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Synthesis of Nor-*C*-linked Neuraminic Acid Disaccharide: A Versatile Precursor of *C*-Analogs of Oligosialic Acids and Gangliosides

Xuejun Yuan, Dino K. Ress, and Robert J. Linhardt*

Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Troy, New York 12180

linhar@rpi.edu

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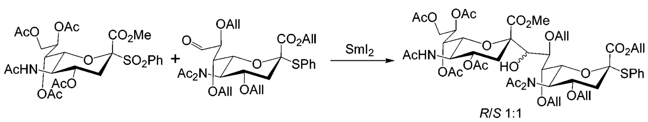

The Neu5Acα(2,8)Neu5Ac disaccharide is an important constituent of tumor related antigen, however, the *O*-linkage is catabolically unstable. Vaccination with a catabolically stable sialic acid *C*-glycoside analog might enhance immunogenicity. The synthesis of Neu5Ac nor-*C*-disaccharide **20***R*/*S*, corresponding to versatile precursors of *C*-analogs of oligosialic acid and gangliosides, is reported. The synthesis of the protected acceptor was not straightforward, as ester, silyl ether, and isopropylidene protection failed to afford desired *C*-linked disaccharide. Allyl ether protection of hydroxyl groups and acetyl protection of the acetamido facilitated the successful synthesis of the 8-aldehyde neuraminyl acceptor. Samarium mediated *C*-glycosylation afforded the desired nor-*C*-disaccharide as a mixture of two separable diastereomers.

Sialic acids, among the most important saccharides in living systems, are often found at nonreducing end of glycans.[1] They are involved in many biological phenomena, such as recognition, cell interactions, neuronal transmission, ion transport, reproduction, differentiation, epitope masking, and epitope protection. Sialic acids are also associated with pathological processes including infection, inflammation, cancer, and in neurological, cardiovascular, endocrinological, and autoimmune diseases.[2]

Polysialic acids (PSAs, **1**) are naturally occurring helical, linear homopolymers composed entirely of negatively charged sialic acid residues joined by α(2→8), α(2→9), or α(2→8)/α-(2→9) alternating ketosidic linkages[3] and are commonly found *N*-linked to a neural cell adhesion molecule (NCAM). NCAM is a cell adhesion molecule that plays a pivotal role in embryogenesis and the developmental biology of organogenesis.[4] PSAs are spatially and temporally expressed during development and disappear soon after birth. In adult mammals, PSA expression is limited to selected regions of hippocampus, where neuronal generation and axonal plasticity persists.[5] PSAs can reappear in adulthood diseases such as Wilms tumor of the kidney,[6] small cell lung carcinoma,[7] and various malignant neuroendocrine tumors, such as neuroblastoma, pheochromocytoma, and medullary thyroid carcinoma.[8] The precise function of PSA has not yet been established. The most well-demonstrated property of PSAs is in cell−cell interaction and adhesion, and it is postulated that alteration of PSA glycans in NCAM reduces cell adhesion and may be involved in invasive metastasis.[7]

PSAs are also expressed widely in bacteria. Structural mimicry of PSAs may result in immune tolerance, attenuating host-tumor and host-pathogen immune reactions.[9a] PSA capsules found in *Escherichia coli* K-235 to the capsular polysaccharides of *Neisseria meningtidis* group B and in *Pasteurella hemeolytica* serotype A2 have identical structures.[10] The role and importance of different capsular polysaccharides in the pathogenicity of several strains of *E. coli* have been established. A large proportion of cases of bacteremia and urinary tract infections are caused by strains containing Neu5Ac in their capsular structure.[11] Similarly, over 80% of neonatal meningitis is caused by strains having PSA capsules. The virulence of these organisms is attributable to structural mimicry between their common α(2→8) PSA capsular polysaccharide and human tissue counterpart, which allows the bacteria to evade immune surveillance. The poor immunogenicity of the group B meningococcal PSA has made it difficult to formulate a protective polysaccharide-based vaccine against meningococcal meningitis.[12]

The glycosidic oxygen linkage in PSAs, susceptible to the enzymatic action of extracellular sialidases,[13] represents an important target for modification in the rational design of PSA-based therapeutics. PSAs are also prone to spontaneous chemical depolymerization through the protonation of glycosidic oxygens by the adjacent internal carboxylic acid residues.[14] Neu5Acα-(2,8)Neu5Ac **2** is also an important constituent of gangliosides GD_2 and GD_3, well-known melanoma-associated antigens,

* To whom correspondence should be addressed. Phone: 518-276-3404. Fax: 518-276-3405. Homepage: http://www-heparin.rpi.edu.

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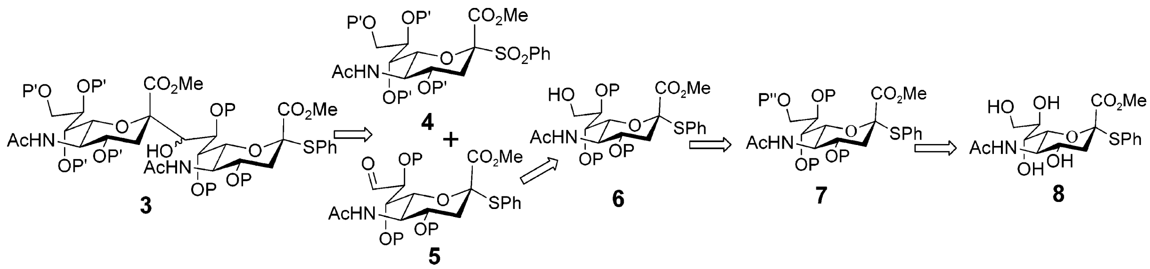
SCHEME 1



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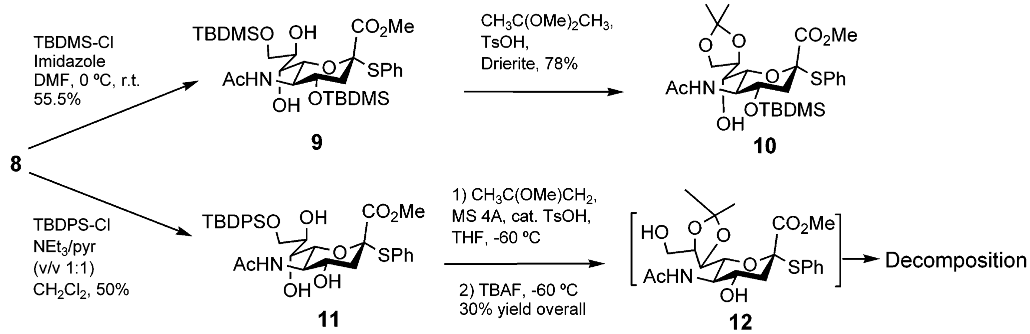

considered attractive targets for vaccine-based anticancer therapy.[15] *C*-Glycosides are resistant to chemical and enzymatic degradation, and vaccination with *C*-glycosides might enhance immunogencity[16] or be of utility in understanding biological recognition at the molecular level.[17] Herein, we report the synthesis of nor-*C*-linked α(2→8) Neu5Ac disaccharide, a versatile precursor of PSA, GD_2, and GD_3 *C*-analogs.

Retrosynthetic analysis (Scheme 1) suggests that glycosylation of acceptor **5** with Neu5Ac phenyl sulfone donor **4** should afford protected nor-*C*-disaccharide target **3**.[16a] The success of this synthetic route relies on the design and application of acceptor **5**, which we envision could be synthesized starting from the previously reported sialic acid thiophenyl glycoside **8**,[16b] using an orthogonal protection strategy followed by exposure and oxidation of the C-9 hydroxyl group.

The stability of trialkylsilyl ether masking group made it an attractive candidate as temporary protecting group (P″) for the 9-hydroxyl group. In initial attempts, starting from Neu5Ac phenyl thioglycoside **8**, C-9 hydroxyl was protected as *t*-butyldimethylsilyl (TBDMS) ether.[17] Peracetylation, followed by selective deprotection of the 9-OH using TBAF,[18] resulted in acetyl migration over a wide range of conditions (pH 3−9).[19] Persilylation of hydroxyl groups in **8** using a more aggressive silylating reagent, TBDMS-OTf,[20] selective deprotection of C-9 hydroxyl group,[21] and Swern oxidation afforded desired aldehyde acceptor **5** (P=TBDMS).[19] SmI_2 mediated *C*-glycosylation with Neu5Ac sulfone donor **4** (P′=Ac), failed to afford the desired *C*-linked Neu5Ac disaccharide **3**.[19] Molecular modeling of **5** (P=TBDMS) suggested the 9-aldehyde group was crowded and suggested the 7,8-hydroxy groups might be better protected as a smaller of isopropylidene ketal. Selective TBDMS protection of 4- and 9-hydroxyl groups resulted in **9** (Scheme 2). Treatment with dimethyl acetone ketal in the presence of a catalytic amount of tosic acid resulted in loss of the 9-*O*-TBDMS group, affording the undesired 8,9-*O*-isopropylidene derivative **10**. The *t*-butyldiphenylsilyl (TBDPS) ether **11** was prepared[22] to enhance the acid stability of the protection group at the C-9. Successful protection of the 7,8-hydroxyl groups as isopropylidene was followed by exposure of the 9-hydroxyl group using TBAF (**11**→**12**). Unfortunately, **12** was insufficiently stable, due to its strained 5-membered ring, showing 50% decomposition within one week at room temperature.

Modeling suggested allyl protection should allow *C*-glycosylation with the bulky nucleophile **4**. The ease of introduction, electron-donating properties, orthogonality, and ease of removal made OAll an ideal protecting group for synthesis of desired aldehyde acceptor **5**.[23] Regioselective protection of 8,9-diol of **8** gave **13** in 94% yield, which was then regioselectively opened[24] affording the 9-*p*-methoxybenzyl (PMB) ether **14** (Scheme 3). Perallylation of **15** under standard conditions

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SCHEME 3

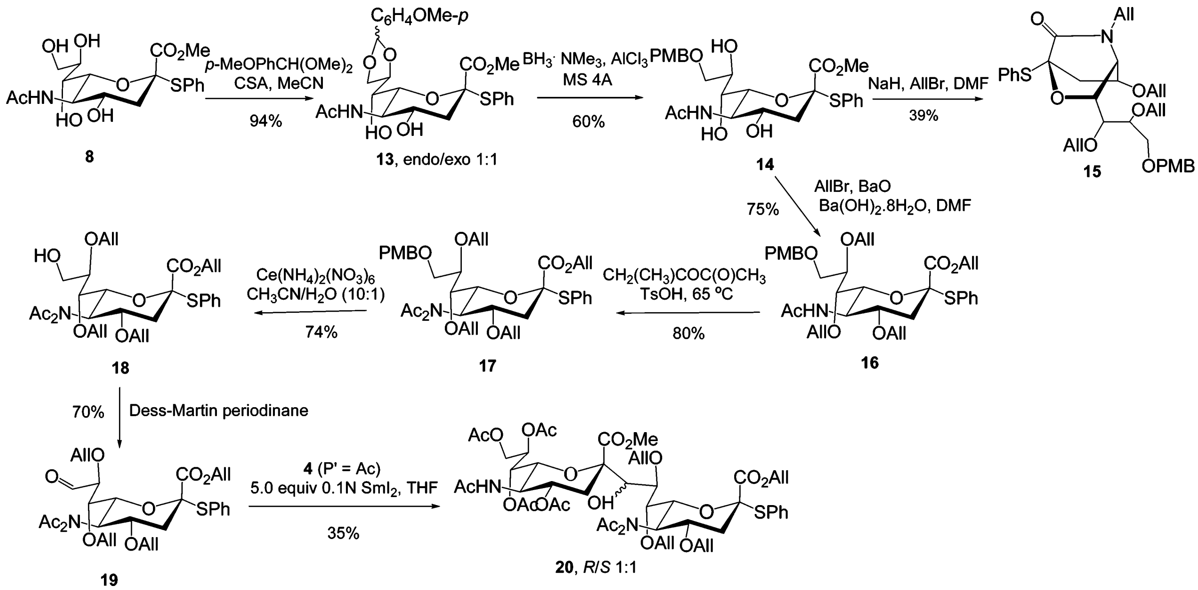
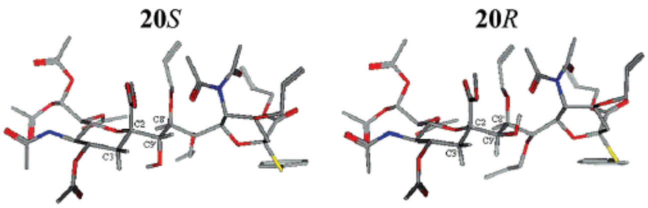


TABLE 1. Modeling on SGI SYBYL 6.0 (TRIPOS Force Field and a Dielectric Constant Set to 4.8) Compared with NMR Experimental Data



	distance (Å)	
H3eq−H9′	2.83	3.03
H3eq−H(OH9′)	3.46	3.20
H3ax−H9′	3.28	2.28, NOE observed, δ_{H3ax} 1.88 ppm
H3ax−H(OH9′)	2.29, NOE observed, δ_{H3ax} 2.25 ppm	3.96 Å
	dihedral angle (deg)	
H9′−C9′−C8′−H8′	178.8	57.9
$J_{H-9',H-8'}$	7.0 Hz	1.5 Hz

resulted in unexpected lactamization affording **15**. A mixture of BaO and $Ba(OH)_2$•$8H_2O$[25] gave the desired, albeit transesterified, allylated compound **16** in 75% yield. If the ratio of BaO and $Ba(OH)_2$•$8H_2O$ was altered in any way, the methyl ester was hydrolyzed. *N*-acetylation of **16** afforded **17** in 80% yield.[26] Deprotection of the PMB gave 9-hydroxyl derivative **18**,[26] which was oxidized to the corresponding aldehyde acceptor **19** in 70% yield.[27] *C*-Glycosylation of the aldehyde **19** with Neu5Ac sulfone donor **4** in the presence of freshly prepared SmI_2[16a] gave the desired nor-α(2,8)-*C*-neuraminic acid disaccharide **20** in 35% yield, as a diastereomeric mixture (*R*/*S* 1:1) at the bridge hydroxymethylene group. The two diastereomers were separated by flash chromatography.

^{1}H NMR shows the expected resonances of the C-3/3′ methylene and the C-4/4′ protons of ulosonic acid skeleton in the $_5C^2$ conformation.[28] The α-configuration of the products was confirmed by a $J_{C1,\ H3ax}$ = 8.5 Hz and $J_{C1,\ H3eq}$ < 1.0 Hz for less polar isomer, and a $J_{C1,\ H3ax}$ = 9.0 Hz and $J_{C1,\ H3eq}$ < 1.0 Hz for the other, as measured by selective ^{13}C NMR decoupling.[16b] The stereochemistry of newly generated bridge-carbon was determined by ROESY, NOESY, and TCOSY experiments and the less polar diastereomer assigned as *S* and the more polar as *R*. Data from computational molecular modeling are in excellent agreement with NMR experimental data (Table 1). NOE was only observed between two protons with the closest through-space distance. Differences observed in the H-3ax chemical shifts coincide with the stereochemistry assignments at the C-9 position in both diastereomers. In the **20***S*, the 9′-hydroxyl group points toward H-3ax, resulting in downfield chemical shift of H-3ax. A large coupling constant between H-9′ and H8′ is consistent with the dihedral angle of 178.8° in the structure of the *S* diastereomer.[16d]

Experimental Section

Methyl[phenyl5-acetamido-*endo*-8,9-*O*-(*p*-methoxy)-benzylidene-3,5-dideoxy-2-thio-d-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (13). Neu5Ac phenyl sulfide **8** (1.00 g, 2.41 mmol) was dissolved in CH_3CN (100 mL), and anisaldehyde dimethyl acetal (3.3 mL, 19.4 mmol) and camphorsulfuric acid (56.0 mg, 0.20 mmol). The reaction mixture was stirred for overnight and neutralized with trimethylamine (pH = 7) and solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (60 mL) and water (3 × 25 mL). The organic phase was dried over anhydr. $MgSO_4$ and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (CH_2Cl_2−CH_3OH, v/v 10:1) to afford **13** as light-yellow foam (1.46 g, 94%, *endo*/*exo* 1:1).

Methyl[phenyl 5-acetamido-9-*O*-(*p*-methoxy)benzyl-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (14). BH_3• NMe_3 (297 mg, 4.10 mmol) and $AlCl_3$ (530 mg, 3.98 mmol) were added to a solution of **13** (360 mg, 0.66 mmol) in anhydrous THF (60 mL) with activated molecular sieves (4 Å, 1.80 g) at 0 °C. After stirring at 0 °C for 4 h and at room temperature overnight, the reaction mixture was filtered over a pad of Celite and solids

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were washed with CH_3CN (3 × 25 mL). The combined filtrate was concentrated in vacuum. The residue was dissolved in ethyl acetate (30 mL) and washed with saturated aqueous $NaHCO_3$ (30 mL) and water (3 × 20 mL). The organic phase was dried over $MgSO_4$ and filtered, and the filtrate was concentrated in vacuum. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 20:1), affording **14** as snow-white foam (190 mg, 52.7%).

Allyl[phenyl 4,7,8-tri-*O*-allyl-5-acetamido-9-*O*-(*p*-methoxy)benzyl-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (16). BaO (420 mg, 2.74 mmol) and $Ba(OH)_2$•$8H_2O$ (564 mg, 1.8 mmol) were added to a solution of **14** (160 mg, 0.30 mmol) in anhydrous DMF (10 mL) under stirring. Half an hour later, AllBr (0.54 mL, 6.2 mmol) was added dropwise to the above mixture. The mixture was stirred under argon at r.t. for 10 h. The reaction was quenched with TsOH, the reaction mixture was filtered over a pad of celite, and the solids were washed with CH_3CN (3 × 20 mL). The combined filtrate was rotary evaporated under vacuum to dryness, leaving a yellow oil-like liquid residue. The residue was subject to flash column chromatography (CH_2Cl_2−MeOH, v/v 35:1) to afford **16** (150 mg, 73.6%) as yellow oil-like liquid.

Allyl[phenyl 4,7,8-tri-*O*-allyl-5-(*N*-acetylacetamido)-9-*O*-(*p*-methoxy)benzyl-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (17). A solution of **16** (150 mg, 0.208 mmol) and TsOH•H_2O (10 mg, 0.05 mmol) in isopropenyl acetate (5 mL) was kept at 60 °C for 6 h. The reaction mixture was neutralized by addition of Et_3N. The resulting solution was concentrated under vacuum. The residue was purified by flash silica gel column chromatography (petroleum ether-EtOAc, v/v 4:1), affording **17** as a light-yellow oil-like liquid (0.123 g, 77.4%).

Allyl [phenyl 4,7,8-tri-*O*-allyl-5-(*N*-acetylacetamido)-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (18). Cerium ammonium nitrate (348 mg, 0.60 mmol) was added to a solution of **17** (120 mg, 0.18 mmol) in a mix solvent (CH_3CN/H_2O 10:1) under stirring. The reaction mixture was stirred for 5 h at r.t. Then it was concentrated under vacuum. The residue was dissolved in ethyl acetate (15 mL), and the resulting solution was washed with saturated Na_2SO_3 aqueous solution (5 mL) and water (3 × 5 mL), consecutively. The organic phase was concentrated to dryness, and the resulting residue was subject to flash chromatography (petroleum ether-EtOAc, v/v 5:1), affording **18** (60 mg, 60%) as a colorless liquid.

Allyl[phenyl 4,7,8-tri-*O*-allyl-5-(*N*-acetylacetamido)-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-(9-oxa-ulopyranosid)]onate (19). Dess-Martin solution (15 wt %) (0.64 mL, 0.30 mmol) was added dropwise to a solution of **18** (48 mg, 0.079 mmol) in anhydr. CH_2Cl_2 (5.0 mL) under stirring at 0 °C. The reaction mixture was kept at 0 °C for 30 min and was stirred overnight at r.t. It was diluted with ethyl ether (15 mL) and poured into 0.1 N sodium thiosulfate saturated with $NaHCO_3$ (5 mL). The organic layer was washed sequentially with saturated aqueous $NaHCO_3$, brine, and water. The organic phase was concentrated under vacuum. The residue was purified on flash column chromatography (petroleum ether-EtOAc, v/v 10:1), giving **19** (33 mg, 70%) as a colorless liquid.

Methyl 5-Acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-2-*C*-{(*S*)-hydroxy-[9′-(allyl(phenyl4′,7′,8′-tri-*O*-allyl-5-(*N*-acetylacetamido)-3′,5′-dideoxy-2′-thio-D-*glycero*-α-D-*galacto*-oct-2′-ulopyranosid)onate)methyl]}-D-erythro-L-*manno*-nononate (20). A solution of compounds **19** (30 mg, 0.050 mmol) and **4** (60 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was evaporated to dryness and the resulting residue dried overnight under high vacuum. The dried residue placed under argon was added a solution of freshly prepared SmI_2 (0.1 N, 5.0 mL) and the reaction mixture was stirred for 1 h at r.t. The reaction mixture was diluted with ethyl ether, washed successively with 0.1 N HCl, saturated aqueous $Na_2S_2O_3$ in $NaHCO_3$, and distilled water, dried over anhydr. $MgSO_4$, and filtered. The filtrate was evaporated under vacuum to dryness and purified by column chromatography (petroleum ether-EtOAc, v/v 3:1→1:1) in a total yield of (*S*)-**20** (9.5 mg) and (*R*)-**20** (9.5 mg) corresponding to 35.0%.

(*S*)-**20**: $[\alpha]_D^{25} = -17.5$ (*c* 0.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.53 (1H, dd, $J_{H-3ax', H-3eq'}$ 12.9 Hz, $J_{H-3ax', H-4'}$ = 10.8 Hz, H-3ax′), 2.01, 2.04, 2.09, 2.17, 2.30, 2.31, 2.36 (21H, 7s, CH_3CO), 2.25 (1H, t, $J_{H-3ax,H-4}$ = 10.5 Hz, H-3ax), 2.78 (1H, t, $J_{H-3eq',H-4}$ = 5.0 Hz, H-3eq′), 2.80 (1H, t, $J_{H-3eq,H-4}$ = 5.0 Hz, H-3eq), 3.45 (1H, m, H-7′), 3.49 (1H, dd, $J_{H-9',OH-9'}$ = 4.5 Hz, $J_{H-9',H-8'}$ = 7.0 Hz, H-9′), 3.70 (1H, m, C*H*$_2$CHAll), 3.72 (3H, s, $COOCH_3$), 3.77 (1H, dd, $J_{H-5',H-4'}$ = 10.0 Hz, $J_{H-5',H-6'}$ = 10.0 Hz, H-5′), 3.78−3.83 (3H, m, C*H*$_2$CHAll), 3.88 (2H, m, C*H*$_2$-CHAll), 3.94 (1H, d, $J_{OH-9',H-9'}$ = 4.5 Hz, OH-9′), 3.96−3.99 (1H, m, C*H*$_2$CHAll), 4.01 (1H, dd, $J_{H-9a,H-8}$ = 5.0 Hz, $J_{H-9a,H-9b}$ = 12.5 Hz, H-9a), 4.03−4.11 (2H, m, C*H*$_2$CHAll), 4.12 (1H, m, H-4′), 4.14 (1H, m, H-6), 4.19 (2H, m, C*H*$_2$CHAll), 4.29 (1H, m, H-8′), 4.34 (1H, dd, $J_{H-7,H-8}$ = 11.0 Hz, $J_{H-7,H-6}$ = 2.5 Hz, H-7), 4.63 (1H, m, C*H*$_2$═CHAll), 4.71 (1H, dd, $J_{H-6',H-7'}$ = 2.5 Hz, $J_{H-6',H-5'}$ = 9.5 Hz, H-6′), 4.75 (1H, d, $J_{NH,H-5}$ = 5.0 Hz, NH), 4.79 (1H, oct, $J_{H-5,H-4}$ = 10.0 Hz, $J_{H-5,H-6}$ = 9.0 Hz, $J_{H-5,NH}$ = 5.0 Hz, H-5), 4.85 (1H, oct, $J_{H-4,H-3ax}$ = 10.5 Hz, $J_{H-4,H-5}$ = 10.0 Hz, $J_{H-4,H-3eq}$ = 5.0 Hz, H-4), 5.16 (5H, m, C*H*$_2$═CHAll), 5.25−5.38 (2H, m, C*H*$_2$═CHAll), 5.41 (1H, m, H-8), 5.48−5.51 (1H, m, CH_2═C*H*All),5.52 (1H, dd, $J_{H-9b,H-9a}$ = 12.5 Hz, $J_{H-9b,H-8}$ = 2.0 Hz, H-9b), 5.66−6.11 (3H, m, CH_2═C*H*All), 7.65−7.77 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): 21.0, 21.5, 23.4, 25.4, 28.0, 29.9, 30.6, 35.4, 40.3, 50.0, 52.6, 60.2, 67.1, 68.0, 70.9, 72.0, 72.3, 73.0, 73.3, 77.4, 84.8, 87.8, 95.2, 116.6, 116.9, 117.6, 120.6, 125.7, 129.2, 130.2, 131.8, 134.3, 135.1, 137.0, 154.3, 168.6, 169.9, 170.4, 170.7, 171.0, 171.2, 175.2, 176.0; HR-ESIMS calcd for $C_{51}H_{68}N_2O_{21}NaS$ $[M + Na]^+$ 1099.3933, found *m/z* 1099.3937.

(*R*)-**20**: $[\alpha]_D^{25} = -5.7$ (*c* 0.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.68 (1H, dd, $J_{H-3ax',H-3eq'}$ = 12.5 Hz, $J_{H-3ax',H-4'}$ = 10.8 Hz, H-3ax′), 1.88 (1H, t, $J_{H-3ax,H-4}$ = 10.5 Hz, H-3ax), 1.89, 1.98, 2.03, 2.04, 2.14, 2.20, 2.24 (15H, s, CH_3CO), 2.48 (1H, $J_{H-3eq,H-4}$ = 5.0 Hz, $J_{H-3eq,H-3ax}$ = 12.5 Hz, H-3eq), 2.78 (1H, $J_{H-3eq',H-4'}$ = 4.5 Hz, $J_{H-3eq',H-3ax'}$ = 12.5 Hz, H-3eq′), 3.49 (2H, m, C*H*$_2$CHAll), 3.51 (1H, m, H-9a), 3.62−3.72 (2H, m, C*H*$_2$CHAll), 3.74 (3H, s, $COOCH_3$), 3.81 (1H, m, H-4′), 3.82−3.87 (2H, m, C*H*$_2$CHAll), 3.92 (1H, dd, $J_{H-9b,H-8}$ = 5.0 Hz, $J_{H-9b,H-9a}$ = 12.5 Hz, H-9b), 3.97 (1H, m, H-7′), 4.02 (1H, m, $J_{H-5,H-4}$ = 10.0 Hz, $J_{H-5,H-6}$ = 10.0 Hz, H-5), 4.06−4.18 (2H, m, C*H*$_2$CHAll), 4.19 (1H, m, H-8′), 4.21 (1H, m, H-6), 4.58−4.63 (1H, m, C*H*$_2$═CHAll), 4.71−4.76 (1H, m, C*H*$_2$═CHAll), 5.08−5.14 (2H, m, C*H*$_2$═CHAll), 4.84 (1H, oct, $J_{H-4,H-3ax}$ = 10.5 Hz, $J_{H-4,H-5}$ = 10.0 Hz, $J_{H-4,H-3eq}$ = 5.0 Hz, H-4), 5.17 (1H, dd, $J_{H-6',H-7'}$ = 2.5 Hz, $J_{H-6',H-5'}$ = 9.5 Hz, H-6′), 5.19−5.28 (2H, m, C*H*$_2$═CHAll), 5.29 (1H, dd, $J_{H-7,H-8}$ = 11.0 Hz, $J_{H-7,H-6}$ = 2.5 Hz, H-7), 5.31 (1H, t, $J_{H-9',H-8'}$ = 1.5 Hz, H-9′), 5.33−5.36 (2H, m, C*H*$_2$═CHAll), 5.38 (1H, dd, $J_{H-5',H-4'}$ = 10.0 Hz, $J_{H-5',H-6'}$ = 10.0 Hz, H-5′), 5.42 (1H, m, OH), 5.43 (1H, m, H-8), 5.57−5.60 (2H, m, H-5 and NH), 5.76−6.00 (4H, m, CH_2═C*H*All), 7.35−7.63 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.1, 21.1, 21.5, 21.6, 23.5, 23.8, 32.0, 35.3, 50.0, 52.6, 53.0, 63.0, 66.5, 68.11, 68.9, 70.0, 70.0, 71.5, 73.2, 73.3, 74.6, 75.7, 80.6, 87.8, 115.8, 116.9, 117.2, 119.6, 129.0, 129.6, 129.7, 131.8, 134.9, 135.3, 135.5, 136.8, 168.5, 169.8, 170.5, 170.6, 170.7, 171.0, 171.1, 171.3; HR-ESIMS calcd for $C_{51}H_{68}N_2O_{21}$-NaS $[M + Na]^+$ 1099.3933, found *m/z* 1099.3939.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **9**−**21** and HR ESI-MS spectra for **20*R*** and **20*S***, general methods, and the synthesis and characterization of **9**−**19**, and **21.** This material is available free of charge via the Internet at http://pubs.acs.org.

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