c** and zanamivir were administered intranasally at doses of 0.3 mmol/kg once beginning 24 h prior to infection. The concentration of 0.3 mmol of **26c** was calculated based on the molar concentration of the monomeric sialidase inhibitor. *c*) $p=0.0009$ *versus* zanamivir (Log-rank test).

strated that all the polymers were much more active than monomeric sialidase inhibitor **25j**, **25k** and zanamivir, regardless of their content of 4-guanidino-Neu5Ac2en molecules and length of the carbon chain. As a control for the biological evaluation, unsubsituted poly-L-glutamic acid was used and showed no inhibitory activity. This enhancement could be explained by the contribution of multivalence or cluster effects.[26—28]

Efficacy of Intranasally Administered Polymeric Sialidase Inhibitor 26c Tested in the Influenza Virus-Infected Mouse Model Furthermore, the efficacy of intranasally administered polymeric sialidase inhibitor **26c** (average MW: 78100) was tested in the influenza virus-infected mouse model in terms of the survival rate of treated and infected mice relative to that of control mice. Compound **26c** was administered intranasally once beginning 24 h prior to infection. It was found that **26c** was much more effective than zanamivir as shown in Table 3 (7/7 survived in the **26c**-treated infected group while there were no survivors in the case of zanamivir). This *in vivo* efficacy is the first such result for polymeric sialidase inhibitors. No *in vitro* cytotoxicity or *in vivo* toxicity in mouse was observed.

In conclusion, we synthesized a series of 7-*O*-alkyl ether derivatives related to zanamivir by direct alkylation of the C-7 alcohol of a sialic acid derivative. Alkyl ether moiety less than 12 carbons in length showed similar activities against influenza A virus sialidase. These compounds showed improved virus growth inhibitory activity compared to zanamivir. We also synthesized poly-L-glutamines carrying 4-guanidino-Neu5Ac2en bound *via* alkyl ether bonds at the C-7 position. All polymers displayed less potent influenza A sialidase inhibitory activity. However, a much greater efficacy against influenza A in the mice model by intranasal administration than zanamivir was observed.

Experimental

General Methods IR spectra were recorded on a Jasco FT-IR 8300 or 8900 spectrometer. NMR spectra were recorded on a JEOL EX 270 (270 MHz) or GSX-400 (400 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a JEOL HX-100, SX-102A or AX-505H mass spectrometer. The melting point (mp) was determined using a Yanagimoto micro-melting point apparatus and was not corrected. Optical rotations were obtained with a Jasco DIP-370 polarimeter. Column chromatography was carried out on Silica gel 60 (230—400 mesh, Art. 9385, Merck). The analytical column for HPLC was an L-Column ODS (5 mm particle size, 4.6 mm i.d.×150 mm).

5-Acetylamino-3,5-dideoxy-2,7-*O*-dimethyl-8,9-*O*-isopropylidene-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-β-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 9a A solution of 5-acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-β-D-*galacto*-2-nonulo-pyranosonic acid methyl ester **8** (1.0 g, 2.03 mmol) in acetonitrile (20 ml) was cooled in an ice bath and slowly mixed with potassium hydroxide (0.67 g, 10.17 mmol). The reaction mixture was stirred at room temperature for 1 h. Then, dimethyl sulfate (0.96 ml, 10.17 mmol) was added dropwise with cooling in an ice bath. The reaction mixture was stirred at room temperature for 1 h, diluted with aqueous ammonium hydrochloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent; CH_2Cl_2 : MeOH=50 : 1) to obtain **9a** as an amorphous solid (510 mg, 1.01 mmol, 50%). mp 160—161 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.33 (3H, s), 1.42 (3H, s), 1.73 (1H, dd, J=13.1, 10.7 Hz), 1.99 (3H, s), 2.28 (1H, dd, J=13.1, 5.1 Hz), 3.22 (3H, s), 3.48—3.56 (1H, m), 3.57 (3H, s), 3.78 (3H, s), 3.80—4.30 (6H, m), 5.16 (1H, d, J=8.2 Hz). FAB-MS m/z: 506 $(M+H)^+$. HR-FAB-MS m/z Calcd for $C_{23}H_{43}O_9NSiNa$ $(M+Na)^+$: 528.2605. Found: 528.2609. IR (KBr) cm^{-1}: 3387, 3291, 3078, 2984, 2954, 2934, 2896, 2857, 1750, 1660, 1554. $[\alpha]_D^{23}$ −13.4° (c=0.10, CH_3OH).

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-methoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 11a **9a** (2.31 g, 4.58 mmol) was treated with acetic anhydride (30 ml), acetic acid (30 ml), sulfuric acid (95%, 3 ml) and the reaction mixture was stirred at room temperature for 16 h. The solvent was poured onto ice-cold aqueous sodium hydrogen carbonate and methylene chloride. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. After adding toluene, the mixture was evaporated, and the residue was dissolved in *N*,*N*-dimethylformamide. To this solution was added sodium azide (2.3 g, 35.4 mmol) and DOWEX 50W X8 (H^+) (2.3 g). The reaction mixture was stirred at 70 °C for 6 h, and filtered. The residue was thoroughly washed with ethyl acetate. The filtrate was combined, washed with aqueous sodium hydrogen carbonate and brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (eluent; CH_2Cl_2 : MeOH=50 : 1) to obtain **11a** as a colorless amorphous solid (1.28 g, 2.99 mmol, 65%). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.51 (3H, s), 3.65 (1H, dd, J=3.0, 2.0 Hz), 3.79 (3H, s), 4.07 (1H, ddd, J=8.8, 8.8, 8.8 Hz), 4.22 (1H, dd, J=12.7, 6.8 Hz), 4.40 (1H, dd, J=8.8, 2.9 Hz), 4.42 (1H, dd, J=8.8, 2.0 Hz), 4.80 (1H, dd, J=12.7, 2.0 Hz), 5.32 (1H, ddd, J=6.8, 3.0, 2.0 Hz), 5.94 (1H, d, J=2.9 Hz), 6.47 (1H, d, J=8.8 Hz). FAB-MS m/z: 429 $(M+H)^+$. HR-FAB-MS m/z Calcd for $C_{17}H_{25}O_9N_4$ $(M+H)^+$: 429.1621. Found: 429.1628. IR (KBr) cm^{-1}: 3334, 3270, 3226, 3073, 2955, 2845, 2099, 1749, 1736, 1684, 1669, 1549, 1439, 1374. $[\alpha]_D^{23}$ +117.4° (c=0.73, $CHCl_3$).

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-(2′,3′-diacetoxy-1′-methyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 12a A solution of **11a** (3.85 g, 8.98 mmol) in ethanol (200 ml) was hydrogenated with Lindlar's catalyst for 2 h. The reaction mixture was filtered through Celite and the precipitate was washed with methanol. The filtrate was combined and evaporated. The residue was dissolved in tetrahydrofuran (50 ml). This solution was mixed with *N*,*N*′-bis-*tert*-butyloxycarbonyl-1*H*-pyrazole-1-carboxamidine (9.6 g, 31.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with aqueous ammonium hydrochlo-

ride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent; hexane : ethyl acetate = 2 : 1) to obtain **12a** as a colorless amorphous solid (4.42 g, 6.86 mmol, 76%). ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.50 (9H, s), 1.97 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.52 (3H, s), 3.54—3.56 (1H, m), 3.78 (3H, s), 4.10 (1H, dd, J=10.5, 1.0 Hz), 4.25—4.40 (2H, m), 4.82 (1H, dd, J=12.0, 3.2 Hz), 5.12 (1H, ddd, J=11.0, 11.0, 2.5 Hz), 5.29—5.31 (1H, m), 5.85 (1H, d, J=2.3 Hz), 6.35 (1H, d, J=8.8 Hz). FAB-MS m/z: 645 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-(2′,3′-dihydroxy-1′-methoxy)propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13a **12a** (53 mg, 0.082 mmol) was treated with methylene chloride (3 ml), and trifluoroacetic acid (30 ml) and the reaction mixture was stirred at room temperature for 4 h. Then, the solvent was removed under reduced pressure. The residue was dissolved in methanol (1 ml) and treated with aqueous sodium hydroxide (1 N, 0.3 ml, 0.3 mmol) with cooling in an ice bath. The reaction was stirred for 30 min and neutralized with DOWEX 50W X8 (H^+). Then, the reaction was filtered and the residue was thoroughly washed with methanol. The filtrate was combined, and the mixture was evaporated under reduced pressure. The crude product was purified by reverse phase cosmosil chromatography (eluent; water : MeOH = 1 : 1) to obtain **13a** as a colorless amorphous solid (24 mg, 0.0693 mmol, 84%). ^{1}H-NMR (D_2O) δ: 2.00 (3H, s), 3.37 (3H, s), 3.55 (1H, d, J=8.5 Hz), 3.65 (1H, dd, J=5.0, 12.0 Hz), 3.80 (1H, dd, J=2.6, 12.0 Hz), 3.90 (1H, m), 4.20 (1H, dd, J=10.0, 10.0 Hz), 4.40—4.50 (2H, m), 5.85 (1H, d, J=1.8 Hz). FAB-MS m/z: 347 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-7-*O*-ethyl-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 10b **8** (6.0 g, 12.2 mmol) in acetonitrile (30 ml) was cooled in an ice bath and mixed with potassium hydroxide (4.0 g, 61.0 mmol). The reaction mixture was stirred at room temperature for 1 h. Then, diethyl sulfate (10.3 g, 67.0 mmol) was added dropwise with cooling in an ice bath and stirred at room temperature for 1 h. The reaction mixture was diluted with aqueous ammonium hydrochloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude ethyl ester was dissolved in methanol, treated with sodium methoxide (4.9 M in methanol, 2.5 ml, 12.0 mmol) at 0 °C, and stirred at room temperature for 1 h. The reaction mixture was diluted with aqueous ammonium hydrochloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent; hexane : ethyl acetate = 1 : 1) to obtain **10b** as an amorphous solid (3.26 g, 6.11 mmol, 50%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.20 (3H, t, J=7.0 Hz), 1.33 (3H, s), 1.42 (3H, s), 1.73 (1H, dd, J=13.1, 10.7 Hz), 1.99 (3H, s), 2.28 (1H, dd, J=13.1, 5.1 Hz), 3.22 (3H, s), 3.40—3.60 (3H, m), 3.79 (3H, s), 3.80—4.30 (6H, m), 5.15 (1H, d, J=8.3 Hz). FAB-MS m/z: 520 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-ethoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 11b Compound **11b** was obtained from **10b** (1.89 g, 3.54 mmol) using the same procedure employed for the preparation of **11a** (colorless amorphous solid, 1.10 g, 2.48 mmol, 70%). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0 Hz), 2.09 (3H, s), 2.10 (3H, s), 2.13 (3H, s), 3.50—3.80 (3H, m), 3.80 (3H, s), 4.05 (1H, m), 4.25 (1H, dd, J=5.0, 12.0 Hz), 4.45—4.55 (2H, m), 4.80 (1H, dd, J=3.2, 12.0 Hz), 5.35 (1H, m), 5.51 (1H, d, J=8.2 Hz), 6.00 (1H, d, J=2.7 Hz). FAB-MS m/z: 443 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-(2′,3′-diacetoxy-1′-ethoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 12b Compound **12b** was obtained from **11b** (580 mg, 1.31 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 530 mg, 0.80 mmol, 61%). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz), 1.49 (9H, s), 1.50 (9H, s), 1.95 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.50—3.80 (3H, m), 3.80 (3H, s), 4.10 (1H, dd, J=1.0, 10.5 Hz), 4.25—4.40 (2H, m), 4.80 (1H, dd, J=3.2, 12.0 Hz), 5.10 (1H, ddd, J=2.5, 11.0, 11.0 Hz), 5.30 (1H, m), 5.83 (1H, d, J=2.3 Hz), 6.20 (1H, d, J=8.8 Hz). FAB-MS m/z: 659 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-(2′,3′-dihydroxy-1′-ethoxy)propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13b Compound **13b** was obtained from **12b** (50 mg, 0.076 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 27 mg, 0.075 mmol, 98%). ^{1}H-NMR (D_2O) δ: 1.05 (3H, t, J=7.0 Hz), 1.97 (3H, s), 3.40 (1H, m), 3.50—3.65 (3H, m), 3.80 (1H, dd, J=5.0, 12.0 Hz), 3.90 (1H, m), 4.15 (1H, dd, J=10.0, 10.0 Hz), 4.40—4.50 (2H, m), 5.55 (1H, d, J=1.8 Hz). FAB-MS m/z: 361 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-7-*O*-*n*-propyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid *n*-Propyl Ester 9c A procedure similar to that used for the preparation of **10b** was employed with di(*n*-propyl)sulfate and **9c** was obtained as a colorless amorphous solid (3.37 g, 5.99 mmol, 49%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 0.86—1.00 (6H, m), 1.33 (3H, s), 1.42 (3H, s), 1.60—1.77 (5H, m), 1.98 (3H, s), 2.27 (1H, dd, J=13.2, 4.6 Hz), 3.23 (3H, s), 3.53—3.68 (3H, m), 3.75—3.98 (2H, m), 4.00—4.30 (6H, m), 5.15 (1H, d, J=7.9 Hz). FAB-MS m/z: 562 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-*n*-propoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid *n*-Propyl Ester 11c Compound **11c** was obtained from **10c** (1.80 g, 3.21 mmol) using the same procedure employed for the preparation of **11a** (colorless amorphous solid, 1.10 g, 2.27 mmol, 71%). ^{1}H-NMR ($CDCl_3$) δ: 0.89—0.99 (6H, m), 1.55—1.80 (4H, m), 2.04 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.40—3.50 (1H, m), 3.55—3.65 (1H, m), 3.70—3.77 (1H, m), 3.92—4.02 (1H, m), 4.29 (1H, dd, J=11.9, 7.3 Hz), 4.45—4.56 (2H, m), 4.63—4.71 (1H, m), 5.30—5.39 (1H, m), 5.68—5.73 (1H, m), 5.98 (1H, d, J=3.3 Hz). FAB-MS m/z: 485 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-(2′,3′-diacetoxy-1′-propoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid *n*-Propyl Ester 12c Compound **12c** was obtained from **11c** (580 mg, 1.20 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 710 mg, 1.01 mmol, 84%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.3 Hz), 0.95 (3H, t, J=7.3 Hz), 1.49 (9H, s), 1.50 (9H, s), 1.55—1.80 (4H, m), 1.95 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.49—3.59 (2H, m), 3.70—3.72 (1H, m), 4.03—4.07 (1H, m), 4.29—4.40 (2H, m), 4.77 (1H, dd, J=12.5, 2.0 Hz), 5.07—5.16 (1H, m), 5.24—5.33 (1H, m), 5.82 (1H, d, J=2.6 Hz), 6.34—6.40 (1H, m), 7.61—7.65 (1H, m), 8.49—8.54 (1H, m). FAB-MS m/z: 701 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-(2′,3′-dihydroxy-1′-propoxy)propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13c Compound **13c** was obtained from **12c** (100 mg, 0.143 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 45 mg, 0.120 mmol, 84%). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.52—1.64 (2H, m), 1.99 (3H, s), 3.37—3.43 (1H, m), 3.51—3.69 (4H, m), 3.81—3.87 (1H, m), 4.00—4.06 (1H, m), 4.29—4.34 (1H, m), 4.39—4.44 (1H, m), 5.56—5.58 (1H, m). FAB-MS m/z: 375 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-7-*O*-*n*-pentyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid *n*-Pentyl Ester 9d A procedure similar to that used for the preparation **10b** was employed with di(*n*-pentyl)sulfate and **9d** was obtained as a colorless amorphous solid (3.70 g, 5.99 mmol, 49%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 0.90—0.94 (6H, m), 1.30—1.38 (8H, m), 1.32 (3H, s), 1.41 (3H, s), 1.53—1.64 (4H, m), 1.73 (1H, dd, J=13.1, 10.7 Hz), 1.97 (3H, s), 2.26 (1H, dd, J=13.1, 5.1 Hz), 3.22 (3H, s), 3.60—3.71 (3H, m), 3.79—3.85 (1H, m), 3.91 (1H, dd, J=10.5, 1.4 Hz), 4.00—4.05 (1H, m), 4.10—4.20 (4H, m), 4.23—4.27 (1H, m), 5.13 (1H, d, J=8.9 Hz). FAB-MS m/z: 618 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-*n*-pentyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 11d Compound **10d** and successively **11d** was obtained from **9d** (440 mg, 0.712 mmol) using the same procedure employed for the preparation of **11a** (colorless amorphous solid, 190 mg, 0.392 mmol, 55%). ^{1}H-NMR ($CDCl_3$) δ: 0.90—0.94 (3H, m), 1.30—1.38 (4H, m), 1.56—1.64 (2H, m), 2.06 (3H, s), 2.07 (3H, s), 2.10 (3H, s), 3.47—3.52 (1H, m), 3.64—3.70 (1H, m), 3.76 (1H, dd, J=4.3, 3.5 Hz), 3.82 (3H, s), 3.96 (1H, ddd, J=8.8, 8.1, 8.1 Hz), 4.23 (1H, dd, J=12.3, 7.1 Hz), 4.49 (1H, dd, J=8.1, 3.0 Hz), 4.55 (1H, dd, J=8.8, 3.5 Hz), 4.73 (1H, dd, J=12.3, 3.0 Hz), 5.36 (1H, ddd, J=7.1, 4.3, 3.0 Hz), 5.69 (1H, br d, J=8.1 Hz), 6.00 (1H, d, J=3.0 Hz). FAB-MS m/z: 485 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-(2′,3′-diacetoxy-1′-pentyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 12d Compound **12d** was obtained from **11d** (109 mg, 0.224 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 115 mg, 0.164 mmol, 73%). ^{1}H-NMR ($CDCl_3$) δ: 0.87—0.91 (3H, m), 1.28—1.35 (4H, m), 1.49 (9H, s), 1.50 (9H, s), 1.56—1.64 (2H, m), 1.94 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.52—3.62 (2H, m), 3.70 (1H, dd, J=4.0, 1.6 Hz), 3.78 (3H, s), 3.92—3.98 (1H, m), 4.07 (1H, dd, J=10.4, 1.6 Hz), 4.26 (1H, dd, J=12.5, 7.6 Hz), 4.83 (1H, dd, J=12.5, 2.4 Hz), 5.07—5.13 (1H, m), 5.28 (1H, ddd, J=7.6, 4.0, 1.6 Hz), 5.82 (1H, d, J=2.4 Hz), 6.36 (1H, br d, J=8.2 Hz), 8.53 (1H, br d, J=8.6 Hz). FAB-MS m/z: 701 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-(2′,3′-dihydroxy-1′-pentyloxy)propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13d Compound **13d** was obtained from **12d** (42 mg, 0.060 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 20 mg, 0.0497 mmol, 83%). ^{1}H-NMR (CD_3OD) δ: 0.87—0.91 (3H, m), 1.27—1.35 (4H, m), 1.49—1.57 (2H, m), 1.99 (3H, s), 3.43—3.54 (2H, m), 3.55—3.59 (1H, m), 3.61 (1H, dd, J=11.3, 4.6 Hz), 3.85 (1H, dd, J=11.3, 3.2 Hz), 3.89—3.94 (1H, m), 4.20—4.23 (1H, m), 4.29—4.33 (2H, m), 5.51 (1H, d, J=2.4 Hz). FAB-MS m/z: 403 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-7-*O*-*n*-octyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 10e A procedure similar to that used for the preparation of compound **10b** was employed with di(*n*-octyl)sulfate and **10e** was obtained as a colorless amorphous solid (3.28 g, 5.43 mmol, 44%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 0.86—0.90 (3H, m), 1.22—1.38 (10H, m), 1.32 (3H, s), 1.41 (3H, s), 1.53—1.64 (2H, m), 1.73 (1H, dd, J=13.1, 10.7 Hz), 1.98 (3H, s), 2.26 (1H, dd, J=13.1, 5.1 Hz), 3.22 (3H, s), 3.60 (1H, dd, J=5.7, 1.4 Hz), 3.62—3.68 (2H, m), 3.79 (3H, s), 3.79—3.86 (1H, m), 3.93 (1H, dd, J=10.6, 1.4 Hz), 4.01 (1H, dd, J=8.6, 7.0 Hz), 4.08—4.17 (2H, m), 4.22—4.28 (1H, m), 5.15 (1H, d, J=8.9 Hz). FAB-MS m/z: 604 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-*n*-octyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 11e Compound **11e** was obtained from **10e** (4.1 g, 5.84 mmol) using the same procedure employed for the preparation of **10a** (colorless amorphous solid, 1.65 g, 3.13 mmol, 53%). ^{1}H-NMR ($CDCl_3$) δ: 0.87—0.91 (3H, m), 1.23—1.35 (10H, m), 1.54—1.64 (2H, m), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.47—3.51 (1H, m), 3.62—3.68 (1H, m), 3.74 (1H, dd, J=4.3, 3.5 Hz), 3.80 (3H, s), 3.95 (1H, ddd, J=8.8, 8.1, 8.1 Hz), 4.22 (1H, dd, J=12.3, 7.1 Hz), 4.47 (1H, dd, J=8.1, 3.0 Hz), 4.52 (1H, dd, J=8.8, 3.5 Hz), 4.72 (1H, dd, J=12.3, 3.0 Hz), 5.33 (1H, ddd, J=7.1, 4.3, 3.0 Hz), 5.79 (1H, br d, J=7.8 Hz), 5.98 (1H, d, J=3.0 Hz). FAB-MS m/z: 527 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-(2′,3′-diacetoxy-1′-octyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 12e Compound **12e** was obtained from **11e** (1.60 g, 3.04 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 1.45 g, 1.95 mmol, 64%). ^{1}H-NMR ($CDCl_3$) δ: 0.86—0.90 (3H, m), 1.24—1.35 (10H, m), 1.49 (9H, s), 1.50 (9H, s), 1.51—1.64 (2H, m), 1.94 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.50—3.62 (2H, m), 3.70 (1H, dd, J=4.0, 1.6 Hz), 3.78 (3H, s), 3.92—3.98 (1H, m), 4.10 (1H, dd, J=10.4, 1.6 Hz), 4.26 (1H, dd, J=12.5, 7.6 Hz), 4.83 (1H, dd, J=12.5, 2.4 Hz), 5.09—5.15 (1H, m), 5.29 (1H, ddd, J=7.6, 4.0, 1.6 Hz), 5.83 (1H, d, J=2.4 Hz), 6.41 (1H, br d, J=9.1 Hz), 8.53 (1H, br d, J=8.7 Hz). FAB-MS m/z: 743 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-(2,3-dihydroxy-1-octyloxy)propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13e Compound **13e** was obtained from **12e** (1.45 g, 1.95 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 840 mg, 1.46 mmol, 75%). ^{1}H-NMR (CD_3OD) δ: 0.87—0.91 (3H, m), 1.25—1.35 (10H, m), 1.49—1.57 (2H, m), 1.99 (3H, s), 3.43—3.56 (2H, m), 3.57 (1H, dd, J=8.3, 2.2 Hz), 3.61 (1H, dd, J=11.3, 4.8 Hz), 3.83 (1H, dd, J=11.3, 3.2 Hz), 3.89—3.95 (1H, m), 4.27—4.32 (2H, m), 4.29—4.37 (1H, m), 5.53 (1H, d, J=1.8 Hz). FAB-MS m/z: 445 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-7-*O*-*n*-dodecyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 10f A procedure similar to that used for the preparation of **10a** was employed with di(*n*-dodecyl)sulfate and **10f** was obtained as a colorless amorphous solid (2.89 g, 4.37 mmol, 36%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 0.86—0.90 (3H, m), 1.22—1.38 (16H, m), 1.32 (3H, s), 1.41 (3H, s), 1.53—1.64 (2H, m), 1.73 (1H, dd, J=13.0, 10.9 Hz), 1.98 (3H, s), 2.26 (1H, dd, J=13.0, 5.0 Hz), 3.22 (3H, s), 3.60 (1H, dd, J=5.6 1.4 Hz), 3.62—3.68 (2H, m), 3.79 (3H, s), 3.79—3.86 (1H, m), 3.93 (1H, dd, J=10.6, 1.4 Hz), 4.01 (1H, dd, J=8.6, 7.0 Hz), 4.09—4.17 (2H, m), 4.22—4.28 (1H, m), 5.14 (1H, d, J=8.9 Hz). FAB-MS m/z: 660 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-*n*-dodecyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 11f Compound **11f** was obtained from **10f** (0.78 g, 1.18 mmol) using the same procedure employed for the preparation of **10b** (colorless amorphous solid, 240 mg, 0.411 mmol, 35%). ^{1}H-NMR ($CDCl_3$) δ: 0.87—0.91 (3H, m), 1.23—1.35 (18H, m), 1.54—1.64 (2H, m), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.47—3.51 (1H, m), 3.62—3.68 (1H, m), 3.74 (1H, dd, J=4.3, 3.5 Hz), 3.80 (3H, s), 3.95 (1H, ddd, J=8.8, 8.1, 8.1 Hz), 4.22 (1H, dd, J=12.3, 7.1 Hz), 4.47 (1H, dd, J=8.1, 3.0 Hz), 4.52 (1H, dd, J=8.8, 3.5 Hz), 4.72 (1H, dd, J=12.3, 3.0 Hz), 5.33 (1H, ddd, J=7.1, 4.3, 3.0 Hz), 5.79 (1H, br d, J=7.8 Hz), 5.98 (1H, d, J=3.0 Hz). FAB-MS m/z: 583 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)-guanidino-6-(2′,3′-diacetoxy-1′-dodecyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 12f Compound **12f** was obtained from **11f** (64 mg, 0.110 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 60 mg, 0.0751 mmol, 68%). ^{1}H-NMR ($CDCl_3$) δ: 0.86—0.90 (3H, m), 1.24—1.35 (18H, m), 1.49 (9H, s), 1.50 (9H, s), 1.51—1.64 (2H, m), 1.94 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.50—3.62 (2H, m), 3.69—3.72 (1H, m), 3.78 (3H, s), 4.10—4.15 (1H, m), 4.25 (1H, dd, J=12.4, 7.4 Hz), 4.28—4.37 (1H, m), 4.83 (1H, dd, J=12.4, 2.4 Hz), 5.12—5.22 (1H, m), 5.26—5.31 (1H, m), 5.82 (1H, d, J=2.4 Hz), 6.41 (1H, br d, J=9.1 Hz), 8.53 (1H, br d, J=8.7 Hz). FAB-MS m/z: 799 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-[2′,3′-dihydroxy-1′-dodecyloxy-propyl]-4-guanidino-4*H*-pyran-2-carboxylic Acid 13f Compound **13f** was obtained from **12f** (24 mg, 30.2 μmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 10 mg, 16.3 μmol, 54%). ^{1}H-NMR (CD_3OD) δ: 0.87—0.92 (3H, m), 1.25—1.35 (18H, m), 1.48—1.57 (2H, m), 2.00 (3H, s), 3.43—3.56 (2H, m), 3.57 (1H, dd, J=9.3, 0.8 Hz), 3.61 (1H, dd, J=11.3, 4.7 Hz), 3.83 (1H, dd, J=11.3, 3.2 Hz), 3.89—3.95 (1H, m), 4.22—4.25 (1H, m), 4.30—4.33 (2H, m), 5.51 (1H, d, J=2.5 Hz). FAB-MS m/z: 501 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-7-*O*-*n*-tetradecyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid *n*-Tetradecyl Ester 9g A procedure similar to that used for the preparation of compound **10a** was employed with di(*n*-tetradecyl)-sulfate and **9g** was obtained as a colorless amorphous solid (2.0 g, 3.00 mmol, 25%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 0.86—0.90 (6H, m), 1.22—1.38 (40H, m), 1.32 (3H, s), 1.41 (3H, s), 1.53—1.64 (4H, m), 1.73 (1H, dd, J=13.0, 10.9 Hz), 1.98 (3H, s), 2.26 (1H, dd, J=13.0, 5.0 Hz), 3.22 (3H, s), 3.60—3.71 (2H, m), 3.78—3.85 (1H, m), 3.92 (1H, dd, J=10.6, 1.5 Hz), 4.01 (1H, dd, J=8.4, 7.3 Hz), 4.10—4.21 (5H, m), 4.22—4.28 (1H, m), 5.15 (1H, d, J=8.8 Hz). FAB-MS m/z: 870 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-*n*-tetradecyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 11g Compound **11g** was obtained from **9g** (1.00 g, 1.14 mmol) using the same procedure employed for the preparation of **11d** (colorless amorphous solid, 190 mg, 0.311 mmol, 27%). ^{1}H-NMR ($CDCl_3$) δ: 0.87—0.91 (3H, m), 1.23—1.35 (22H, m), 1.54—1.64 (2H, m), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.47—3.51 (1H, m), 3.62—3.68 (1H, m), 3.74 (1H, dd, J=4.3, 3.5 Hz), 3.80 (3H, s), 3.95 (1H, ddd, J=8.8, 8.1, 8.1 Hz), 4.22 (1H, dd, J=12.3, 7.1 Hz), 4.47 (1H, dd, J=8.1, 3.0 Hz), 4.52 (1H, dd, J=8.8, 3.5 Hz), 4.72 (1H, dd, J=12.3, 3.0 Hz), 5.33 (1H, ddd, J=7.1, 4.3, 3.0 Hz), 5.79 (1H, br d, J=7.8 Hz), 5.98 (1H, d, J=3.0 Hz). FAB-MS m/z: 611 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)-guanidino-6-(2′,3′-diacetoxy-1′-tetradecyloxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 12g Compound **12g** was obtained from **11g** (87 mg, 0.142 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 62 mg, 0.075 mmol, 53%). ^{1}H-NMR ($CDCl_3$) δ: 0.86—0.90 (3H, m), 1.24—1.35 (22H, m), 1.49 (9H, s), 1.50 (9H, s), 1.51—1.64 (2H, m), 1.94 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.50—3.60 (2H, m), 3.70—3.73 (1H, m), 3.78 (3H, s), 4.10—4.15 (1H, m), 4.25 (1H, dd, J=12.4, 7.5 Hz), 4.31—4.40 (1H, m), 4.83 (1H, dd, J=12.4, 2.4 Hz), 5.09—5.17 (1H, m), 5.26—5.31 (1H, m), 5.82 (1H, d, J=2.4 Hz), 6.80 (1H, br d, J=9.4 Hz), 8.55 (1H, br d, J=8.5 Hz). FAB-MS m/z: 827 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-(2′,3′-dihydroxy-1′-tetradecyloxy)propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13g Compound **13g** was obtained from **12g** (17 mg, 20.5 μmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 10 mg, 18.9 μmol, 92%). ^{1}H-NMR (CD_3OD) δ: 0.88—0.92 (3H, m), 1.25—1.35 (22H, m), 1.48—1.57 (2H, m), 1.99 (3H, s), 3.43—3.56 (2H, m), 3.56 (1H, dd, J=8.5, 1.9 Hz), 3.61 (1H, dd, J=11.3, 4.7 Hz), 3.81 (1H, dd, J=11.3, 3.2 Hz), 3.89—3.94 (1H, m), 4.21—4.24 (1H, m), 4.30—4.33 (2H, m), 5.51 (1H, d, J=2.5 Hz). FAB-MS m/z: 529 $(M+H)^+$.

5-Acetylamino-7-*O*-cyclohexylmethyl-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Cyclohexylmethyl Ester 9h A procedure similar to that used for the preparation of compound **10b** was employed with di(*n*-tetradecyl)sulfate and **9h** was obtained as a colorless amorphous solid (2.0 g, 2.99 mmol, 25%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s),

0.86 (9H, s), 0.90—1.04 (4H, m), 1.12—1.30 (6H, m), 1.31 (3H, s), 1.41 (3H, s), 1.58—1.80 (13H, m), 1.97 (3H, s), 2.25 (1H, dd, *J*=13.1, 5.1 Hz), 3.22 (3H, s), 3.40—3.51 (2H, m), 3.59—3.62 (1H, m), 3.80—3.86 (1H, m), 3.87—3.91 (1H, m), 3.97—4.05 (3H, m), 4.08—4.15 (2H, m), 4.22—4.26 (1H, m), 5.15 (1H, d, *J*=9.0 Hz). FAB-MS *m/z*: 670 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(1′-cyclohexylmethoxy-2′,3′-diacetoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Cyclohexylmethyl Ester 11h Compound **11h** was obtained from **9h** (1.0 g, 1.49 mmol) using the same procedure employed for the preparation of **11d** (colorless amorphous solid, 250 mg, 0.422 mmol, 28%). ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.03 (4H, m), 1.10—1.32 (6H, m), 1.53—1.80 (12H, m), 2.04 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.29 (1H, dd, *J*=8.5, 6.1 Hz), 3.47 (1H, dd, *J*=8.5, 6.5 Hz), 3.71 (1H, dd, *J*=3.8, 3.6 Hz), 3.95 (1H, ddd, *J*=8.6, 8.0, 7.8 Hz), 4.00 (2H, d, *J*=6.6 Hz), 4.28 (1H, dd, *J*=12.3, 7.4 Hz), 4.48 (1H, dd, *J*=8.0, 3.0 Hz), 4.52 (1H, dd, *J*=8.6, 3.6 Hz), 4.65 (1H, dd, *J*=12.3, 3.0 Hz), 5.34 (1H, ddd, *J*=7.4, 3.8, 3.0 Hz), 5.77 (1H, br d, *J*=7.8 Hz), 5.96 (1H, d, *J*=3.0 Hz). FAB-MS *m/z*: 593 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)guanidino-6-(1′-cyclohexylmethoxy-2′,3′-diacetoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Cyclohexylmethyl Ester 12h Compound **12h** was obtained from **11h** (243 mg, 0.410 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 232 mg, 0.286 mmol, 70%). ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.03 (4H, m), 1.10—1.32 (6H, m), 1.49 (9H, s), 1.50 (9H, s), 1.56—1.76 (12H, m), 1.94 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.35—3.42 (2H, m), 3.69 (1H, dd, *J*=3.6, 1.3 Hz), 3.95 (1H, dd, *J*=10.7, 6.7 Hz), 4.03 (1H, dd, *J*=10.7, 6.7 Hz), 4.07 (1H, dd, *J*=10.3, 1.3 Hz), 4.24—4.32 (1H, m), 4.36 (1H, dd, *J*=12.4, 7.9 Hz), 4.75 (1H, dd, *J*=12.4, 2.4 Hz), 5.06—5.13 (1H, m), 5.27 (1H, ddd, *J*=7.9, 3.6, 2.4 Hz), 5.79 (1H, d, *J*=2.3 Hz), 6.80 (1H, br d, *J*=9.1 Hz), 8.53 (1H, br d, *J*=9.1 Hz). FAB-MS *m/z*: 809 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-(1′-cyclohexylmethoxy-2′,3′-dihydroxy)propyl-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid 13h Compound **13h** was obtained from **12h** (113 mg, 0.139 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 56 mg, 0.130 mmol, 94%). ^{1}H-NMR (CD_3OD) δ: 0.88—1.03 (2H, m), 1.10—1.32 (3H, m), 1.47—1.81 (6H, m), 1.99 (3H, s), 3.24—3.38 (2H, m), 3.54 (1H, dd, *J*=8.3, 1.3 Hz), 3.63 (1H, dd, *J*=11.3, 4.6 Hz), 3.81 (1H, dd, *J*=11.3, 3.0 Hz), 3.89—4.05 (1H, m), 4.28—4.32 (2H, m), 4.35—4.42 (1H, m), 5.68—5.70 (1H, m). FAB-MS *m/z*: 429 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-7-*O*-phenylethyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulopyranosonic Acid Phenylethyl Ester 9i A procedure similar to that used for the preparation of compound **9a** was employed with di(phenylethyl)sulfate and **9i** was obtained as a colorless amorphous solid (343 mg, 0.50 mmol, 24%). ^{1}H-NMR ($CDCl_3$) δ: −0.03 (3H, s), 0.16 (3H, s), 0.88 (9H, s), 1.29 (3H, s), 1.43 (3H, s), 1.47 (1H, dd, *J*=13.0, 10.8 Hz), 1.70 (3H, s), 2.16 (1H, dd, *J*=13.0, 5.0 Hz), 2.82—2.97 (2H, m), 2.98—3.05 (3H, m), 3.07 (3H, s), 3.57—3.65 (2H, m), 4.03—4.06 (1H, m), 4.15—4.21 (2H, m), 4.22—4.48 (6H, m), 7.21—7.35 (10H, m). FAB-MS *m/z*: 686 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-azide-6-(2′,3′-diacetoxy-1′-phenethoxy)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Phenethyl Ester 11i Compound **11i** was obtained from **9i** (710 mg, 1.03 mmol) using the same procedure employed for the preparation of **11a** (colorless amorphous solid, 220 mg, 0.361 mmol, 35%). ^{1}H-NMR ($CDCl_3$) δ: 1.71 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.85—3.09 (4H, m), 3.33—3.39 (1H, m), 3.41—3.43 (1H, m), 4.08—4.12 (1H, m), 4.30—4.42 (4H, m), 4.66—4.71 (2H, m), 4.75 (1H, dd, *J*=12.3, 2.6 Hz), 5.33—5.38 (1H, m), 5.82 (1H, d, *J*=2.7 Hz) 7.20—7.45 (10H, m). FAB-MS *m/z*: 609 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)guanidino-6-(2′,3′-diacetoxy-1′-phenethyl)propyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Phenethyl Ester 12i Compound **12i** was obtained from **11i** (138 mg, 0.226 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 140 mg, 0.169 mmol, 75%). ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.53 (9H, s), 1.89 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.83—3.00 (4H, m), 3.64—3.72 (2H, m), 3.86—3.93 (1H, m), 3.98—4.07 (1H, m), 4.11—4.15 (1H, m), 4.22 (1H, dd, *J*=12.5, 7.4 Hz), 4.36 (2H, t, *J*=7.3 Hz), 4.76 (1H, dd, *J*=12.5, 2.2 Hz), 5.07—5.13 (1H, m), 5.28 (1H, ddd, *J*=7.4, 4.3, 2.2 Hz), 5.73 (1H, d, *J*=2.3 Hz), 7.02 (1H, br d, *J*=8.8 Hz), 7.17—7.33 (10H, m), 8.53 (1H, br d, *J*=9.1 Hz). FAB-MS *m/z*: 825 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-[2′,3′-dihydroxy-1′-phenethoxy-propyl]-4-guanidino-4*H*-pyran-2-carboxylic Acid 13i Compound **13i** was obtained from **12i** (110 mg, 0.133 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 33 mg, 0.076 mmol, 57%). ^{1}H-NMR (CD_3OD) δ: 1.99 (3H, s), 2.78—2.92 (2H, m), 3.52 (1H, dd, *J*=11.3, 4.5 Hz), 3.61—3.65 (1H, m), 3.65—3.77 (3H, m), 3.87—3.91 (1H, m), 4.29—4.41 (3H, m), 5.66 (1H, d, *J*=2.2 Hz), 7.13—7.27 (10H, m). FAB-MS *m/z*: 437 $(M+H)^+$.

5-Acetylamino-7-*O*-(2′-benzyloxy)ethyl-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 14j A procedure similar to that used for the preparation of compound **10b** was employed with di(2-benzyloxyethyl)sulfate and **14j** was obtained as a colorless amorphous solid (11.4 g, 18.3 mmol, 30%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.32 (3H, s), 1.41 (3H, s), 1.59 (1H, dd, *J*=13.1, 10.8 Hz), 1.70 (3H, s), 2.30 (1H, dd, *J*=13.1, 5.0 Hz), 3.18 (3H, s), 3.22—3.36 (1H, m), 3.52—3.56 (1H, m), 3.67—3.78 (2H, m), 3.78 (3H, s), 3.79—3.82 (1H, m), 4.05—4.29 (4H, m), 4.35 (1H, dd, *J*=10.3, 2.5 Hz), 4.56 (2H, s), 4.70—4.81 (1H, m), 6.43 (1H, br d, *J*=7.3 Hz), 7.28—7.38 (5H, m). MS (FAB) *m/z* 625 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{31}H_{51}O_{10}NSiNa$: 648.3180; Found 648.3173 $(M+Na)^+$.

5-Acetylamino-3,5-dideoxy-7-*O*-(2′-hydroxy)ethyl-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 15j Compounds **14j** (27.3 g, 43.5 mmol) was hydrogenated with palladium carbon (10 g) in methanol (500 ml) at room temperature for 3 h and filtrated. The residue was washed with methanol thoroughly and evaporated under reduced pressure. The residue was purufied by silica gel chromatography (eluent; ethyl acetate) to give compound **15j** as an amorphous solid (21.0 g, 39.1 mmol, 90%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.85 (9H, s), 1.32 (3H, s), 1.42 (3H, s), 1.75 (1H, dd, *J*=13.1, 10.8 Hz), 1.99 (3H, s), 2.27 (1H, dd, *J*=13.1, 4.8 Hz), 3.21 (3H, s), 3.64—3.79 (4H, m), 3.80 (3H, s), 3.80—3.88 (1H, m), 3.92—4.02 (2H, m), 4.03—4.18 (3H, m), 4.23—4.31 (1H, m), 5.47 (1H, br d, *J*=8.9 Hz). MS (FAB) *m/z* 536 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{24}H_{46}O_{10}NSi$: 536.2891; Found 536.2880 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-6-[1′-(2″-Acetoxy)ethoxy-2′,3′-diacetoxy]propyl-5-acetylamino-4-azide-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 17j Compound **17j** was obtained from **15j** (20.2 g, 37.7 mmol) using the same procedure employed for the preparation of **11a** (colorless amorphous solid, 15.1 g, 30.2 mmol, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.05 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 2.13 (3H, s), 3.69—3.89 (3H, m), 3.80 (3H, s), 3.92—4.01 (1H, m), 4.20—4.30 (3H, m), 4.58—4.66 (2H, m), 4.75 (1H, dd, *J*=12.4, 2.9 Hz), 5.34—5.40 (1H, m), 5.97 (1H, d, *J*=2.7 Hz), 6.14 (1H, br d, *J*=7.9 Hz). MS (FAB) *m/z* 501 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{20}H_{29}O_{11}N_4$: 501.1833; Found 501.1807 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-6-[1′-(2″-Acetoxy)ethoxy-2′,3′-diacetoxy]propyl-5-acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 18j Compound **18j** was obtained from **17j** (14.9 g, 29.7 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 18.7 g, 26.1 mmol, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.48 (9H, s), 1.49 (9H, s), 1.95 (3H, s), 2.06 (3H, s), 2.10 (6H, s), 3.72—3.77 (1H, m), 3.78 (3H, s), 3.80—3.87 (2H, m), 4.09 (1H, dd, *J*=11.0, 2.8 Hz), 4.22—4.28 (3H, m), 4.29—4.40 (1H, m), 4.84 (1H, dd, *J*=12.6, 2.4 Hz), 5.07—5.17 (1H, m), 5.27—5.33 (1H, m), 5.83 (1H, d, *J*=2.4 Hz), 6.63 (1H, br d, *J*=9.0 Hz), 8.55 (1H, br d, *J*=8.8 Hz). IR ($CDCl_3$) ν_{max} 4213, 3425, 2955, 2101, 1740, 1681, 1602, 1510, 1439 cm^{-1}. MS (FAB) *m/z* 717 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{31}H_{49}O_{15}N_4$: 717.3215; Found 717.3202 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-[2′,3′-dihydroxy-1′-(2″-hydroxy)ethoxy]propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13j Compound **13j** was obtained from **18j** (50 mg, 0.0846 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 15 mg, 0.0397 mmol, 47%). ^{1}H-NMR (400 MHz, D_2O) δ: 2.04 (3H, s), 3.55—3.76 (6H, m), 3.90 (1H, dd, *J*=11.8, 2.9 Hz), 3.97—4.06 (1H, m), 4.19—4.28 (1H, m), 4.38—4.48 (2H, m), 5.63 (1H, d, *J*=2.2 Hz). MS (FAB) *m/z* 377 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{14}H_{25}O_8N_4$: 377.1672; Found 377.1683 $(M+H)^+$.

5-Acetylamino-7-*O*-(5′-benzyloxy)pentyl-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 14k A procedure similar to that used for the preparation of compound **10b** was employed with di(5-benzyloxypentyl)sulfate and **14k** was obtained as a colorless amorphous solid (5.70 g, 8.53 mmol, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.31 (3H, s), 1.33—1.51 (2H, m), 1.41 (3H, s), 1.58—1.79 (5H, m), 1.96 (3H, s), 2.27 (1H, dd, *J*=13.1, 5.0 Hz), 3.22 (3H, s), 3.42—3.50 (2H, m), 3.55—3.83 (4H, m), 3.77 (3H, s), 3.94—4.06 (2H, m), 4.09—4.28 (3H, m), 4.50 (2H, s), 5.28 (1H, d, *J*=8.8 Hz), 7.26—7.38 (5H, m). MS (FAB) *m/z* 668 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{34}H_{58}O_{10}NSi$:

668.3830; Found 668.3818 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-7-*O*-(5′-hydroxy)pentyl-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 15k Compound **15k** was obtained from **14k** (6.52 g, 9.76 mmol) using the same procedure employed for the preparation of **15j** (colorless amorphous solid, 4.72 g, 8.17 mmol, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (3H, s), 0.06 (3H, s), 0.85 (9H, s), 1.31 (3H, s), 1.41 (3H, s), 1.48—1.79 (7H, m), 1.97 (3H, s), 2.26 (1H, dd, J=13.0, 5.0 Hz), 3.22 (3H, s), 3.55—3.87 (6H, m), 3.79 (3H, s), 3.85—4.19 (4H, m), 4.20—4.29 (1H, m), 5.46 (1H, br d, J=8.7 Hz). MS (FAB) m/z 578 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{27}H_{52}O_{10}NSi$: 578.3361; Found 578.3360 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-6-[1′-(5″-Acetoxy)pentyloxy-2′,3′-diacetoxy]-propyl-5-acetylamino-4-azide-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 17k Compound **17k** was obtained from **15k** (4.60 g, 7.96 mmol) using the same procedure employed for the preparation of **15j** (colorless amorphous solid, 2.51 g, 4.62 mmol, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35—1.49 (2H, m), 1.56—1.71 (4H, m), 2.04 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.43—3.52 (1H, m), 3.67—3.77 (2H, m), 3.80 (3H, s), 3.80—3.92 (1H, m), 4.05—4.13 (2H, m), 4.21 (1H, dd, J=12.4, 7.2 Hz), 4.50 (1H, dd, J=8.2, 3.0 Hz), 4.58 (1H, dd, J=9.0, 3.2 Hz), 4.72 (1H, dd, J=12.3, 3.0 Hz), 5.28—5.38 (1H, m), 5.97 (1H, d, J=2.8 Hz), 6.01 (1H, br d, J=8.0 Hz). MS (FAB) m/z 543 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{23}H_{34}O_{11}N_4K$: 581.1861; Found 581.1849 $(M+K)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-6-[1′-(5″-Acetoxy)pentyloxy-2′,3′-diacetoxy]-propyl-5-acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 18k Compound **18k** was obtained from **17k** (2.51 g, 4.63 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 2.50 g, 3.29 mmol, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40—1.55 (2H, m), 1.49 (9H, s), 1.50 (9H, s), 1.60—1.75 (4H, m), 1.94 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.50—3.65 (2H, m), 3.67—3.71 (1H, m), 3.78 (3H, s), 4.02—4.12 (2H, m), 4.21—4.34 (2H, m), 4.83 (1H, dd, J=12.5, 2.3 Hz), 5.08—5.16 (1H, m), 5.23—5.32 (1H, m), 5.83 (1H, d, J=2.5 Hz), 6.29 (1H, br d, J=8.6 Hz), 8.53 (1H, br d, J=8.6 Hz). MS (FAB) m/z 759 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{34}H_{55}O_{15}N_4$: 759.3664; Found 759.3657 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-[2′,3′-dihydroxy-1′-(5″-hydroxy)pentyloxy]propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13k Compound **13k** was obtained from **18k** (70 mg, 0.104 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 33 mg, 0.0788 mmol, 76%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.26—1.38 (2H, m), 1.44—1.58 (4H, m), 2.00 (3H, s), 3.38—3.48 (1H, m), 3.51—3.68 (5H, m), 3.85 (1H, dd, J=11.8, 2.3 Hz), 3.90—4.00 (1H, m), 4.09—4.20 (1H, m), 4.32—4.41 (2H, m), 5.57 (1H, d, J=2.2 Hz). MS (FAB) m/z 419 $(M+H)^+$.

5-Acetylamino-3,5-dideoxy-8,9-*O*-isopropylidene-2-*O*-methyl-4-*O*-*tert*-butyldimethylsilyl-7-*O*-[10′-(tetrahydro-pyran-2″-yloxy)decyl]-D-*glycero*-D-*galacto*-2-nonulo-pyranosonic Acid Methyl Ester 16 A solution of **8** (30.0 g, 61.0 mmol) in *N*,*N*-dimethyl formamide (180 ml) was cooled in an ice bath and mixed with sodium hydride (5.33 g, 122.0 mmol). The reaction mixture was stirred at room temperature for 30 min. Then the mixture was mixed with 2-(10-bromo-decyloxy)tetrahydropyran (22.9 g, 73.2 mmol) dropwise and stirred at 50 °C for 3 h. The reaction mixture was diluted with aqueous ammonium hydrochloride and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent; hexane : ethyl acetate=2 : 1) to give compound **16** as a colorless amorphous solid (16.6 g, 22.7 mmol, 37%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.25—1.38 (16H, m), 1.31 (3H, s), 1.41 (3H, s), 1.48—1.65 (6H, m), 1.79—1.87 (1H, m), 1.97 (3H, s), 2.26 (1H, dd, J=13.0, 5.0 Hz), 3.22 (3H, s), 3.34—3.41 (1H, m), 3.47—3.53 (1H, m), 3.57—3.95 (7H, m), 3.78 (3H, s), 3.97—4.04 (1H, m), 4.08—4.17 (2H, m), 4.21—4.28 (1H, m), 4.57—4.60 (1H, m), 5.14 (1H, br d, J=8.9 Hz). MS (FAB) m/z 754 $(M+Na)^+$. HR-MS (FAB) Calcd for $C_{37}H_{69}O_{11}NSiNa$: 754.4537; Found 754.4520 $(M+Na)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-6-[1′-(10″-Acetoxy)decyloxy-2′,3′-diacetoxy]-propyl-5-acetylamino-4-azide-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 17l Compound **17l** was obtained from **16** (16.6 g, 22.7 mmol) using the same procedure employed for the preparation of **11a** (colorless amorphous solid, 8.02 g, 13.1 mmol, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24—1.38 (12H, m), 1.53—1.65 (4H, m), 2.04 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.44—3.52 (1H, m), 3.60—3.68 (1H, m), 3.71—3.75 (1H, m), 3.80 (3H, s), 3.92—4.00 (1H, m), 4.05 (2H, t, J=6.8 Hz), 4.21 (1H, dd, J=12.4, 7.2 Hz), 4.43—4.55 (2H, m), 4.75 (1H, dd, J=12.4, 2.9 Hz), 5.28—5.37 (1H, m), 5.81 (1H, br d, J=8.1 Hz), 5.97 (1H, d, J=2.8 Hz). MS (FAB) m/z 613 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{28}H_{45}O_{11}N_4$: 613.3084; Found 613.3094 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,2′*R*)-6-[1′-(10″-Acetoxy)decyloxy-2′,3′-diacetoxy]-propyl-5-acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 18l Compound **18l** was obtained from **17l** (8.20 g, 13.4 mmol) using the same procedure employed for the preparation of **12a** (colorless amorphous solid, 7.85 g, 9.47 mmol, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25—1.40 (12H, m), 1.49 (9H, s), 1.50 (9H, s), 1.55—1.70 (4H, m), 1.94 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.50—3.63 (2H, m), 3.67—3.71 (1H, m), 3.78 (3H, s), 4.00—4.12 (3H, m), 4.21—4.36 (2H, m), 4.82 (1H, dd, J=12.5, 2.3 Hz), 5.08—5.16 (1H, m), 5.23—5.32 (1H, m), 5.83 (1H, d, J=2.4 Hz), 6.22 (1H, br d, J=8.7 Hz), 8.52 (1H, br d, J=8.7 Hz). MS (FAB) m/z 829 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{39}H_{64}O_{15}N_4Na$: 851.4266; Found 851.4282 $(M+Na)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-5,6-dihydro-6-[2′,3′-dihydroxy-1′-(10″-hydroxy)decyloxy]propyl-4-guanidino-4*H*-pyran-2-carboxylic Acid 13l Compound **13l** was obtained from **18l** (100 mg, 0.120 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 33 mg, 0.067 mmol, 56%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.23—1.40 (12H, m), 1.44—1.58 (4H, m), 2.00 (3H, s), 3.38—3.48 (1H, m), 3.51—3.68 (5H, m), 3.85 (1H, dd, J=11.8, 2.3 Hz), 3.90—4.00 (1H, m), 4.09—4.20 (1H, m), 4.32—4.41 (2H, m), 5.57 (1H, d, J=2.2 Hz). MS (FAB) m/z 489 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)-guanidino-6-[(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)-(2‴-hydroxy-ethyloxy)]methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 19j A solution of **18j** (18.7 g, 26.1 mmol) in methanol (200 ml) was cooled in an ice bath and mixed with a solution of sodium methoxide in methanol (4.9 N, 2.6 ml, 13.0 mmol). The reaction mixture was stirred for 1 h. Then, the reaction mixture was cooled in an ice bath and neutralized with DOWEX 50W X8 (H^+). The reaction mixture was filtered and the precipitate was washed with methanol. The filtrate was evaporated and the residue was dissolved in acetone (200 ml). To the solution, dimethoxypropane (40 ml) and *p*-toluene sulfonic acid monohydrate (500 mg, 2.62 mmol) were added and the mixture was stirred for 2 h. The reaction mixture was combined with sodium hydrogen carbonate (3 g) with cooling in an ice bath. Then, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, the precipitate was washed with ethyl acetate, and the filtrate was evaporated. The residue was dissolved in ethyl acetate (200 ml) and mixed with aqueous hydrogen chloride (1 N, 100 ml). The reaction mixture was stirred for 5 min, and then extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: ethyl acetate) to give compound **19j** as a colorless amorphous solid (12.1 g, 19.1 mmol, 73%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.44 (3H, s), 1.48 (9H, s), 1.50 (9H, s), 1.96 (3H, s), 3.59—3.82 (3H, m), 3.79 (3H, s), 3.85—3.89 (1H, m), 3.95—4.04 (1H, m), 4.10—4.27 (3H, m), 4.29—4.42 (2H, m), 5.10—5.20 (1H, m), 5.83 (1H, d, J=2.3 Hz), 6.65 (1H, br d, J=8.9 Hz), 8.54 (1H, br d, J=8.6 Hz). MS (FAB) m/z 631 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{28}H_{46}O_{12}N_4Na$: 653.3110; Found 653.2990 $(M+Na)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)guanidino-6-[(2‴-azido-ethyloxy)-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)]methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 20j Compound **19j** (12.1 g, 19.2 mmol) was dissolved in anhydrous pyridine (150 ml), cooled in an ice bath, and mixed with *p*-toluenesulfonyl chloride (7.32 g, 38.4 mmol). The reaction mixture was stirred for 2 h at room temperature, then the reaction mixture was diluted with brine and extracted with ethyl acetate. The organic layer was washed with 1 N aqueous hydrogen chloride, aqueous sodium hydrogen carbonate, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in *N*,*N*-dimethylformamide (100 ml) and mixed with sodium azide (2.49 g, 38.4 mmol). The reaction mixture was stirred for 5 h at 50 °C. Then, the reaction mixture was diluted with brine and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: hexane : ethyl acetate=1 : 2) to give compound **20j** as a colorless amorphous solid (10.7 g, 16.3 mmol, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, s), 1.45 (3H, s), 1.48 (9H, s), 1.50 (9H, s), 1.94 (3H, s), 3.31—3.41 (1H, m), 3.47—3.58 (1H, m), 3.75—3.86 (2H, m), 3.78 (3H, s), 3.95—4.05 (1H, m), 4.10—4.32 (5H, m), 5.12—5.22 (1H, m), 5.82 (1H, d, J=2.4 Hz), 6.47 (1H, br d, J=8.0 Hz), 8.53 (1H, br d,

J=8.6 Hz). MS (FAB) m/z 656 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(2″-azido)ethyloxy-2′,3′-dihydroxy]propyl-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid 21j Compound **21j** was obtained from **20j** (110 mg, 0.168 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 46 mg, 0.114 mmol, 68%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.99 (3H, s), 3.33—3.52 (2H, m), 3.55—3.80 (4H, m), 3.86 (1H, dd, J=11.9, 2.6 Hz), 3.92—4.01 (1H, m), 4.17—4.27 (1H, m), 4.33—4.42 (2H, m), 5.57 (1H, d, J=2.1 Hz). MS (FAB) m/z 401 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{14}H_{23}O_7N_7K$: 440.1296; Found 440.1286 $(M+K)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)-guanidino-6-[(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)-(5‴-hydroxy-pentyloxy)]methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 19k Compound **19k** was obtained from **18k** (2.45 g, 3.23 mmol) using the same procedure as that for the preparation of **19j** (colorless amorphous solid, 46 mg, 0.114 mmol, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.43 (3H, s), 1.49 (9H, s), 1.50 (9H, s), 1.50—1.60 (2H, m), 1.65—1.75 (4H, m), 1.92 (3H, s), 3.49—3.75 (4H, m), 3.77 (3H, s), 3.75—3.81 (1H, m), 4.00—4.08 (1H, m), 4.10—4.32 (4H, m), 5.12—5.21 (1H, m), 5.85 (1H, d, J=2.3 Hz), 6.63 (1H, br d, J=8.3 Hz), 8.41 (1H, br d, J=8.7 Hz). MS (FAB) m/z 673 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{31}H_{53}O_{12}N_4$: 673.3680; Found 673.3679 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)-guanidino-6-[(5‴-azido-pentyloxy)-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 20k Compound **20k** was obtained from **19k** (1.03 g, 1.53 mmol) using the same procedure as that for the preparation of **20j** (colorless amorphous solid, 46 mg, 0.114 mmol, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.43 (3H, s), 1.49 (9H, s), 1.50 (9H, s), 1.53—1.75 (6H, m), 1.94 (3H, s), 3.27 (2H, t, J=6.9 Hz), 3.54—3.63 (1H, m), 3.74—3.84 (2H, m), 3.78 (3H, s), 4.02—4.35 (5H, m), 5.08—5.17 (1H, m), 5.82 (1H, d, J=2.5 Hz), 6.05 (1H, br d, J=8.8 Hz), 8.51 (1H, br d, J=8.7 Hz). MS (FAB) m/z 698 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{31}H_{52}O_{11}N_7$: 698.3725; Found 698.3731 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(5″-azido)propyloxy-2′,3′-dihydroxy]propyl-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid 21k Compound **21k** was obtained from **20k** (100 mg, 0.143 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 43 mg, 0.0969 mmol, 68%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.29—1.43 (2H, m), 1.48—1.65 (4H, m), 2.00 (3H, s), 3.23—3.33 (2H, m), 3.36—3.49 (1H, m), 3.52—3.68 (3H, m), 3.79—3.90 (1H, m), 3.89—4.00 (1H, m), 4.10—4.22 (1H, m), 4.30—4.42 (2H, m), 5.55—5.58 (1H, m). MS (FAB) m/z 444 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{17}H_{29}O_7N_7Na$: 466.2026; Found 466.2007 $(M+Na)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-[(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)-(10‴-hydroxy-decyloxy)]methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 19l Compound **19l** was obtained from **18l** (7.85 g, 9.47 mmol) using the same procedure employed for the preparation of **19j** (colorless amorphous solid, 43 mg, 0.0969 mmol, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25—1.40 (12H, m), 1.35 (3H, s), 1.43 (3H, s), 1.49 (9H, s), 1.50 (9H, s), 1.50—1.65 (4H, m), 1.93 (3H, s), 3.49—3.75 (4H, m), 3.74—3.77 (1H, m), 3.77 (3H, s), 4.00—4.08 (1H, m), 4.00—4.35 (4H, m), 5.12—5.21 (1H, m), 5.83 (1H, d, J=2.5 Hz), 6.06 (1H, br d, J=9.0 Hz), 8.51 (1H, br d, J=8.7 Hz). MS (FAB) m/z 743 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{36}H_{62}O_{12}N_4Na$: 765.4262; Found 765.4258 $(M+Na)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*″-*tert*-butyloxycarbonyl)guanidino-6-[(10‴-azido-decyloxy)-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)]methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 20l Compound **20l** was obtained from **19l** (5.11 g, 6.88 mmol) using the same procedure employed for the preparation of **20j** (colorless amorphous solid, 3.92 g, 5.10 mmol, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25—1.40 (12H, m), 1.35 (3H, s), 1.43 (3H, s), 1.49 (9H, s), 1.50 (9H, s), 1.55—1.65 (4H, m), 1.93 (3H, s), 3.25 (2H, t, J=6.9 Hz), 3.54—3.63 (1H, m), 3.68—3.75 (1H, m), 3.75—3.77 (1H, m), 3.78 (3H, s), 4.00—4.11 (2H, m), 4.14—4.22 (3H, m), 5.08—5.16 (1H, m), 5.82 (1H, d, J=2.5 Hz), 6.00 (1H, br d, J=9.0 Hz), 8.51 (1H, br d, J=8.7 Hz). MS (FAB) m/z 768 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{36}H_{61}O_{11}N_7Na$: 790.4327; Found 790.4343 $(M+Na)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(10″-azido)decyloxy-2′,3′-dihydroxy]propyl-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid 21l Compound **21l** was obtained from **20l** (300 mg, 0.390 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 101 mg, 0.196 mmol, 50%). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.25—1.40 (12H, m), 1.47—1.65 (4H, m), 1.99 (3H, s), 3.22—3.30 (2H, m), 3.40—3.65 (4H, m), 3.81 (1H, dd, J=13.3, 3.0 Hz), 3.87—3.96 (1H, m), 4.20—4.27 (1H, m), 4.30—4.34 (2H, m), 5.51 (1H, d, J=2.4 Hz). MS (FAB) m/z 514 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{22}H_{40}O_7N_7$: 514.2989; Found 514.3016 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-[(2‴-amino-ethyoxy)-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)]methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 22j Compound **20j** (640 mg, 0.976 mmol) in ethanol (20 ml) was hydrogenated with Lindlar's catalyst for 5 h. The reaction mixture was filtered through Celite and the precipitate was washed with methanol. The filtrate was combined and evaporated. The residue was purified by silica gel chromatography (eluent; 2-propanol : ethyl acetate : distilled water=2 : 5 : 1) to give compound **22j** as a colorless amorphous solid (330 mg, 0.523 mmol, 54%). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.33 (3H, s), 1.41 (3H, s), 1.46 (9H, s), 1.52 (9H, s), 1.95 (3H, s), 2.72—2.80 (2H, m), 3.40—3.50 (1H, m), 3.78 (3H, s), 3.80—3.90 (2H, m), 4.03—4.10 (1H, m), 4.15—4.30 (3H, m), 4.40—4.48 (1H, m), 5.00—5.06 (1H, m), 5.88 (1H, d, J=2.4 Hz). MS (FAB) m/z 630 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(2″-amino)ethyloxy-2′,3′-dihydroxy]propyl-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid Trifluoroacetic Acid Salt 23j Compound **23j** was obtained from **22j** (930 mg, 1.48 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 503 mg, 1.02 mmol, 70%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.90 (3H, s), 3.02—3.08 (2H, m), 3.43—3.57 (2H, m), 3.62 (1H, dd, J=7.3, 2.9 Hz), 3.71 (1H, dd, J=11.7, 3.7 Hz), 3.72—3.80 (1H, m), 3.83—3.89 (1H, m), 4.12—4.16 (1H, m), 4.21 (1H, dd, J=8.1, 2.2 Hz), 4.27 (1H, dd, J=8.8, 2.9 Hz), 5.55 (1H, d, J=2.9 Hz). MS (FAB) m/z 376 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{14}H_{26}O_7N_5$: 376.1832; Found 376.1842 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)-guanidino-6-[(5‴-amino-pentyloxy)-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)]methyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 22k Compound **22k** was obtained from **20k** (2.01 g, 2.88 mmol) using the same procedure employed for the preparation of **22j** (colorless amorphous solid, 1.94 g, 2.88 mmol, quant.). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.30—1.65 (6H, m), 1.33 (3H, s), 1.40 (3H, s), 1.46 (9H, s), 1.53 (9H, s), 1.94 (3H, s), 2.60—2.67 (1H, m), 3.40—3.50 (1H, m), 3.73—3.83 (2H, m), 3.78 (3H, s), 4.02—4.09 (2H, m), 4.13—4.35 (5H, m), 4.96—5.02 (1H, m), 5.86 (1H, d, J=2.4 Hz), 6.14 (1H, br d, J=8.6 Hz), 8.51 (1H, br d, J=8.7 Hz). MS (FAB) m/z 672 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(5″-amino)pentyloxy-2′,3′-dihydroxy-propyl]-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid Trifluoroacetic Acid Salt 23k Compound **23k** was obtained from **22k** (1.00 g, 1.49 mmol) using the same procedure employed for the preparation of **13a** (colorless amorphous solid, 430 mg, 0.809 mmol, 54%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.30—1.43 (2H, m), 1.50—1.70 (4H, m), 2.00 (3H, s), 2.92—3.00 (2H, m), 3.38—3.47 (1H, m), 3.55—3.67 (3H, m), 3.80—3.88 (1H, m), 3.90—3.99 (1H, m), 4.10—4.22 (1H, m), 4.32—4.42 (2H, m), 5.58 (1H, d, J=2.0 Hz). MS (FAB) m/z 418 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{17}H_{32}O_7N_5$: 418.2302; Found 418.2307 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(10″-amino)decyloxy-2′,3′-dihydroxy]propyl-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid Trifluoroacetic Acid Salt 23l Compound **22l** was obtained from **20l** (100 mg, 0.195 mmol) using the same procedure employed for the preparation of **22j**. Compound **23l** was obtained from **22l** (100 mg, 0.195 mmol) using the same procedure employed for the preparation of **23j** (colorless amorphous solid, 71 mg, 0.145 mmol, 75%). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.18—1.40 (12H, m), 1.43—1.61 (4H, m), 1.98 (3H, s), 2.80—2.95 (2H, m), 3.35—3.46 (1H, m), 3.50—3.68 (3H, m), 3.79—3.89 (1H, m), 3.89—3.98 (1H, m), 4.09—4.18 (1H, m), 4.30—4.40 (2H, m), 5.55 (1H, m). MS (FAB) m/z 488 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{22}H_{42}O_7N_5$: 488.3084; Found 488.3091 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*S*,4″*R*)-5-Acetylamino-6-[(2‴-acetylamino-ethyloxy)-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)]methyl-4-(bis-*N*,*N*′-*tert*-butyloxycarbonyl)guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 24j **22j** (76 mg, 0.121 mmol) was treated with acetic anhydride (1 ml) and pyridine (1 ml). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured into brine and extracted with methylene chloride. The organic layer was washed with aqueous hydrogen chloride (1 N), aqueous sodium hydrogen carbonate, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent; ethyl acetate : methanol=10 : 1) to give compound **24j** as a colorless amorphous solid (77 mg, 0.114 mmol, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H,

s), 1.43 (3H, s), 1.48 (9H, s), 1.49 (9H, s), 1.98 (3H, s), 1.99 (3H, s), 3.25—3.35 (1H, m), 3.41—3.60 (2H, m), 3.79 (3H, s), 3.80—3.90 (1H, m), 3.96—4.40 (7H, m), 5.05—5.16 (1H, m), 5.84 (1H, d, J=2.4 Hz), 6.52 (1H, br d, J=9.2 Hz), 7.44 (1H, m), 8.57 (1H, br d, J=8.8 Hz). MS (FAB) m/z 672 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(2″-acetylamino)ethyloxy-2′,3′-dihydroxy-propyl]-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid 25j. Method A Compound **25j** was obtained from **24j** (50 mg, 0.0745 mmol) using the same procedure as that for the preparation of **13a** (colorless amorphous, 26 mg, 0.0623 mmol, 84%).

Method B Compound **23j** (10.0 mg, 0.0204 mmol) was dissolved in distilled water (1 ml) and mixed with 1-(acetoxy)benzotriazole (7.2 mg, 0.0408 mmol) and pyridine (0.1 ml). The reaction mixture was stirred for 2 h at room temperature, and then concentrated under reduced pressure. The crude product was purified by reverse phase cosmosil chromatography (eluent; water : MeOH=4 : 1) to obtain **25j** as a colorless amorphous (7.0 mg, 0.0168 mmol, 82%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.95 (3H, s), 1.98 (3H, s), 3.20—3.40 (2H, m), 3.43—3.52 (1H, m), 3.55—3.70 (3H, m), 3.81 (1H, dd, J=11.8, 2.7 Hz), 3.92—3.99 (1H, m), 4.12—4.22 (1H, m), 4.30—4.39 (2H, m), 5.58 (1H, d, J=2.9 Hz). MS (FAB) m/z 418 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{16}H_{28}O_8N_5$: 418.1937; Found 418.1935 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,4″*S*)-5-Acetylamino-6-[(5‴-acetylamino-pentyloxy)-(2″,2″-dimethyl-[1″,3″]dioxolan-4″-yl)]methyl]-4-(bis-*N*,*N*″-*tert*-butyloxy-carbonyl)guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester 24k Compound **24k** was obtained from **22k** (140 mg, 0.201 mmol) using the same procedure as that for the preparation of **24j** (colorless amorphous, 110 mg, 0.154 mmol, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, s), 1.43 (3H, s), 1.49 (9H, s), 1.50 (9H, s), 1.53—1.75 (6H, m), 1.94 (3H, s), 1.95 (3H, s), 3.21—3.28 (2H, m), 3.40—3.52 (1H, m), 3.74—3.84 (2H, m), 3.78 (3H, s), 4.02—4.35 (5H, m), 5.10—5.19 (1H, m), 5.84 (1H, d, J=2.4 Hz), 6.14 (1H, br d, J=8.6 Hz), 8.51 (1H, br d, J=8.7 Hz). MS (FAB) m/z 714 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{33}H_{56}O_{12}N_5$: 714.3926; Found 714.3942 $(M+H)^+$.

(4*S*,5*R*,6*R*,1′*R*,2′*R*)-5-Acetylamino-6-[1′-(5″-acetylamino)pentyloxy-2′,3′-dihydroxy]propyl-5,6-dihydro-4-guanidino-4*H*-pyran-2-carboxylic Acid 25k Compound **25k** was obtained from **24k** (110 mg, 0.154 mmol) using the same procedure as that for the preparation of **13a** (colorless amorphous, 46 mg, 0.100 mmol, 65%). ^{1}H-NMR (400 MHz, D_2O) δ: 1.20—1.38 (2H, m), 1.40—1.60 (4H, m), 1.92 (3H, s), 1.99 (3H, s), 3.05—3.17 (2H, m), 3.35—3.47 (1H, m), 3.52—3.72 (3H, m), 3.75—3.98 (2H, m), 4.09—4.18 (1H, m), 4.32—4.40 (2H, m), 5.55—5.58 (1H, m). MS (FAB) m/z 460 $(M+H)^+$. HR-MS (FAB) Calcd for $C_{19}H_{34}O_8N_5$: 460.2407; Found 460.2432 $(M+H)^+$.

Polymer Carrying 7-*O*-Ethyl-4-guanidino-Neu5Ac2en 26a To a solution of poly-L-glutamic acid sodium salt (50 mg, 0.331 mol/unit) in distilled water (1 ml), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (70 mg, 0.364 mmol) and a solution of 1-hydroxybenzotriazole (111 mg, 0.728 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 30 min. Then, the precipitate was separated by filtration, washed with water, and dried under vacuum. The residue was dissolved in *N*,*N*-dimethylformamide (2 ml) and combined with compound **23j** (20 mg, 0.041 mmol) and pyridine (0.1 ml). The reaction mixture was stirred at room temperature for 2 h. Then, to the reaction, aqueous ammonia (25%, 3 ml) was added and the mixture was stirred at room temperature for 2 d. The reaction mixture was concentrated under reduced pressure. To the residue, 2-propanol was added and the precipitate was separated by filtration. The residue was dissolved in water, dialyzed for 2 d in water (MW 12000 cut off), and lyophilized to afford **26a** as a colorless powder (43 mg, 0.268 mmol, 81%). Mol fraction of sugar unit=0.076. ^{1}H-NMR (400 MHz, D_2O) δ: 1.85—2.18 (26.4H, m), 1.98 (3H, s), 2.22—2.48 (26.4H, m), 3.20—3.40 (2H, m), 3.42—3.70 (4H, m), 3.78—3.88 (1H, m), 3.92—4.00 (1H, m), 4.12—4.52 (16.2H, m), 5.58—5.62 (1H, m).

Polymer Carrying 7-*O*-Ethyl-4-guanidino-Neu5Ac2en 26b Polymer **26b** was obtained from **23j** (56 mg, 0.116 mmol) using the same procedure as that for the preparation of **26a** (52 mg, 0.24 mmol, 73%). Mol fraction of sugar unit=0.25. ^{1}H-NMR (400 MHz, D_2O) δ: 1.85—2.18 (8H, m), 1.98 (3H, s), 2.22—2.48 (8H, m), 3.20—3.40 (2H, m), 3.42—3.70 (4H, m), 3.78—3.88 (1H, m), 3.92—4.00 (1H, m), 4.12—4.52 (7H, m), 5.58—5.62 (1H, m).

Polymer Carrying 7-*O*-Pentyl-4-guanidino-Neu5Ac2en 26c Polymer **26c** was obtained from **23k** (22 mg, 0.041 mmol) using the same procedure as that for the preparation of **26a** (45 mg, 0.27 mmol, 81%). Mol fraction of sugar unit=0.09. ^{1}H-NMR (400 MHz, D_2O) δ: 1.15—1.35 (2H, m), 1.38—1.55 (4H, m), 1.85—2.18 (22H, m), 1.98 (3H, s), 2.22—2.48 (22H, m), 3.20—3.40 (2H, m), 3.42—3.70 (4H, m), 3.78—3.88 (1H, m), 3.92—4.00 (1H, m), 4.12—4.52 (14H, m), 5.58—5.62 (1H, m).

Polymer Carrying 7-*O*-Decyl-4-guanidino-Neu5Ac2en 26d Polymer **26d** was obtained from **23l** (25 mg, 0.041 mmol) using the same procedure as that for the preparation of **26a** (45 mg, 0.26 mmol, 79%). Mol fraction of sugar unit=0.09. ^{1}H-NMR (400 MHz, D_2O) δ: 1.15—1.35 (12H, m), 1.38—1.55 (4H, m), 1.85—2.18 (22H, m), 1.98 (3H, s), 2.22—2.48 (22H, m), 3.20—3.40 (2H, m), 3.42—3.70 (4H, m), 3.78—3.88 (1H, m), 3.92—4.00 (1H, m), 4.12—4.52 (14H, m), 5.58—5.62 (1H, m).

Cells and Viruses Madin-Darby canine kidney (MDCK) cells obtained from Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan) were grown in Earle's Minimum Essential Medium (MEM) (Invitrogen corp.) supplemented with 10% fetal bovine serum (Hyclone), and the antibiotics penicillin G (50 units/ml) and streptomycin sulfate (50 μg/ml) (Invitrogen corp.). Cells were routinely cultured in flasks at 37 °C and 5% CO_2. The influenza virus strains A/PR/8/34 (H1N1) was provided by Dr. Peter Palese, and A/Yamagata/32/89 (H1N1) was obtained from Chiba Serum Institute (Japan). The A/PR/8/34 (H1N1) virus used for neuraminidase inhibition assays (the source of enzyme) was propagated in the allantoic sacs of embryonated eggs and purified by sucrose density gradient centrifugation. The A/Yamagata/32/89 (H1N1) virus used for plaque reduction assay was in the allantoic sacs of embryonated eggs. The viral stocks were stored at −80 °C. Influenza virus A/PR/8/34 was adapted to mice by passaging the virus several times in mice (MAIV, Mouse Adapted Influenza Virus).

Neuraminidase Inhibition Assay A standard colorimetric assay was used to measure influenza virus neuraminidase activity. The substrate, 2′-(4-nitrophenyl)-α-D-*N*-acetylneuraminic acid, was cleaved by neuraminidase to yield nitrophenol, which was quantified. The assay mixture contained inhibitors at various concentrations and the substrate in 20 mM 2-(*N*-morpholino)ethanesulfonic acid (MES) and buffer (50 mM calcium chloride at pH 6.0 and 10 mg/ml bovine serum albumin) and was incubated for 5 min at 37 °C. The reaction was started by the addition of enzyme. After incubation for 20 min, the reaction was terminated by adding 0.2 M glycine/sodium hydroxide (pH 10.2). Then, the absorbance at 450 nm was measured using the microplate reader. The substrate blanks were subtracted from the sample readings. The IC_{50} was calculated by plotting the percent inhibition of neuraminidase activity versus the inhibitor concentration.

Plaque Reduction Assays in MDCK Cells Anti-influenza virus activity was measured as described by Hayden *et al.*,[29] with some modifications. Briefly, confluent growing MDCK cells on 35 mm dish were washed with phosphate buffered saline (PBS) (Invitrogen Corp.), inoculated with virus (80 to 150 PFU/well) and incubated in a 5% CO_2 incubator at 37 °C for 1 h. The virus inoculum was then discarded, and the cell monolayers were overlaid with MEM supplemented with 0.22% sodium hydrogen carbonate, 10 mM HEPES (pH 7.2) (Invitrogen Corp.), 0.21% bovine serum albumin (Dainippon Pharmaceuticals Co. Ltd.), 1 μg/ml of trypsin, 0.01% DEAE Dextran, 0.6% agarose (Sigma Aldrich Corp.) and the test compound. After 30 to 38 h of incubation at 37 °C, the agar overlay was removed and the cell monolayers were stained with 0.1% crystal violet in 19% methanol.

The antiviral efficacy of the test compounds was assessed by counting the plaque number visually or measuring plaque size with PIXEL CATHER & ANALYZER PCA-11 (SYSTEM SCIENCE CO., Japan) at each compound concentration.

The IC_{50} was calculated by plotting the percent inhibition of plaque number or size versus the inhibitor concentration.

***In Vivo* Antiviral Experiments** Mice (BALB/c CrSlc, female, 5 weeks old) were purchased from Japan SLC, Inc. (Shizuoka, Japan). Compounds were prepared with saline. Mice were anesthetized with chloroform/diethyl ether (1 : 1) 24 h before infection and each group of 7 or 8 mice received 50 μl of **26c** or zanamivir solution intranasally at doses of 0.3 μmol/kg, respectively. The control group (n=8) was administered saline. Then, 500 plaque-forming units (pfu)/mouse of MAIV in 50 μl of phosphate-buffered saline (pH 7.4) containing 0.42% bovine serum albumin was inoculated intranasally to mice anesthetized with chloroform/diethyl ether (1 : 1) (day 0). The number of surviving mice was counted everyday for 20 d after infection. The statistical analyses were performed using the SAS System Release 8.2 for Windows (SAS Institute Inc.,). The Log-Rank test based on the joint ranking method was carried out to compare the prolonged effects of **26c** and zanamivir.

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