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Synthesis of non-natural glycosylamino acids containing tumor-associated carbohydrate antigens

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Dedicated in honor of the award of the Tetrahedron Prize to Professor K. C. Nicolaou and in recognition of his many contributions to the assembly of oligosaccharides.

Abstract—The synthesis of biologically relevant glycosylamino acids using a non-natural amino acid as the glycosyl acceptor is described. The glycosylation reaction of a monosaccharide tri-chloroacetimidate donor with Fmoc-L-hydroxynorleucine benzyl ester provided the α-*O*-linked product. Conversely, when the glycosylation reaction was carried out with a glycal epoxide donor, the β-*O*-linked product predominated. We have used these two complementary glycosylation reactions to synthesize five different glycosylamino acids, each containing the Tn, TF, STn, Lewis^y or Globo-H tumor-associated carbohydrate antigens.

1. Introduction

Certain carbohydrate epitopes are often significantly over-expressed on the surface of transformed cells.[1] The isolation and identification of these differential antigens has allowed for their use in the development of anti-cancer vaccines.[2] These vaccines, normally consisting of the carbohydrate antigen attached through a linker domain to an immunogenic carrier protein, have been investigated for their ability to generate an immune response directed at eliminating circulating tumor cells and micrometastases.[3] One of the limiting factors in exploring the utility of these cell-free glycoconjugate vaccines is the limited availability of purified tumor-associated carbohydrate antigens. Many laboratories have increasingly come to rely on total chemical synthesis for producing probe structures to be evaluated in such constructs.[4] We have become progressively active in developing multiple synthetic methods for the syntheses of these antigens as well as investigating the ideal technique for creating vaccine constructs.

Based on our earlier investigations, we have come to prefer the display of tumor antigens on a peptide backbone. The desired *N*-protected glycoamino acids are individually synthesized and then the vaccine assembled by iterative peptide couplings. The strategy in our laboratory for introducing amino acid functionality to tumor-associated carbohydrate antigens first involved glycosylations utilizing natural amino acids (Ser, Thr) to provide core mucin structures.[5] More recently, our efforts in the total synthesis of carbohydrate-based anti-tumor vaccines have led us to favor non-natural amino acids as components of our peptide-linked vaccines.[6] In principle, such unnatural linkages might result in an enhanced immune response. Additionally, the use of non-natural amino acids, in particular those containing long, aliphatic side chains that create greater distance between the peptide backbone and the glycosides, may be critical to the success of the glycopeptide synthesis. One vaccine employing these non-natural amino acids as linkers to carbohydrate domains has undergone preliminary investigation and demonstrated proof of principle in its effectiveness at inducing immunogenicity in murine hosts.[7]

We have come to depend on three different protocols for facilitating the introduction of the non-natural amino acid moiety to the carbohydrate domain. Specifically, transformation of *O*-pentenyl glycosides via an ozonolysis-Wittig-asymmetric hydrogenation sequence,[6] cross-metathesis of *O*-allyl glycosides with allylglycine[8] and the most recently disclosed direct glycosylation of hydroxynorleucine with a suitable glycosyl donor[9] all result in the same type and length of side chain, four methylene units, between the α-carbon of the amino acid and the carbohydrate antigen. We have previously shown that 2-azido galactose trichloroacetimidate donor **2**, when treated with a Lewis acid in the presence of Fmoc-L-hydroxynorleucine benzyl ester **1**

Keywords: hydroxynorleucine; glycosylation; carbohydrate antigen; glycosylamino acid; carbohydrate-based antitumor vaccines.

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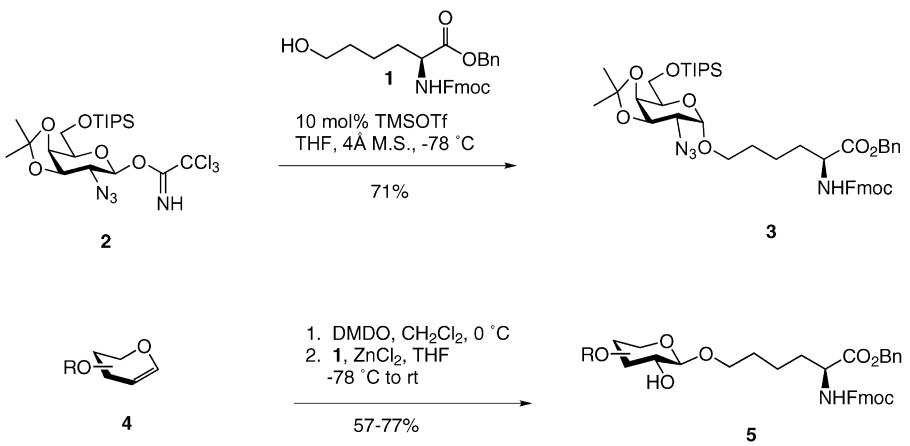
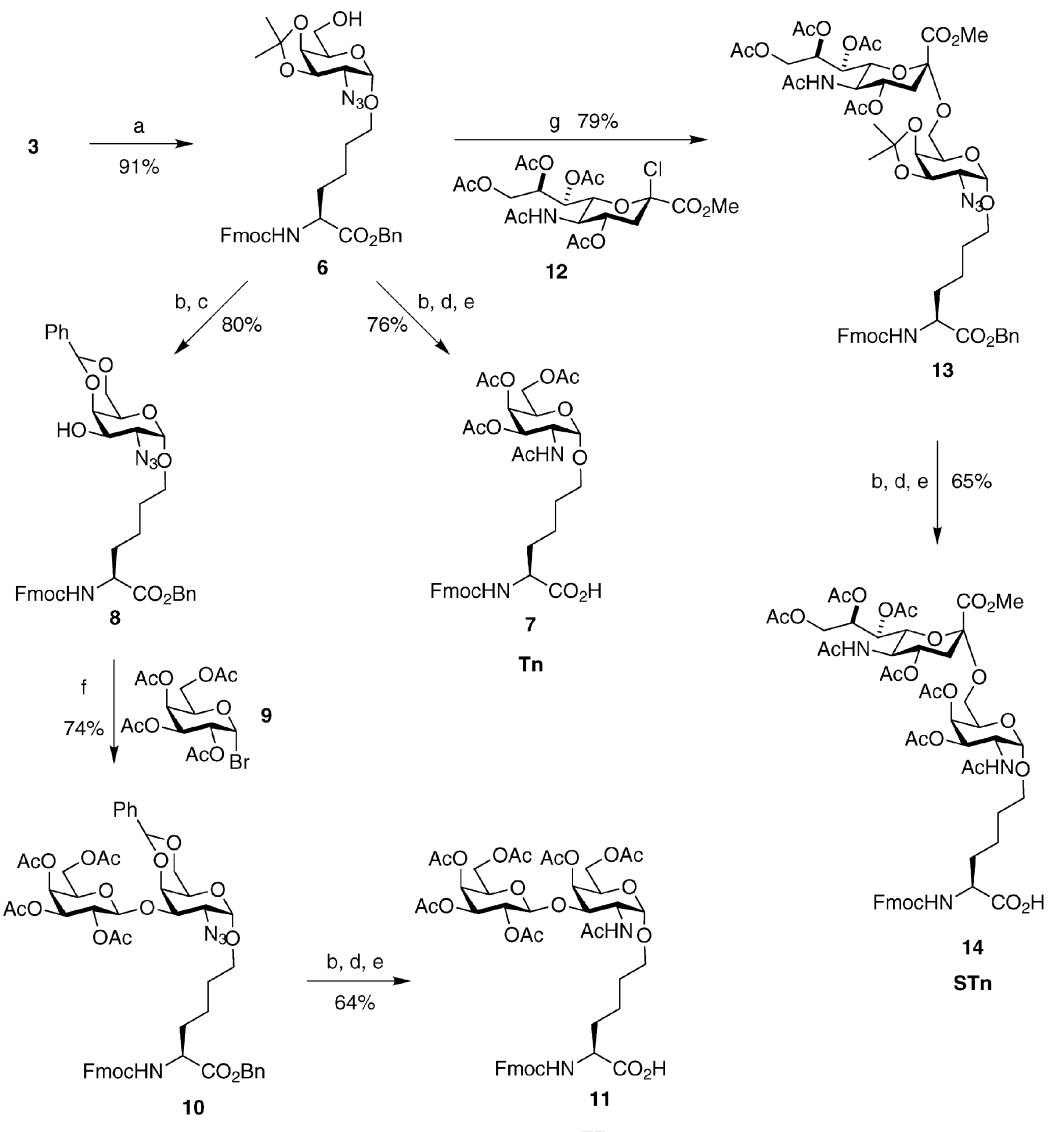
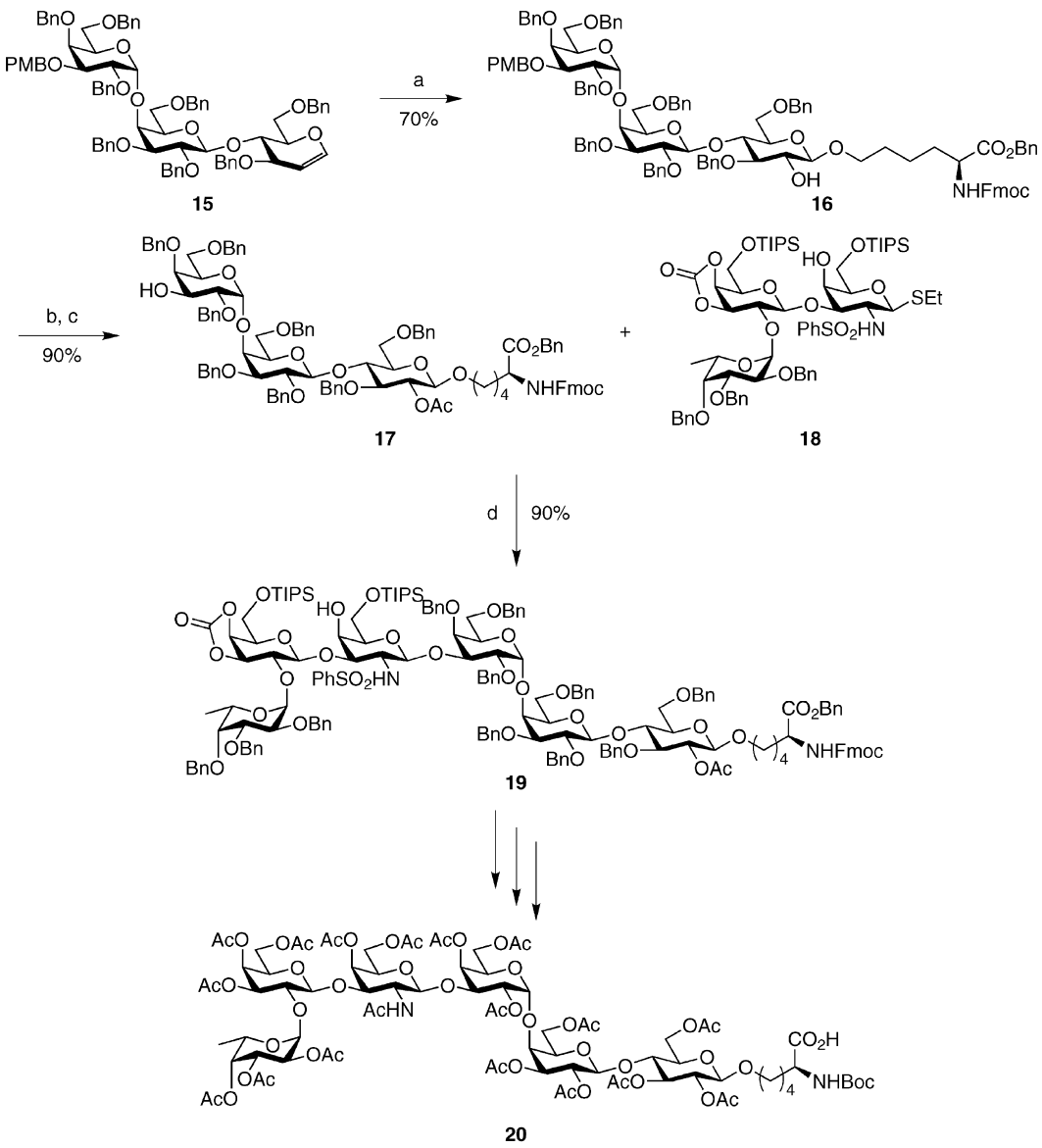


Scheme 1. α- and β-selective hydroxynorleucine based glycosylations.



Scheme 2. Synthesis Tn, TF and STn glycosylamino acids. *Reagents*: (a) TBAF, AcOH, THF; (b) 80% AcOH (aq.), 70°C; (c) benzaldehyde dimethyl acetal, $MeNO_2$, cat. *p*-TsOH; (d) (i) Ac_2O, pyr, cat. DMAP, CH_2Cl_2, (ii) pyr, AcSH; (e) 10% Pt/C, 1 atm H_2, $MeOH/H_2O$; (f) **9**, AgOTf, 4 Å MS, $PhCH_3/CH_2Cl_2$, −30°C (g) **12**, AgOTf, DTBP, $CaSO_4$, THF, −78 to −10°C.



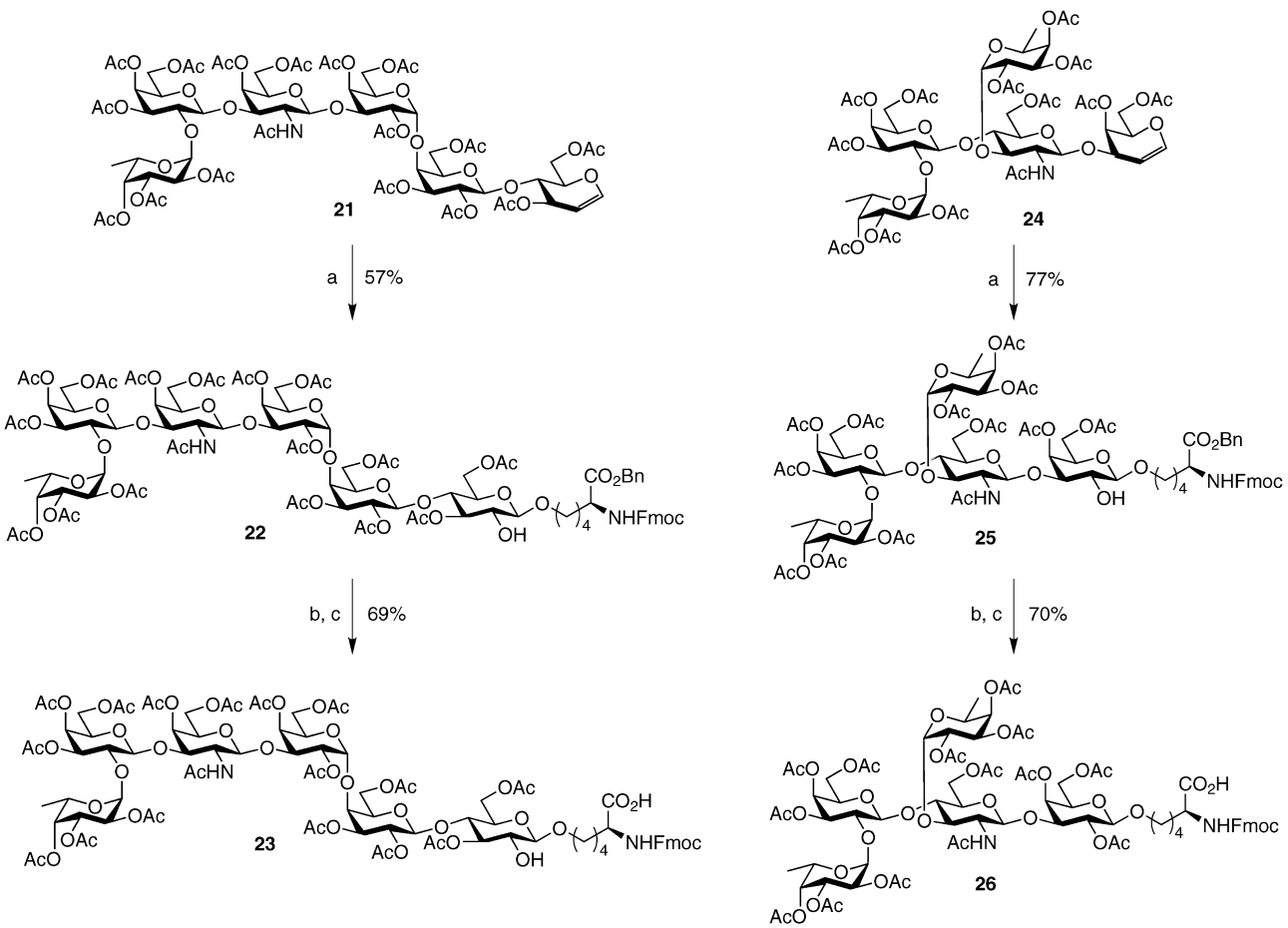
Scheme 3. Synthesis of Globo-H glycosylamino acid via ABC-hydroxynorleucine coupling. *Reagents*: (a) (i) DMDO, CH_2Cl_2, 0°C, (ii) **1**, $ZnCl_2$, THF, 0°C to rt; (b) Ac_2O, pyr., cat. DMAP; (c) DDQ, CH_2Cl_2/H_2O, 0°C; (d) MeOTf, 4 Å MS, CH_2Cl_2, −20 to 0°C.

resulted in a 71% yield of the desired α-anomer **3**, along with 18% of the β-anomer as shown in Scheme 1. The carbohydrate domain of protected monosaccharidic amino acid **3** can be further transformed to provide many different α-linked glycosylamino acids of biological interest. We report here the synthesis of glycosylamino acids containing the Tn, TF and STn tumor-associated carbohydrate domains. Conversely, when the donor is changed to a glycal epoxide, derived from glycal **4**, and $ZnCl_2$ activator, the hydroxynorleucine glycosylation resulted in the formation of β-anomer **5**. We have used this method to synthesize Lewis^y (Le^y) and Globo-H containing amino acids.

2. Results and discussion

The synthesis of the three different glycosylamino acids shown in Scheme 2 started from the common building block, **3**, with the removal of the silyl protecting group to generate the primary alcohol **6**. The synthesis of the Tn antigen glycosylamino acid involved acidic removal of the acetonide and peracetylation of the hydroxyls followed by azide reduction and acylation. Finally, hydrogenolysis of the benzyl ester using Pt/C provided the free acid **7** for use in peptide synthesis. The use of palladium instead of platinum during hydrogenolysis caused undesired partial cleavage of the Fmoc protecting group. The disaccharide TF antigen synthesis involved AgOTf mediated glycosylation between benzylidene protected acceptor **8** and tetra-*O*-acetyl-α-bromo galactosyl donor **9**[10] gave β-linked disaccharide **10** in 74% yield with no indication of ortho ester formation. Acidolytic removal of the benzylidene group, followed by acetate protection, azide reduction-protection and hydrogenolysis generated the Fmoc protected TF glycosyl acid **11**.

The disaccharide STn antigen contains a sialic acid residue that was incorporated into our scheme via the chloro donor **12**,[11] using AgOTf as the activator and acceptor **6**. The



Scheme 4. Synthesis of Globo-H and Le^y glycosylamino acids from late stage glycals. *Reagents*: (a) (i) DMDO, CH_2Cl_2, 0°C, (ii) **1**, $ZnCl_2$, THF, −78 to 23°C; (b) Ac_2O, pyr., cat. DMAP, CH_2Cl_2; (c) 10% Pt/C, 1 atm H_2, MeOH/H_2O.

glycosylation reaction proceeded in 97% yield with good anomeric 4.5:1 (α/β) selectivity. Transformation of disaccharide **13** to acid **14** occurs, as previously described for the Tn antigen. We have clearly demonstrated the usefulness of intermediate **3** in the synthesis of three antigen containing glycosylamino acids. One can also envision its further utility in the synthesis of other carbohydrate antigen analogs that contain a GalNAc monosaccharide such as glycophorin, 2,3-ST, 2,6-ST and F1α.[12]

Globo-H and Le^y are two of the more complex carbohydrate antigens which we have repeatedly incorporated into our vaccine constructs.[3a] We completed the first total synthesis and, thereby proof of stereochemistry of the Globo-H antigen in our laboratory in 1996.[13] Since then, we have been actively pursuing more convenient and convergent syntheses of this hexasaccharide antigen to enable the generation of sufficient quantities for clinical trials. Based on our previous knowledge, we chose to first investigate uniting the hydroxynorleucine **1** moiety with the ABC glycal **15** as shown in Scheme 3. The glycosylation occurred in 70% yield and generated the desired β-anomer **16** selectively. The free hydroxyl was protected as the acetate, and the PMB ether was oxidatively removed with DDQ to liberate **17**. This compound is necessary for the glycosylation with the DEF ethylsulfide donor **18**. Using 2 equiv. DEF donor, the glycosylation between the two trisaccharide domains generated the hexasaccharide glycosylamino acid **19** in good yield. Unfortunately, the global deprotection and peracylation sequence[13] along with the amino protection pattern shown in **20** did not generate the desired product cleanly. Most often the desired product was contaminated with species corresponding to differentials +42 and +84 mass units from ideality. These peaks would seem to arise from acetylation of the acetamide and carbamate moieties. Attempts to hydrolyze, isolate or confirm the byproducts were not successful. Ultimately, these difficulties resulted in the abandonment of this route and an alternative, albeit less convergent synthesis, was investigated. In this case we looked at incorporating the amino acid motif late in the synthesis, specifically at the hexasaccharide glycal stage as shown in Scheme 4.

The peracetylated Globo-H hexasaccharide glycal **21**[13] was treated with DMDO to generate the glycal epoxide. The latter was subsequently coupled to hydroxynorleucine **1**, to generate adduct **22** in 57% yield for the two steps with the byproduct (19%) being α-manno type adduct originating from undesired β-epoxidation of the glycal. This methodology was also applied to the synthesis of the Le^y bearing amino acid **26**. Le^y glycoconjugates, both to protein and lipid immunogens, have been extensively studied for their effects.[14] Starting from the Le^y pentasaccharide **24**,[14a] containing the glycal linkage, glycosylamino acid **25** was generated in 77% yield via the glycal epoxide donor method. In order to utilize these glycosylamino acids in

glycopeptide construction, the free hydroxyl groups were protected as their acetates and deprotection of the benzyl esters provided the free acids **23** and **26**.

3. Conclusion

In conclusion, we have described herein the utility of hydroxynorleucine as a glycosyl acceptor for the incorporation of amino acid functionality into carbohydrates. This procedure directly affords the *N*- and *C*-protected glycosylamino acid for further functionalization of the carbohydrate domain or for deprotection and use in the preparation of glycopeptides. We have clearly demonstrated that multiple carbohydrate antigens, both α- and β-linked, can be produced depending upon the nature of the carbohydrate donor. These glycosylamino acids are currently being used for incorporation into vaccine constructs for immunological investigation. The results of these investigations will be forthcoming.

4. Experimental

4.1. General procedures

All commercial materials were used without further purification. Anhydrous THF, diethyl ether, CH_2Cl_2, toluene, and benzene were obtained from a dry solvent system (passed through column of alumina) and used without further drying. All reactions were performed under an atmosphere of pre-purified dry Ar(g). NMR spectra (^1H and ^{13}C) were recorded on a Bruker AMX-400 MHz or Bruker Advance DRX-500 MHz, referenced to TMS or residual solvent. Optical rotations were measured with a Jasco DIP-370 digital polarimeter using a 10 cm path length cell. Low-resolution mass spectral analyses were performed with a JOEL JMS-DX-303-HF mass spectrometer or Waters Micromass ZQ mass spectrometer. Analytical TLC was performed on E. Merck silica gel 60 F254 plates and flash column chromatography was performed on E. Merck silica gel 60 (40–63 mm).

4.1.1. Glycal epoxidation and hydroxynorleucine glycosylation. A solution of glycal in CH_2Cl_2 (0.15 M) at 0°C was treated with dimethyldioxirane (assumed 0.07 M in acetone, 2.0 equiv.), and the mixture was stirred at 0°C until all of the glycal was consumed (20–30 min). After removal of solvent, the crude epoxide was combined with hydroxynorleucine **1** (5.0 equiv.), azeotroped with toluene (2×), and further dried under high vacuum for 30 min. The mixture was dissolved in THF containing freshly activated 4 Å molecular sieves (1 g/0.25 mmol glycal), stirred at room temperature for 30 min, cooled to −78°C, treated with $ZnCl_2$ (1.0 M solution in Et_2O, 4.0 equiv.), and finally allowed to warm to room temperature. After stirring overnight, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and filtered through celite, and the filtrate was extracted with EtOAc. Organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography of the residue provided the desired compound.

4.1.2. Acetonide, benzylidene deprotection. Acetonide or benzylidene protected compounds were dissolved in 80% aq. acetic acid and heated to 70°C until starting material was consumed. The solution was concentrated in vacuo and azeotroped with toluene (3×) and the resulting residue used directly without purification.

4.1.3. Acetylation. To the hydroxyl dissolved in CH_2Cl_2 (0.1 M) was added pyridine (5–10 equiv.), acetic anhydride (5–10 equiv.) and a catalytic amount of DMAP. The solution was stirred at room temperature until complete as judged by TLC. The solution was concentrated and the residue purified by chromatography.

4.1.4. Azide reduction–acylation. To the azide at 0°C was added equal amounts of pyridine then thiolacetic acid (0.1 M final concentration). The reaction was allowed warm slowly to room temperature and stirred for 24–48 h, concentrated and purified by chromatography.

4.1.5. Benzyl ester hydrogenolysis. The benzyl ester was dissolved in MeOH/H_2O (15:1, 0.001 M concentration). 20% (w/w) of 10% Pt/C was added and the reaction was stirred under 1 atm H_2 for 24 h. The reaction mixture was filtered and concentrated in vacuo.

4.2. Specific procedures

4.2.1. Compound 3. β-Trichloroacetimidate **2** (2.89 g, 5.29 mmol) and Fmoc-L-hydroxynorleucine benzyl ester **1** (3.65 g, 7.94 mmol) were azeotroped in benzene (3×) and dried in vacuo for 2 h. The solution of acceptor and donor were dissolved in THF (53 mL total) and transferred via cannula to flame dried 4 Å molecular sieves. The solution was cooled to −78°C and TMSOTf (96 μL) was added dropwise. The reaction was stirred at −78°C for 2 h, quenched by addition of solid $NaHCO_3$, filtered through celite and concentrated in vacuo. Purification by flash column chromatography (0.5–20% ethyl acetate in hexanes) provided the α-anomer (3.12 g, 3.70 mmol, 70%) and β-anomer (0.78 g, 0.926 mmol, 18%). α-anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, J=7.5 Hz), 7.59 (d, 2H, J=7.2 Hz), 7.25–7.41 (m, 9H), 5.37 (d, 1H, J=8.2 Hz), 5.18 (dd, 1H, J=14.7, 12.5 Hz), 4.81 (d, 1H, J=3.2 Hz), 4.33–4.46 (m, 4H), 4.27 (dd, 1H, J=5.1, 2.2 Hz), 4.21 (t, 1H, J=7.1 Hz), 3.85–4.04 (m, 3H), 3.70 (m, 1H), 3.36 (m, 1H), 3.26 (dd, 1H, J=8.5, 3.3 Hz), 1.21–1.95 (m, 6H), 1.50 (s, 3H), 1.34 (s, 3H), 0.89–1.21 (m, 21H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.46, 156.08, 144.08, 143.95, 141.46, 135.46, 128.80, 128.66, 128.48, 127.86, 127.24, 125.31, 120.14, 109.78, 97.96, 73.48, 72.87, 68.68, 67.95, 67.34, 67.26, 62.71, 61.53, 53.98, 47.31, 32.41, 28.95, 28.57, 26.39, 21.89, 18.12, 12.09; MS (LR-ESI) calculated for $C_{46}H_{63}N_4O_9Si$ $[M+H]^+$ 843.4, found 843.4.

4.2.2. Compound 6. To a solution of **3** (1.30 g, 1.54 mmol) in 15.4 mL THF at 0°C was added glacial acetic acid (5.3 mL, 92.4 mmol) and 1.0 M TBAF in THF (23.1 mL, 23.1 mmol). The reaction was stirred at 0°C for 1 h, room temperature for 48 h and concentrated in vacuo. The crude residue was diluted with EtOAc and washed successively with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by

flash column chromatography (25–50% EtOAc in hexanes) provided 0.962 g (1.40 mmol, 91%) of the desired compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, J=7.5 Hz), 7.59 (d, 2H, J=7.1 Hz), 7.25–7.41 (m, 9H), 5.46 (d, 1H, J=7.7 Hz), 5.18 (dd, 1H, J=16.5, 12.4 Hz), 4.86 (d, 1H, J=3.2 Hz), 4.33–4.41 (m, 4H), 4.14–4.21 (m, 2H), 4.02 (m, 1H), 3.79–3.93 (m, 2H), 3.69 (m, 1H), 3.41 (m, 1H), 3.28 (dd, 1H, J=8.6, 3.3 Hz), 2.62 (bs, 1H), 1.27–1.92 (m, 6H), 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.47, 156.15, 144.04, 143.91, 141.46, 135.42, 128.81, 128.70, 128.47, 127.90, 127.26, 125.27, 120.16, 110.24, 98.04, 73.87, 73.70, 68.24, 68.09, 67.40, 67.27, 62.74, 61.29, 53.99, 47.30, 32.34, 28.90, 28.45, 26.46, 21.95; MS (LR-ESI) calculated for $C_{37}H_{42}N_4O_9Na$ $[M+Na]^+$ 709.3, found 709.3.

4.2.3. Compound 7. Obtained from **6** according to the general procedures as a white solid in 76% yield (0.261 g). $[\alpha]_D^{26}$=+59.3° (c 1.01, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.77 (d, 2H, J=7.5 Hz), 7.66 (t, 2H, J=6.7 Hz), 7.37 (t, 2H, J=7.4 Hz), 7.27–7.31 (m, 2H), 5.40 (d, 1H, J=2.6 Hz), 5.15 (dd, 1H, J=11.6, 3.2 Hz), 4.86 (d, 1H, J=3.6 Hz), 4.44 (dd, 1H, J=11.6, 3.5 Hz), 4.34 (d, 2H, J=7.0 Hz), 4.16–4.22 (m, 3H), 4.03–4.10 (m, 2H), 3.69 (dt, 1H, J=9.8, 6.4 Hz), 3.44 (dt, 1H, J=9.8, 6.1 Hz), 2.12 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H), 1.41–2.01 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.81, 174.08, 172.68, 172.59, 172.37, 159.00, 145.77, 145.69, 143.01, 129.26, 128.65, 128.63, 126.73, 121.42, 99.38, 70.14, 69.85, 69.27, 68.35, 68.20, 63.68, 55.96, 48.84, 33.09, 30.33, 24.12, 23.03, 22.66, 21.18, 21.14, 21.03; MS (HR-FAB) calculated for $C_{35}H_{42}N_2O_{13}Na$ $[M+Na]^+$ 721.2585, found 721.2586.

4.2.4. Compound 8. Obtained from **6** according to the general procedures and purified (25–50% EtOAc in hexanes) to provide a white solid in 80% yield (0.620 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 2H, J=7.5 Hz), 7.61 (d, 2H, J=6.4 Hz), 7.25–7.49 (m, 14H), 5.53 (s, 1H), 5.39 (d, 1H, J=8.3 Hz), 5.19 (dd, 2H, J=15.2, 12.4 Hz), 4.96 (d, 1H, J=3.3 Hz), 4.37–4.44 (m, 3H), 4.01–4.25 (m, 5H), 3.68 (m, 2H), 3.53 (dd, 1H, J=10.5, 3.1 Hz), 3.45 (m, 1H), 2.30 (bs, 1H), 1.24–1.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.48, 156.13, 144.05, 143.97, 141.48, 137.48, 135.44, 129.55, 128.85, 128.74, 128.52, 127.93, 127.29, 126.41, 125.30, 120.20, 101.44, 98.90, 75.68, 69.42, 68.26, 67.43, 67.29, 62.99, 60.83, 54.00, 47.32, 32.48, 28.99, 22.01; MS (LR-ESI) calculated for $C_{41}H_{42}N_4O_9Na$ $[M+Na]^+$ 757.3, found 757.2.

4.2.5. Compound 10. To a suspension of acceptor **8** (0.300 g, 0.408 mmol), bromo donor **9** (0.230 g, 0.560 mmol), and 4 Å MS (400 mg) in CH_2Cl_2 (5.3 mL) at −30°C was added dropwise a solution of AgOTf (0.154 g, 0.600 mmol) in toluene (3.0 mL) and stirred for 90 min. The reaction was quenched by the addition of pyridine, warmed to room temperature, diluted with EtOAc and filtered through celite. The organics were washed with $Na_2S_2O_3$ (0.5 M aq.) and saturated $NaHCO_3$, filtered, concentrated in vacuo and the residue purified by chromatography (25–40% EtOAc in hexanes) to provide 0.323 g (0.303 mmol, 74%) of the product as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 2H, J=7.5 Hz), 7.59 (t, 2H, J=6.4 Hz), 7.29–7.53 (m, 14H), 5.52 (s, 1H), 5.41 (d, 1H, J=8.1 Hz), 5.36 (d, 1H, J=2.9 Hz), 5.27 (dd, 1H, J=10.3, 7.9 Hz), 5.19 (dd, 2H, J=18.0, 12.2 Hz), 4.95–5.05 (m, 2H), 4.72 (d, 1H, J=7.9 Hz), 4.35–4.52 (m, 4H), 3.95–4.23 (m, 6H), 3.76–3.89 (m, 2H), 3.63–3.71 (m, 2H), 3.45 (m, 1H), 2.13 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.40–1.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.36, 170.42, 170.36, 170.22, 169.54, 156.02, 144.02, 143.77, 141.40, 137.80, 137.66, 135.35, 128.97, 128.79, 128.69, 128.40, 128.23, 127.90, 127.22, 126.63, 126.25, 125.23, 125.17, 120.17, 102.51, 100.73, 98.83, 77.43, 71.14, 70.84, 69.27, 68.80, 68.25, 67.33, 67.16, 67.09, 63.23, 61.50, 58.89, 53.95, 47.28, 32.43, 29.79, 29.61, 28.96, 21.97, 20.81, 20.78, 20.68; MS (LR-ESI) calculated for $C_{55}H_{61}N_4O_{18}$ $[M+H]^+$ 1065.4, found 1065.4.

4.2.6. Compound 11. Obtained from **10** according to the general procedures as a white solid in 64% yield (0.223 g). $[\alpha]_D^{24}$=+54.9° (c 1.04, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.79 (d, 2H, J=7.5 Hz), 7.67 (t, 2H, J=8.6 Hz), 7.38 (t, 2H, J=7.4 Hz), 7.30 (t, 2H, J=7.4 Hz), 5.39 (d, 1H, J=2.7 Hz), 5.33 (d, 1H, J=2.6 Hz), 4.96–5.02 (m, 2H), 4.76 (m, 2H), 3.96–4.43 (m, 12H), 3.68 (m, 1H), 3.44 (m, 1H), 2.11 (s, 3H), 2.10, (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.93 (s, 3H), 1.43–1.95 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.94, 173.30, 172.54, 172.18, 172.16, 171.59, 171.34, 158.59, 145.48, 145.30, 142.67, 128.96, 128.33, 126.41, 121.12, 102.43, 99.20, 74.77, 72.26, 71.88, 71.44, 70.29, 69.42, 68.74, 68.59, 68.00, 64.24, 62.54, 55.89, 50.56, 32.87, 29.91, 23.86, 23.03, 20.97, 20.90, 20.84, 20.63; MS (HR-FAB) calculated for $C_{47}H_{59}N_2O_{21}$ $[M+H]^+$ 987.3610, found 987.3609.

4.2.7. Compound 13. A suspension of acceptor **6** (0.410 g, 0.597 mmol), AgOTf (0.306 g, 1.19 mmol), $CaSO_4$ (820 mg) and DTBP (267 μL, 0.768 mmol) in THF (6.0 mL) was cooled to −78°C and stirred for 45 min. A solution of chloro donor **12** (0.607 g, 1.19 mmol) in THF (6.0 mL) was added slowly over 60 min to the acceptor suspension and slowly allowed to warm to room temperature over 12 h. The reaction was quenched with Et_3N, diluted with Et_2O, filtered through celite, concentrated in vacuo and the residue purified by chromatography (0–1.5% MeOH in CH_2Cl_2) to provide 0.546 g (0.471 mmol, 79%) of the α-anomer as a white solid along with 0.123 g (0.106 mmol, 18%) of the undesired β-anomer. α-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, J=7.5 Hz), 7.60 (d, 2H, J=6.9 Hz), 7.27–7.41 (m, 9H), 5.51 (d, 1H, J=8.1 Hz), 5.38–5.42 (m, 2H), 5.35 (dd, 1H, J=7.6, 1.6 Hz), 5.19 (dd, 2H, J=18.6, 12.2 Hz), 4.89 (m, 1H), 4.82 (d, 1H, J=3.3 Hz), 4.31–4.44 (m, 5H), 4.05–4.21 (m, 6H), 3.92 (dd, 1H, J=9.7, 6.3 Hz), 3.63–3.81 (m, 2H), 3.77 (s, 3H), 3.37 (m, 1H), 3.27 (dd, 1H, J=8.5, 3.3 Hz), 2.63 (dd, 1H, J=12.8, 4.7 Hz), 2.13 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H), 1.23–1.94 (m, 6H), 1.49 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.45, 171.06, 170.74, 170.39, 170.14, 168.05, 156.10, 144.05, 143.93, 141.40, 136.08, 135.47, 128.75, 128.62, 128.44, 127.82, 127.20, 125.25, 120.09, 115.32, 109.69, 98.93, 97.81, 73.25, 72.87, 72.70, 69.25, 69.12, 68.05, 67.60, 67.25, 67.19, 66.37, 63.63, 62.43, 61.17, 54.00, 53.59, 52.91, 49.44, 47.27, 37.81, 32.27, 30.26, 28.91, 28.41,

26.32, 23.29, 21.89, 21.20, 20.96, 20.93, 20.88; MS (LR-ESI) calculated for $C_{57}H_{69}N_5O_{21}Na$ $[M+Na]^+$ 1182.5, found 1182.5.

4.2.8. Compound 14. Obtained from **13** according to the general procedures as white solid in 65% yield (0.219 g). $[\alpha]_D^{24}=+28.8°$ (*c* 1.01, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 7.78 (d, 2H, *J*=7.5 Hz), 7.66 (t, 2H, *J*=7.0 Hz), 7.38 (t, 2H, *J*=7.4 Hz), 7.30 (t, 2H, *J*=7.4 Hz), 5.31–5.48 (m, 3H), 5.14 (dd, 1H, *J*=11.5, 2.9 Hz), 4.77–4.96 (m, 3H), 4.42 (dd, 1H, *J*=11.6, 3.4 Hz), 4.35 (d, 1H, *J*=6.9 Hz), 4.05–4.40 (m, 7H), 3.99 (m, 1H), 3.65–3.93 (m, 2H), 3.78 (s, 3H), 3.45 (m, 1H), 3.34 (m, 1H), 2.58 (dd, 1H, *J*=12.7, 4.6 Hz), 2.15 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.93 (s, 6H), 1.83 (s, 3H), 1.35–1.85 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.04, 173.73, 173.57, 172.50, 172.34, 172.05, 171.92, 171.72, 171.55, 169.33, 158.55, 145.47, 145.32, 142.65, 128.91, 128.30, 126.38, 121.06, 100.00, 98.95, 73.39, 70.72, 69.97, 69.55, 69.36, 69.09, 68.84, 68.57, 67.93, 64.44, 63.51, 56.01, 53.58, 50.11, 39.01, 32.99, 30.04, 23.72, 22.85, 22.71, 21.37, 21.05, 20.92, 20.88, 20.84; MS (HR-FAB) calculated for $C_{53}H_{67}N_3O_{24}Na$ $[M+Na]^+$ 1152.4012, found 1152.4007.

4.2.9. Compound 16. Obtained from **15** according to the general procedure. Purification by flash column chromatography (3:7 EtOAc/hexane) of the residue provided a white foam (0.341 g, 70% for two steps). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, 2H, *J*=7.5 Hz), 7.50 (d, 2H, *J*=7.3 Hz), 7.35–7.05 (m, 49H), 6.92 (d, 2H, *J*=8.5 Hz), 6.68 (d, 2H, *J*=8.5 Hz), 5.35 (d, 1H, *J*=8.2 Hz), 5.12 (d, 1H, *J*=7.5 Hz), 5.08 (d, 1H, *J*=7.5 Hz) 4.97 (d, 1H, *J*=3.3 Hz), 4.94 (d, 1H, *J*=11.8 Hz), 4.82–4.75 (m, 2H), 4.72 (d, 1H, *J*=4.6 Hz), 4.70 (d, 1H, *J*=4.6 Hz), 4.69 (d, 1H, *J*=10.6 Hz), 4.67 (d, 1H, *J*=15.1.Hz), 4.58 (d, 1H, *J*=15.1 Hz), 4.45–4.40 (m, 3H), 4.38 (d, 1H, *J*=6.9 Hz), 4.37–4.20 (m, 7H), 4.20–4.09 (m, 3H), 4.09–3.98 (m, 3H), 3.98–3.90 (m, 3H), 3.88–3.80 (m, 2H), 3.79–3.70 (m, 2H), 3.69 (s, 3H), 3.61 (d, 1H, *J*=7.3 Hz), 3.57 (dd, 2H, *J*=7.0, 6.5 Hz), 3.46–3.25 (m, 6H), 3.25–3.18 (m, 2H), 3.10 (dd, 1H, *J*=7.2, 3.6 Hz), 2.30 (s, 1H), 1.85–1.70 (m, 2H), 1.72–1.55 (m, 2H), 1.40–1.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.85, 159.27, 156.43, 144.37, 144.24, 141.71, 139.50, 139.38, 139.14, 139.10, 139.01, 138.74, 138.48, 135.75, 131.26, 129.18, 129.04, 128.91, 128.80, 128.70, 128.67, 128.54, 128.48, 128.26, 128.16, 128.11, 127.93, 127.52, 125.58, 120.38, 114.09, 113.97, 103.17, 103.01, 100.98, 82.51, 81.88, 79.80, 77.68, 77.08, 77.01, 75.77, 75.65, 75.30, 74.99, 74.81, 74.30, 73.68, 73.61, 73.50, 73.45, 72.70, 72.48, 69.83, 69.55, 68.68, 68.33, 68.10, 67.54, 67.44, 55.65, 54.35, 47.58, 32.45, 29.23, 22.21; MS (LR-ESI) 1809 $[M+Na]^+$.

4.2.10. Compound 17. Obtained from **16** according to the general procedures in 90% yield (0.296 g). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, 2H, *J*=7.4 Hz), 7.52 (d, 2H, *J*=7.3 Hz), 7.35–7.03 (m, 49H), 5.29 (d, 1H, *J*=7.8 Hz), 5.12 (d, 1H, *J*=12.3 Hz), 5.08 (d, 1H, *J*=12.3 Hz), 5.00 (d, 1H, *J*=3.3 Hz), 4.87 (d, 1H, *J*=11.4 Hz), 4.85 (d, 1H, *J*=7.5 Hz), 4.83 (d, 1H, *J*=8.0 Hz), 4.77 (d, 1H, *J*=11.3 Hz), 4.72 (d, 1H, *J*=12.4 Hz), 4.69 (d, 1H, *J*=11.1 Hz), 4.62 (d, 1H, *J*=11.4 Hz), 4.53 (d, 1H, *J*=11.5 Hz), 4.52 (d, 1H, *J*=11.9 Hz), 4.48 (d, 1H, *J*=11.4 Hz), 4.45 (d, 1H, *J*=11.4 Hz), 4.43 (d, 1H, *J*=11.4 Hz), 4.37–4.25 (m, 7H), 4.21 (d, 1H, *J*=10.5 Hz), 4.20–4.12 (m, 3H), 4.07 (d, 1H, *J*=11.7 Hz), 4.02 (d, 1H, *J*=11.7 Hz), 3.97 (m, 1H), 3.95–3.84 (m, 4H), 3.76–3.60 (m, 4H), 3.52 (dd, 1H, *J*=10.0, 7.7 Hz), 3.44 (d, 1H, *J*=9.0 Hz), 3.42 (d, 1H, *J*=9.0 Hz), 3.35–3.24 (m, 3H), 3.24–3.17 (m, 2H), 3.12 (dd, 1H, *J*=9.4, 4.8 Hz), 1.80 (s, 3H), 1.82–1.68 (m, 2H), 1.73 (d, 1H, *J*=5.3 Hz), 1.67–1.50 (m, 2H), 1.30–1.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.78, 169.92, 156.40, 144.37, 144.23, 141.71, 139.82, 139.17, 139.01, 138.94, 138.74, 138.60, 138.51, 138.45, 135.74, 129.04, 128.88, 128.85, 128.70, 128.69, 128.67, 128.58, 128.42, 128.36, 128.33, 128.25, 128.13, 128.03, 127.97, 127.93, 127.88, 127.51, 125.61, 125.55, 120.38, 103.02, 101.35, 99.84, 81.77, 81.08, 79.70, 77.98, 77.67, 77.36, 77.32, 75.76, 75.66, 75.62, 74.76, 73.58, 73.52, 73.49, 73.45, 73.26, 72.87, 72.52, 70.48, 69.56, 69.12, 68.55, 68.22, 67.85, 67.59, 67.46, 54.41, 47.57, 32.53, 29.32, 22.11, 21.30; MS (LR-ESI) 1731 $[M+Na]^+$.

4.2.11. Compound 19. A mixture of acceptor **17** (49.0 mg, 0.029 mmol, 1 equiv.), donor **18** (73.8 mg, 0.058 mmol, 2.0 equiv.), and freshly activated 4 Å molecular sieves (120 mg) was dissolved in CH_2Cl_2 (0.60 mL), and the resultant slurry was stirred at room temperature for 30 min. MeOTf (19.0 μL, 0.017 mmol, 6 equiv.) was added to the mixture at −20°C and the reaction mixture was allowed to warm to 0°C. After 4 h, the reaction was quenched with Et_3N (50 μL), filtered through celite, and partitioned between EtOAc and saturated $NaHCO_3$ solution. Organic phase was dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (3:7 EtOAc/hexane) of the residue gave the desired product (76.0 mg, 90%) as a white foam: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, 2H, *J*=7.5 Hz), 7.61 (d, 2H, *J*=7.4 Hz), 7.52 (d, 2H, *J*=7.3 Hz), 7.35–6.92 (m, 67H), 5.28 (d, 1H, *J*=8.3 Hz), 5.10 (d, 1H, *J*=7.5 Hz), 5.07 (d, 1H, *J*=7.5 Hz), 5.05–4.99 (m, 2H), 4.98 (d, 1H, *J*=3.5 Hz), 4.93 (d, 1H, *J*=11.5 Hz), 4.88 (d, 1H, *J*=11.4 Hz), 4.84–4.73 (m, 6H), 4.73–4.4.49 (m, 2H), 4.69–4.65 (m, 3H), 4.64 (d, 1H, *J*=7.4 Hz), 4.63–4.53 (m, 5H), 4.50–4.37 (m, 5H), 4.36 (d, 1H, *J*=4.5 Hz), 4.35–4.30 (m, 3H), 4.30–4.23 (m, 2H), 4.23 (d, 1H, *J*=11.5 Hz), 4.19 (d, 1H, *J*=6.7 Hz), 4.13 (m, 1H), 4.12 (d, 1H, *J*=11.8 Hz), 4.07 (d, 1H, *J*=8.1 Hz), 4.07–3.96 (m, 6H), 3.95–3.92 (m, 2H), 3.92–3.75 (m, 3H), 3.74–3.65 (m, 6H), 3.65–3.56 (m, 6H), 3.53 (dd, 1H, *J*=9.8, 8.6 Hz), 3.43 (dd, 1H, *J*=8.6, 8.6 Hz), 3.36 (dd, 1H, *J*=8.2, 8.2 Hz), 3.33–3.23 (m, 2H), 3.20–3.12 (m, 2H), 2.81 (dd, 1H, *J*=9.3, 1.9 Hz), 2.78 (s, 1H), 2.65 (m, 1H), 1.83–1.70 (m, 2H), 1.73 (s, 3H), 1.52–1.43 (m, 2H), 1.29–1.17 (m, 2H), 1.13 (d, 3H, *J*=6.4 Hz), 1.15–0.80 (m, 42H); MS (LR-ESI) 2948 $[M+Na]^+$.

4.2.12. Compound 22. Obtained from **21** according to the general procedures in 57% yield (5.4 mg) ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, 2H, *J*=7.4 Hz), 7.52 (d, 2H, *J*=7.3 Hz), 7.40–7.18 (m, 14H), 6.62 (d, 1H, *J*=6.6 Hz), 5.52 (d, 1H, *J*=3.0 Hz), 5.39 (d, 1H, *J*=3.5 Hz), 5.36 (d, 1H, *J*=8.5 Hz), 5.33 (d, 1H, *J*=3.1 Hz), 5.22 (dd, 1H, *J*=10.9, 3.0 Hz), 5.20–5.05 (m, 6H), 4.99–4.85 (m, 4H), 4.68 (dd, 1H, *J*=10.9, 2.3 Hz), 4.50–4.20 (m, 11H), 4.20–3.95 (m, 10H), 3.94–3.87 (m, 3H), 3.85–3.73 (m, 3H), 3.67 (m, 1H),

3.59 (m, 1H), 3.52 (m, 1H), 3.43 (m, 1H), 3.33 (m, 1H), 2.81 (s, 1H), 2.20–1.72 (m, 51H), 1.85–1.73 (m, 2H), 1.69–1.55 (m, 2H), 1.35–1.20 (m, 2H), 1.10 (d, 3H, J=6.5 Hz); MS (LR-ESI) 2152 $[M+Na]^+$.

4.2.13. Compound 23. Obtained from **22** according to the general procedures in 69% yield (3.8 mg) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, 2H, J=7.5 Hz), 7.52 (d, 2H, J=7.3 Hz), 7.38–7.30 (m, 2H), 7.30–7.22 (m, 2H), 6.70 (d, 1H, J=6.5 Hz), 5.56 (d, 1H, J=3.0 Hz), 5.50 (d, 1H, J=8.0 Hz), 5.41 (d, 1H, J=3.3 Hz), 5.33 (d, 1H, J=3.2 Hz), 5.23 (dd, 1H, J=10.9, 3.1 Hz), 5.20–5.10 (m, 4H), 5.10 (d, 1H, J=8.1 Hz), 5.02 (dd, 1H, J=10.7, 7.7 Hz), 4.98–4.91 (m, 3H), 4.87 (dd, 1H, J=10.8, 3.5 Hz), 4.80 (dd, 1H, J=9.0, 8.0 Hz), 4.69 (dd, 1H, J=10.8, 2.5 Hz), 4.52–4.26 (m, 11H), 4.21 (dd, 1H, J=10.8, 2.5 Hz), 4.19–3.96 (m, 11H), 3.92 (d, 1H, J=3.0 Hz), 3.89 (t, 1H, J=6.5 Hz), 3.82 (t, 1H, J=8.0 Hz), 3.78–3.72 (m, 3H), 3.75–3.30 (m, 5H), 2.25–1.85 (m, 54H), 1.85–1.73 (m, 2H), 1.69–1.55 (m, 2H), 1.35–1.20 (m, 2H), 1.10 (d, 3H, J=6.5 Hz); ^{1}H NMR (CD_3OD, 125 MHz) δ 171.42, 170.81, 170.52, 170.48, 170.42, 170.35, 170.15, 170.06, 169.93, 169.85, 169.71, 169.55, 169.30, 156.78, 143.58, 143.46, 140.79, 127.02, 126.41, 124.56, 124.51, 119.15, 101.82, 101.00, 100.31, 99.72, 98.80, 95.65, 76.25, 73.05, 72.72, 72.25, 72.08, 71.59, 71.39, 70.97, 70.64, 70.47, 70.01, 69.74, 69.53, 69.01, 68.03, 67.13, 67.03, 66.95, 66.13, 64.48, 61.80, 61.40, 60.87, 60.74, 28.18, 21.72, 21.60, 16.45; MS (LR-ESI) 2104 $[M+Na]^+$.

4.2.14. Compound 25. Obtained from **24** according to the general procedures and purified (50–90% EtOAc in CH_2Cl_2) to provide a white solid in 77% yield (18 mg). $[\alpha]_D^{24}=-61.0°$ (c 0.71, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 2H, J=7.4 Hz), 7.60 (d, 2H, J=7.3 Hz), 7.26–7.43 (m, 9H), 5.44 (d, 1H, J=8.6 Hz), 5.32–5.39 (m, 7H), 4.93–5.22 (m, 8H), 4.81 (d, 1H, J=8.1 Hz), 4.71 (d, 1H, J=10.6 Hz), 4.52 (d, 1H, J=7.8 Hz), 4.39–4.49 (m, 5H), 4.29 (dd, 1H, J=11.4, 8.0 Hz), 4.18–4.24 (m, 3H), 4.10 (d, 2H, J=6.3 Hz), 3.67–3.95 (m, 9H), 3.50 (m, 2H), 2.92 (bs, 1H), 2.19 (s, 3H), 2.15 (s, 6H), 2.14 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.89 (s, 3H), 1.25–1.90 (m, 6H), 1.18 (app. t, 6H, J=6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.68, 171.47, 171.42, 170.95, 170.89, 170.78, 170.75, 170.70, 170.59, 170.30, 169.98, 156.18, 144.05, 143.92, 141.49, 135.40, 128.85, 128.74, 128.49, 127.94, 127.29, 125.28, 120.22, 103.32, 101.61, 100.77, 96.46, 96.06, 79.26, 77.43, 74.97, 74.28, 73.59, 73.45, 72.97, 71.64, 71.58, 71.15, 70.00, 69.31, 68.19, 68.10, 67.90, 67.68, 67.43, 67.16, 67.12, 65.19, 64.23, 62.24, 61.63, 60.90, 60.59, 57.15, 54.00, 47.37, 43.05, 40.19, 32.37, 29.88, 28.91, 23.57, 22.01, 21.24, 21.04, 21.00, 20.94, 20.89, 20.85, 20.80, 16.13, 15.92, 14.38, 14.34, 13.28; MS (LR-ESI) calculated for $C_{84}H_{107}N_2O_{40}$ $[M+H]^+$ 1783.6, found 1783.6.

4.2.15. Compound 26. Obtained from **25** according to the general procedures as a white solid in 70% yield (12.2 mg). $[\alpha]_D^{23}=-65.2°$ (c 0.67, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.80 (d, 2H, J=7.5 Hz), 7.69 (t, 2H, J=6.9 Hz), 7.40 (t, 2H, J=7.4 Hz), 7.32 (t, 2H, J=7.5 Hz), 5.44 (d, 1H, J=3.3 Hz), 5.42 (d, 1H, J=2.9 Hz), 5.34 (d, 2H, J=3.3 Hz), 5.32 (d, 1H, J=3.9 Hz), 5.30 (d, 1H, J=3.9 Hz), 5.17–5.24 (m, 3H), 5.07 (m, 1H), 4.92–5.01 (m, 3H), 4.74 (d, 1H, J=7.9 Hz), 3.76–4.50 (m, 21H), 3.60 (m, 1H), 2.50 (m, 1H), 2.18 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 2.06 (s, 6H), 2.05 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.83 (s, 3H), 1.28–1.90 (m, 6H), 1.20 (d, 3H, J=6.4 Hz), 1.20 (d, 3H, J=6.4 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.90, 173.40, 172.80, 172.71, 172.57, 172.55, 172.44, 172.41, 172.32, 172.20, 171.92, 171.77, 171.68, 171.39, 158.73, 145.56, 145.38, 142.74, 128.95, 128.35, 126.47, 121.07, 103.29, 102.58, 101.87, 97.84, 97.41, 78.16, 75.94, 75.17, 74.68, 74.43, 73.05, 72.49, 72.38, 72.23, 72.02, 71.77, 70.63, 69.67, 69.46, 69.22, 69.06, 68.94, 68.05, 66.51, 65.51, 63.31, 62.84, 62.62, 57.53, 56.08, 48.03, 32.88, 30.40, 23.69, 23.37, 21.43, 21.34, 21.24, 21.20, 21.15, 21.14, 20.98, 20.90, 20.85, 20.74, 20.60, 20.46, 16.72, 16.35, 9.35; MS (LR-ESI) calculated for $C_{79}H_{102}N_2O_{41}Na$ $[M+Na]^+$ 1757.6, found 1757.7.

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