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Synthesis of Oligomers Derived from Amide-Linked Neuraminic Acid Analogues[#]

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N-Fluoren-9-ylmethoxycarbonyl-protected sugar amino acids derived from α-*O*-methoxy- and 2,3-dehydroneuraminic acids have been prepared. Incorporation of these monomer units into solid-phase synthesis led to the efficient synthesis of two series of oligomers varying from one to eight units in length. The (1→5)-linked amides of 2,3-dehydroneuraminic acid were further subjected to hydrogenation giving a third series of oligomers with a β-hydrido substituent at the anomeric carbon.

Introduction

In 1998, we first reported that amide-linked homooligomers, derived from neuraminic acid (NeuAc) analogues, adopt stable secondary structures in solution depending upon the oligomer length.[1] The oligomer series (Figure 1) was composed of (1→5) amide-linked β-*O*-methoxy neuraminic acids ranging from one to eight residues in length. These materials were efficiently prepared using solid-phase peptide synthesis employing *N*-fluoren-9-ylmethoxycarbonyl (Fmoc) protecting groups. A C-terminus ϵ-amino caproic acid linker was also introduced in order to prevent fraying of the terminal residue, which might disturb important hydrogen-bonding interactions required for stable secondary structure.[2]

We chose neuraminic acid because it is a readily available naturally occurring δ amino acid with a trihydroxy C-6 side chain, which we anticipated would increase water solubility in higher order oligomers. Moreover, *O*-glycoside oligomers of NeuAc have stable secondary structure,[3] and it seemed plausible that amide-linked analogues might exhibit similar properties. Indeed, these hypotheses proved correct, and our report was

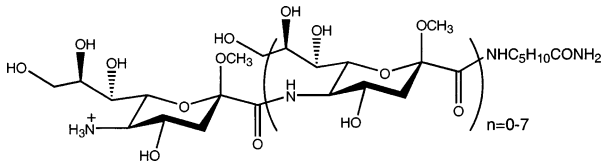

FIGURE 1. Amide-linked β-*O*-methoxy neuraminic acid oligomer series A.

the first to demonstrate that neutral amide-linked carbohydrate-based materials possess stable secondary structures in water. Shortly thereafter, Fleet and co-workers reported that furanose-derived amide-linked oligomers also adopt stable secondary structures in solution,[4] and more recent investigations have demonstrated the general utility of sugar amino acids[5] in foldamer research.[6]

In continuing investigations, we have targeted the synthesis of three other homooligomer series in order to probe the consequences of introducing variable functionality at C-2. In the first series (B) (Scheme 2), conditions for the synthesis of (1→5) amide-linked α-*O*-methoxy neuraminic acids are established in order to compare reversal in anomeric stereochemistry. The second series (C) (Scheme 3) introduces a 2,3 dehydro analogue of NeuAc, which changes the hybridization of the anomeric carbon. And finally, the third series (D) (Scheme 4) incorporates a β-hydrogen atom at the anomeric center

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(1) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074.

(2) Fraying refers to disruption of secondary structure due to solvation effects. A hydrophobic linker such as caproamide diminishes solvation relative to a simple primary amide. Solvation can disrupt helicity in small oligomers.

(3) (a) Brisson, J.-R.; Baumann, H.; Imberty, A.; Pérez, S.; Jennings, H. J. *Biochemistry* **1992**, *31*, 4996. (b) Yamasaki, R.; Bacon, B. *Biochemistry* **1991**, *30*, 851.

(4) (a) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *J. Chem. Commun.* **1998**, 2041. (b) Long, D. D.; Smith, M. D.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1998**, *39*, 9293.

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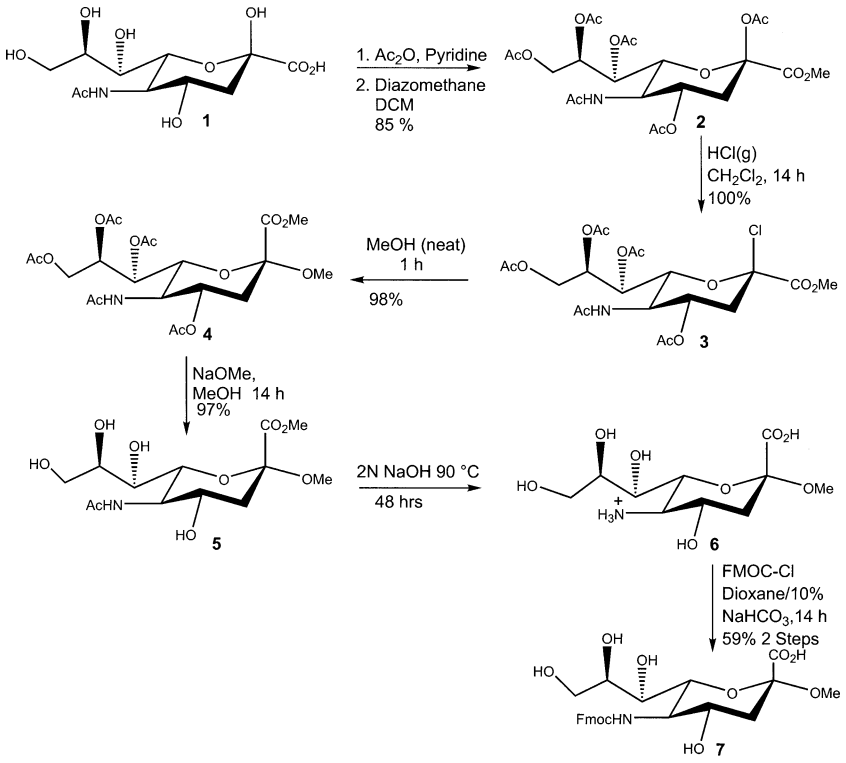
SCHEME 1



in place of the original methoxy group. Studies leading to the production of these systems are reported herein.

Results and Discussion

Synthesis of the monomer required for series B began with acetylation of *N*-acetyl neuraminic acid (**1**)[7] followed by methyl ester formation using diazomethane to give **2** (Scheme 1).[8] Subsequently, the anomeric acetate was quantitatively converted to a chloride (**3**) by the action of HCl.[9] The next critical step in the synthesis employed a procedure first reported by Magnusson[10] in which methanol displaces the axial chloride with inversion of stereochemistry providing the α-OCH_3 glycoside **4**. Deacetylation of **4** was performed in a two-step process, which began with Zemplén[11] hydrolysis of the esters to give **5**, followed by the more extreme conditions required to remove the *N*-acetyl group.[12] The crude sugar amino acid (**6**) was neutralized with HCl, filtered, and lyophilized to give a salt. Two different methods were used to protect the amine. Initially, we employed the procedure we reported in our first paper,[1] which incorporated a 1:1 mixture of 10% $NaHCO_3$ in water with dioxane, but we encountered reproducibility problems. Further investigations revealed that using 4 equiv of Hünigs base (*N*,*N*-diisopropylethylamine) in place of aqueous sodium bicarbonate greatly increased the yield of **7**, possibly due to the increased solubility of Hünigs base in dioxane relative to sodium bicarbonate. Subsequent reactions on the solid-phase support progressed more cleanly and efficiently using this method of Fmoc protection.

Coupling of **7** to the resin continued using traditional solid-phase peptide techniques (Scheme 2). Rink resin[13] was employed, because mild acidic conditions sufficiently cleave the oligomers from the resin without sugar decomposition. Series B oligomer synthesis began with condensation of Fmoc-protected ϵ-amino caproic acid to the resin, which was accomplished using 5 equiv of the

(5) (a) Van Well, R. M.; Marinelli, L.; Altona, C.; Erkelens, K.; Siegal, G.; Van Raaij, M.; Llamas-Saiz, A. L.; Kessler, H.; Novellino, E.; Lavecchia, A.; Van Boom, J. H.; Overhand, M. *J. Am. Chem. Soc.* **2003**, *125*, 10822. (b) Chakraborty, T. K.; Srinivasu, P.; Bikshapathy, E.; Nagaraj, R.; Vairamani, M.; Kumar, S. K.; Kunwar, A. C. *J. Org. Chem.* **2003**, *68*, 6257. (c) van Well, R. M.; Meijer, M. E. A.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A.; Overhand, M. *Tetrahedron* **2003**, *59*, 2423−2434. (d) Xie, J. *Carbohydr. Res.* **2003**, *338*, 399. (e) Gervay-Hague, J.; Weathers, T. M., Jr. *J. Carbohydr. Chem.* **2002**, *21*, 867 and references therein. (f) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stockle, M.; Kessler, H. *Chem.—Eur. J.* **2002**, *8*, 4365. (g) Chakraborty, T. K.; Jayaprakash, S.; Ghosh, S. *Comb. Chem. High Throughput Screening* **2002**, 5, 373. (h) Stoeckle, M.; Voll, G.; Guenther, R.; Lohof, E.; Locardi, E.; Gruner, S.; Kessler, H. *Org. Lett.* **2002**, *4*, 2501. (i) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421. Chakraborty, T. K.; Jayaprakash, S.; Srinivasu, P.; Madhavendra, S. S.; Ravi Sankar, A.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 2853. (j) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491 and references therein. (k) Suhara, Y.; Masayuki, I.; Ichikawa, M.; Penno, M.; Ichikawa, Y. *Tetrahedron Lett.* **1997**, *41*, 7167. (l) Suhara, Y.; Hildreth, J.; Ichikawa, Y. *Chem. Commun.* **1998**, 617.

(6) (a) Baldauf, C.; Guenther, R.; Hofmann, H.-J. *Helv. Chim. Acta* **2003**, *86*, 2573. (b) Raguse, T. L.; Lai, J. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 5592. (c) Garric, J.; Leger, J.-M.; Grelard, A.; Ohkita, M.; Huc, I. *Tetrahedron Lett.* **2003**, *44*, 1421. (d) Tomasini, C.; Trigari, V.; Lucarini, S.; Bernardi, F.; Garavelli, M.; Peggion, C.; Formaggio, F.; Toniolo, C. *Eur. J. Org. Chem.* **2003**, *2*, 259. (e) de Jong, R.; Rijkers, D. T. S.; Liskamp, R. M. J. *Helv. Chim. Acta* **2002**, *85*, 4230. (f) Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650. (g) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893 and references therein.

(7) Marra, A.; Sinay, P. *Carbohydr. Res.* **1989**, *190*, 317.

(8) Kuhn, R.; Lutz, P.; MacDonald, D. L. *Chem. Ber.* **1966**, *99*, 611.

(9) Meindl, P.; Tuppy, H. *Monatsh. Chem.* **1965**, *96*, 802.

(10) Kononov, L. O.; Magnusson, G. *Acta Chem. Scand.* **1998**, *52*, 141.

(11) Szurmai, Z.; Kerekgyarto, J.; Harangi, J.; Liptak, A. *Carbohydr. Res.* **1987**, *164*, 313.

(12) Roy, R.; Pon, R. A. *Glycoconjugate J.* **1990**, *7*, 3.

(13) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787.

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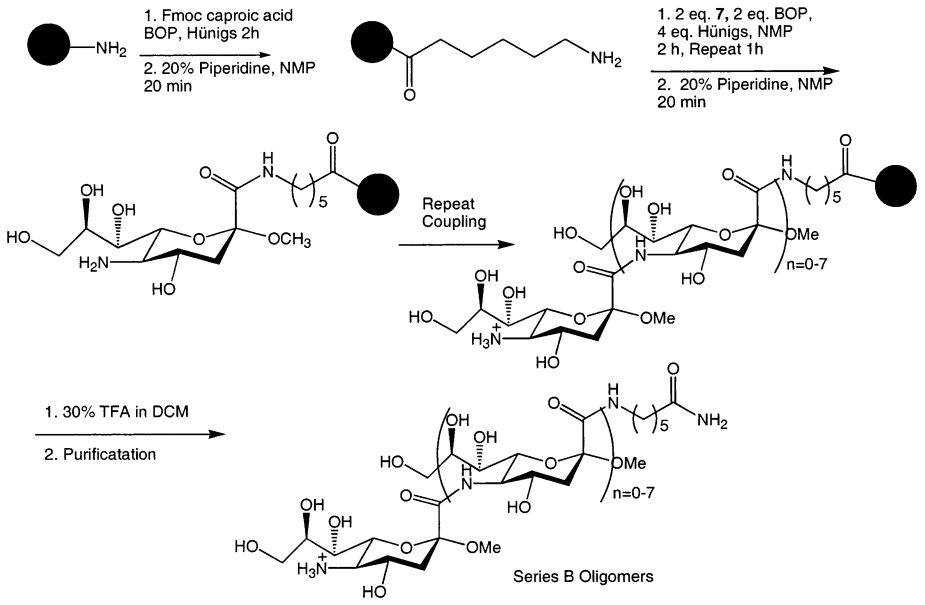

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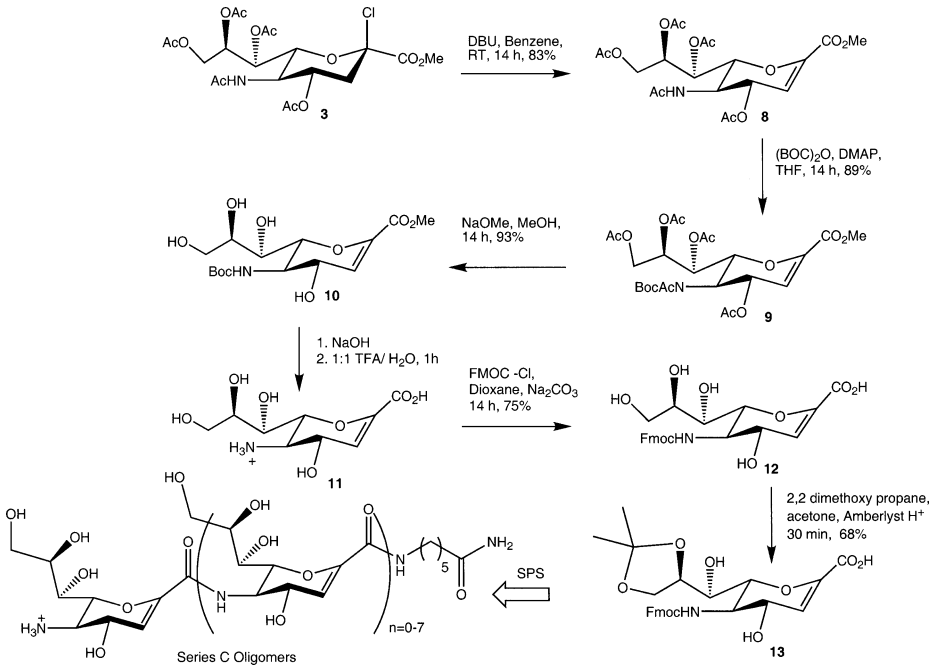

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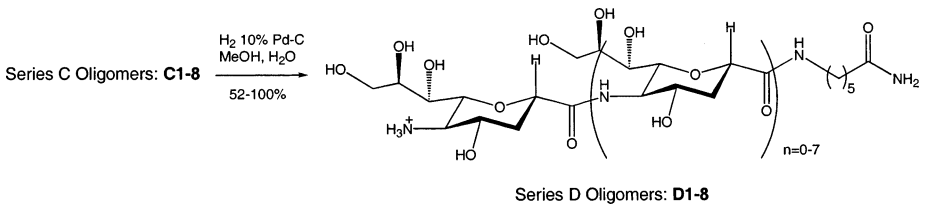

protected amino acid with 5 equiv of benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate[14] (BOP or Castro's reagent) and 5 equiv of Hünigs base in NMP for 2 h. After completion of the reaction, as indicated by the Kaiser test,[15] the Fmoc was removed using 20% piperidine in NMP, and the resin was subsequently washed with NMP (5 × 2 mL × 2 min), methanol (5 × 2 mL × 2 min), and finally with dichloromethane

(14) Nguyen, D. L.; Seyer, R.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1025.

(15) Kaiser, E.; Colescat, R. L.; Bossinge, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.

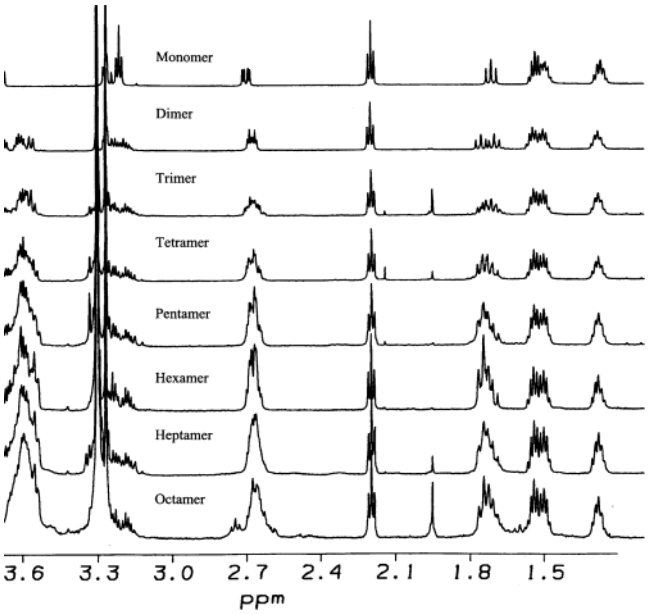

FIGURE 2. Stack plot of 1D proton NMR spectra for **B1**−**8** at 600 MHz in D_2O. Note acetone impurity at ~2.0 ppm.

(5 × 2 mL × 2 min). Compound **7** (2 equiv), BOP (2 equiv), and Hünig's base (4 equiv) were added to the caproamide-linked resin in 1.5 mL of NMP, and the reaction proceeded for 2 h. Routinely, a second coupling reaction was performed using 1 equiv of the sugar amino acid (**7**), 1 equiv of BOP, and 4 equiv of Hünigs base in 1.5 mL of NMP for 1 h to ensure complete loading of the resin. Reaction completion was confirmed by the Kaiser test, and the resin was washed with dichloromethane prior to deprotection of the Fmoc functionality. This procedure was repeated as required to build the oligomer library.

Final cleavage of the sugar from the solid support was accomplished using 30% trifluoroacetic acid (TFA) in dichloromethane (DCM) for 30 min, which was mild enough to remove the sugar without causing any decomposition or epimerization of the OCH_3 at the anomeric center as evidenced by NMR. Purification was accomplished by one of two methods. The procedure developed by Szabo et al.[1] incorporating size exclusion chromatography on P-10 gel worked well but took about 24 h for each oligomer. Instead, we found that reverse phase high-performance liquid chromatography (HPLC) on a C-18 column provided more efficient separation.

Figure 2 shows a stack plot of one-dimensional (1D) NMR spectra for all eight oligomers (**B1**−**8**), which revealed insightful, yet limited, information. Beginning with the monomer (**B-1**), all proton and carbon resonances were assigned by correlation spectroscopy (COSY) and heteronuclear single quantum coherence (HSQC) experiments, respectively. The dimer (**B-2**) and trimer (**B-3**) tested the limits of resolution of the NMR ^1H spectra even at 600 MHz, making it impossible to assign protons in the remaining oligomers.

Having successfully completed the synthesis and purification of series B, we next turned our attention to the synthesis of Fmoc-protected 2,3-dehydroneuraminic acid analogue **13** (Scheme 3). Chloride **3** was dissolved in benzene and reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to provide the unsaturated sugar **8**. A modification of the procedure to remove the *N*-acetyl group was required for this analogue, as 2 N NaOH at 90 °C caused decomposition. In this event, compound **8** was treated with *tert*-butyloxycarbonyl anhydride ($(BOC)_2O$) and catalytic *N*,*N*-(dimethylamino)pyridine (DMAP) in THF to form the *N*-acetyl-*N*-Boc product **9**.[16] Zemplén conditions ($NaOCH_3/CH_3OH$) removed the *N*-acetyl as well as the *O*-acetates to give **10**, a Boc-protected δ amino acid methyl ester. Treatment of the protected amino acid with sodium hydroxide in water converted the methyl ester to a free carboxylate, which upon neutralization with acid resin and treatment with 1:1 TFA/water provided the amine **11**. Fmoc protection of **11** proceeded nicely to give **12**, which we then protected as the 8,9 acetonide. Protection was necessary because previous studies in our laboratory indicated that the C-9 hydroxyl undergoes cyclocondensation forming a lactone under the coupling conditions.[17]

With the required monomer unit in hand, we focused on preparing the series C oligomers, which was accomplished using the same method as with series B oligomers. Overall, the coupling times were less for **13**, suggesting enhanced steric accessibility. As anticipated, the acetonide protecting groups were removed upon cleavage of the series C oligomers from the solid support, and purification was performed as previously described (vide supra).

NMR characterization of the series C oligomers was also complicated with significant overlap in the proton and carbon spectra (Figure 3). It was possible to make complete assignments for the monomer (C-1), dimer (C-2), and trimer (C-3) proton and carbon resonances. Beyond the trimer, the HSQC experiment showed that the carbon peaks were divided into two unique regions: those assigned to the terminal sugars and all other internal residues in the oligomer. The remaining carbons in the sugar chain overlapped with each other. This is similar to the pattern found in the α-OMe series. However, the proton spectra show a unique pattern for the H-3 protons, and it is possible to distinguish three regions for the H-3 protons including those assigned to the internal residues (5.78 ppm), the amino terminus residue (5.83 ppm), and the carboxy terminus sugar attached to the caproamide linker (5.71 ppm). The utility of H-3 as a reporter group in conformational studies is currently under investigation in our laboratories as are circular dichroism studies.

The α−β unsaturated functionality in the C series oligomers proved useful in the synthesis of the β-hydrido series D compounds (Scheme 4). Hydrogenation of the double bond was effected with a catalytic amount of 10% Pd−C with the substrate dissolved in a mixture of methanol and water. Shorter oligomers were soluble in methanol and did not require the addition of water. As the length of the oligomer increased, more and more water was needed to complete the reaction in a 12-h period. After the reaction was complete, the solution was filtered through a tight packing of glass wool and the solvent removed in vacuo. Water was added and subsequently removed via lyophilization to give a white solid.

(16) Gervay, J.; Flaherty, T. M.; Nguyen, C. P. *Tetrahedron Lett.* **1997**, *38*, 1493.
(17) Nguyen, C. P. M.S. Thesis, The University of Arizona, 1998.

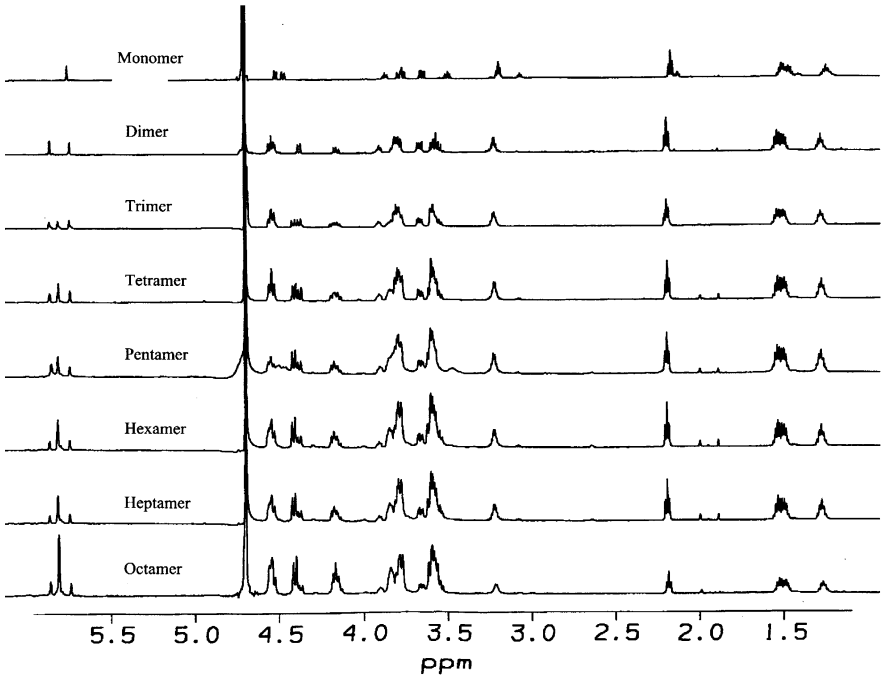

FIGURE 3. Stack plot of 1D proton NMR spectra for **C1**−**8** at 600 MHz in D_2O. Note acetate and acetone impurity at 1.8 and 2 ppm, respectively.

Hydrogenation of unsaturated sialic acids is reported to occur from the top face to give the β (axial)-hydride, and product distribution can be determined by NMR.[18] The most discriminating spectroscopic feature is the H2, H3 coupling constant, which is on the order of 10 Hz for the β-hydrido anomer ($J_{H2ax,H3ax}$) and 3.5 Hz for the equatorial α-hydrido anomer ($J_{H2eq,H3ax}$). $J_{H2,H3}$ is ≥10 Hz for all of the series D oligomers, indicating that oligomer conformations do not interfere with stereoselective β-face hydrogenation.

The NMR spectra for the β-hydrido compounds displayed a complicated series of peaks with significant overlap (Figure 4). The general pattern for regions in the proton dimension correlated with the unsaturated series. In a manner similar to the H3 proton of the C series, the H2 anomeric proton doublets display unique regions for the amino terminus residue (3.99 ppm), the internal sugars (4.06 ppm), and the carboxy terminus residue attached to the caproamide linker (4.14 ppm). As before, the pattern of increasing the middle anomeric doublet serves as a reporter group of the conformation of the oligomer chain. The gradual increase of the middle peak indicates the gradual increase of defined chemical equivalency within the sugar chain. All sugar residues displayed similar carbon chemical shifts with the exception of the terminal residues in a manner consistent with the α−β unsaturated oligomers.

Conclusion

Two novel Fmoc-protected neuraminic acid analogues have been prepared and incorporated into solid-phase synthesis (SPS). A caproamide linker was introduced at the carboxy terminus in an effort to minimize hydration that might disrupt interactions required for a stable secondary structure. For the most part, oligomer synthesis proceeded smoothly, although reactions incorporating 2,3-dehydroneuraminic acid (series C) were most efficient. Two different series (B and C) of compounds were prepared with oligomer lengths varying from one to eight units. A third series (D) was obtained upon hydrogenation of the 2,3-dehydro oligomers. These reactions yielded only oligomers resulting from axial delivery of hydrogen. Each component of the three series was characterized by ^1H and ^{13}C NMR. In most cases, resolution of the peaks for monomer−trimer was possible, as the amino and carboxy terminal residues have distinct chemical shifts. The resonances corresponding to the internal residues were not resolved in longer oligomers (≥4). Importantly, all of the oligomers were soluble in water and all except **C4**−**8** were soluble in methanol. Conformational analyses of the series B−D oligomers using circular dichroism and NH/ND exchange NMR experiments are currently under investigation in our laboratories.

Experimental Section

***N*-Acetyl-α-2-*O*-methyl Neuraminic Acid Methyl Ester (5).** According to the method of Magnusson et al.,[10] 2-α-*O*-methyl-4,7,8,9-tetra-*O*-acetyl-neuraminic acid methyl ester (**4**) (7.41 g, 14.1 mmol) was dissolved in 150 mL of dry methanol. Sodium methoxide (200 mg, 3.7 mmol) was added. The reaction vessel was sealed and stirred overnight at room temperature. After 14 h, the reaction was complete as indicated by TLC (7:3 benzene/acetone) and the solution was neutralized with Dowex H^+ resin and filtered. The solvent was removed in vacuo to give 4.66 g of **5**. Yield: 97%.

α-*O*-Methyl-neuraminic Acid (6). *N*-Acetyl-α-*O*-methyl neuraminic acid methyl ester (**5**) (500 mg, 1.47 mmol) was dissolved in 3.5 mL of 2 N NaOH (4.4 mmol) and heated at 90 °C for 48 h. The solution was cooled and checked by TLC (4:1 propanol/H_2O). The solution was neutralized to pH = 7 and

(18) (a) Bandgar, B. P.; Zbiral, E. *Carbohydr. Res.* **1995**, *270*, 201. (b) Gervay, J.; Gregar, T. Q. *Tetrahedron Lett.* **1997**, *38*, 5921.

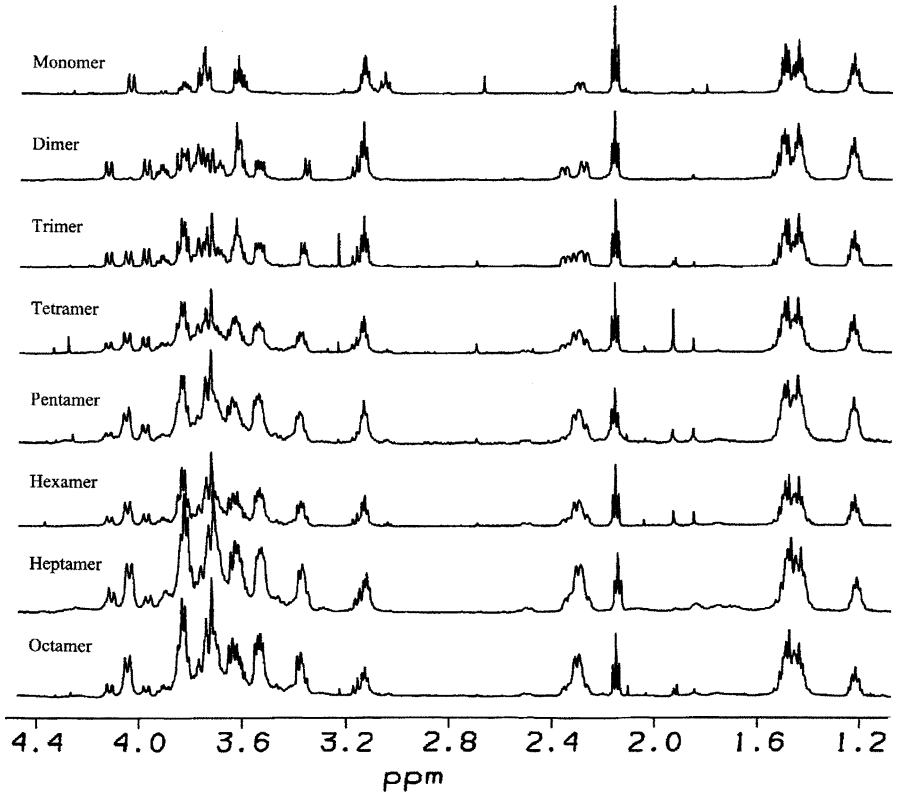

FIGURE 4. Stack plot of 1D proton NMR spectra for **D1**−**8** at 600 MHz in D_2O. Note acetate, acetone, acetonitrile, and methanol impurity at 1.8, 2.0, 2.8, and 3.3 ppm, respectively.

freeze-dried. A determination of total yield and mass spectrometric analysis were not possible because of the large amount of sodium chloride salt present. The remaining brown solid was used, as is, for the next reaction. ^{1}H NMR (D_2O, 600 MHz): δ 3.57−3.57 (m, 2H, H8 and H9), 3.60−3.49 (m, 3H, H4, H7, H9′), 3.37 (d, J = 9.0 Hz, 1H, H6), 3.24 (at., J = 8.5 Hz, 1H, H5), 3.22 (s, 3H, OCH_3), 2.59 (dd, J = 4.0 and 10.5 Hz, 1H, $H3_{eq}$), 1.49 (at., J = 10.0 Hz, 1H, $H3_{ax}$). ^{13}C NMR (D_2O referenced to TSP-d_6, 125 MHz): δ 176.7, 103.7, 77.3, 74.8, 72.8, 71.6, 65.8, 65.6, 63.4, 57.4, 54.5, 43.5.

***N*-(9-Fluorenylmethoxycarbonyl)-2-α-*O*-methylneuraminic Acid (7).** α-*O*-Methyl-neuraminic acid (**6**) (1.477 g, 5.2 mmol) was dissolved in 35 mL of $NaHCO_3$, 50 mL of H_2O, and 85 mL of dioxane. The solution was stirred briskly and cooled to 0 °C. 9-Fluorenylmethyl chloroformate was dissolved in dioxane and added dropwise over 30 min. The solution was warmed to room temperature and stirred for 16 h. The solution was diluted with water (50 mL) and extracted with diethyl ether (3 × 20 mL). The aqueous phase was adjusted to pH = 3 with the addition of a 10% HCl solution. The acidic solution was then extracted with EtOAc (3 × 20 mL). The organic layers were combined and dried with $MgSO_4$. The solution was filtered and the solvent was removed in vacuo giving 1.82 g of **7**. Yield: 59% from **5**. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.78−7.28 (m, 8H, ArH), 4.36 (dd, J = 4.4 and 8.5 Hz, 2H, Fmoc CH_2), 4.21 (t, J = 6.5 Hz, 1H, Fmoc CH), 3.86−3.84 (m, 2H, H8, H9), 3.68−3.53 (m, 5H, H4, H5, H6, H7, H9′), 2.67 (dd, J = 4.6 and 12.7 Hz, 1H, $H3_{eq}$), 1.70 (at., J = 12.6 Hz, 1H, $H3_{ax}$). ^{13}C NMR (CD_3OD, 125 MHz): δ 171.8, 159.8, 145.4, 145.2, 142.6, 128.8, 128.2, 126.3, 120.9, 100.0, 75.0, 73.2, 70.2, 68.8, 68.1, 67.4, 55.1, 51.9, 41.7. FABHRMS: [M + H$^+$] calcd for $C_{25}H_{30}O_{10}N$, 504.1870; found, 504.1886.

General Procedure for (1→5) Amide-Linked Neuraminic Acid Oligomers Conjugated to ϵ-Amino Caproamide. (1→5) Amide-linked oligomers were assembled using Fmoc chemistry on solid-phase support. Rink resin (4-(2′,4′-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxy resin) was used for the solid-phase synthesis. The extent of the reactions was confirmed using the Kaiser test. A typical procedure for the building of oligomers was the following: Fmoc rink resin (100 mg, 0.7 mmol/g) was treated with 2 mL of 20% piperidine in *N*-methyl pyrrolidinone (NMP) and agitated to remove Fmoc (2 × 20 min). The resin was washed with NMP (6 × 2 mL × 2 min) and finally with CH_2Cl_2 (1 × 1 mL × 2 min). The Fmoc-protected ϵ-amino caproic acid (5 equiv), BOP (5 equiv), and *i*-Pr_2NEt (5 equiv) was added to the resin in 2 mL of NMP and agitated for 2 h. Completion was confirmed by the Kaiser test. Subsequently, the Fmoc was removed per previous conditions, and the washing step was performed as before. Addition of the first neuraminic acid unit was accomplished by the addition, in order, of the following: Fmoc amino acid (2 equiv), BOP (2 equiv), *i*-Pr_2NEt (4 equiv) in NMP (2 mL). The reaction mixture was agitated for 2 h at room temperature, and the procedure was repeated to ensure complete coupling. Deprotection was the same as before, and the procedure was repeated as desired. Removal of oligomer from the resin was accomplished by first washing the resin with MeOH (2 × 2 mL × 2 min) followed by CH_2Cl_2 (5 × 2 mL × 2 min). Cleavage was performed with 30% CF_3COOH in CH_2Cl_2 (3:7, 40 mL), and the solvent was allowed to pass through the funnel into a flask below. Seepage through the funnel took approximately 30 min. The solvent was removed in vacuo, 5 mL of H_2O was added, and the filtrate was lyophilized.

Purification of these compounds initially used a size exclusion chromatography gel. A buffer system of 0.03 N NH_4HCO_3 was used to elute the sugar off the column with a flow rate of 12%, which reflects the percentage of the maximum flow rate for the fraction collector pump, approximately 0.5 mL/min. The column had a diameter of 1 in. and a length of 60 in. With this length and flow rate, each fraction took about 4 min to fill. The sugar was detected using a UV/vis detector set at 222 nm to detect the amide absorbance. Material eluted at approximately fraction 30 and ended at approximately fraction 80 depending on the amount of material placed on the column.

These numbers varied depending on the oligomer length with the longer oligomers eluting before the shorter chain lengths. Size exclusion chromatography works well when it is used to separate two compounds where the molecular weight of one compound is at least twice that of the other. The separation of the monomer and dimer sugar proved to be most effective using this technique. As the oligomer length increased and the differences in molecular weight decreased, the efficiency of purification by size exclusion chromatography decreased. Fractions collected were lyophilized to give a fluffy white amorphous solid.

Reverse phase HPLC was also used to purify these oligomers as it took less time and resulted in a more uniform separation between oligomers. A C-18 column was used with a flow rate of 2.5 mL/min with a UV/vis detector set to 230 to detect the amide absorbance. The water phase contained 0.1% TFA. A gradient of 0−10% acetonitrile over 20 min was used to elute the oligomer with the retention time of approximately 13 min. Peaks were very broad and generally trailed. The solvent was then lyophilized to give fluffy white solids.

Monomer (B-1): obtained in 31% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 3.96 (d, J = 1.7, 10.3 Hz, 1H), 3.85−3.82 (m, 1H, H8), 3.79 (dd, J = 2.5, 12.2 Hz, 1H), 3.74 (dd, J = 1.6, 9.1 Hz, 1H, H7), 3.71−3.65 (m, 2H, H4, H9′), 3.25 (s, 3H, OCH_3), 3.19 (t, J = 7.0 Hz, 2H, CH_2 caproamide), 2.69 (dd, J = 4.7, 13.1 Hz, 1H, $H3_{eq}$), 2.18 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.769 (apt, J = 12.4 Hz, 1H, $H3_{ax}$), 1.56−1.47 (m, 4H, $2CH_2$ caproamide), 1.30−1.24 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 178.0, 168.3, 99.8, 72.0, 70.8, 67.2, 65.5, 62.4, 52.0, 51.1, 39.3, 38.2, 34.7, 27.9, 25.5, 24.6. FABHRMS: [M + H$^+$] calcd for $C_{16}H_{32}O_8N_3$, 394.2189; found, 394.2191.

Dimer (B-2): obtained in 12% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.00 (d, J = 1.7 and 10.3 Hz, 1H, H6), 3.96 (t, J = 10.3 Hz, 1H, H5), 3.83−3.80 (m, 1H, H8), 3.78−3.75 (m, 5H, H4, H6, H7, H8, H9), 3.66 (dd, J = 5.1, 12.2 Hz, 1H), 3.61−3.57 (m, 2H), 3.57 (d, J = 9.5 Hz, 1H, H9′), 3.28 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.26−3.16 (m, 3H, H5, CH_2 caproamide), 2.68 (dt, J = 4.7 and 13.0 Hz, 2H, $H3_{eq}$), 2.21 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.74 (apt, J = 12.8 Hz, 1H, $H3_{ax}$), 1.68 (apt, J = 12.5 Hz, 1H, $H3_{ax}$), 1.55−1.45 (m, 4H, $2CH_2$ caproamide), 1.28−1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 178.0, 169.9, 168.7, 99.8, 73.0, 72.0, 71.0, 70.8, 67.7, 67.3, 66.9, 65.5, 62.6, 62.4, 52.0, 51.8, 51.2, 51.0, 39.3, 38.5, 37.8, 34.7, 27.9, 25.9, 25.6, 24.6. FABHRMS: [M + H$^+$] calcd for $C_{26}H_{49}O_{15}N_4$, 657.3194; found, 657.3196.

Trimer (B-3): obtained in 15% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.00 (d, J = 10.4 Hz, 1H, H6), 3.98−3.92 (m, 2H, H5), 3.83−3.53 (m, 17H), 3.29 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 3.22−3.13 (m, 3H, H5, CH_2 caproamide), 2.71−2.64(m, 3H, $H3_{eq}$), 2.18 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.74−1.65 (m, 3H, $H3_{ax}$), 1.61−1.47 (m, 4H, $2CH_2$ caproamide), 1.31−1.27 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 180.0, 170.3, 169.8, 168.7, 99.9, 99.8, 73.1, 73.0, 72.0, 71.1, 70.9, 67.8, 67.7, 67.3, 67.1, 67.1, 65.5, 62.8, 62.7, 62.6, 62.4, 52.0, 51.9, 51.8, 51.7, 51.2, 51.1, 51.0, 39.3, 38.5, 38.2, 37.8, 34.7, 27.9, 25.6, 24.6. FABHRMS: [M + H$^+$] calcd for $C_{36}H_{66}O_{22}N_5$, 920.4205; found, 920.4199.

Tetramer (B-4): ^{1}H NMR (D_2O, 600 MHz): δ 4.00 (dd, J = 1.8 and 10.3 Hz, 1H, H6), 3.98 (m, 3H, H5), 3.83−3.70 (m, 13H), 3.66 (dd, J = 5.6, 12.4 Hz, 1H, H9), 3.63−3.52 (m, 9H), 3.29, 3.28, 3.28, 3.25 (4s, 12H, OCH_3), 3.22−3.13 (m, 3H, H5, CH_2 caproamide), 2.69−2.63 (m, 4H, $H3_{eq}$), 2.19 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.76−1.67 (m, 4H, $H3_{ax}$), 1.56−1.47 (m, 4H, $2CH_2$ caproamide), 1.29−1.24 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 180.0, 170.3, 170.2, 169.8, 168.7, 163.1, 117.4, 115.1, 99.89, 99.87, 99.8, 73.1, 72.0, 71.1, 71.1, 70.8, 67.8, 67.8, 67.7, 67.3, 67.2, 67.1, 67.1, 65.5, 62.7, 62.7, 62.6, 62.4, 52.0, 51.8, 51.7, 51.2, 51.1, 51.0, 39.3, 38.6, 38.2, 38.1, 37.8, 34.7, 27.9, 25.6, 24.6. FABHRMS: [M + H$^+$] calcd for $C_{46}H_{83}O_{29}N_6$, 1183.5217; found, 1183.5204.

Pentamer (B-5): obtained in 32% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.00 (d, J = 10.1 Hz), 3.81−3.70 (m, 4H, H5), 3.81−3.70 (m, 14H), 3.66 (dd, J = 5.3, 12.1 Hz), 3.64−3.51 (m, 14H), 3.28 (s, 12H, OCH_3), 3.24 (s, 3H, OCH_3), 3.23−3.13 (m, 3H, H5, CH_2 caproamide), 2.69−2.63 (m, 5H, $H3_{eq}$), 2.19 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.75−1.69 (m, 5H, $H3_{ax}$), 1.55−1.46 (m, 4H, $2CH_2$ caproamide), 1.29−1.24 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 180.0, 170.3, 170.2, 169.9, 168.7, 99.9, 99.8, 73.1, 72.0, 71.2, 71.1, 70.8, 67.8, 67.7, 67.3, 67.2, 67.1, 65.5, 62.7, 62.4, 52.0, 51.8, 51.7, 51.2, 51.1, 51.0, 39.3, 38.6, 38.2, 37.8, 34.8, 27.9, 25.6, 24.6. FABHRMS: [M + H$^+$] calcd for $C_{56}H_{100}O_{36}N_7$, 1466.6228; found, 1446.6205.

Hexamer (B-6): obtained in 24% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.00−3.93 (m, 6H, H6, H5), 3.82−3.70 (m, 17H), 3.65 (dd, J = 5.4, 12.2 Hz, 1H, H9), 3.64−3.52 (m, 17H), 3.28 (s, 15 H, OCH_3), 3.25 (s, 3H, OCH_3), 3.24−3.15 (m, 3H, H5, CH_2 caproamide), 2.68−2.63 (m, 6H, $H3_{eq}$), 2.19 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.75−1.68 (m, 6H, $H3_{ax}$), 1.54−1.46 (m, 4H, $2CH_2$ caproamide), 1.28−1.24 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 150 MHz): δ 180.0, 170.3, 170.2, 170.1, 168.7, 99.9, 99.8, 73.1, 71.2, 71.1, 67.9, 67.7, 67.4, 67.1, 67.0, 62.7, 52.0, 51.8, 51.7, 51.1, 51.0, 39.3, 38.5, 38.3, 38.2, 38.0, 34.7, 27.9, 25.6, 24.6. FABHRMS: [M + H$^+$] calcd for $C_{66}H_{117}O_{43}N_8$, 1709.7275; found, 1709.7215.

Heptamer (B-7): obtained in 9% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 8.25 4.02−4.00 (m, 7H, H5, H6), 3.99−3.93 (m, 22H), 3.67−3.52 (m, 19H), 3.28 (s, 18H, OCH_3), 3.25 (s, 3H, OCH_3), 3.22−3.13 (m, 3H, H5, CH_2 caproamide), 2.76−2.65 (m, 7H, $H3_{eq}$), 2.19 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.75−1.67 (m, 7H, $H3_{ax}$), 1.55−1.46 (m, 4H, $2CH_2$ caproamide), 1.29−1.24 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.0, 173.3, 173.2, 172.8, 171.7, 166.1, 165.8, 102.9, 102.8, 76.1, 75.0, 74.2, 74.1, 74.0, 70.9, 70.7, 70.5, 70.3, 70.2, 70.1, 70.0, 69.9, 68.5, 65.7, 65.4, 55.0, 54.8, 54.7, 54.7, 54.2, 54.3, 54.0, 42.3, 41.2, 40.8, 37.7, 30.9, 28.6, 27.6. FABHRMS: [M + H$^+$] calcd for $C_{76}H_{134}O_{50}N_9$, 1972.8220; found, 1972.8329.

Octomer (B-8): obtained in 31% yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.01−3.95 (m, 8H, H5, H6), 3.82−3.72 (m, 24H), 3.66−3.53 (m, 23H), 3.29 (s, 21H, OCH_3), 3.26−3.15 (m, 3H, H5, CH_2 caproamide), 2.68−2.65 (m, 8H, $H3_{eq}$), 2.19 (t, J = 7.6 Hz, 2H, CH_2 caproamide), 1.75 (m, 8H, $H3_{ax}$), 1.55−1.46 (m, 4H, $2CH_2$ caproamide), 1.29−1.24 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 150 MHz): δ 180.0, 170.3, 179.2, 169.8, 168.7, 99.9, 99.8, 73.1, 72.0, 71.14, 71.09, 70.8, 67.9, 67.8, 67.7, 67.3, 67.2, 67.1, 65.5, 62.7, 62.6, 62.4, 52.0, 51.8, 51.70, 51.67, 51.2, 51.1, 51.0, 39.3, 38.5, 38.2, 37.8, 34.7, 27.9, 25.6, 24.6. MALDI: [M + Na$^+$] calcd for $C_{86}H_{149}O_{57}N_{10}Na$, 2257.9069; found, 2257.8844.

***N*-(9-Fluorenylmethoxycarbonyl)-2,3-dehydroneuraminic Acid (12).** 2,3-Dehydrido neuraminic acid (**11**) (1.78 g, 7.16 mmol) was dissolved in 70 mL of H_2O, 20 mL of saturated Na_2CO_3, and 100 mL of dioxane. The solution was cooled to 0 °C, and a solution of Fmoc-Cl (2.23 g, 8.62 mmol) dissolved in 25 mL of dioxane was added dropwise over 30 min. The solution was warmed to room temperature and stirred for 14 h. Once the reaction was complete as determined by TLC (4:1 propanol/water), the solution was extracted with diethyl ether (3 × 20 mL) and the aqueous layer was concentrated to half its original volume in vacuo. The aqueous solution was acidified with 10% HCl to pH = 3, and the sugar was extracted into ethyl acetate (3 × 30 mL). The solvent was removed in vacuo giving 2.53 g of a yellow amorphous solid (75% yield). ^{1}H NMR (CD_3OD, 600 MHz): δ 7.77−7.28 (m, 8H, Fmoc−Ar), 5.95 (d, J = 2.4 Hz, 1H, H3), 4.43 (dd, J = 2.5 and 8.7 Hz, 1H, H4), 4.38 (d, J = 6.9 Hz, 2H, CH_2−Fmoc), 4.24 (m, 2H, H6, CH−Fmoc), 3.91 (m, 1H, H8), 3.84 (dd, J = 3.1 and 4.4 Hz, 1H, H9), 3.82 (t, J = 10.1 Hz, 1H, H5), 3.67−3.64 (m, 2H, H7,

H9′). ^{13}C NMR (CD_3OD, 150 MHz): δ 165.7, 159.4, 145.3, 145.1, 142.6, 128.8, 128.2, 126.18, 120.9, 113.6, 78.2, 71.3, 70.1, 68.2, 68.1, 65.0, 52.9, 48.3. FABHRMS: [M + Na^+] calcd for $C_{24}H_{25}O_9Na$, 494.1427; found, 494.1431.

***N*-(9-Fluorenylmethoxycarbonyl)-2,3-dehydro-8,9-isopropylidine Neuraminic Acid (13).** *N*-(9-Fluorenylmethoxycarbonyl) 2,3-dehydro neuraminic acid (**12**) (2.53 g, 5.36 mmol) was dissolved in 150 mL of dry acetone. To this, 400 mg Amberlyst H^+resin was added and stirred. 2,2-Dimethoxy propane (2.63 mL, 25.3 mmol) was added via syringe and stirred for 2 h. The solution was filtered and concentrated giving 1.88 g of white amorphous solid (68% yield). ^{1}H NMR (acetone-d_6, 600 MHz): δ 7.84−7.30 (m, 8H, Fmoc−Ar), 6.91 (d, J = 8.2 Hz, 1H, CONH), 5.98 (d, J = 2.1 Hz, 1H, H3), 4.59 (dd, J = 2.2 and 8.5 Hz, 1H, H4), 4.50 (dd, J = 7.3 and 10.5 Hz, 1H, CH−Fmoc), 4.39 (dd, J = 6.7 and 10.6 Hz, 1H, CH_2−Fmoc), 4.31 (dd, J = 6.2 and 13.2 Hz, 1H, H8), 4.24 (t, J = 6.9 Hz, 1H, CH_2−Fmoc), 4.12−4.09 (m, 2H, H6, H9), 4.01 (dd, J = 5.1 and 8.4 Hz, 1H, H9′), 3.84 (dt, J = 8.6 and 10.3 Hz, 1H, H5), 3.69 (d, J = 7.8 Hz, 1H, H7). ^{13}C NMR (acetone-d_6, 150 MHz): δ 163.8, 159.3, 145.5,142.6, 129.1, 126.6, 113.9, 79.0, 76.1, 75.1, 71.3, 53.7, 49.8, 48.5, 32.5, 27.9, 26.3. FABHRMS: [M + H^+] calcd for $C_{27}H_{30}O_9N$, 512.1921; found, 512.1938.

Series C Synthesis. Assignments for each oligomer are based upon the following: the sugar chain attached to the caproamide linker is labeled as sugar a, with the terminal sugar with the free amine labeled as sugar x. Absolute assignment is given where possible. AB-X refers to the α−β unsaturated oligomers with length x.

Monomer (C-1): obtained in 63% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.77 (d, J = 2.6 Hz, 1H,), 4.52 (dd, J = 6.0, 8.4 Hz, 1H, H4), 4.48 (dd, J = 1.2, 9.6 Hz, 1H, H6), 3.87 (m, 1H, H8), 3.79 (dd, J = 4.8, 9.0 Hz, 1H, H9), 3.75 (dd, J = 0.6, 8.8 Hz, 1H, H7), 3.65 (dd, J = 5.5, 12.0 Hz, 1H, H9′), 3.51 (dd, J = 8.6, 9.7 Hz, 1H, H5), 3.20 (t, J = 6.6 Hz, 2H, NCH_2), 2.17 (t, J = 7.2 Hz, 2H, CH_2), 1.53−1.44 (m, 4H, $2CH_2$), 1.27−1.23 (m, 2H, CH_2). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 166.0, 148.7, 110.1, 77.8, 72.8, 70.7, 67.6, 65.5, 53.8, 50.2, 42.2, 42.0, 38.6, 37.8, 30.9, 28.4, 28.0, 27.7. FABHRMS: [M + H^+] calcd for $C_{15}H_{28}O_7N_3$, 362.1927; found, 362.1922.

Dimer (C-2): obtained in 77% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.87 (d, J = 2.7 Hz, 1H, H3b), 5.75 (d, J = 2.4 Hz, 1H, H3a), 4.56−4.52 (m, 3H, H4a,b, H6b), 4.38 (d, J = 10.8 Hz, 1H, H6a), 4.16 (dd, J = 8.9, 10.7 Hz, 1H, H5a), 3.90 (m, 1H, H8b), 3.84−3.78 (m, 5H, H7b, H8a, H9a, H9′a, H9b), 3.67 (dd, J = 5.6, 12.0 Hz, 1H, H9′b), 3.60−3.53 (m, 2H, H5b, H7a), 3.22 (m, 2H, NCH_2), 2.19 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.56−1.48 (m, 4H, $2CH_2$ caproamide), 1.30−1.26 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 166.7, 166.5, 148.8, 148.3, 110.9, 110.8, 79.0, 77.9, 72.9, 72.8, 70.7, 70.0, 67.5, 65.9, 65.4, 53.8, 53.1, 42.1, 37.8, 30.9, 28.4, 27.7. FABHRMS: [M + H^+] calcd for $C_{24}H_{41}O_{13}N_4$, 593.2670; found, 593.2717.

Trimer (C-3): obtained in 35% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.83 (d, J = 2.7 Hz, 1H, H3c), 5.78 (d, J = 2.3 Hz, 1H, H3), 5.71 (d, J = 2.3 Hz, 1H, H3), 4.53−4.49 (m, 4H, H4a−c, H6c), 4.35 (d, J = 10.4 Hz, 1H, H6), 4.31 (d, J = 10.9 Hz, 1H, H6), 4.14−4.09 (m, 2H, H5a,b), 3.88−3.86 (m, 1H, H8c), 3.82−3.73 (m, 7H, H7c, H8a,b, H9a,b, H9′b,c), 3.63 (dd, J = 5.5 and 12.0 Hz, 1H, H9c), 3.56−3.52 (m, 4H, H7a,b, H9′a), 3.51 (t, J = 8.3 Hz, 1H, H5c), 3.20−3.17 (m, 2H, NCH_2), 2.15 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.51−1.44 (m, 4H, CH_2 caproamide), 1.26−1.22 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 167.3, 166.7, 166.5, 148.8, 148.5, 148.4, 111.8, 110.9, 79.1, 79.1, 77.9, 72.8, 70.7, 70.0, 67.5, 66.0, 65.8, 65.4, 53.8, 53.1, 53.0, 42.2, 37.8, 30.9, 28.4, 27.7. FABHRMS: [M + H^+] calcd for $C_{33}H_{54}O_{19}N_5$, 824.3413; found, 824.3408.

Tetramer (C-4): obtained in 35% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.85 (d, J = 2.5 Hz, 1H, H3d), 5.79 (s, 2H, H3b,c), 5.72 (d, J = 1.9 Hz, 1H, H3a), 4.54−4.51 (m, 5H, H4a−d, H6d), 4.39 (d, J = 10.8 Hz, 2H, H6), 4.35 (d, J = 10.9 Hz, 1H, H6), 4.17−4.11 (m, 3H, H5a−c), 3.88−3.87 (m, 1H, H8d), 3.82−3.75 (m, 10H, H7d, H8a−c, H9a−c, H9′b−d), 3.64 (dd, J = 5.5 and 11.9 Hz, 1H, H9d), 3.59−3.51 (m, 4H, H7a−c, H9′a), 3.53 (t, J = 8.8 Hz, 1H, H5d), 3.21−3.18 (m, 2H, NCH_2), 2.17 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.53−1.46 (m, 4H, $2CH_2$ caproamide), 1.27−1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 167.3, 166.7, 166.5, 148.8, 148.5, 148.3, 111.8, 110.9, 79.2, 79.1, 79.1, 77.9, 72.9, 72.8, 70.7, 70.0, 67.5, 65.94, 65.87, 65.8, 65.4, 53.8, 53.1, 53.0, 42.1, 37.8, 30.9, 28.4, 27.7. FABHRMS: [M + Na^+] calcd for $C_{42}H_{66}O_{25}N_6Na$, 1055.4156; found, 1055.4164.

Pentamer (C-5): obtained in 66% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.85 (d, J = 2.6 Hz, 1H, H3e), 5.80 (s, 3H, H3b−d), 5.73 (d, J = 2.2 Hz, 1H, H3a), 4.54−4.49 (m, 6H, H4a−e, H6e), 4.39 (d, J = 10.9 Hz, 3H, H6), 4.36 (d, J = 10.9 Hz, 1H, H6), 4.18−4.11 (m, 4H, H5a−d), 3.90−3.87 (m, 1H, H8e), 3.84−3.75 (m, 13H, H7e, H8a−d, H9a−d, H9′b−e), 3.64 (dd, J = 5.5, 11.9 Hz, 1H, H9e), 3.62−3.54 (m, 5H, H7a−d, H9′a), 3.53 (t, J = 8.8 Hz, 1H, H5e), 3.24−3.18 (m, 2H, NCH_2), 2.17 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.54−1.46 (m, 4H, $2CH_2$ caproamide), 1.28−1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 167.3, 166.7, 166.5, 165.7, 148.8, 148.5, 148.3, 111.8, 110.9, 79.1, 79.1, 79.0, 77.9, 72.8, 70.7, 70.0, 67.5, 66.0, 65.9, 65.8, 65.4, 53.8, 53.03, 52.98, 42.1, 37.8, 30.8, 28.4, 27.7. MALDI: [M + Na^+] calcd for $C_{51}H_{81}O_{31}N_7Na$, 1308.4714; found, 1308.4685.

Hexamer (C-6): obtained in 50% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.85 (d, J = 2.6 Hz, 1H, H3f), 5.80 (s, 4H, H3b−e), 5.73 (d, J = 2.2 Hz, 1H, H3a), 4.54−4.49 (m, 7H, H4a−f, H6f), 4.39 (d, J = 10.9 Hz, 4H, H6), 4.36 (d, J = 10.9 Hz, 1H, H6), 4.18−4.11 (m, 5H, H5a−e), 3.90−3.87 (m, 1H, H8f), 3.84−3.75 (m, 16H, H7f, H8a−e, H9a−e, H9′b−f), 3.64 (dd, J = 5.5, 11.9 Hz, 1H, H9f), 3.62−3.54 (m, 6H, H7a−e, H9′a), 3.53 (t, J = 8.8 Hz, 1H, H5f), 3.24−3.18 (m, 2H, CH_2), 2.17 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.54−1.46 (m, 4H, $2CH_2$ caproamide), 1.28−1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 167.3, 166.7, 166.5, 148.8, 148.5, 148.3, 111.8, 110.9, 79.2, 79.0, 77.9, 72.9, 70.7, 70.0, 67.4, 65.9, 65.3, 53.8, 53.0, 42.1, 37.8, 30.8, 28.4, 27.7, 26.8. MALDI: [M + Na^+] calcd for $C_{60}H_{93}O_{37}N_8$, 1539.5457; found, 1539.5521.

Heptamer (C-7): obtained in 86% purified yield. ^{1}H NMR (D_2O, 600 MHz): δ 5.85 (d, J = 2.6 Hz, 1H, H3g), 5.80 (s, 5H, H3b−f), 5.73 (d, J = 2.2 Hz, 1H, H3a), 4.54−4.49 (m, 8H, H4a−g, H6g), 4.39 (d, J = 10.9 Hz, 5H, H6), 4.36 (d, J = 10.9 Hz, 1H, H6), 4.18−4.11 (m, 6H, H5a−f), 3.90−3.87 (m, 1H, H8g), 3.84−3.75 (m, 19H, H7g, H8a−f, H9a−f, H9′b−g), 3.64 (dd, J = 5.5 and 11.9 Hz, 1H, H9g), 3.62−3.54 (m, 7H, H7a−f, H9′a), 3.53 (t, J = 8.8 Hz, 1H, H5g), 3.24−3.18 (m, 2H, NCH_2), 2.17 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.54−1.46 (m, 4H, $2CH_2$ caproamide), 1.28−1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 167.3, 166.7, 166.5, 148.8, 148.5, 148.3, 111.8, 110.9, 79.2, 79.0, 77.9, 72.9, 70.7, 70.0, 67.50, 65.9, 65.9, 65.4, 65.2, 53.8, 53.0, 42.1, 37.8, 30.8, 28.40, 27.7. FABHRMS: [M + Na^+] calcd for $C_{69}H_{106}O_{43}N_9Na$, 1770.6200; found, 1770.6080.

Octamer (C-8): obtained in 84% purified yield. ^{1}H NMR (D_2O, 600 MHz) δ 5.85 (d, J = 2.6 Hz, 1H, H3h), 5.80 (s, 6H, H3b−g), 5.73 (d, J = 2.2 Hz, 1H, H3a), 4.54−4.49 (m, 9H, H4a−h, H6h), 4.39 (d, J = 10.9 Hz, 5H, H6), 4.36 (d, J = 10.9 Hz, 1H, H6), 4.18−4.11 (m, 6H, H5a−f), 3.90−3.87 (m, 1H, H8h), 3.84−3.75 (m, 22H, H7h, H8a−g, H9a−g, H9′b−h), 3.64 (dd, J = 5.5 and 11.9 Hz, 1H, H9g), 3.62−3.54 (m, 6H, H7a−f, H9′a), 3.53 (t, J = 8.8 Hz, 1H, H5h), 3.24−3.18 (m, 2H, NCH_2), 2.17 (t, J = 7.4 Hz, 2H, NCH_2 caproamide), 1.54−1.46 (m, 4H, $2CH_2$ caproamide), 1.28−1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.0, 167.2, 166.6, 166.4, 148.7, 148.4, 148.3, 111.8, 110.8, 79.1, 79.0, 77.8, 72.8, 70.6, 69.9, 67.4, 65.8, 65.3, 53.7, 52.9, 42.1, 37.8,

30.8, 28.3, 27.6. MALDI: [M + Na^+] calcd for $C_{78}H_{118}O_{49}N_{10}Na$, 2001.6943; found, 2001.6901.

General Procedure for the Synthesis of Series D Oligomers. Series C oligomers were dissolved in 5 mL of methanol. Water was added for the longer oligomers to aid solubility. To the reaction mixture, 10 mg of 10% Pd-on-carbon was added to the reaction mixture, and hydrogen gas was bubbled through the methanol solution for 5 min. The flask was placed under a balloon of hydrogen for 14 h. The solution was then filtered through tight glass wool to remove the Pd-on-carbon. The glass wool was washed several times with water and methanol. The filtrate was removed in vacuo, and the remaining sugar was dissolved in water and lyophilized to give a white amorphous solid.

Monomer (D-1): obtained in 79% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.08 (dd, J = 2.1, 12.0 Hz, 1H, H2), 3.89 (dt, J = 4.8, 10.7 Hz, 1H, H4), 3.82−3.76 (m, 2H, H6, H9), 3.64 (m, 2H, H7, H8), 3.16 (m, 2H, H9′, NCH_2), 3.13 (t, J = 10.1 Hz, 1H, H5), 2.34 (ddd, J = 2.2, 4.8, 12.9 Hz, 1H, $H3_{eq}$), 2.19 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.55−1.45 (m, 5H, $H3_{ax}$, CH_2 caproamide), 1.25 (m, 2H, $2CH_2$ caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 175.5, 77.8, 77.8, 73.0, 71.7, 70.9, 65.8, 55.5, 41.7, 39.6, 37.8, 30.8, 28.3, 27.7. FABHRMS: [M + H^+] calcd for $C_{15}H_{30}O_7N_3$, 364.2084; found, 364.2068.

Dimer (D-2): obtained in 94% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.14 (dd, J = 1.9 and 11.9 Hz, H2), 3.99 (d, J = 11.9 Hz, 1H, H2), 3.93 (dt, J = 4.8 and 10.7 Hz, 1H, H4), 3.87−3.69 (m, 7H, H4, H5, H6, H8, H9), 3.64−3.61 (m, 3H, H7, H8, H9), 3.54 (dd, J = 5.9, 11.8 Hz, 1H, H9′), 3.37 (d, J = 9.2 Hz, 1H, H7), 3.19 (t, J = 10.2 Hz, 1H, H5), 3.15 (m, 2H, NCH_2), 2.37 (ddd, J = 2.6, 4.8, 10.8 Hz, 1H, $H3_{eq}$), 2.29 (d, J = 12.5 Hz, 1H, $H3_{eq}$), 2.17 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.53−1.42 (m, 5H, $H3_{ax}$, $2CH_2$ caproamide), 1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 176.3, 176.0, 78.4, 77.9, 77.8, 77.3, 73.1, 72.9, 72.7, 71.1, 71.0, 70.8, 66.0, 65.7, 55.4, 54.6, 41.7, 39.8, 37.8, 30.8, 28.3, 27.7. FABHRMS: [M + H^+] calcd for $C_{24}H_{45}O_{13}N_4$, 597.2983; found, 597.3000.

Trimer (D-3): obtained in 100% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.14 (dd, J = 2.0, 11.0 Hz, 1H, H2), 4.06 (dd, J = 1.8, 12.0 Hz, 1H, H2), 3.99 (dd, J = 1.5, 11.9 Hz, 1H, H2), 3.93 (dt, J = 4.8, 10.6 Hz, 1H, H4), 3.87−3.61 (m, 12H), 3.57−3.50 (m, 2H, H9′), 3.40−3.37 (m, 2H, H7), 3.18 (t, J = 10.2 Hz, 1H, H5), 3.15 (m, 2H, NCH_2), 2.38−2.28 (m, 3H, $H3_{eq}$), 2.17 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.56−1.42 (m, 7H, $H3_{ax}$, $2CH_2$ caproamide), 1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 177.0, 176.3, 176.0, 78.4, 77.9, 77.9, 77.8, 77.3, 73.2, 72.9, 72.7, 72.6, 71.1, 71.1, 70.9, 70.8, 66.0, 65.9, 65.7, 55.4, 54.6, 41.7, 39.9, 39.8, 39.7, 37.8, 33.2, 30.8, 28.3, 27.7. FABHRMS: [M + H^+] calcd for $C_{33}H_{60}O_{19}N_5$, 830.3883; found, 830.3886.

Tetramer (D-4): obtained in 70% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.13 (d, J = 11.9 Hz, 1H, H2), 4.06 (d, J = 11.9 Hz, 2H, H2), 3.99 (d, J = 12.0 Hz, 1H, H2), 3.92 (dt, J = 6.0, 10.7 Hz, 1H, H4), 3.87−3.61 (m, 17H), 3.57−3.53 (m, 3H, H9′), 3.48−3.37 (m, 3H, H7), 3.15 (m, 3H, H5, NCH_2), 2.37−2.28 (m, 4H, $H3_{eq}$), 2.17 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.55−1.41 (m, 8H, $H3_{ax}$, $2CH_2$ caproamide), 1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.0, 176.9, 176.2, 175.9, 78.3, 77.82, 77.78, 77.7, 77.2, 73.2, 73.1, 72.8, 72.6, 72.5, 71.0, 70.8, 70.7, 65.9, 65.8, 65.6, 55.3, 54.5, 54.5, 41.6, 39.8, 39.7, 39.6, 37.8, 30.7, 28.2, 27.6. MALDI: [M + Na^+] calcd for $C_{42}H_{74}O_{25}N_6Na$, 1085.4597; found, 1085.4540.

Pentamer (D-5): obtained in 82% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.14 (d, J = 10.5 Hz, 1H, H2), 4.06 (d, J = 11.7 Hz, 3H, H2), 3.99 (d, J = 12.0 Hz, 1H, H2), 3.95−3.67 (m, 22H), 3.65−3.54 (m, 4H, H9′), 3.44−3.37 (m, 4H, H7), 3.23−3.08 (m, 3H, H5, NCH_2), 2.20−2.16 (m, 5H, $H3_{eq}$), 2.17 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.55−1.36 (m, 9H, $H3_{ax}$, $2CH_2$ caproamide), 1.26−1.23 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.0, 176.9, 176.3, 175.9, 84.6, 78.4, 77.8, 77.7, 77.4, 73.1, 72.9, 72.5, 71.0, 70.7, 65.9, 65.7, 55.4, 54.50, 54.46, 41.6, 39.8, 39.7, 39.6, 37.8, 30.7, 28.2, 27.6. MALDI: [M + Na^+] calcd for $C_{51}H_{89}O_{31}N_7Na$ 1318.5496; found, 1318.5383.

Hexamer (D-6): obtained in 63% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.14 (d, J = 10.7 Hz, 1H, H2), 4.06 (d, J = 11.9 Hz, 4H, H2), 3.99 (d, J = 12.0 Hz, 1H, H2), 3.92 (m, 1H, H4), 3.87−3.61 (m, 27H), 3.57−3.54 (m, 5H, H9′), 3.41−3.37 (m, 5H, H7), 3.19−3.13 (m, 3H, H5, CH_2 caproamide), 2.33−2.28 (m, 6H, $H3_{eq}$), 2.17 (t, J = 10.8 Hz, 2H, CH_2 caproamide), 1.53−1.41 (m, 10H, $H3_{ax}$, $2CH_2$), 1.26−1.21 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 183.1, 177.0, 176.3, 176.0, 166.1, 84.7, 78.4, 77.9, 77.8, 77.7, 77.3, 73.3, 73.19, 73.15, 72.9, 72.7, 72.6, 71.1, 70.90, 70.85, 70.8, 66.04, 65.95, 65.7, 54.6, 54.5, 54.4, 41.7, 39.9, 39.7, 39.7, 37.8, 30.8, 28.3, 27.7, 20.9. MALDI: [M + Na^+] calcd for $C_{60}H_{104}O_{37}N_8Na$, 1551.6396; found, 1551.6317.

Heptamer (D-7): obtained in 52% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.14 (d, J = 9.7 Hz, 1H, H2), 4.07 (d, J = 11.8 Hz, 6H, H2), 3.99 (d, J = 12.0 Hz, 1H, H2), 3.92 (m, 1H, H4), 3.87−3.60 (m, 32H), 3.57−3.51 (m, 6H, H9), 3.43−3.39 (m, 6H, H7), 3.18−3.13 (m, 3H, H5, CH_2 caproamide), 2.33−2.28 (m, 7H, H3eq), 2.17 (t, J = 7.3 Hz, 2H, CH_2 caproamide), 1.53−1.42 (m, 11H, $H3_{ax}$, $2CH_2$ caproamide), 1.26−1.18 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 180.1, 174.0, 173.3, 173.0, 163.1, 162.8, 75.6, 75.4, 74.9, 74.8, 74.7, 74.3, 71.5, 70.3, 69.9, 69.6, 68.1, 67.9, 67.8, 63.0, 62.7, 52.4, 51.5, 38.7, 36.9, 36.7, 36.6, 34.8, 27.8, 25.3, 24.7. MALDI: [M + Na^+] calcd for $C_{69}H_{119}O_{43}N_9Na$, 1784.7295; found, 1784.7273.

Octamer (D-8): obtained in 85% isolated yield. ^{1}H NMR (D_2O, 600 MHz): δ 4.13 (d, J = 12.1 Hz, 1H, H2), 4.06 (d, J = 12.1 Hz, 6H, H2), 3.99 (d, J = 13.5 Hz, 1H, H2), 3.85 (m, 1H, H4), 3.81−3.37 (m, 37H), 3.57−3.54 (m, 7H, H9′), 3.41−3.37 (m, 7H, H7), 3.19−3.13 (m, 3H, H5, CH_2 caproamide), 2.37−2.28 (m, 8H, $H3_{eq}$), 2.17 (t, J = 7.4 Hz, 2H, CH_2 caproamide), 1.53−1.44 (m, 12H, $H3_{ax}$, $2CH_2$ caproamide), 1.26−1.22 (m, 2H, CH_2 caproamide). ^{13}C NMR (D_2O referenced to external TSP std, 125 MHz): δ 174.0, 75.4, 74.9, 74.7, 70.3, 69.6, 68.1, 63.0, 62.7, 52.4, 51.5, 38.7, 36.9, 34.8, 27.8, 25.3, 24.7. MALDI: [M + Na^+] calcd for $C_{78}H_{134}O_{49}N_{10}Na$, 2017.8195; found, 2017.8375.

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Supporting Information Available: General experimental procedures and carbon NMR spectra for **6**, **7**, **B1**−**8**, **12**, **13**, **C1**−**8**, and **D1**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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