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Convergent stereoselective synthesis of multiple sulfated GlcNα(1,4)GlcAβ(1,4) dodecasaccharides†

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In this paper, we describe an effective method for the elongation of a GlcNα(1,4)GlcAβ(1,4) sequence using a GlcNTrocα(1,4)GlcA disaccharide unit and the synthesis of the *N*- and/or *O*-sulfated GlcNα(1,4)-GlcAβ(1,4) oligosaccharides. *N*-Troc protection of GlcNα(1,4)GlcA units was effective for the synthesis of the GlcNα(1,4)GlcAβ(1,4) oligosaccharides in comparison with the azido substituent. The GlcNα(1,4)-GlcAβ(1,4) dodecasaccharide was successfully prepared by the direct β-selective glycosidation of glucuronate in the GlcNα(1,4)GlcAβ(1,4)GlcNα(1,4)GlcAβ(1,4) tetrasaccharide. In addition, the synthesis of the *N*- and/or *O*-sulfated GlcNα(1,4)GlcAβ(1,4) oligosaccharides was accomplished by fluorous-assisted deprotection and sulfation. The fluorous-assisted synthetic technology applied to the highly polar sulfated oligosaccharide permits it to be more easily separated from the highly polar reagents, such as SO_3·NEt_3.

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Introduction

Heparan sulfates (HS) and heparins (H) are partially sulfated heterogeneous polysaccharides that are composed of α-glucosamine (GlcN) and β-glucuronic acid (GlcA) or β-iduronic acid (IdoA) units and are biologically synthesized by the partial enzymatic modification of heparosan, a homopolymer composed of a GlcNα(1,4)GlcAβ(1,4) sequence. These sulfated oligosaccharides play crucial roles in a variety of biological systems such as bacterial infections, growth factor regulation, angiogenesis, cell adhesion and lipid metabolism[1] and promote the growth of human embryonic stem cells in a defined serum-free medium.[2] However, elucidating the structure–activity relationships of such oligosaccharides is a daunting task, since a great deal of heterogeneity can exist, because of the sugars contained by the oligosaccharide and the fact that the number and position of sulfate esters and IdoA units can vary greatly. Methodology for the chemical synthesis of structurally defined pure HS/H related oligosaccharides would greatly contribute not only to the elucidation of their structure–activity relationships, but could also lead to the development of new drug candidates based on the structure of HS/H.

Recent developments in synthetic carbohydrate chemistry now permit various sulfated oligosaccharides to be prepared.[3,4] However, the synthesis of relatively large sulfated oligosaccharides which are expected to have enhanced biological activity compared to smaller oligosaccharides[5] is still a difficult task, because (1) uronic acids are relatively unreactive towards both glycosylation and glycosidation due to the strong electron-withdrawing effect of the carboxyl group at the 6 position,[6] (2) difficulties associated with producing an α-glucosamine linkage[7] and (3) the high polarity of multiply sulfated oligosaccharides. A post-glycosylation oxidation approach where the oligosaccharide backbone is built up prior to the installment of the carboxylate functions is an effective way to avoid these difficulties. However, this approach requires the oxidation of multiple C6 hydroxyl groups of complex oligosaccharides at the last stage in the synthesis of sulfated oligosaccharides. On the other hand, an IdoAβ(1,4)$GlcN_3$ disaccharide represents an effective building block for the synthesis of the oligosaccharides based on a pre-glycosylation oxidation approach.[8] Lortat-Jacob *et al.* successfully synthesized a heparin GlcNα(1,4)IdoAβ(1,4) dodecasaccharide containing 18 sulfate esters using a building block approach.[9] However, it is still difficult to prepare oligosaccharides containing alternating GlcN and GlcA units that serve as substrates for enzymatic modification as well as ligands of the heparin receptors.[10] The corresponding GlcAβ(1,4)$GlcN_3$ unit did not function well, since glycosylation of the C4 equatorial hydroxyl group of the $^4C_1$ conformer of the D-glucuronyl acceptor with the $GlcN_3$ donor frequently resulted in the formation of anomeric mixtures.[11] Therefore, an effective method for the synthesis of these heparosan oligosaccharides continues to be needed. Herein we proposed the GlcNTrocα(1,4)GlcA disaccharide unit as a new building block for the synthesis of sulfated dodecasaccharides composed of alternating GlcNα(1,4)GlcAβ(1,4) sequences.[12]

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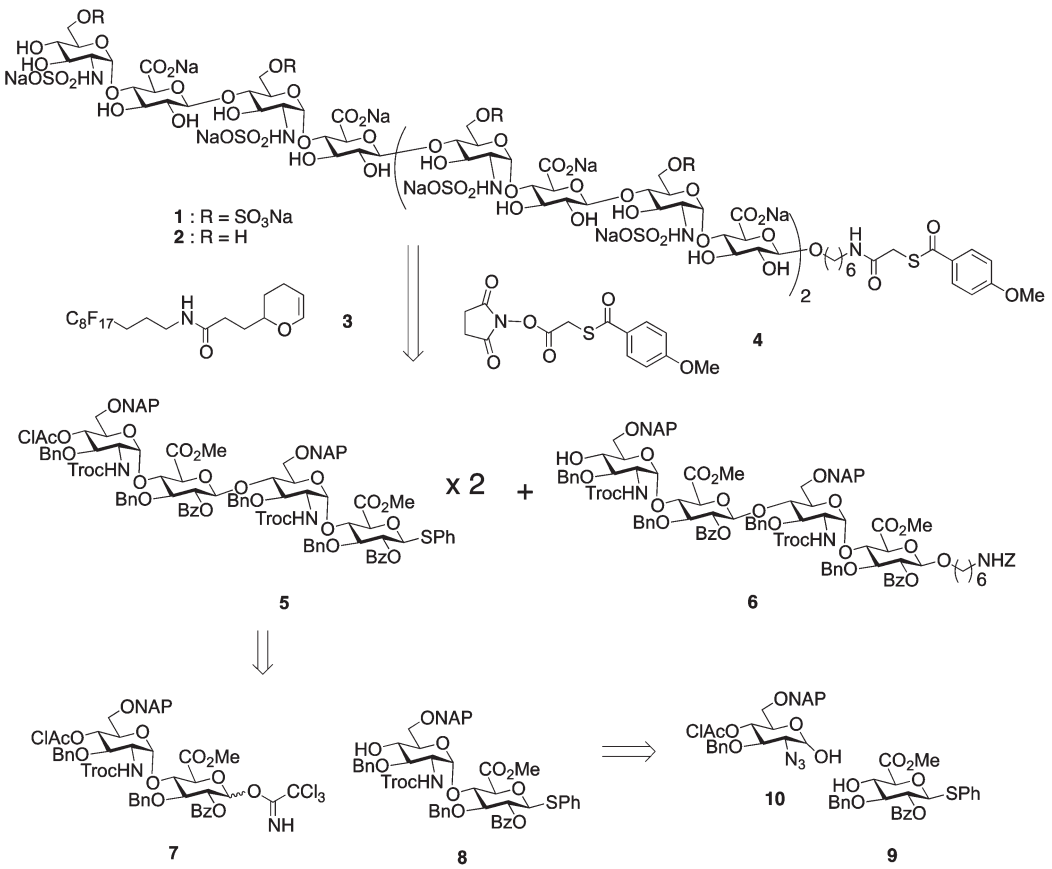
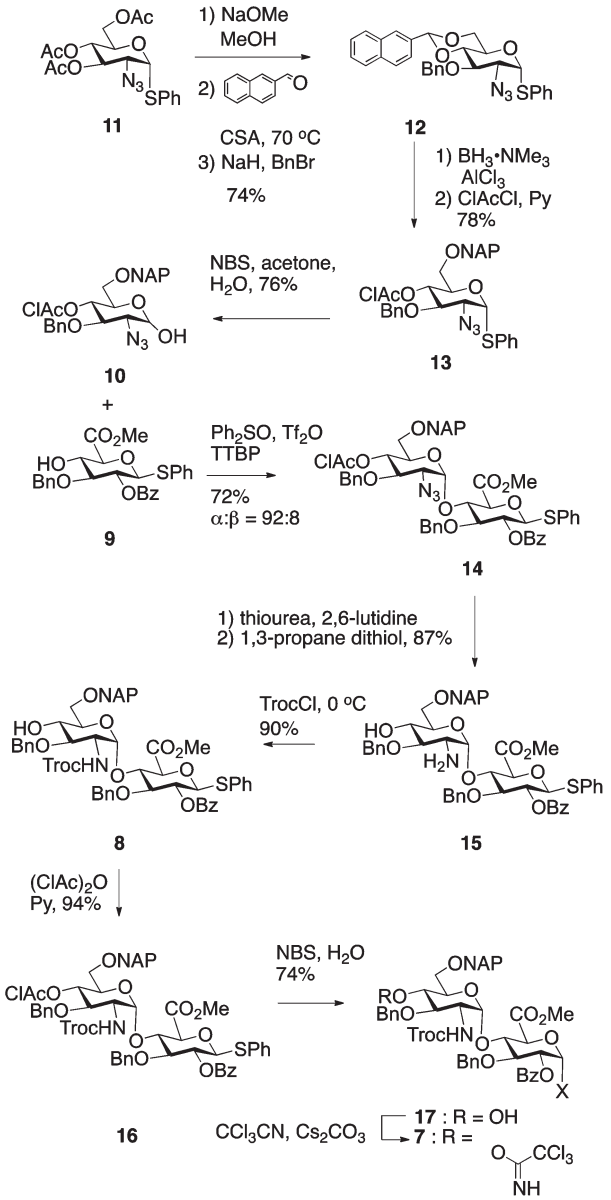
Results and discussion

We planned the synthesis of the *N*- and *O*-sulfated GlcNα(1,4)-GlcAβ(1,4) dodecasaccharides **1** and **2** containing a thioester at the reducing end (Scheme 1). The *N*-sulfated oligosaccharides **1** and **2** are expected to act as substrates for enzymatic modification as well as ligands of the heparin receptors. The thiobenzoate moiety acts as a chromophore for detecting the final product as well as a linking device for further derivatization *via* S-alkylation. Strategy for the synthesis of the sulfated oligosaccharides **1** and **2** is based on a [4 + 4 + 4] coupling strategy using the tetrasaccharide **5** and a fluorous-assisted deprotection using the fluorous tag **3**. The dodecasaccharides **1** and **2** would be prepared from two tetrasaccharide donors **5** and tetrasaccharide acceptor **6**. The C2 benzoate of the glucuronate unit in **5** promotes β-selectivity in the glycosidation of tetrasaccharide **5**. The *N*-Troc protecting group improves the reactivity of the C4 hydroxyl group towards glycosylation.[12] The chloroacetyl group can be selectively removed without affecting any other protecting groups for conversion to a glycosyl acceptor. The use of large building blocks improves the efficiency of the synthesis of oligosaccharides and facilitates the separation of the product from the substrates by size exclusion chromatography.[13] The sulfation, deprotection and installation of the chromophore with the activated ester **3** would be achieved after attaching a light-fluorous tag. Attaching a light-fluorous tag to the protected oligosaccharides facilitates their purification and improves efficiency of the deprotection process with minimal effects on their reactivity.[14] We previously reported on a methodology for the solid- and fluorous-assisted deprotection of oligosaccharides that ease the manipulation of highly polar substrates.[15] The 2-naphthylmethyl (NAP) ethers and the *N*-trichloroethylcarbonyl (Troc) protecting groups are selectively removed for the partial sulfation of the oligosaccharides. The tetrasaccharide **5** was prepared by the chemoselective and β-selective glycosylation of the disaccharide donor **7** and acceptor **8**. The disaccharide is prepared by the chemoselective and α-selective glycosylation of **9** with **10**.

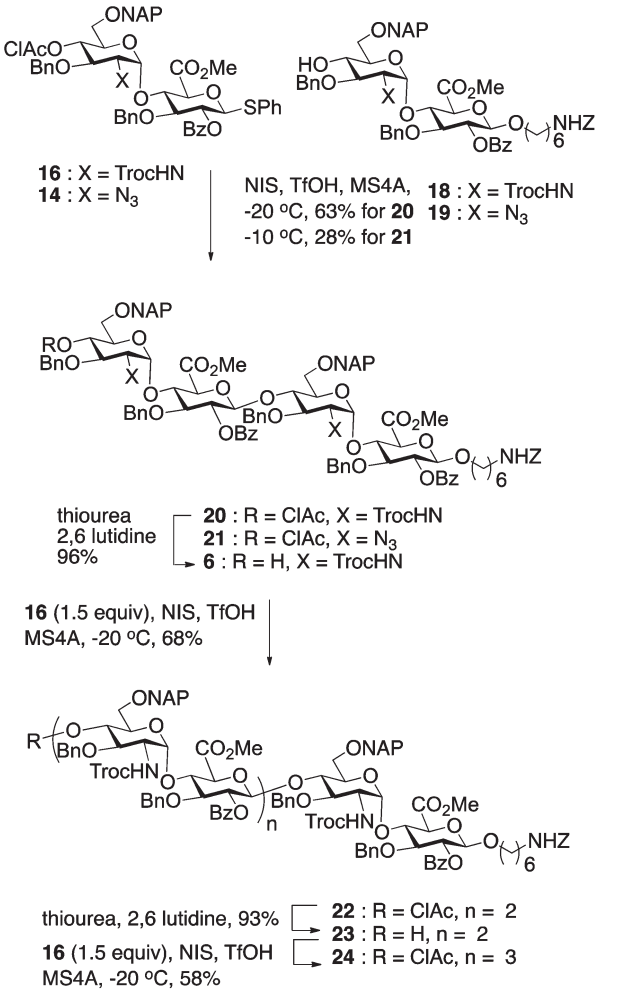
Scheme 2 shows preparation of the GlcNα(1,4)GlcAβ(1,4) disaccharides **7** and **8** from **11**. The α-thioglycoside **11** was converted to acetal **12** by hydrolysis of the acetates, acetalization of C4,6 dihydroxyl groups with 2-naphthylaldehyde and etherification of the C3 hydroxyl group with benzyl bromide. Regioselective cleavage of the acetal with $BH_3{\cdot}NMe_3$ and $AlCl_3$, followed by protection of the resulting C4 hydroxyl group with chloroacetyl chloride provided the naphthylmethylether **13** in 78% yield. Oxidative hydrolysis of the thioglycoside with NBS provided hemiacetal **10** in 76% yield. Treatment of the hemiacetal **10** and thioglycoside **9** with Tf_2O, Ph_2SO and TTBP provided the α-linked disaccharide **14** in 72% yield with excellent α-selectivity (α/β = 92/8). Removal of the chloroacetyl group with thiourea, followed by reduction of azide to amine with



Scheme 1 Strategy for the synthesis of the sulfated GlcNα(1,4)GlcAβ(1,4) dodecasaccharides **1** and **2**.



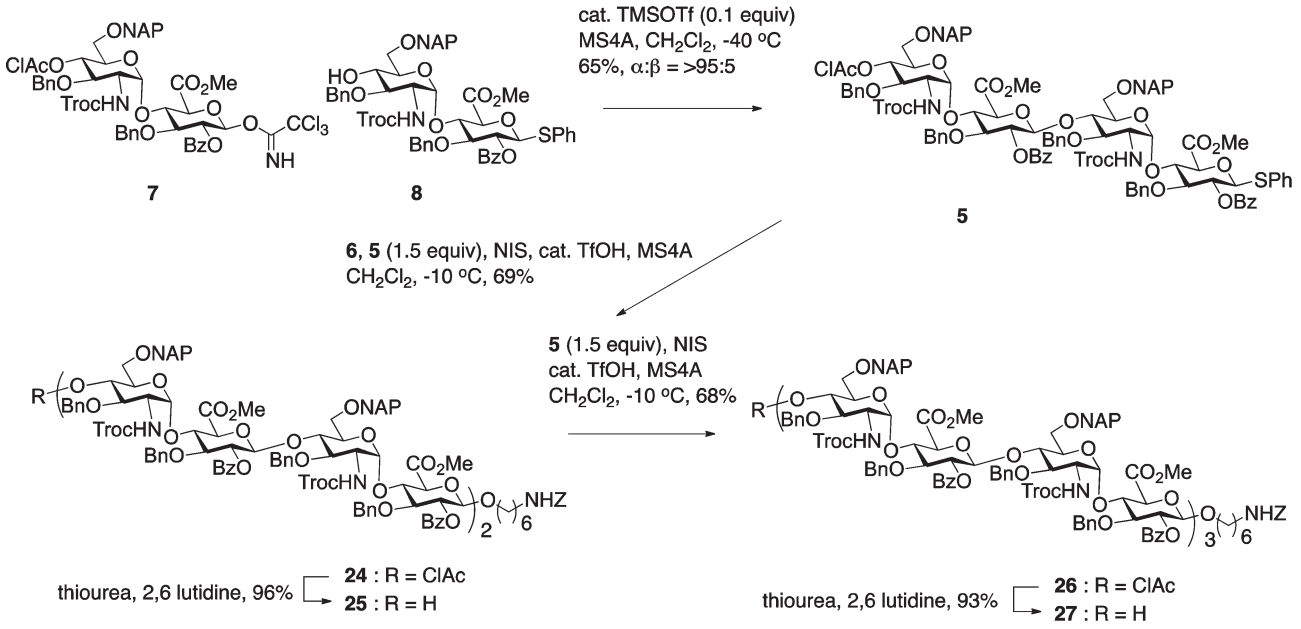
Scheme 2 Preparation of the disaccharide building blocks **9** and **10**.



Scheme 3 Synthesis of the octasaccharide **25** from *N*-Troc protected disaccharide.

1,3-propane dithiol provided the amino alcohol **15** in 87% overall yield. Treatment of the amino alcohol **15** with *N*-TrocCl without base chemoselectively provided the *N*-Troc protected thioglycoside **8** in 90% yield. The remaining alcohol **8** was acylated with chloroacetyl unhydride to afford the thioglycoside **16** in 94% yield. Hydrolysis of the thioglycoside **16** with NBS (74%), followed by treatment of the hemiacetal **17** with trichloroacetonitrile under basic conditions provided the glycosyl imidate **7**. The glycosyl imidate **7** was used for the glycosidation after brief purification.

We next examined the effect of the 2-azide and 2-(2,2,2-trichloroethyloxy)carbonylamino groups of a glucosamine unit on the coupling of disaccharides (Scheme 3). Both of the substituents are known to improve the reactivity of the C4 hydroxyl group towards glycosylation.[12,13] Glycosylation of the *N*-Troc disaccharide **18** with 1.5 equivalents of the *N*-Troc thioglycoside **16** provided the tetrasaccharide **20** in 63% yield with complete β selectivity, along with the recovery of the acceptor **18** (30%). On the other hand, when attempts were made to couple the azide derivatives **14** and **19**, the tetrasaccharide **21** was produced in a reduced yield (25%) with a significant amount of the acceptor **19** being recovered (59%). The electron withdrawing azide substituent that directs the α-selective glycosylation of the glucosamine unit would reduce the reactivity of the C4 hydroxyl group towards glycosylation to a considerable extent in comparison with the (2,2,2-trichloroethyloxy)carbonylamino substituent. The synthesis of the hexa- and octa-saccharides **22** and **24** from the *N*-Troc protected tetrasaccharide **20** was examined. Selective hydrolysis of the chloroacetyl ester of **20** was achieved by treatment with thiourea to provide the tetrasaccharide acceptor **6** in 96% yield. Glycosylation of the tetrasaccharide **6** with the disaccharide donor **16** proceeded smoothly under the same glycosylation conditions to provide the hexasaccharide **22** in 68% yield. The desired hexasaccharide **22** was separated from the tetrasaccharide acceptor **6** by preparative HPLC using a gel



Scheme 4 Synthesis of the protected dodecasaccharide **28** by glycosidation of the tetrasaccharide donor **5**.

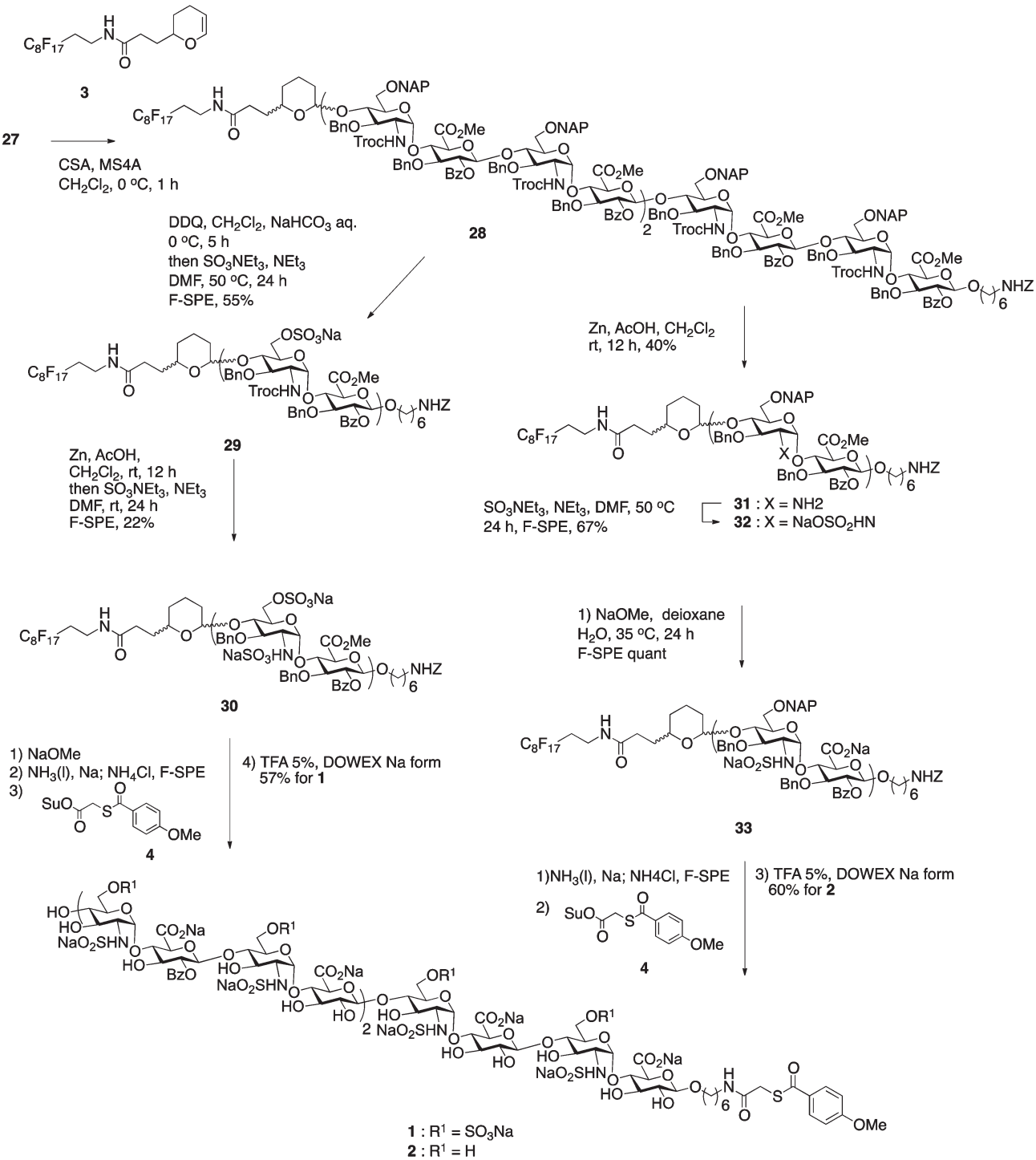
permeable chromatography column. Hydrolysis of the chloroacetyl ester of **22** by treatment with thiourea provided the hexasaccharide acceptor **23** in 93% yield. Glycosylation of the hexasaccharide acceptor **23** with the disaccharide donor **16** provided the octasaccharide **24** in 58% yield. These results indicate that the *N*-Troc protected glucosamines **18**, **6** and **23** should be effective glycosyl acceptors for the synthesis of HS/H derivatives. Although the conversion of the amino substituent needs additionally two steps, the improved coupling efficiency would be effective for the synthesis of large oligosaccharides. However, the purification of the octasaccharide **24** from the remaining hexasaccharide acceptor **23** was laborious, due to the small difference in both their molecular weights and their R_f values on the TLC plate.

Synthesis of the protected dodecasaccharide **27** from the tetrasaccharide donor **5** was also examined (Scheme 4). The tetrasaccharide **5** was prepared by chemoselective glycosylation of thioglycoside **8** with glycoyl imidate **7**. Treatment of the tetrasaccharide acceptor **6** with 1.5 equivalents of the tetrasaccharide donor **5** in the presence of NIS and a catalytic amount of TfOH at −20 °C for 2 h provided octasaccharide **24** in 69% yield. Treatment of the octasaccharide **24** with thiourea under basic conditions provided the octasaccharide glycosyl acceptor **25** in 96% yield. Treatment of the octasaccharide acceptor **25** and 1.5 equivalents of the tetrasaccharide donor **5** with NIS and a catalytic amount of TfOH at −20 °C for 2 h provided the dodecasaccharide **26** in 68% yield. Removal of the chloroacetyl group of **26** afforded the tetrasaccharide acceptor **27** in 96% yield in which the hydroxyl group would be used as a functional group for attaching with the fluorous tag.

Fluorous-assisted modification of the protected oligosaccharides to multiple sulfated GlcNα(1,4)GlcAβ(1,4) oligosaccharides **1** and **2** was examined (Scheme 5). Coupling of the fluorous tag **3** with an attached DHP moiety and the dodecasaccharide **27** *via* acetalization provided the fluorous tag-attached dodecasaccharide **28** in 91% yield. Removal of the NAP esters of **28** by treatment with DDQ under mildly basic conditions to provide hexaol, followed by *O*-sulfation of the resulting hydroxyl groups with a large excess of $SO_3{\cdot}NEt_3$ in the presence of NEt_3 at 50 °C for 24 h provided the 6-*O*-sulfated oligosaccharide **29** in 55% yield in 2 steps. Removal of the Troc groups was achieved by treatment with Zn in acetic acid to provide the hexaamine, followed by *N*-sulfation with a large excess amount of $SO_3{\cdot}NEt_3$, which provided the *N*- and *O*-sulfated dodecasaccharide **30** in 22% yield. De-monochlorination of the 2,2,2-trichloroethyl carbamate to the 2,2-dichloroethyl carbamate reduced the yield of **30**. Work-up and purification for the *O*- and *N*-sulfated compounds that were prepared using a large excess of sulfating reagents was simply achieved by a fluorous solid-phase extraction (F-SPE). Removal of the remaining protecting group of **30** under Birch reduction conditions after hydrolysis of the methyl esters, acylation of the resulting primary amine with the activated ester **4**, followed by cleavage of the fluorous tag under acidic conditions provided the *N*- and 6-*O*-sulfated dodecasaccharide **1** in 60% yield. Omitting the 6-*O*-sulfation provided the *N*-sulfated dodecasaccharide **2** in 11% overall yield based on **28**.

Conclusions

In conclusion, an efficient synthesis of the *N*- and 6-*O*-sulfated heparosan dodecasaccharide **18** composed of a GlcNα(1,4)-GlcAβ(1,4) sequence based on the coupling of GlcNTrocα(1,4)-GlcA disaccharides is described. *N*-Troc protection of glycosamine was effective for improving reactivity towards



Scheme 5 Fluorous-assisted synthesis of the sulfated oligosaccharides **1** and **2** from the protected disaccharide **31**.

glycosylation at the C4 hydroxyl group in comparison with that of the 2-azide derivative of glucosamine. These building blocks would be effective for the synthesis of not only the sulfated heparosan oligosaccharides, but also the HS/S related oligosaccharide containing both GlcA and IdoA. In addition, this method provided various heparosan oligosaccharide derivatives as effective substrates for enzymatic modification to produce various HS/S derivatives.

Experimental

Phenylthio 2-azido-3-*O*-benzyl-2-deoxy-4,6-*O*-naphthylidene-α-D-glucopyranoside (12)

To a solution of **11** (1.22 g, 2.90 mmol) in MeOH (10 mL) was added 1 M NaOMe in MeOH (3 mL). The reaction mixture was left to stand at room temperature for 5 h, and neutralized with acetic acid. After removal of the solvent *in vacuo*, the residue

was used for the next reaction without further purification. To a stirred solution of the residue in dry DMF (5.80 mL) was added 2-naphthaldehyde (6.79 g, 4.35 mmol), $HC(OMe)_3$ (6.09 mL, 5.80 mmol) and CSA (2.02 g, 8.70 mmol) at room temperature. After being stirred at 70 °C for 36 h, the reaction mixture was neutralized with NEt_3 and poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with a saturated aq. $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was used for the next reaction without further purification. To a stirred solution of the residue in dry THF (29.0 mL) was added NaH (139 mg, 3.19 mmol) and benzyl bromide (508 mg, 3.04 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was neutralized with MeOH and poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane : ethyl acetate = 70 : 30) to give **12** (1.13 g, 2.15 mmol, 3 steps 74%): $[\alpha]_D^{30}$ +108 (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.98 (m, 17H, aromatic), 5.71 (s, 1H), 5.55 (d, 1H, J = 5.3 Hz), 4.98 (d, 1H, J = 11.1 Hz), 4.83 (d, 1H, J = 11.1 Hz), 4.46 (ddd, 1H, J = 9.7 Hz, J = 4.8, 5.3 Hz), 4.25 (dd, 1H, J = 5.3, 10.1 Hz), 3.75–4.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 134.5, 133.7, 133.0, 132.9, 132.5, 129.2, 128.5, 128.4, 128.2, 128.0, 127.8, 126.6, 126.3, 125.6, 123.7 (101.7 anomeric), 87.9, 82.8, 77.9, 77.3, 75.2, 68.7, 63.9, 63.6; IR (KBr) 2903, 2109, 1478, 1363, 1093, 1022, 741, 698 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{30}H_{28}N_3O_4S$ $[M + H]^+$ 526.1805, found 526.1801.

Phenylthio 2-azido-3-*O*-benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-α-D-glucopyranoside (13)

To a stirred solution of **12** (3.13 g, 5.95 mmol) and pulverized activated MS-4A (5.95 g) in dry THF (29.8 mL) was added $BH_3{\cdot}NMe_3$ (2.60 g, 35.7 mmol) and $AlCl_3$ (4.76 g, 35.7 mmol) at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was poured into an ice-cooled solution of 1 M H_2SO_4 and ethyl acetate for 20 min at 0 °C. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was used for the next reaction without further purification. To a stirred solution of the residue in dry CH_2Cl_2 (59.5 mL) was added dry pyridine (0.959 mL, 59.5 mmol) and chloroacetyl chloride (1.14 mL, 14.3 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane : ethyl acetate = 90 : 10) to **13** (2.80 g, 4.64 mmol, 2 steps 78%): $[\alpha]_D^{29}$ +119 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.83 (m, 17H, aromatic), 5.61 (d, 1H, J = 5.3 Hz), 5.21 (dd, 1H, J = 9.2, 10.1 Hz), 4.90 (d, 1H, J = 11.1 Hz), 4.66 (d, 1H, J = 11.6 Hz), 4.63 (d, 1H, J = 11.1 Hz), 4.56 (d, 1H, J = 11.6 Hz), 4.49 (ddd, 1H, J = 1.9, 4.3, 10.1 Hz), 4.01 (dd, 1H, J = 5.3, 9.7 Hz), 3.80 (dd, 1H, $J_{2,3}$ = 9.2, 9.7 Hz), 3.61 (d, 1H, J = 15.0 Hz), 3.52–3.56 (m, 2H), 3.51 (d, 1H, J = 15.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 137.5, 135.0, 133.2, 133.1, 132.9, 132.3, 129.2, 128.7, 128.2 × 2, 128.0 × 2, 127.8, 126.8, 126.2, 126.0 × 2 (87.0 anomeric), 79.3, 77.3, 75.4, 73.8, 72.5, 69.8, 68.7, 64.0, 40.5; IR (KBr) 3459, 3060, 2109, 1770, 1743, 1365, 1253, 1167, 741, 699 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{32}H_{34}N_4O_5SCl$ $[M + NH_4]^+$ 621.1941, found 621.1938.

2-Azido-3-*O*-benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-D-glucopyranose (10)

To a stirred solution of **13** (560 mg, 0.929 mmol) in acetone (4.65 mL) and H_2O (0.465 mL) was added NBS (500 mg, 2.71 mmol) at 0 °C. After being stirred at the same temperature for 6 h, the reaction mixture was poured into a mixture of saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane : ethyl acetate = 80 : 20) to give **10** (361 mg, 0.706 mmol, 76%) as an anomeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$) α anomer (major); δ 7.25–7.83 (m, 12H, aromatic), 5.33 (d, 1H, J = 3.3 Hz), 5.07 (dd, 1H, J = 9.2, 9.6 Hz), 4.50–4.86 (m, 4H), 4.14 (m, 1H), 3.98 (dd, 1H, J = 9.2, 9.7 Hz), 3.75 (dd, 1H, J = 3.3, 9.7 Hz), 3.38–3.59 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.2, 137.7, 134.8, 134.7, 133.3, 133.2 × 2, 128.6 × 2, 128.4, 128.1 × 3, 128.0, 127.8, 127.1 × 2, 126.3 × 2, 126.2 × 2, 126.1, 126.0 (96.3, 91.9 anomeric), 80.2, 75.1, 73.9, 72.9, 72.7, 72.2, 69.1, 69.0, 68.7, 67.1, 63.7, 40.4 × 2; IR (KBr) 3428, 2879, 2109, 1760, 1319, 1142, 1059, 754, 700 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{26}H_{30}N_4O_6Cl$ $[M + NH_4]^+$ 529.1855, found 529.1854.

Phenylthio 2-azido-3-*O*-benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate (14)

A mixture of **10** (300 mg, 0.586 mmol), Ph_2SO (331 mg, 1.64 mmol), TTBP (436 mg, 1.76 mmol) and pulverized activated MS-4A (586 mg) in dry CH_2Cl_2 (9.00 mL) was stirred at room temperature for 30 min under argon to remove trace amounts of water. Then the reaction mixture was cooled to −60 °C. Tf_2O (114 μL, 0.820 mmol, 1.40 equiv.) was added to the reaction mixture at the same temperature. After being stirred at −40 °C for 30 min, a solution of **9** (273 mg, 0.391 mmol) in dry CH_2Cl_2 (3.00 mL) was added at −60 °C and the reaction mixture was allowed to warm slowly to room temperature. After being stirred at the same temperature for 5 h, the reaction mixture was neutralized with NEt_3 and filtered through a pad of Celite®. The filtrate mixture was poured into brine. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and

evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with $CHCl_3$: MeOH = 98 : 2) and by gel permeation chromatography (GPC) to give **14** (417 mg, 0.422 mmol, 72%, β/α = 92/8). The β,α-isomers were separated by column chromatography on silica gel to give the α-isomer (elution with toluene : ethyl acetate = 99 : 1) and the β-isomer (elution with toluene : ethyl acetate = 98 : 2): $[\alpha]_D^{20}$ +45.1 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–8.08 (m, 27H, aromatic), 5.54 (d, 1H, *J* = 3.8 Hz), 5.34 (dd, 1H, *J* = 9.2, 9.7 Hz), 5.22 (dd, 1H, *J* = 9.7, 9.7 Hz), 4.88 (d, 1H, *J* = 9.7 Hz), 4.82 (d, 1H, *J* = 11.1 Hz), 4.76 (d, 1H, *J* = 10.6 Hz), 4.68 (d, 1H, *J* = 10.6 Hz), 4.67 (d, 1H, *J* = 12.1 Hz), 4.59 (d, 1H, *J* = 11.1 Hz), 4.55 (d, 1H, *J* = 12.1 Hz), 4.25 (dd, 1H, *J* = 8.7, 9.7 Hz), 4.11 (d, 1H, *J* = 9.7 Hz), 4.03 (dd, 1H, *J* = 8.7, 9.2 Hz), 3.87 (dd, 1H, *J* = 9.7, 10.1 Hz), 3.72 (s, 3H), 3.60 (ddd, 1H, *J* = 3.4, 4.8, 9.7 Hz), 3.56 (m, 1H), 3.55 (d, 1H, *J* = 14.5 Hz), 3.48 (d, 1H, *J* = 14.5 Hz), 3.46 (dd, 1H, *J* = 3.4, 9.7 Hz), 3.36 (dd, 1H, *J* = 3.8, 10.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.9, 165.0, 137.6, 137.1, 135.0, 133.6, 133.3, 133.1, 132.9, 132.2, 129.9, 129.6, 129.1, 129.0, 128.7, 128.6, 128.5, 128.3 × 3, 128.1 × 2, 128.0, 127.9 × 2, 127.7, 127.0, 126.2, 126.1 × 2 (97.5, 87.0 anomeric), 83.9, 78.1, 77.4, 77.3, 74.9, 74.8, 74.7, 74.0, 72.7, 72.2, 69.0, 68.6, 62.9, 52.8, 40.5; IR (KBr) 3028, 2108, 1735, 1453, 1263, 1068, 772, 710 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{53}H_{54}N_4O_{12}ClS$ $[M + NH_4]^+$ 1005.3147, found 1005.3159.

Phenylthio 2-amino-3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate) (15)

To a stirred solution of **14** (6.37 g, 6.44 mmol, 1.00 equiv.) in DMF (65.0 mL) was added thiourea (4.91 g, 64.4 mmol) and 2,6-lutidine (1.15 mL, 7.73 mmol) at room temperature. After being stirred at 50 °C for 12 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aq. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the residue in MeOH (64.0 mL) and THF (5.0 mL) was added 1,3-propanedithiol (3.2 mL) and NEt_3 (1.6 mL) at room temperature. After being stirred at the same temperature for 24 h, to the reaction mixture was added 1,3-propanedithiol (3.2 mL) and NEt_3 (1.6 mL) at the same temperature. After being stirred at the same temperature for another 24 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with toluene : ethyl acetate : NEt_3 = 75.5 : 20 : 0.5) to give **15** (4.96 g, 5.60 mmol, 87%): $[\alpha]_D^{20}$ +57.8 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–8.06 (m, 27H, aromatic), 5.32 (dd, 1H, *J* = 8.7, 9.7 Hz), 5.27 (d, 1H, *J* = 3.4 Hz), 4.92 (d, 1H, *J* = 11.6 Hz), 4.86 (d, 1H, *J* = 9.7 Hz), 4.71–4.78 (m, 3H), 4.69 (d, 1H, *J* = 12.1 Hz), 4.59 (d, 1H, *J* = 10.6 Hz), 4.24 (dd, 1H, *J* = 9.2, 9.2 Hz), 4.05 (d, 1H, *J* = 9.2 Hz), 3.91 (dd, 1H, *J* = 8.7, 9.2 Hz), 3.79 (dd, 1H, *J* = 3.4, 9.7 Hz), 3.71 (s, 3H), 3.68–3.71 (m, 1H), 3.62 (dd, 1H, *J* = 5.8, 9.7 Hz), 3.53–3.58 (m, 1H), 3.32 (dd, 1H, *J* = 8.7, 10.1 Hz), 2.70 (dd, 1H, *J* = 3.4, 10.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 165.0, 138.9, 137.2, 135.1, 133.5, 133.3, 133.1, 132.8, 132.4, 129.9, 129.7, 129.0, 128.6, 128.4 × 2, 128.2, 128.1, 128.0, 127.9, 127.8, 126.8, 126.3, 126.1 (100.2, 86.9 anomeric), 83.4, 83.0, 78.8, 77.3, 75.2, 75.1, 74.5, 74.0, 73.5, 72.1, 70.6, 55.1, 52.8; IR (KBr) 3502, 2868, 1747, 1718, 1452, 1268, 1218, 772 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{51}H_{52}NO_{11}S$ $[M + H]^+$ 886.3274, found 886.3261.

Phenylthio 3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate) (8)

To a stirred solution of **15** (3.88 g, 4.38 mmol) in THF (60.0 mL) and H_2O (20.0 mL) was added $NaHCO_3$ (3.60 g, 43.8 mmol) and TrocCl (708 μL, 5.26 mmol) at 0 °C. After being stirred at the same temperature for 10 min, the reaction mixture was poured into brine. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was precipitated from ethyl acetate–hexane to **8** (4.20 g, 3.96 mmol, 90%): $[\alpha]_D^{20}$ +41.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.07–8.06 (m, 27H, aromatic), 5.41 (d, 1H, *J* = 10.2 Hz), 5.30–5.35 (m, 2H), 4.90 (d, 1H, *J* = 9.7 Hz), 4.78 (d, 1H, *J* = 12.5 Hz), 4.77 (d, 1H, *J* = 11.1 Hz), 4.71–4.74 (m, 2H), 4.68 (d, 1H, *J* = 11.6 Hz), 4.62 (s, 2H), 4.56 (d, 1H, *J* = 12.1 Hz), 4.21 (dd, 1H, *J* = 9.2, 9.2 Hz), 4.06 (d, 1H, *J* = 9.2 Hz), 3.98 (dd, 1H, *J* = 8.7, 9.2 Hz), 3.93 (ddd, 1H, *J* = 3.9, 10.2, 10.2 Hz), 3.80–3.86 (m, 2H), 3.76 (s, 3H), 3.69 (dd, 1H, *J* = 4.8, 10.1 Hz), 3.56–3.60 (m, 1H), 3.48 (dd, 1H, *J* = 9.2, 10.2 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.3, 165.2, 154.5, 138.9, 137.1, 135.8, 133.9, 133.6, 133.4, 132.8, 132.7, 130.1, 129.8, 129.4, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0 × 2, 126.9, 126.6, 126.4, 126.1 (98.8, 95.9 anomeric), 87.5, 83.5, 79.8, 78.6, 77.9, 75.2, 75.0, 74.9, 74.7, 74.2, 72.8, 72.4, 71.2, 70.5, 54.8, 53.2; IR (KBr) 3370, 2953, 1736, 1511, 1264, 1069, 768, 711 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{54}H_{53}NO_{13}SCl_3$ $[M + H]^+$ 1060.2296, found 1060.2303.

Phenylthio 3-*O*-benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate) (16)

To a stirred solution of **16** (5.42 g, 5.11 mmol) in dry CH_2Cl_2 (51.0 mL) was added dry pyridine (2.07 mL, 25.6 mmol) and chloroacetic anhydride (1.05 g, 6.13 mmol) at 0 °C. After being stirred at the same temperature for 2 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was precipitated from ethyl acetate–hexane to **16** (5.45 g, 4.79 mmol, 94%): $[\alpha]_D^{20}$ +41.4 (*c* 1.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.07–8.01 (m, 27H, aromatic), 5.35 (s, 1H), 5.28–5.33 (m, 2H), 5.24 (dd, 1H, *J* = 9.7, 9.7 Hz), 4.85 (d, 1H, *J* = 9.7 Hz), 4.66 (d, 1H, *J* = 12.1 Hz), 4.55–4.63 (m, 6H), 4.51 (d, 1H, *J* = 11.6 Hz), 4.23 (dd, 1H, *J* = 9.2, 9.2 Hz),

3.94–4.05 (m, 3H), 3.73 (s, 3H), 3.66–3.70 (m, 4H), 3.63 (dd, 1H, J = 3.9, 14.5 Hz), 3.56 (dd, 1H, J = 4.8, 14.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 165.8, 164.9, 154.0, 137.8, 136.4, 135.1, 133.6, 133.3, 133.1, 133.0, 132.1, 129.9, 129.5, 129.1, 128.6 × 2, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8 × 2, 127.0, 126.2, 126.1 × 2 (98.4, 95.4 anomeric), 87.2, 82.8, 78.5, 77.4, 77.3, 75.5, 74.7, 74.4, 74.0, 73.4, 72.6, 72.2, 69.6, 69.0, 54.5, 52.9, 40.6; IR (KBr) 3029, 2925, 1736, 1510, 1262, 1069, 752, 710 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{56}H_{54}NO_{14}SCl_4$ $[M + H]^+$ 1136.2003, found 1136.2019.

3-*O*-Benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl)-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-D-glucopyranosyluronate) (17)

To a stirred solution of **16** (308 mg, 0.270 mmol) in acetone (3.00 mL) and H_2O (0.300 mL) was added NBS (72.5 mg, 0.405 mmol) at 0 °C. After being stirred at the same temperature for 1 h, to the reaction mixture was added NBS (72.5 mg, 0.405 mmol) at 0 °C. After being stirred at the same temperature for another 1 h, the reaction mixture was poured into a mixture of saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with hexane : ethyl acetate = 87 : 13) to give **17** (210 mg, 0.706 mmol, 74%, α/β = >95/5) as an anomeric mixture; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.12–8.06 (m, 22H, aromatic), 5.61 (dd, 1H, J = 3.9, 3.9 Hz), 5.41 (d, 1H, J = 10.1 Hz), 5.40 (d, 1H, J = 3.9 Hz), 5.25 (dd, 1H, J = 9.7, 9.7 Hz), 5.17 (dd, 1H, J = 3.9, 9.2 Hz), 4.82 (d, 1H, J = 11.1 Hz), 4.75 (d, 1H, J = 12.1 Hz), 4.74 (d, 1H, J = 11.6 Hz), 4.58–4.70 (m, 4H), 4.53 (d, 1H, J = 11.1 Hz), 4.47 (d, 1H, J = 11.6 Hz), 3.37 (dd, 1H, J = 8.2, 9.2 Hz), 4.22 (dd, 1H, J = 8.2, 8.7 Hz), 4.06 (ddd, 1H, H-2′, J = 3.9, 10.1, 10.6 Hz), 3.71–3.82 (m, 3H), 3.68 (s, 3H), 3.55–3.67 (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 169.7, 166.3, 165.9, 154.4, 138.3, 137.6, 135.7, 133.9, 133.6, 133.4, 130.1, 129.7, 129.3, 129.0, 128.8, 128.7, 128.5, 128.4, 128.2 × 3, 128.1 × 2, 128.0, 127.9, 126.5, 126.3 (98.9, 95.8 anomeric), 90.8, 78.4, 78.1, 77.9, 75.9, 74.9, 74.5, 74.1, 73.7, 72.9, 71.3, 69.8, 69.3, 53.0, 41.1; IR (KBr) 3359, 2926, 1736, 1523, 1271, 1063, 754, 713 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{50}H_{50}NO_{15}Cl_4$ $[M + H]^+$ 1044.1956, found 1044.1935.

N-Benzyloxycarbonyl-6-aminohexyl 3-*O*-benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate) (20)

A mixture of **16** (59.2 mg, 52.0 μmol, 1.50 equiv.), **18** (41.7 mg, 34.7 μmol) and pulverized activated MS-4A (140 mg) in dry CH_2Cl_2 (1.00 mL) was stirred at room temperature for 30 min under argon to remove trace amounts of water. Then the reaction mixture was cooled to −40 °C. NIS (11.7 mg, 52.0 μmol) and TfOH (0.93 μL, 10.4 μmol) were added to the reaction mixture at the same temperature. After being stirred at −20 °C for 3 h, the reaction mixture was neutralized with NEt_3 and filtered through a pad of Celite®. The filtrate mixture was poured into a mixture of saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (elution with $CHCl_3$: MeOH = 98 : 2) to give **20** (48.6 mg, 21.8 μmol, 63%, α/β = >95/5): $[\alpha]_D^{28}$ +41.2 (c 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.93–8.05 (m, 49H, aromatic), 5.41 (d, 1H, J = 3.9 Hz), 5.37–5.41 (m, 1H), 5.16–5.32 (m, 5H), 5.07 (s, 2H, A), 5.02 (d, 1H, J = 12.6 Hz), 5.01 (d, 1H, J = 11.6 Hz), 4.75 (d, 1H, J = 12.1 Hz), 4.68 (d, 1H, J = 11.6 Hz), 4.51–4.64 (m, 12H), 4.35 (d, 1H, J = 10.6 Hz), 4.21 (d, 1H, J = 11.1 Hz), 4.02–4.13 (m, 4H), 3.85–3.91 (m, 3H), 3.67–3.83 (m, 6H), 3.64 (s, 3H), 3.56–3.61 (m, 3H), 3.51 (d, 1H, J = 10.6 Hz), 3.34–3.42 (m, 2H), 3.25 (s, 3H), 3.20–3.23 (m, 2H), 2.98 (t, 2H, J_2 = 6.3 Hz), 1.06–1.47 (m, 8H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.8, 168.4, 166.2, 165.2, 164.8, 156.5, 154.4 × 2, 139.1, 138.3, 137.5, 137.2, 137.0, 136.4, 135.7, 134.1, 133.8, 133.7, 133.6, 133.5, 133.4, 130.0, 129.9 × 2, 129.3, 129.1, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.0 × 2, 127.7, 127.5, 127.0, 126.8, 126.5, 126.3 × 2 (101.5, 100.4, 98.4, 98.0 anomeric), 95.8, 82.6, 82.5, 77.9, 77.8, 77.8, 76.9, 75.3 × 2, 75.2, 75.0, 74.9, 74.8, 74.7 × 2, 74.5, 74.4, 74.1, 74.0, 73.9, 73.8, 72.9, 71.5, 70.4, 69.9, 69.3, 67.3, 66.6, 55.0, 54.9, 53.0, 52.5, 41.1, 30.0, 29.5, 26.5, 25.8; IR (KBr) 3029, 2951, 1736, 1512, 1264, 1070, 1041, 821, 755 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{112}H_{115}N_3O_{30}Cl_7$ $[M + H]^+$ 2226.5385, found 2226.5374.

N-Benzyloxycarbonyl-6-aminohexyl 3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate) (6)

To a stirred solution of **20** (2.54 g, 1.14 mmol) in DMF (22.8 mL) was added thiourea (260 mg, 3.42 mmol) and 2,6-lutidine (158 μL, 1.37 mmol) at room temperature. After being stirred at 50 °C for 12 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aq. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo.* The residue was purified by MPLC (elution with toluene : ethyl acetate = 88 : 12 to 78 : 22) to give **6** (2.36 g, 1.09 mmol, 96%): $[\alpha]_D^{26}$ +42.2 (c 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.90–8.04 (m, 49H, aromatic), 5.41 (d, 1H, J = 3.9 Hz), 5.32–5.35 (m, 1H), 5.24 (d, 1H, J = 2.9 Hz), 5.16–5.24 (m, 3H), 5.07 (s, 2H), 5.02 (d, 1H, J = 12.6 Hz), 5.00 (d, 1H, J = 11.1 Hz), 4.82 (d, 1H, J = 11.6 Hz), 4.78 (d,

1H, *J* = 12.1 Hz), 4.70–4.74 (m, 3H), 4.62 (d, 1H, *J* = 12.1 Hz), 4.50–4.57 (m, 8H), 4.34 (d, 1H, *J* = 10.6 Hz), 4.16 (d, 1H, *J* = 11.1 Hz), 4.04–4.13 (m, 3H), 3.82–3.95 (m, 6H), 3.66–3.79 (m, 4H), 3.63 (s, 3H), 3.54–3.59 (m, 1H), 3.45–3.50 (m, 2H), 3.34–3.41 (m, 2H), 3.24 (s, 3H), 3.14–3.21 (m, 2H), 3.05 (d, 1H, *J* = 1.9 Hz), 2.98 (t, 2H, *J* = 6.7 Hz), 1.05–1.48 (m, 8H, aliphatic); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.8, 168.4, 165.2, 164.7, 162.7, 156.5, 154.5, 139.1, 139.0, 137.5, 137.2, 137.1, 136.3, 135.8, 134.0, 133.8, 133.7, 133.6, 133.5, 133.4, 130.0, 129.9 × 2, 129.3, 129.0, 128.9 × 2, 128.8, 128.7 × 2, 128.6 × 2, 128.5, 128.3 × 2, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 127.0, 126.8, 126.5, 126.3, 126.1 (101.5, 100.4, 98.7, 98.0 anomeric), 95.9, 95.8, 82.6 × 2, 79.8, 77.9, 77.7, 76.8, 75.2, 74.9, 74.8, 74.7 × 2, 74.5, 74.4, 74.2, 74.0, 73.9, 73.8, 72.9, 71.5, 71.2, 70.5, 70.4, 67.2, 66.6, 54.8 × 2, 53.0, 52.5, 41.2, 36.5, 31.4, 30.0, 29.5, 26.5, 25.8; IR (KBr) 3431, 3018, 2946, 1736, 1509, 1265, 1091, 768, 711 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{110}H_{117}N_4O_{29}Cl_6$ [M + NH_4]$^+$ 2167.5935, found 2167.5945.

Phenylthio 3-*O*-benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate) (5)

To a stirred solution of **17** (1.33 g, 1.20 mmol) in dry CH_2Cl_2 (3.5 mL) was added Cs_2CO_3 (390 mg, 1.20 mmol) and CCl_3CN (1.70 g, 12.0 mmol, 10.0 equiv.) at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was filtered through a pad of Celite®. The residue was briefly purified by column chromatography on a small amount of silica gel (elution with $CHCl_3$: MeOH = 98 : 2) and used for the next reaction without further purification. A mixture of the residue, **8** (850 mg, 801 μmol) and pulverized activated MS-4A (3.2 g) in dry CH_2Cl_2 (16.0 mL) was stirred at room temperature for 30 min under argon to remove trace amounts of water. Then the reaction mixture was cooled to −40 °C. TMSOTf (14.5 μL, 80.1 μmol) was added to the reaction mixture at the same temperature. After being stirred at −20 °C for 1 h, the reaction mixture was neutralized with NEt_3 and filtered through a pad of Celite®. The filtrate mixture was poured into a mixture of saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : ethyl acetate = 90 : 10 to 80 : 20) and by gel permeation chromatography (GPC) to give **5** (1.08 g, 519 μmol, 65% based on **8**, α/β = >95/5): $[\alpha]_D^{29}$ +30.0 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.95–8.07 (m, 49H, aromatic), 5.42 (d, 1H, *J* = 3.4 Hz), 5.41 (d, 1H, *J* = 7.2 Hz), 5.29–5.33 (m, 2H), 5.23–5.29 (m, 2H), 5.17 (d, 1H, *J* = 10.1 Hz), 5.05 (d, 1H, *J* = 12.1 Hz), 5.03 (d, 1H, *J* = 11.6 Hz), 4.83 (d, 1H, *J* = 10.1 Hz), 4.78 (d, 1H, *J* = 12.1 Hz), 4.70 (d, 1H, *J* = 12.1 Hz), 4.53–4.65 (m, 11H), 4.36 (d, 1H, *J* = 11.1 Hz), 4.22 (d, 1H, *J* = 10.6 Hz), 4.05–4.14 (m, 4H), 3.86–3.93 (m, 3H), 3.75–3.81 (m, 4H), 3.68–3.73 (m, 2H), 3.66 (s, 3H), 3.57–3.64 (m, 2H), 3.53 (d, 1H, *J* = 10.1 Hz), 3.40 (dd, 1H, *J* = 9.2, 10.6 Hz), 3.28 (s, 3H), 3.20–3.25 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.4, 168.3, 166.2, 165.2, 164.7, 154.4 × 2, 139.0, 138.2, 136.9, 136.3, 135.7, 134.1, 133.9, 133.8, 133.6, 133.5, 133.4, 132.7, 132.6, 130.1, 129.9, 129.7, 129.3 × 2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5 × 3, 128.4, 128.3, 128.2 × 2, 128.1, 128.0 × 2, 127.8, 127.7, 127.5, 127.1, 127.0 × 2, 126.9, 126.8, 126.5, 126.3 × 2, 126.2 (100.3, 98.3, 98.0, 95.7 anomeric), 87.4, 84.0, 82.5, 78.1, 77.9, 77.8, 77.6, 76.8, 75.3, 75.2 × 2, 74.9 × 2, 74.6, 74.4, 74.1, 74.0, 73.7, 72.9, 72.3, 71.5, 69.8, 69.2, 67.2, 55.0, 54.8, 53.0, 52.6, 41.1; IR (KBr) 2920, 2850, 1736, 1509, 1262, 1069, 753, 711 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{104}H_{100}N_2O_{27}SCl_7$ [M + H]$^+$ 2085.4054, found 2085.4004.

***N*-Benzyloxycarbonyl-6-aminohexyl 3-*O*-benzyl-4-*O*-chloroacetyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-*O*-benzyl-2-deoxy-6-*O*-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate) (25)**

A mixture of **5** (937 mg, 449 μmol), **6** (600 mg, 299 μmol) and pulverized activated MS-4A (1.2 g) in dry CH_2Cl_2 (6.0 mL) was stirred at room temperature for 30 min under argon to remove trace amounts of water. Then the reaction mixture was cooled to −40 °C. NIS (166 mg, 738 μmol) and TfOH (8.21 μL, 92.2 μmol) were added to the reaction mixture at the same temperature. After being stirred at −20 °C for 2 h, the reaction mixture was neutralized with NEt_3 and filtered through a pad of Celite®. The filtrate mixture was poured into a mixture of saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : ethyl acetate = 90 : 10 to 80 : 20) and by gel permeation chromatography (GPC) to give **25** (890 mg, 206 μmol, 69%, α/β = >95/5): $[\alpha]_D^{28}$ +52.3 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.79–8.13 (m, 93H, aromatic), 5.39 (d, 1H, *J* = 12.6 Hz), 5.37 (d, 1H, *J* = 3.9 Hz), 5.27–5.32 (m, 4H), 5.23 (d, 1H, *J* = 3.4 Hz), 5.00–5.19 (m, 11H), 4.95 (d, 1H, *J* = 11.6 Hz), 4.88 (d, 1H, *J* = 11.6 Hz), 4.76 (d, 1H, *J* = 12.1 Hz), 4.68 (d, 1H, *J* = 12.1 Hz), 4.46–4.66 (m, 20H), 4.44 (d, 1H, *J* = 11.6 Hz), 4.32–4.37 (m, 2H), 4.29 (d, 1H, *J* = 7.7 Hz), 4.19–4.25 (m, 3H), 4.06–4.14 (m, 4H), 3.74–4.02 (m, 14H), 3.72–3.56 (m, 9H), 3.43–3.52 (m, 5H), 3.29–3.40 (m, 4H), 3.11–3.26 (m, 13H), 2.92–3.00 (m, 3H), 2.89 (dd, 1H, H-3c, *J* = 9.2, 9.7 Hz),

1.07–1.49 (m, 8H, aliphatic); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.8, 168.4, 168.3 × 2, 166.2, 165.2, 164.7 × 2, 156.5, 154.5 × 2, 154.4, 139.1, 139.0 × 2, 138.3, 137.5, 137.2, 137.0, 136.4, 136.2, 135.7, 134.2, 134.1 × 2, 133.8, 133.7 × 2, 133.6, 133.5 × 2, 133.4, 130.0, 129.9 × 2, 129.8, 129.3, 129.2, 129.1, 129.0, 128.9 × 2, 128.8, 128.7, 128.6, 128.5, 128.4 × 2, 128.3, 128.2, 128.1 × 2, 128.0 × 2, 127.9, 127.8 × 2, 127.7 × 2, 127.5, 127.1 × 2, 127.0, 126.9, 126.8, 126.5, 126.3 × 2 (101.5, 100.4, 100.2, 98.3, 98.2, 98.0, 95.8, 95.7 anomeric), 82.8 × 2, 82.6, 77.7, 77.5, 77.4, 76.9, 76.7, 76.6, 75.6, 75.3, 75.2, 75.0, 74.9, 74.8, 74.7, 74.5, 74.4, 74.3, 74.1, 74.0, 73.9 × 3, 73.7, 72.9, 71.5, 71.4, 70.4, 69.9, 69.2, 67.2, 67.0, 66.6, 55.0, 54.8, 53.1, 52.5, 52.4 × 2, 41.2, 30.0, 29.5, 26.6, 25.8; IR (KBr) 3019, 2929, 1736, 1509, 1264, 1219, 1042, 769, 711 (cm^{-1}).

_N_-Benzyloxycarbonyl-6-aminohexyl 3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1→4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1→4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1→4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate) (26)

To a stirred solution of **25** (890 mg, 206 μmol) in DMF (4.0 mL) was added thiourea (47.0 mg, 618 μmol) and 2,6-lutidine (28.5 μL, 247 μmol) at room temperature. After being stirred at 50 °C for 12 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aq. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : ethyl acetate = 88 : 12 to 78 : 22) to give **26** (795 mg, 196 μmol, 96%): $[\alpha]_D^{29}$ +47.6 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.87–8.08 (m, 93H, aromatic), 5.44 (d, 1H, *J* = 2.9 Hz), 5.39 (d, 1H, *J* = 9.7 Hz), 5.19–5.32 (m, 6H), 5.00–5.16 (m, 10H), 4.95 (d, 1H, *J* = 11.6 Hz), 4.88 (d, 1H, *J* = 11.6 Hz), 4.49–4.84 (m, 22H), 4.39–4.41 (m, 2H), 4.35 (d, 1H, *J* = 7.7 Hz), 4.21–4.32 (m, 3H), 3.69–4.18 (m, 23H), 3.61–3.65 (m, 1H), 3.46–3.56 (m, 6H), 3.35–3.44 (m, 4H), 3.17–3.27 (m, 16H), 2.95–3.03 (m, 4H), 1.15–1.52 (m, 8H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.7, 168.4, 168.3 × 2, 166.2, 165.2, 164.7, 156.5, 154.5, 154.4, 139.1, 139.0, 138.9, 137.5, 137.2, 137.1, 137.0, 136.2 × 2, 135.8, 134.1, 133.7 × 2, 133.6, 133.5, 133.4, 130.0, 129.8, 129.3, 129.2, 129.0, 128.9, 128.8 × 2, 128.7 × 2, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.1 × 2, 126.9, 126.5, 126.3 (101.5, 100.4, 100.2, 98.7, 98.2, 98.0, 95.9, 95.8 anomeric), 82.8, 82.7 × 2, 82.6, 79.7, 77.6, 77.5, 77.4, 76.9, 76.6, 75.6, 75.2, 75.0, 74.9, 74.8, 74.7, 74.6, 74.5, 74.3, 74.1, 74.0, 73.9, 73.8 × 2, 72.9, 71.4, 71.3, 70.4, 70.3, 67.1, 66.9, 66.6, 60.6, 54.8, 54.3, 53.0, 52.5, 52.4, 41.1, 30.0, 29.9; IR (KBr) 3425, 3030, 2952, 1736, 1511, 1264, 1070, 755, 711 (cm^{-1}).

_N_-Benzyloxycarbonyl-6-aminohexyl 3-_O_-benzyl-4-_O_-chloroacetyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate) (27)

A mixture of **5** (102.1 mg, 48.9 μmol), **26** (132 mg, 32.6 μmol) and pulverized activated MS-4A (130 mg) in dry CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min under argon to remove trace amounts of water. Then the reaction mixture was cooled to −40 °C. NIS (12.5 mg, 55.4 μmol) and TfOH (0.87 μL, 9.78 μmol) were added to the reaction mixture at the same temperature. After being stirred at −20 °C for 2 h, the reaction mixture was neutralized with NEt_3 and filtered through a pad of Celite®. The filtrate mixture was poured into a mixture of saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : ethyl acetate = 90 : 10 to 80 : 20) and by gel permeation chromatography (GPC) to give **27** (134 mg, 17.7 μmol, 68%, α/β = >95/5): $[\alpha]_D^{29}$ +56.8 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.84–8.13 (m, 137H), 5.42 (d, 1H, *J* = 9.7 Hz), 5.39 (d, 1H, *J* = 3.4 Hz), 5.24–5.35 (m, 7H), 4.95–5.21 (m, 19H), 4.90 (d, 1H, *J* = 12.6 Hz), 4.81 (d, 1H, *J* = 13.0 Hz), 4.45–4.76 (m, 34H), 4.22–4.39 (m, 9H), 3.58–4.17 (m, 35H), 3.29–3.54 (m, 15H), 3.09–3.27 (m, 24H), 2.90–3.02 (m, 6H), 1.06–1.49 (m, 8H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.8, 168.4, 168.3 × 2, 166.2, 165.2, 164.7 × 2, 156.5, 154.5 × 2, 154.4, 139.1, 139.0, 138.3, 137.5, 137.2, 137.0, 136.4, 136.2, 136.0, 135.7, 134.2, 134.1, 134.0, 133.8, 133.7, 133.6, 133.5 × 2, 133.4, 130.0, 129.9, 129.8, 129.3, 129.2, 129.0, 128.9 × 2, 128.8, 128.7, 128.6, 128.5, 128.4 × 2, 128.3, 128.2, 128.1, 128.0 × 2, 127.9, 127.8 × 2, 127.7, 127.5, 127.1 × 2, 127.0, 126.9, 126.5, 126.3 × 2 (101.5, 100.4, 100.2, 98.3, 98.2, 98.0, 95.8, 95.7 anomeric), 82.8 × 2, 82.6, 77.8, 77.7, 77.5, 77.4, 76.9, 76.7, 75.6, 75.3, 75.0, 74.9, 74.8, 74.7, 74.5 × 2, 74.4, 74.1, 74.0, 73.9, 73.8, 73.7, 72.9, 71.5, 71.4, 70.4, 69.9, 69.3, 67.2, 66.9, 66.6, 55.0,

54.9, 54.8, 53.1, 52.5, 52.4, 41.1, 30.0 × 2, 29.5, 26.5, 25.8, 14.3; IR (KBr) 3028, 2952, 1736, 1510, 1264, 1070, 756, 711 (cm^{-1}).

_N_-Benzyloxycarbonyl-6-aminohexyl 3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate)-(1 → 4)-3-_O_-benzyl-2-deoxy-6-_O_-naphthylmethyl-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl-(1 → 4)-(methyl 2-_O_-benzoyl-3-_O_-benzyl-β-D-glucopyranosyluronate) (28)

To a stirred solution of **27** (125 mg, 20.7 μmol) in DMF (0.50 mL) was added thiourea (5.0 mg, 62.1 μmol) and 2,6-lutidine (3.0 μL, 24.8 μmol) at room temperature. After being stirred at 50 °C for 12 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aq. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : ethyl acetate = 88 : 12 to 78 : 22) to give **28** (115 mg, 19.3 μmol, 93%): $[\alpha]_D^{31}$ +46.1 (*c* 0.08, $CHCl_3$); ^1H NMR (400 MHz, CD_2Cl_2)δ 6.82–8.04 (m, 137H, aromatic), 5.38 (d, 1H, *J* = 3.4 Hz), 5.34 (d, 1H, *J* = 6.8 Hz), 5.23–5.32 (m, 6H), 4.94–5.20 (m, 19H), 4.89 (d, 1H, *J* = 12.1 Hz), 4.83 (d, 1H, *J* = 12.1 Hz), 4.77 (d, 1H, *J* = 11.6 Hz), 4.47–4.75 (m, 31H), 4.45 (d, 1H, *J* = 11.1 Hz), 4.17–4.37 (m, 9H), 3.65–4.12 (m, 32H), 3.59 (m, 1H), 3.29–3.51 (m, 16H), 3.12–3.23 (m, 24H), 2.88–3.01 (m, 6H), 1.07–1.53 (m, 8H, aliphatic); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.8, 168.5, 168.3 × 2, 165.2, 164.8, 164.7, 156.5, 154.5 × 2, 154.4, 139.1, 139.0 × 2, 137.5, 137.2, 137.1, 137.0, 136.3, 136.2, 136.0, 135.8, 134.1 × 2, 133.8, 133.7, 133.6 × 2, 133.5, 133.4, 130.0, 129.9, 129.8, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 127.1, 127.0, 126.9, 126.6, 126.4, 126.1 (101.5, 100.4, 100.2, 98.7, 98.2, 98.0, 95.9, 95.8 anomeric), 82.8 × 2, 82.7, 82.6, 79.8, 77.9, 77.6, 77.5, 77.4, 76.9, 76.7, 75.6, 75.3, 75.0 × 2, 74.8, 74.7 × 2, 74.5 × 2, 74.4, 74.2, 74.1, 74.0, 73.9 × 2, 73.8, 73.1, 71.5, 71.4, 71.1, 70.6, 70.4, 67.2, 67.0, 66.6, 54.8, 52.5, 52.4, 41.2, 30.1, 29.7, 29.5, 26.6, 25.8, 14.3; IR (KBr) 3426, 2927, 1736, 1510, 1264, 1071, 758, 711 (cm^{-1}).

Dodecamer attached with a fluorous tag 29

A mixture of **28** (207 mg, 34.8 μmol), **3** (32.1 mg, 52.2 μmol), and pulverized activated MS-4A (35 mg) in dry CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min under argon to remove trace amounts of water. Then the reaction mixture was cooled to 0 °C. CSA (2.4 mg, 10.4 μmol, 0.30 equiv.) was added to the reaction mixture at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : ethyl acetate = 88 : 12 to 75 : 25) to give **29** (189 mg, 317 μmol, 91%): ^1H NMR (400 MHz, $CDCl_3$) δ 6.74–8.05 (m, 548H, aromatic), 5.99 (t, 1H, *J* = 6.3 Hz), 5.63 (t, 1H, *J* = 6.3 Hz), 5.39–5.50 (m, 5H), 5.14–5.35 (m, 28H), 4.65–5.12 (m, 90H), 4.18–4.63 (m, 116H), 2.85–4.15 (m, 351H), 1.01–2.20 (m, 88H); ^{19}F NMR (373 MHz, $CDCl_3$) δ −112.4, −120.0, −120.2, −121.0, −121.6, −124.4; IR (KBr) 3423, 2951, 1752, 1452, 1264, 1041, 756, 710 (cm^{-1}).

6-_O_-Sulfated dodecamer attached with a fluorous tag (30)

To a stirred solution of **29** (148 mg, 24.2 μmol) in CH_2Cl_2 (2.5 mL) and saturated aq. $NaHCO_3$ (0.5 mL) was added DDQ (55.0 mg, 242 μmol) at 0 °C. After being stirred at 0 °C for 1 h, to the reaction mixture was added DDQ (55.0 mg, 242 μmol) at 0 °C. After being stirred at 0 °C for another 1 h, to the reaction mixture was added DDQ (55.0 mg, 242 μmol) at 0 °C. After being stirred at 0 °C for another 1 h, the reaction mixture was filtered through a pad of Celite®. The filtrate mixture was poured into saturated aq. $NaHCO_3$ with cooling. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : ethyl acetate = 90 : 10 to 75 : 25) to give glucopyranoside-linking-fluorous tag. To a stirred solution of the residue in dry DMF (2.5 mL) was added $SO_3 \cdot NEt_3$ (450 mg) and NEt_3 (120 μL) at room temperature. After being stirred at 50 °C for 24 h, the reaction mixture was neutralized with 5% aq. $NaHCO_3$ and evaporated *in vacuo*. The residue was purified by fluorous column chromatography (Fluoro *Flash*® SPE) to give **30** (81.7 mg, 13.3 μmol, 2 steps 55%): ^1H NMR (400 MHz, CD_3OD) δ 6.74–8.05 (m, 548H, aromatic), 5.24–5.53 (m, 16H), 4.93–5.22 (m, 52H), 3.68–4.87 (m, 259H), 3.45–3.68 (m, 45H), 3.15–3.44 (m, 37H), 2.61–3.10 (m, 125H), 0.89–2.31 (m, 88H); ^{19}F NMR (373 MHz, CD_3OD) δ −111.8, −119.4, −119.5, 120.4, −121.0, −123.9; IR (KBr) 3427, 2956, 1730, 1453, 1218, 1064, 738, 712 (cm^{-1}).

_N_- and 6-_O_-Sulfated dodecamer attached with a fluorous tag 31

To a stirred solution of **30** (62.7 mg, 10.2 μmol) in CH_2Cl_2 (1.0 mL) and AcOH (50.0 μL) was added Zn dust (150 mg) at room temperature. After being stirred at the same temperature for 1 h or 12 h, the reaction mixture was poured into ice-cooled saturated aq. $NaHCO_3$ and filtered through a pad of Celite®. The filtrate was evaporated *in vacuo*. The residue was purified by MPLC (elution with toluene : acetone : formic acid = 93.75 : 6 : 0.25 to 79.75 : 20 : 0.25) and by reversed phase HPLC (Develosil® ODS-UG-5 column, eluent: H_2O–MeOH, gradient: 0.00 min $[H_2O]:[CH_3CN]$ = 30 : 70, 2.00 min

[H_2O] : [CH_3CN] = 30 : 70, 12.0 min [H_2O] : [CH_3CN] = 10 : 90, 10 mL min^{-1}) to give the amino derivative. To a stirred solution of the residue in dry DMF (1.0 mL) was added SO_3·NEt_3 (181 mg) and NEt_3 (50 μL) at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was neutralized with 5% $NaHCO_3$ aq. and evaporated *in vacuo*. The residue was purified by fluorous column chromatography (Fluoro *Flash*® SPE) to give **31** (12.8 mg, 2.25 μmol, 2 steps 22%): ^{1}H NMR (400 MHz, CD_3OD) δ 6.90–8.18 (m, 548H, aromatic), 5.35–5.69 (m, 22H), 4.90–5.30 (m, 69H), 4.29–4.79 (m, 113H), 3.55–4.25 (m, 165H), 3.35–3.54 (m, 49H), 3.12–3.25 (m, 32H), 2.70–3.00 (m, 46H), 0.86–2.37 (m, 88H); ^{19}F NMR (373 MHz, CD_3OD) δ −111.8, −119.4, −119.5, 120.4, −121.0, −123.9; IR (KBr) 3449, 2926, 1728, 1454, 1260, 1035, 751, 716 (cm^{-1}).

***N*-(*S*-(4-Methoxyphenylcarbonyl)thioacetyl)-6-aminohexyl 2-deoxy-2-sulfoamino-6-*O*-sulfonate-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyluronate-(1 → 4)-2-deoxy-2-sulfoamino-6-*O*-sulfonate-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyluronate-(1 → 4)-2-deoxy-2-sulfoamino-6-*O*-sulfonate-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyluronate-(1 → 4)-2-deoxy-2-sulfoamino-6-*O*-sulfonate-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyluronate-(1 → 4)-2-deoxy-2-sulfoamino-6-*O*-sulfonate-α-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyluronate (1)**

To a stirred solution of **31** (11.5 mg, 2.02 μmol) in 1,4-dioxane (0.60 mL) and H_2O (0.30 mL) was added NaOMe (10.0 mg) at room temperature. After being stirred at 35 °C for 24 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by size exclusion column chromatography on Sephadex PD-10 to give carboxylate attached with a fluorous tag. The carboxylate was stirred in dry THF (0.500 mL) at room temperature for 5 min. Then liq. NH_3 (4.5 mL) and Na (20.0 mg) were added at −78 °C. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with NH_4Cl. After removal of liquid ammonia and the solvents *in vacuo*, the residue was purified by size exclusion column chromatography on Sephadex PD-10 to give the amino derivative. To a stirred solution of the amino derivative in 1,4-dioxane (0.60 mL) and H_2O (0.30 mL) was added **4** (8.0 mg, 20.2 μmol) and $NaHCO_3$ (10.0 mg) at room temperature. After being stirred at the same temperature for 6 h, TFA (0.050 mL) was added to the reaction mixture at 0 °C. After being stirred at the same temperature for 20 min, the reaction mixture was diluted with ethyl acetate (10.0 mL) and H_2O (5.0 mL). After being stirred at room temperature for 5 min, the aqueous layer was quenched with $NaHCO_3$ aq. and evaporated *in vacuo*. To a stirred solution of the residue in H_2O (1.00 mL) was added DOWEX cation exchange resin Na form (10.0 mg) at room temperature. After being stirred at the same temperature for 5 min, the reaction mixture was filtered and purified by size exclusion column chromatography on Sephadex PD-10 to give **1** (4.40 mg, 1.15 μmol, 57%): $[\alpha]_D^{23}$ +43.2 (*c* 0.22, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 7.99 (d, 2H, *J* = 9.2 Hz), 7.10 (d, 2H, *J* = 9.2 Hz), 5.59–5.62 (m, 6H), 4.57–4.60 (d, 5H), 4.41–4.45 (m, 5H), 4.32–4.36 (m, 2H), 4.13–4.18 (m, 6H), 3.97–4.03 (m, 5H), 3.91 (s, 3H), 3.64–3.89 (m, 37H), 3.61 (dd, 1H, *J* = 9.7, 13.0 Hz), 3.56 (dd, 1H, *J* = 9.2, 9.7 Hz), 3.46–3.53 (m, 1H), 3.34–3.39 (m, 5H), 3.25–3.31 (m, 6H), 3.17–3.23 (m, 3H), 1.43–1.51 (m, 4H), 1.22–1.31 (m, 4H); ^{13}C NMR (100 MHz, D_2O) δ 192.6, 175.1, 175.0, 171.2, 164.3, 129.0, 128.7, 114.5 (102.1, 101.9, 97.6, 97.2, 97.0 anomeric), 77.1, 76.9, 76.8, 76.7, 76.6, 76.5, 76.3, 75.9, 72.8 × 2, 72.6, 71.1, 70.4, 69.8, 69.6, 69.4, 69.0, 68.6 × 2, 66.3, 65.8, 58.0, 57.5, 55.8, 39.7, 32.7, 29.0, 28.6, 28.0, 25.5, 24.9, 24.6; IR (KBr) 3437, 2926, 1606, 1418, 1227, 1046, 941, 636 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{88}H_{136}N_7O_{100}S_{13}$ $[M - H]^-$ 3306.2141, found 3306.2141.

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