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Syntheses of new peptidic glycoclusters derived from β-alanine: di- and trimerized glycoclusters and glycocluster–clusters ☆

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Abstract—Fluorescence-labeled glycoclusters **1** and **2** have been synthesized to elongate glycocluster units that contain β-alanine derivative **6** and sugar unit **7**. Similarly, di- and trimerized glycoclusters **3** and **4** have been obtained by coupling glycocluster **17** with succinyl chloride and/or trimesoyl chloride, respectively. Furthermore, glycocluster–cluster **5** was also synthesized by a convergent growth approach.

Keywords: Glycocluster; Glycocluster–cluster; Elongation cycle; D-Galactose; Fluorescence label

1. Introduction

Carbohydrate chains are known to interact with protein receptors as natural clusters (molecular assemblies) to form rafts (glycolipids),[1] modified proteins (glycoproteins)[2] and repeating structures (polysaccharides),[3] and these express strong molecular recognition properties. This has been called the multivalent or cluster effect. On the other hand, synthetic or isolated carbohydrate chains have low affinities towards the receptors in many cases.[4] Therefore, the elucidation of their bioactivity has been complicated in glycoscience. For resolution of this problem, various multivalent carbohydrates and glycoconjugates including glycoclusters,[5–16] glycodendrimers[17–26] and glycopolymers[27–30] have been synthesized with the aim of creating 'glycoside cluster effects'. However, almost all of these cluster molecules have been randomly functionalized, and these have symmetric or repeating structures arising from their synthetic strategies. If the steric structure and geometry of the binding site on the targeted carbohydrate-binding protein could be analyzed and designed, a carbohydrate ligand might be developed with high affinity to the specific receptor due to the entropic gain. Recently, artificial carbohydrate ligands to the receptors of AB_5 heat-labile enterotoxin and also Shiga-like toxin based on the molecular design described above have been developed by two independent groups,[31,32] but still, there are few other such examples. When structural information on protein receptors is poor, it is necessary to give diversity to the structure for searching out suitable ligands. For this purpose, we synthesized new peptidic glycoclusters and a glycodendron consisting of a β-alanine derivative, a sugar unit and an ω-amino acid.[33,34] By this method, it is possible to create diverse 'glycocluster units' by only replacing the ω-amino acid with another one as spacer, which is advantageous for the synthesis of diverse glycoclusters in which the distance from the main chain to the carbohydrate residue and/or the distance between the side chain branch points can be readily modulated. By giving diversity to glycoclusters, the construction of a glycocluster library may be possible, and such a library can be expected to aid in determining the elucidation of the higher-order structure of the receptors.

In this paper, first, we report on the conventional tri- and pentavalent fluorescence-labeled glycoclusters (**1** and **2**), which do not incorporate an ω-amino acid as a spacer, then we describe the synthesis of di- and

☆ Part 3 of the series.

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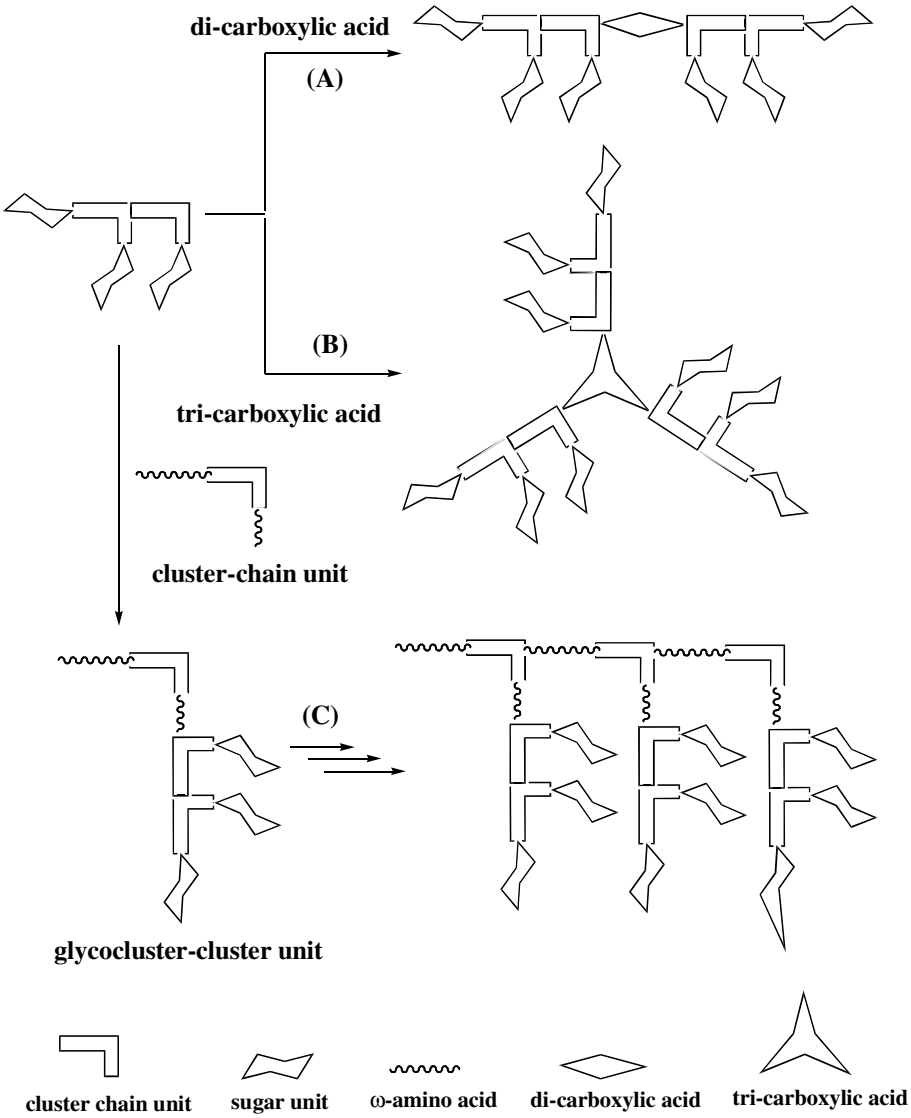


Figure 1. Polymerization of glycocluster: (A) dimerization with a dicarboxylic acid as the dendrimer core; (B) trimerization with a tricarboxylic acid as the dendrimer core; (C) clusterization of glycocluster–cluster unit.

trimerized glycoclusters (**3** and **4**) by coupling with the precursor trivalent glycocluster **17** and a di- or tricarboxylic acid in anticipation of higher affinity as an application of our method (Fig. 1A and B). Finally, the conversion of a simple sugar unit to a glycocluster unit in order to synthesize a novel 'glycocluster–cluster (**5**)' is carried out using a glycocluster–cluster unit in which a condensed glycocluster unit is condensed with a cluster chain unit (Fig. 1C). These target compounds **1**–**5** are depicted in Figure 2.

2. Results and discussion

In our previous work,[33,34] we exploited glycoclusters either attached to or inserted into an ω-amino acid for modulating steric distribution. However, this time we have formed the conventional glycocluster unit **8** by using only cluster–chain unit **6** and sugar unit **7** to simplify the process. Cluster–chain unit **6** and sugar unit **7** were prepared according to the previous paper.[33] Elongation of the glycocluster is composed of three reactions: peptide coupling, deprotection of the *tert*-butyloxycarbonyl (Boc) group and deprotection of the trichloroethyl ester (Tce) group. Coupling of cluster–chain unit **6** with the sugar unit **7** in the presence of diethyl phosphorocyanidate (DEPC) in dry DMF yielded 80% of the glycocluster **8**. Subsequent removal of the Boc group with 50% TFA in CH_2Cl_2 or the Tce group with Zn–AcOH afforded glycocluster **9** (quant) with an amino group or glycocluster **10** (90%) with a carboxylic acid, respectively. Coupling of **9** with **10** as described for **8** gave a dimer derivative **11** in 80% yield. By repeating the coupling and deprotection, the 'elongation cycle'

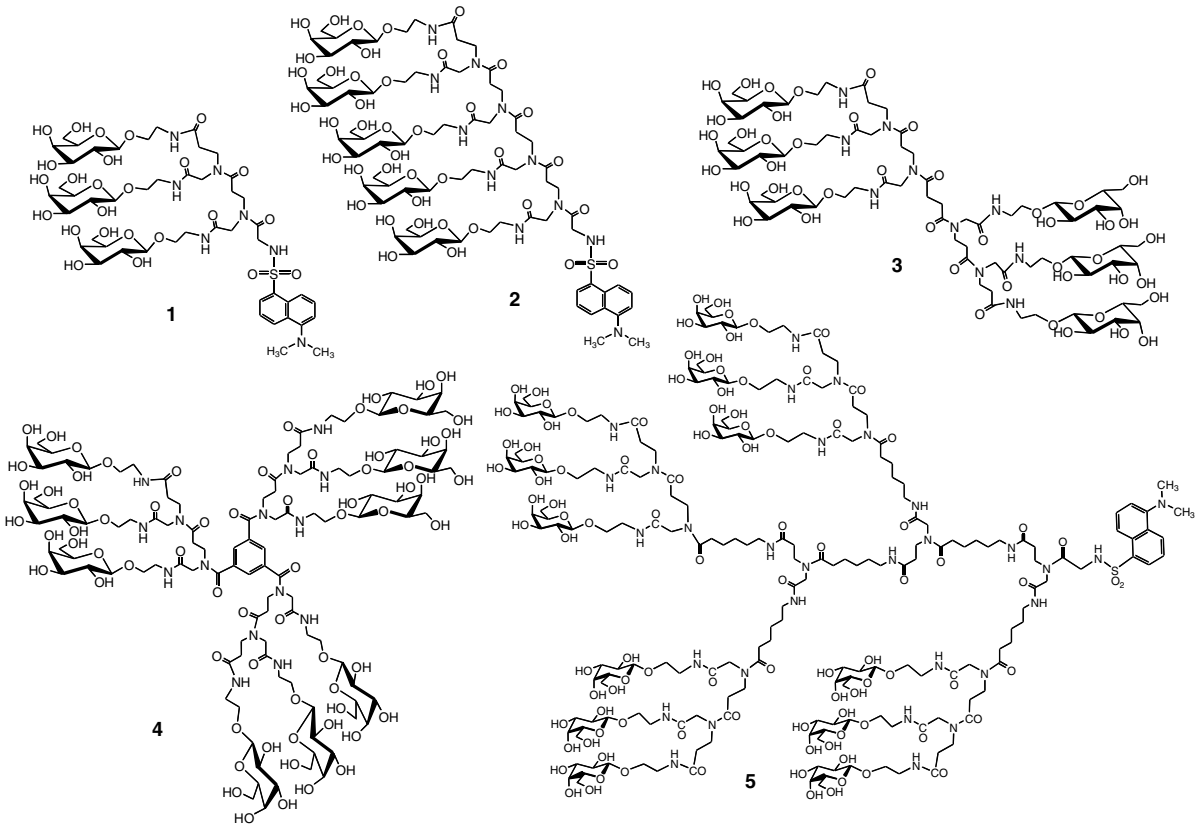
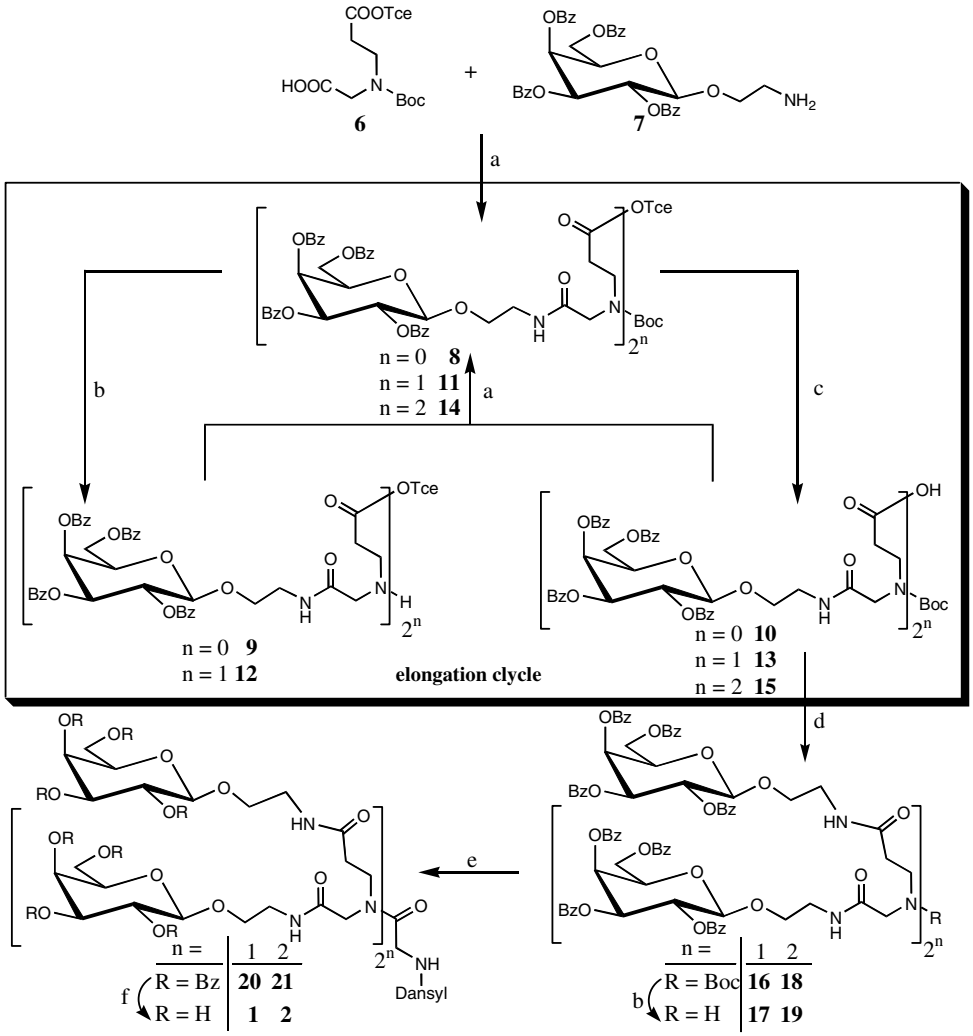


Figure 2. Structures of synthetic glycoclusters.

was completed and the sugar residues on the glycocluster were increased exponentially. The C-terminal ends of the glycoclusters were closed by coupling with sugar unit **7**. When the elongation cycle was terminated, the free acid glycoclusters **13** and **15** gave **16** (78%) and **18** (79%), respectively. Subsequent treatment with 50% TFA to remove the Boc groups gave **17** (79%) and **19** (86%), respectively. Alternatively, the N-terminal end of the glycocluster could be elaborated by modifying the free amine. The free amine trimer **17** and pentamer **19** were treated with dansyl glycine in the presence of DEPC, and complete removal of the *O*-benzoyl groups provided the target compound **1** (quant) and **2** (96%) with free hydroxyl groups on all the fluorescence-labeled glycoclusters (Scheme 1).

Glycocluster compound **17** with a free amine can be coupled with poly(carboxylic) acid derivatives as the dendrimer cores to increase valency and to enhance affinity. If the higher valency glycoclusters are needed in the glycocluster library, the glycoclusters with deprotected amines can be used. Therefore, the trimer derivative **17** was coupled with succinyl chloride and trimesoyl chloride as the dendrimer cores to give the di- and trimerized trimer derivatives **22** (85%) and **23** (81%), respectively. Subsequent removal of the acyl groups from **22** and **23** afforded the di- and trimerized trimer glycocluster **3** (95%) and **4** (quant), respectively (Scheme 2).

The sugar unit with a free amine and a cluster–chain unit with a free carboxylate of the glycocluster unit made the additional clustering of the glycoclusters possible leading to the synthesis of a 'glycocluster–cluster unit'. Compound **17** was used as the glycocluster derivative to synthesize a glycocluster–cluster unit. Since the unit seemed to be too bulky, a cluster–chain unit was attached by means of a spacer. In brief, compound **6** was coupled with benzyl 6-aminohexanoate to give compound **24** in 77% yield. Removal of the Tce group as described for **10** subsequently afforded compound **25** (80%), which was then converted to **26** by coupling with 2,2,2-trichloroethyl 6-aminohexanoate in 64% yield. Finally, removal of the benzyl group in **26** under neutral conditions by hydrogenation over 10% Pd–C afforded compound **27** (39%) as a spacer-modulated cluster–chain unit. Glycocluster–cluster unit **28** was synthesized by coupling **27** with **17**. Subsequent removal of the Tce group as described for **10** gave compound **29** (85%), the C-terminal free acid of which was coupled with **17** to give compound **30** (89%). Removal of the Boc group as described for **9** afforded compound **31** in 73% yield, and it was subsequently coupled with **29** to give compound **32** (66%), which is elongated by one unit relative to **30**. Removal of the Boc group and coupling with **29** were carried out repeatedly, and the resulting compound was again coupled with dansyl glycine as



Scheme 1. Reagents: (a) DEPC, Et_3N, DMF; (b) 50% TFA, CH_2Cl_2; (c) Zn–AcOH; (d) **7**, DEPC, Et_3N, DMF; (e) dansyl Gly, DEPC, Et_3N, DMF; (f) NaOMe, MeOH-1,4-dioxane.

described for **20** to give compound **36** (51%), similar to the fluorescence-labeled compound **17**. Finally, complete removal of the acyl groups afforded the fluorescence-labeled glycocluster–cluster **5** in 36% yield (Scheme 3).

In conclusion, construction of the bioactive glycocluster and glycoclusters with the higher affinities for receptor binding could be expected using this method. Moreover, it is worthwhile to synthesize various kinds of glycoclusters using common synthetic routes and inexpensive materials.

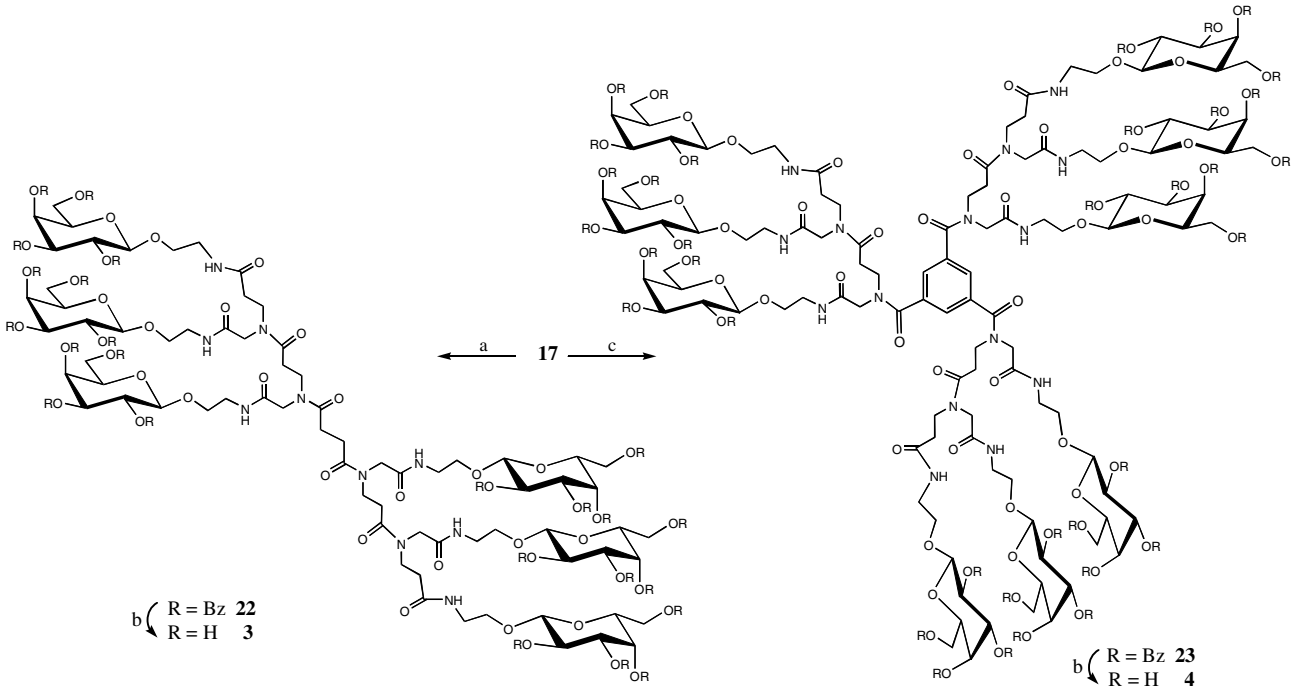
3. Experimental

3.1. General

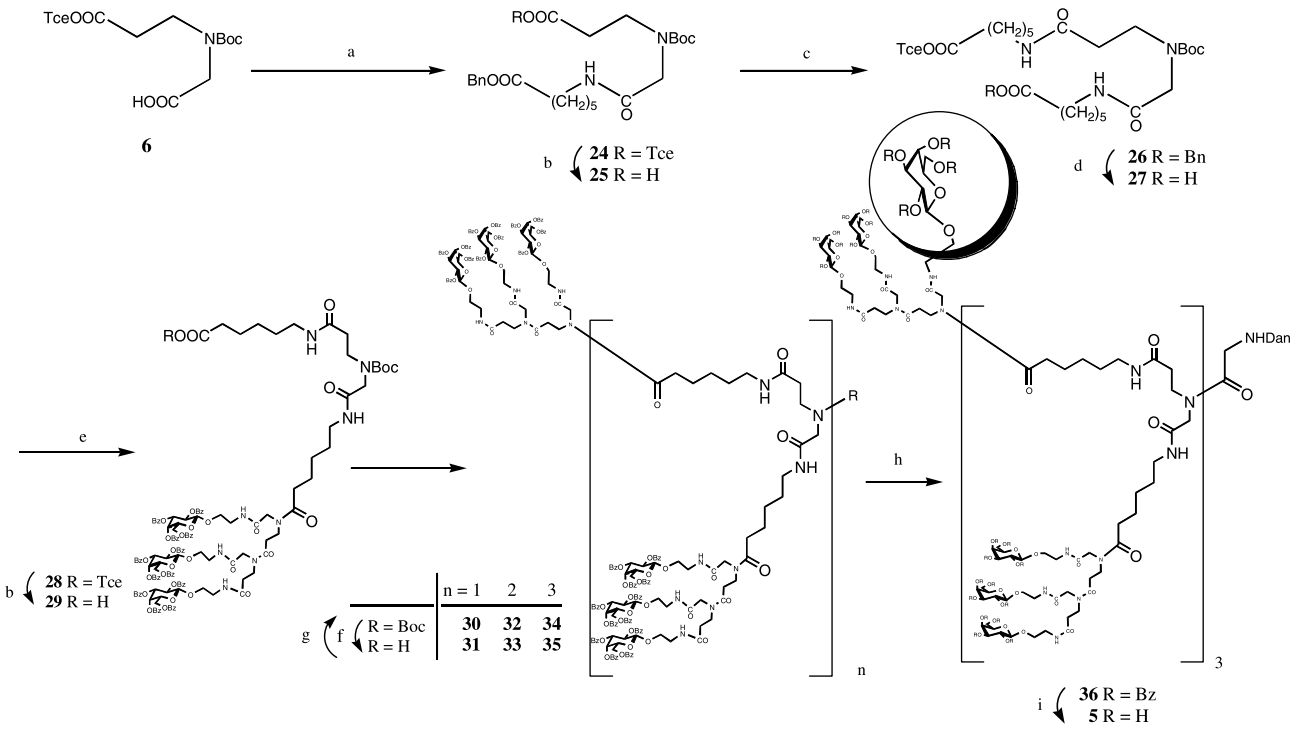
Optical rotations were determined with a Jasco digital polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded with a JNM A 500 FT NMR spectrometer with Me_4Si as the internal standard for solutions in $CDCl_3$ or CD_3OD. MALDI-TOF MS was recorded on a Perceptive Voyager RP mass spectrometer. TLC was performed by Silica Gel 60-F_{254} (E. Merck) with detection by quenching of UV fluorescence and by spraying with 5% ninhydrin and 10% H_2SO_4. Column chromatography was carried out on Silica Gel 60 (E. Merck).

3.2. Typical procedure for the peptide condensation reaction

To a solution of cluster–chain unit **6** (202 mg, 0.53 mmol) and sugar unit **7** (434 mg, 0.64 mmol) in DMF (2 mL) were added diethyl phosphorocyanidate (DEPC, 90 μL, 0.59 mmol) and Et_3N (110 μL, 0.79 mmol). The mixture was stirred for 16 h at room temperature. After completion of the reaction (TLC



Scheme 2. Reagents: (a) succinyl chloride, Et_3N, CH_2Cl_2; (b) NaOMe, MeOH-1,4-dioxane; (c) trimesoyl chloride, Et_3N, CH_2Cl_2.



Scheme 3. Reagents: (a) benyl 6-aminohexanoate tosylate, Et_3N, DEPC, DMF; (b) Zn–AcOH; (c) 2,2,2-trichloroethyl 6-aminohexanoate tosylate, Et_3N, DEPC, DMF; (d) Pd–C, H_2, THF; (e) **17**, Et_3N, DEPC, DMF; (f) 50% TFA; (g) **29**, Et_3N, DEPC, DMF; (h) Dansyl Gly, DEPC, Et_3N, DMF; (i) NaOMe, MeOH-1,4-dioxane.

monitoring), the mixture was extracted with EtOAc, washed with H_2O, dried (Na_2SO_4), and concentrated. The product was purified by silica gel column chromatography (5:1 benzene–acetone as eluent) to give **8** (157 mg, 79.6%): $[\alpha]_D^{23}$ +59.0 (*c* 1.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.10–7.23 (m, 20H, Ar-*H*), 6.25 (br t, 1H, N*H*), 6.00 (br d, 1H, *H*-4), 5.77 (br dd, 1H, *H*-2), 5.63 (br dd, 1H, *H*-3), 4.87 (br d, 1H, *H*-1), 4.72

(br s, 2H, CH_2CCl_3), 4.67 (br dd, 1H, *H*-6a), 4.45 (br dd, 1H, *H*-6b), 4.36 (m, 1H, *H*-5), 3.98 and 3.76 (m, 2H, OCH_2 of sugar unit), 3.65 (br s, 2H, NCH_2CO), 3.55–3.49 (m, 4H, NCH_2 of sugar unit, NCH_2 of β-Ala), 2.72 (br t, 2H, $COCH_2$ of β-Ala), 1.43 (9H, br s, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 166.0, 165.5, 165.3, 133.7, 133.5, 133.4, 133.3, 130.0, 129.7, 129.3, 129.2, 129.0, 128.7, 128.6, 128.5, 128.3, 101.7, 94.8, 80.9, 74.1, 71.6, 71.5, 69.8, 68.9, 68.1, 62.1, 51.7, 44.9, 39.2, 33.0, 28.3. MALDI-TOF MS: Calcd for $C_{48}H_{49}Cl_3N_2NaO_{15}$: *m*/*z* 1021.2. Found: *m*/*z* 1021.9 $[M+Na]^+$.

3.2.1. Compounds 11, 14, 16, 18, 20, 21, 24, 26, 28, 30, 32, 34 and 36. These compounds were obtained in a similar manner by purification by column chromatography using a gradient of 40:1→20:1 $CHCl_3$–MeOH as eluent.

3.2.2. Data for 11. Yield: 112 mg (80%); $[\alpha]_D^{23}$ +63.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.08–7.24 (m, 40H, Ar-*H*), 6.00 (br d, 2H, *H*-4), 5.76 (br dd, 2H, *H*-2), 5.63 (br dd, 2H, *H*-3), 4.89 (br d, 2H, *H*-1), 4.73 (s, 2H, CH_2CCl_3), 4.68 (m, 2H, *H*-6a), 4.42–4.34 (m, 4H, *H*-5, *H*-6b), 3.98–3.31 (m, 16H, OCH_2 of sugar unit, NCH_2 of sugar unit, NCH_2CO, NCH_2 of β-Ala), 2.72–2.05 (m, 4H, $COCH_2$ of β-Ala), 1.39 and 1.32 (2s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 170.2, 166.0, 165.5, 165.3, 165.2, 133.6, 133.5, 133.3, 130.0, 129.7, 129.3, 129.2, 129.0, 128.6, 128.5, 128.3, 101.0, 94.8, 74.1, 71.6, 71.4, 69.84, 69.76, 68.1, 67.6, 61.8, 45.8, 43.8, 39.2, 38.9, 31.7, 28.2. MALDI-TOF MS: Calcd for $C_{89}H_{87}Cl_3N_4NaO_{27}$: *m*/*z* 1771.5. Found: *m*/*z* 1771.8 $[M+Na]^+$.

3.2.3. Data for 14. Yield: 45 mg (41%); $[\alpha]_D^{23}$ +55.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.07–7.05 (m, 80H, Ar-*H*), 6.00 (br d, 4H, *H*-4), 5.76 (br dd, 4H, *H*-2), 5.66 (br dd, 4H, *H*-3), 4.91 (br d, 4H, *H*-1), 4.73–4.65 (m, 6H, CH_2CCl_3, *H*-6a), 4.43–4.38 (m, 8H, *H*-5, H-6b), 3.95–3.41 (m, 32H, OCH_2, NCH_2), 2.69–2.02 (m, 8H, CCH_2), 1.46 1.38, 1.36 1.34, 1.33, 1.31 (6s, 9H, *t*-Bu). MALDI-TOF MS: Calcd for $C_{171}H_{163}Cl_3N_8NaO_{51}$: *m*/*z* 3272.9. Found: *m*/*z* 3272.1 $[M+Na]^+$.

3.2.4. Data for 16. Yield: 53 mg (78%); $[\alpha]_D^{23}$ +75.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.08–7.21 (m, 60H, Ar-*H*), 6.00 (br d, 3H, *H*-4), 5.76 (br dd, 3H, *H*-2), 5.64 (br dd, 3H, *H*-3), 4.89 (br d, 3H, *H*-1), 4.67 (m, 3H, *H*-6a), 4.41–4.35 (m, 6H, *H*-5, *H*-6b), 3.97–3.43 (m, 20H, OCH_2, NCH_2), 2.48–2.09 (m, 4H, CCH_2), 1.31 (s, 9H, *t*-Bu). MALDI-TOF MS: Calcd for $C_{123}H_{117}N_5NaO_{36}$: *m*/*z* 2262.7. Found: *m*/*z* 2262.9 $[M+Na]^+$.

3.2.5. Data for 18. Yield: 31 mg (79%); $[\alpha]_D^{23}$ +75.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.06–7.20 (m, 100H, Ar-*H*), 6.00 (br d, 5H, *H*-4), 5.76 (br dd, 5H, *H*-2), 5.66 (br dd, 5H, *H*-3), 4.91 (br d, 5H, *H*-1), 4.65 (m, 5H, *H*-6a), 4.38 (m, 10H, *H*-5, *H*-6b), 3.94–3.36 (m, 36H, NCH_2,OCH_2), 2.53–2.08 (m, 8H, CCH_2), 1.37, 1.31 (2s, 9H, *t*-Bu). MALDI-TOF MS: Calcd for $C_{205}H_{193}N_9NaO_{60}$: *m*/*z* 3763.2. Found: *m*/*z* 3763.2 $[M+Na]^+$.

3.2.6. Data for 20. Yield: 15 mg (98%); $[\alpha]_D^{23}$ +61.1 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.26–7.21 (m, 66H, Ar-*H*), 5.99 (br d, 3H, *H*-4), 5.76 (br dd, 3H, *H*-2), 5.65 (br dd, 3H, *H*-3), 4.89 (br d, 3H, *H*-1), 4.66 (m, 3H, *H*-6a), 4.41 (m, 6H, *H*-5, *H*-6b), 3.95–2.04 (m, 32H, CH_2, NCH_3). MALDI-TOF MS: Calcd for $C_{132}H_{123}N_7NaO_{37}S$: *m*/*z* 2452.8. Found: *m*/*z* 2452.5 $[M+Na]^+$.

3.2.7. Data for 21. Yield, 9 mg (83%); $[\alpha]_D^{23}$ +75.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.38–7.22 (m, 106H, Ar-*H*), 5.99 (br d, 5H, *H*-4), 5.75 (br dd, 5H, *H*-2), 5.66 (br dd, 5H, *H*-3), 4.91 (br d, 5H, *H*-1), 4.66 (m, 5H, *H*-6a), 4.37 (m, 10H, *H*-5, *H*-6b), 3.94–2.04 (m, 52H, CH_2). MALDI-TOF MS: Calcd for $C_{214}H_{199}N_{11}NaO_{61}S$: *m*/*z* 3953.3. Found: *m*/*z* 3953.8 $[M+Na]^+$.

3.2.8. Data for 24. Yield: 963 mg (77%); ^{1}H NMR ($CDCl_3$): δ 7.37–7.17 (m, 5H, Ar-*H*), 6.27 (br t, 1H, N*H*), 5.11 (s, 2H, CH_2Ph), 4.74 (s, 2H, CH_2CCl_3), 3.85 (s, 2H, NCH_2CO), 3.63 (t, 2H, *J* 6.7 Hz, NCH_2 of β-Ala), 3.25 (m, 2H, NCH_2 of 6-aminohexanoic acid), 2.76 (t, 2H, CH_2CO of β-Ala), 2.36 (t, 2H, *J* 6.1 Hz, CH_2CO of 6-aminohexanoic acid), 1.69–1.34 (m, 6H, CH_2), 1.45 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 173.3, 169.2, 136.0, 128.5, 128.2, 94.7, 81.2, 74.1, 66.1, 52.6, 45.0, 39.1, 34.0, 33.2, 29.2, 28.3, 26.3, 24.4. MALDI-TOF MS: Calcd for $C_{25}H_{35}Cl_3N_2NaO_7$: *m*/*z* 603.2. Found: *m*/*z* 603.7 $[M+Na]^+$.

3.2.9. Data for 26. Yield: 547 mg (64%); ^{1}H NMR ($CDCl_3$): δ 7.35–7.27 (m, 5H, Ar-*H*), 6.95 (br t, 1H, N*H*), 5.11 (s, 2H, CH_2Ph), 4.74 (s, 2H, CH_2CCl_3), 4.05 (s, 2H, NCH_2CO), 3.79 (br t, 2H, NCH_2), 3.25–3.21 (m, 4H, NCH_2), 2.47–2.36 (m, 6H, CH_2CO), 1.78–1.33 (m, 12H, CH_2), 1.43 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 173.4, 171.8, 136.0, 128.5, 128.2, 128.1, 95.0, 80.8, 73.8, 66.1, 62.2, 52.6, 41.1, 39.4, 39.2, 34.1, 33.7, 29.1, 29.0, 28.3, 26.3, 26.0, 24.4, 24.3. MALDI-TOF MS: Calcd for $C_{31}H_{46}Cl_3N_3NaO_8$: *m*/*z* 716.2. Found: *m*/*z* 716.6 $[M+Na]^+$.

3.2.10. Data for 28. Yield: 239 mg (83%); $[\alpha]_D^{23}$ +59.6 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.09–7.21 (m, 60H, Ar-*H*), 5.99 (br d, 3H, *H*-4), 5.75 (br dd, 3H, *H*-2), 5.65 (br dd, 3H, *H*-3), 4.89 (br d, 3H, *H*-1), 4.73 (s, 2H, CH_2CCl_3), 4.66 (m, 3H, *H*-6a), 4.43–4.36 (m, 6H, *H*-5, *H*-6b), 3.95–3.18 (m, 28H, OCH_2, NCH_2), 2.45–2.03

(m, 10H, CCH_2), 1.70–1.36 (m, 12H, CH_2), 1.40 (s, 9H, *t*-Bu). MALDI-TOF MS: Calcd for $C_{142}H_{147}Cl_3N_8NaO_{41}$: *m*/*z* 2747.9. Found: *m*/*z* 2748.1 $[M+Na]^+$.

3.2.11. Data for 30. Yield: 83 mg (89%); $[\alpha]_D^{23}$ +67.0 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.08–7.20 (m, 120H, Ar-*H*), 6.00 (br d, 6H, *H*-4), 5.75 (br dd, 6H, *H*-2), 5.66 (br dd, 6H, *H*-3), 4.90 (br d, 6H, *H*-1), 4.67 (m, 6H, *H*-6a), 4.41–4.37 (m, 12H, *H*-5, *H*-6b), 3.96–3.20 (m, 48H, OCH_2, NCH_2), 2.58–2.04 (m, 14H, CH_2CO), 1.58–1.34 (m, 12H, CH_2), 1.37 (s, 9H, *t*-Bu). MALDI-TOF MS: Calcd for $C_{258}H_{253}N_{13}NaO_{74}$: *m*/*z* 4739.6. Found: *m*/*z* 4740.4 $[M+Na]^+$.

3.2.12. Data for 32. Yield: 61 mg (66%); $[\alpha]_D^{23}$ +63.3 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.11–7.18 (m, 180H, Ar-*H*), 5.99 (br d, 9H, *H*-4), 5.75 (br dd, 9H, *H*-2), 5.66 (br dd, 9H, *H*-3), 4.91 (br d, 9H, *H*-1), 4.66 (m, 9H, *H*-6a), 4.40–4.37 (m, 18H, *H*-5, *H*-6b), 3.96–3.15 (m, 76H, OCH_2, NCH_2), 2.53–2.06 (m, 24H, CH_2CO), 1.56–1.35 (m, 33H, CH_2 and *t*-Bu).

3.2.13. Data for 34. Yield: 24 mg (54%); $[\alpha]_D^{23}$ +51.9 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.05–7.21 (240H, m, Ar-*H*), 5.99 (12H, br d, *H*-4), 5.75 (12H, br dd, *H*-2), 5.65 (12H, br dd, *H*-3), 4.90 (12H, br d, *H*-1), 4.65 (12H, m, *H*-6a), 4.41–4.25 (24H, m, *H*-5, *H*-6b), 3.96–3.13 (104H, m, OCH_2, NCH_2), 2.57–2.00 (34H, m, CH_2CO), 1.53–1.25 (45H, m, CH_2 and *t*-Bu). MALDI-TOF MS: Calcd for $C_{528}H_{525}N_{29}NaO_{150}$: *m*/*z* 9693.4. Found: *m*/*z* 9693.6 $[M+Na]^+$.

3.2.14. Data for 36. Yield: 6 mg (51%); $[\alpha]_D^{23}$ +34.5 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.04–7.20 (m, 246H, Ar-*H*), 5.99 (br d, 12H, *H*-4), 5.74 (br dd, 12H, *H*-2), 5.65 (br dd, 12H, *H*-3), 4.90 (br d, 12H, *H*-1), 4.65 (m, 12H, *H*-6a), 4.40–4.38 (m, 24H, *H*-5, *H*-6b), 3.95–3.12 (m, 112H, OCH_2, NCH_2, NCH_3), 2.36–2.00 (m, 34H, CH_2CO), 1.60–1.25 (m, 36H, CH_2). MALDI-TOF MS: Calcd for $C_{537}H_{531}N_{31}NaO_{151}S$: *m*/*z* 9883.5. Found: *m*/*z* 9884.4 $[M+Na]^+$.

3.3. Typical procedure for removal of the Boc group

To a solution of compound **8** (116 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added 50% aq TFA (1 mL). The reaction mixture was stirred for 1 h at room temperature. After completion of the reaction (TLC monitoring), the mixture was concentrated and purified by silica gel column chromatography (1:1 benzene–acetone as eluant) to give **9** (109 mg, quant): $[\alpha]_D^{23}$ +68.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.09–7.23 (m, 20H, Ar-*H*), 6.00 (br d, 1H, *H*-4), 5.78 (br dd, 1H, *H*-2), 5.62 (br dd, 1H, *H*-3), 4.87 (br d, 1H, *H*-1), 4.75 (s, 2H, CH_2CCl$_3$), 4.68 (m, 1H, *H*-6a), 4.43 (m, 1H, *H*-6b), 4.35 (m, 1H, *H*-5), 4.00 and 3.77 (m, 2H, OCH_2 of sugar unit), 3.55 and 3.46 (m, 2H, NCH_2 of sugar unit), 3.10 (br t, 2H, NHCH_2CO), 2.81 (m, 2H, NCH_2 of β-Ala), 2.60 (br t, 2H, COCH_2 of β-Ala); ^{13}C NMR ($CDCl_3$): δ 170.5, 170.3, 166.0, 165.5, 165.2, 133.6, 133.4, 133.32, 133.28, 130.0, 129.7, 129.3, 129.2, 129.0, 128.6, 128.5, 128.3, 101.4, 94.7, 74.0, 71.54, 71.46, 69.8, 68.7, 68.1, 62.0, 51.4, 44.4, 38.8, 33.5. MALDI-TOF MS: Calcd for $C_{46}H_{48}N_2NaO_{15}$: *m*/*z* 921.2. Found: *m*/*z* 921.4 $[M+Na]^+$.

3.3.1. Deprotection of compounds 12, 17, 19, 31, 33 and 35. These compounds were deprotected using the procedure outlined in Section 3.3, above.

3.3.2. Data for 12. Yield: 56 mg (quant); $[\alpha]_D^{23}$ +65.2 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.10–7.14 (m, 40H, Ar-*H*), 6.00 (br d, 2H, *H*-4), 5.75 (br dd, 2H, *H*-2), 5.65 (br dd, 2H, *H*-3), 4.88 (br d, 2H, *H*-1), 4.72–4.66 (m, 4H, CH_2CCl$_3$, *H*-6a), 4.47–4.33 (m, 4H, *H*-5, *H*-6b), 3.99–3.09 (m, 16H, OCH_2 of sugar unit, NCH_2 of sugar unit, NCH_2CO, NCH_2 of β-Ala), 2.86–2.63 (m, 4H, COCH_2 of β-Ala); ^{13}C NMR ($CDCl_3$): δ 170.7, 169.6, 168.3, 166.1, 165.5, 165.4, 133.6, 133.3, 130.0, 129.7, 129.2, 129.0, 128.6, 128.5, 128.3, 101.7, 101.5, 74.1, 71.6, 71.4, 70.0, 69.9, 69.5, 68.8, 68.6, 68.3, 68.2, 68.1, 62.1, 61.9, 52.1, 49.7, 44.4, 39.4, 39.1, 32.6. MALDI-TOF MS: Calcd for $C_{84}H_{79}Cl_3N_4NaO_{25}$: *m*/*z* 1671.4. Found: *m*/*z* 1671.9 $[M+Na]^+$.

3.3.3. Data for 17. Yield: 94 mg (99%); $[\alpha]_D^{23}$ +85.9 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.08–7.23 (m, 60H, Ar-*H*), 6.01 (br d, 3H, *H*-4), 5.78 (br dd, 3H, *H*-2), 5.66 (br dd, 3H, *H*-3), 4.89 (br d, 3H, *H*-1), 4.68 (m, 3H, *H*-6a), 4.43–4.37 (m, 6H, *H*-5, *H*-6b), 3.67–3.08 (m, 20H, OCH_2, NCH_2), 2.74–2.16 (m, 4H, CCH_2); MALDI-TOF MS: Calcd for $C_{118}H_{109}N_5NaO_{34}$: *m*/*z* 2162.7. Found: *m*/*z* 2163.2 $[M+Na]^+$.

3.3.4. Data for 19. Yield: 26 mg (86%); $[\alpha]_D^{23}$ +78.1 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.06–7.22 (m, 100H, Ar-*H*), 6.00 (br d, 5H, *H*-4), 5.75 (br dd, 5H, *H*-2), 5.66 (br dd, 5H, *H*-3), 4.90 (br d, 5H, *H*-1), 4.67 (m, 5H, *H*-6a), 4.39 (m, 10H, *H*-5, *H*-6b), 3.93–2.06 (m, 44H, CH_2). MALDI-TOF MS: Calcd for $C_{200}H_{185}N_9NaO_{58}$: *m*/*z* 3663.2. Found: *m*/*z* 3663.9 $[M+Na]^+$.

3.3.5. Data for 31. Yield: 59 mg (73%); $[\alpha]_D^{23}$ +70.3 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.06–7.20 (m, 120H, Ar-*H*), 6.00 (br d, 6H, *H*-4), 5.75 (br dd, 6H, *H*-2), 5.66 (br dd, 6H, *H*-3), 4.94 (br d, 6H, *H*-1), 4.67 (m, 6H, *H*-6a), 4.42–4.39 (m, 12H, *H*-5, *H*-6b), 3.96–3.18 (m, 48H, OCH_2, NCH_2), 2.80–2.03 (m, 14H, CH_2CO), 1.54–1.26 (m, 12H, CH_2). MALDI-TOF MS: Calcd for $C_{253}H_{245}N_{13}NaO_{72}$: *m*/*z* 4639.6. Found: *m*/*z* 4640.1 $[M+Na]^+$.

3.3.6. Data for 33. Yield: 33 mg (55%); $[\alpha]_D^{23}$ +64.6 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.06–7.20 (m, 180H, Ar-*H*), 5.99 (br d, 9H, *H*-4), 5.75 (br dd, 9H, *H*-2), 5.66 (br dd, 9H, *H*-3), 4.90 (br d, 9H, *H*-1), 4.66 (m, 9H, *H*-6a), 4.41–4.37 (m, 18H, *H*-5, *H*-6b), 3.96–3.17 (m, 76H, OCH_2, NCH_2), 2.57–2.01 (m, 24H, CH_2CO), 1.54–1.25 (m, 24H, CH_2). MALDI-TOF MS: Calcd for $C_{388}H_{381}N_{21}NaO_{110}$: *m*/*z* 7116.5. Found: *m*/*z* 7117.8 $[M+Na]^+$.

3.3.7. Data for 35. Yield: 12 mg (49%); $[\alpha]_D^{23}$ +42.7 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.05–7.21 (240H, m, Ar-*H*), 5.99 (12H, br d, *H*-4), 5.75 (12H, br dd, *H*-2), 5.66 (12H, br dd, *H*-3), 4.90 (12H, br d, *H*-1), 4.65 (12H, m, *H*-6a), 4.40–4.38 (24H, m, *H*-5, *H*-6b), 3.95–3.12 (104H, m, OCH_2, NCH_2), 2.57–2.00 (34H, m, CH_2CO), 1.75–1.25 (36H, m, CH_2). MALDI-TOF MS: Calcd for $C_{523}H_{518}N_{29}O_{148}$: *m*/*z* 9571.5. Found: *m*/*z* 9572.3 $[M+H]^+$.

3.4. Typical procedure for the removal of the 2,2,2-trichloroethyl (Tce) group

To a solution of compound **8** (189 mg, 0.19 mmol) in HOAc (2 mL) was added Zn powder (104 mg), and the reaction mixture was stirred for 1 h at room temperature. After completion of the reaction (TLC monitoring), the mixture was filtered through Celite. The filtrate was concentrated and purified by silica gel column chromatography (30:1:0.1 $CHCl_3$–MeOH–HOAc) to give **10** (147 mg, 90%): $[\alpha]_D^{23}$ +67.9 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.11–7.22 (m, 20H, Ar-*H*), 6.00 (d, 1H, *H*-4), 5.78 (dd, 1H, $J_{2,3}$ 9.8 Hz, *H*-2), 5.62 (dd, 1H, $J_{3,4}$ 3.7 Hz, *H*-3), 4.87 (d, 1H, $J_{1,2}$ 7.9 Hz, *H*-1), 4.67 (m, 1H, *H*-6a), 4.46 (m, 1H, *H*-6b), 4.38 (m, 1H, *H*-5), 3.99–3.50 (m, 8H, OCH_2 of sugar unit, NCH_2 of sugar unit, NCH_2CO, NCH_2 of β-Ala), 2.49 (br t, 2H, $COCH_2$ of β-Ala), 1.43 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 166.1, 165.51, 165.46, 155.2, 133.7, 133.6, 133.4, 133.3, 130.8, 130.0, 129.7, 129.2, 129.0, 128.9, 128.64, 128.56, 128.5, 128.3, 101.7, 81.3, 71.6, 71.4, 70.0, 68.8, 68.1, 62.1, 51.4, 45.9, 39.6, 35.1, 28.9. MALDI-TOF MS: Calcd for $C_{46}H_{48}N_2NaO_{15}$: *m*/*z* 891.3. Found: *m*/*z* 891.7 $[M+Na]^+$.

3.4.1. Removal of the Tce group to give compounds 13, 15, 25 and 29. Removal of the Tce group was carried out to give these compounds according to the procedure in Section 3.4.

3.4.2. Data for 13. Yield: 53 mg (quant); $[\alpha]_D^{23}$ +61.6 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.09–7.14 (m, 40H, Ar-*H*), 6.00 (br d, 2H, *H*-4), 5.77 (br dd, 2H, *H*-2), 5.65 (br dd, 2H, *H*-3), 4.90 (br d, 2H, *H*-1), 4.66 (m, 2H, *H*-6a), 4.42–4.35 (m, 4H, *H*-5, *H*-6b), 3.98–3.44 (m, 16H, OCH_2 of sugar unit, NCH_2 of sugar unit, NCH_2CO, NCH_2 of β-Ala), 2.59–2.35 (m, 4H, $COCH_2$ of β-Ala), 1.44, 1.38 and 1.32 (3s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 173.7, 172.7, 168.7, 166.0, 165.5, 133.6, 133.4, 133.3, 129.9, 129.7, 129.2, 129.1, 129.0, 128.6, 128.5, 128.2, 101.4, 80.9, 71.6, 71.3, 69.8, 69.7, 68.1, 62.0, 52.8, 39.1, 32.4, 31.7, 29.6, 28.2. MALDI-TOF MS: Calcd for $C_{87}H_{86}N_4NaO_{27}$: *m*/*z* 1641.6. Found: *m*/*z* 1642.3 $[M+Na]^+$.

3.4.3. Data for 15. Yield: 35 mg (81%); $[\alpha]_D^{23}$ +65.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.07–7.22 (m, 80H, Ar-*H*), 6.00 (br d, 4H, *H*-4), 5.76 (br dd, 4H, *H*-2), 5.65 (br dd, 4H, *H*-3), 4.90 (br d, 4H, *H*-1), 4.66 (m, 4H, *H*-6a), 4.42–4.37 (m, 8H, *H*-5, *H*-6b), 3.96–3.41 (m, 32H, OCH_2, NCH_2), 2.45–2.05 (m, 8H, CCH_2), 1.36, 1.34, 1.33, 1.30 (4s, 9H, *t*-Bu). MALDI-TOF MS: Calcd for $C_{169}H_{162}N_8NaO_{51}$: *m*/*z* 3142.0. Found: *m*/*z* 3142.9 $[M+Na]^+$.

3.4.4. Data for 25. Yield: 568 mg (80%); ^1H NMR ($CDCl_3$): δ 7.34–7.25 (m, 5H, Ar-*H*), 7.01 (br t, 1H, N*H*), 5.11 (s, 2H, CH_2Ph), 4.01 (s, 2H, NCH_2CO), 3.62 (br t, 2H, NCH_2 of β-Ala), 3.29 (m, 2H, NCH_2 of 6-aminohexanoic acid), 2.61 (br t, 2H, CH_2CO of β-Ala), 2.35 (br t, 2H, CH_2CO of 6-aminohexanoic acid), 1.64–1.34 (m, 6H, $CH_2 \times 3$), 1.44 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 173.9, 171.8, 135.9, 128.6, 128.2, 82.2, 66.4, 52.5, 45.8, 39.7, 34.0, 28.6, 28.2, 26.1, 24.3. MALDI-TOF MS: Calcd for $C_{23}H_{34}N_2NaO_7$: *m*/*z* 473.2. Found: *m*/*z* 473.7 $[M+Na]^+$.

3.4.5. Data for 29. Yield: 140 mg (85%); $[\alpha]_D^{23}$ +62.1 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.09–7.21 (m, 60H, Ar-*H*), 6.00 (br d, 3H, *H*-4), 5.75 (br dd, 3H, *H*-2), 5.66 (br dd, 3H, *H*-3), 4.90 (br d, 3H, *H*-1), 4.66 (m, 3H, *H*-6a), 4.42–4.36 (m, 6H, *H*-5, *H*-6b), 3.94–3.20 (m, 28H, OCH_2, NCH_2), 2.40–2.05 (m, 10H, CH_2CO), 1.60–1.34 (m, 12H, CH_2), 1.41 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 166.0, 165.5, 165.4, 133.6, 133.53, 133.47, 133.34, 133.3, 130.0, 129.7, 129.3, 129.22, 129.17, 129.0, 128.6, 128.5, 128.3, 101.7, 101.6, 101.4, 80.8, 71.6, 71.54, 71.46, 71.4, 69.9, 68.9, 68.6, 68.1, 61.9, 39.2, 29.0, 28.3, 26.3, 26.0, 24.2. MALDI-TOF MS: Calcd for $C_{140}H_{146}N_8NaO_{41}$: *m*/*z* 2618.0. Found: *m*/*z* 2618.4 $[M+Na]^+$.

3.5. Typical procedure for the preparation of fully deprotected peptidic glycoclusters

To a solution of **20** (15 mg, 6.17 μ mol) in 1:1 1,4-dioxane–MeOH (2 mL) was added NaOMe (24 mg), and the mixture was stirred for 4 h at room temperature and then neutralized with Amberlite IR-120 (H^+) resin. The resin was filtered off and washed with MeOH and water. The filtrate and washings were combined and concentrated. Column chromatography (1:1 MeOH–H_2O) of the residue on Sephadex LH-20 gave **1**

(8.5 mg, quant): ^{13}C NMR (D_2O): δ 128.5, 128.4, 123.6, 102.5, 74.7, 72.3, 70.4, 68.2, 67.9, 67.8, 60.6, 48.4, 44.6, 39.01, 38.96, 39.9, 38.8. MALDI-TOF MS: Calcd for $C_{48}H_{75}N_7NaO_{25}S$: *m*/*z* 1204.5. Found: *m*/*z* 1204.5 $[M+Na]^+$.

3.5.1. Deacylated compounds 2, 3, 4 and 5. These compounds were obtained using the procedure in Section 3.5.

3.5.2. Data for 2. Yield: 4 mg (96%); MALDI-TOF MS: Calcd for $C_{74}H_{119}N_{11}NaO_{41}S$: *m*/*z* 1872.7. Found: *m*/*z* 1872.7 $[M+Na]^+$.

3.5.3. Data for 3. Yield: 4 mg (95%); ^{13}C NMR (D_2O): δ 170.6, 102.5, 74.7, 72.3, 70.4, 68.2, 67.9, 67.8, 60.6, 48.4, 39.1, 39.0, 38.9. MALDI-TOF MS: Calcd for $C_{72}H_{124}N_{10}NaO_{46}$: *m*/*z* 1887.8. Found: *m*/*z* 1888.2 $[M+Na]^+$.

3.5.4. Data for 4. Yield: 7 mg (quant); MALDI-TOF MS: Calcd for $C_{111}H_{183}N_{15}NaO_{69}$: *m*/*z* 2853.1. Found: *m*/*z* 2853.5 $[M+Na]^+$.

3.5.5. Data for 5. Yield: 1.1 mg (36%); ^{13}C NMR (1:1 CD_3OD-D_2O): δ 171.7, 171.6, 171.4, 171.3, 104.4, 76.3, 74.1, 72.9, 72.1, 69.8, 62.1, 61.7, 49.1, 40.5, 40.4. MALDI-TOF MS: Calcd for $C_{202}H_{343}N_{31}NaO_{103}S$: *m*/*z* 4906.3. Found: *m*/*z* 4907.2 $[M+Na]^+$.

3.6. The coupling reaction with acyl chloride

To a solution of compound **17** (23 mg, 10.6 μmol) in CH_2Cl_2 (2 mL) was added succinyl chloride (0.5 μL, 4.54 μmol) and Et_3N (4.5 μL, 32.3 μmol). The mixture was stirred for 1 h at room temperature. After completion of the reaction, the mixture was concentrated and purified by silica gel column chromatography (40:1 $CHCl_3$–MeOH) to give **22** (16 mg, 85%): $[\alpha]_D^{23}$ +65.9 (*c* 0.4, $CHCl_3$); MALDI-TOF MS: Calcd for $C_{240}H_{220}N_{10}NaO_{70}$: *m*/*z* 4384.4. Found: *m*/*z* 4384.8 $[M+Na]^+$.

3.6.1. Data for 23. Yield: 12 mg (81%); $[\alpha]_D^{23}$ +74.0 (*c* 0.3, $CHCl_3$); MALDI-TOF MS: Calcd for $C_{363}H_{327}N_{15}O_{105}Na$: *m*/*z* 6598.1. Found: *m*/*z* 6598.5 $[M+Na]^+$.

3.7. Hydrogenation of compound 26

A solution of compound **26** (520 mg, 0.75 mmol) in THF (5 mL) was hydrogenated over 10% Pd–C (250 mg) for 2 h at room temperature and then filtered through Celite. The filtrate was concentrated and purified by silica gel column chromatography (10:1 $CHCl_3$–MeOH) to give **27** (175 mg, 39%): ^{1}H NMR ($CDCl_3$): δ 4.75 (s, 2H, CH_2CCl_3), 3.84 (s, 2H, NCH_2CO), 3.57 (t, 2H, *J* 6.7 Hz, NCH_2), 3.31–3.21 (m, 4H, NCH_2), 2.49–2.33 (m, 6H, CH_2CO), 1.75–1.37 (m, 12H, CH_2), 1.44 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 176.2, 171.9, 81.0, 73.9, 68.4, 52.2, 39.4, 38.9, 33.7, 33.5, 28.9, 28.7, 28.2, 26.2, 25.8, 24.3, 24.1. MALDI-TOF MS: Calcd for $C_{24}H_{40}Cl_3N_3NaO_8$: *m*/*z* 626.2. Found: *m*/*z* 626.6 $[M+Na]^+$.

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