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Synthesis of *N*-(fluoren-9-ylmethoxycarbonyl)glycopyranosylamine uronic acids

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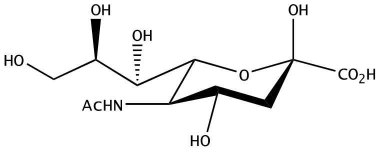
Abstract—The synthesis of 10 *N*-(fluoren-9-ylmethoxycarbonyl)glycopyranosylamine uronic acids that are amenable to solid-phase synthesis is described. The general synthetic strategy involves initial incorporation of the protected amine, followed by selective TEMPO oxidation of C-6 hydroxyl groups to give the corresponding Fmoc-protected sugar amino acids. Amine incorporation may be accomplished from aminolysis of the free sugar or from glycosyl azide reduction. The reactions can be carried out on multigram scale, providing access to unique monomer units for future incorporation into combinatorial library syntheses.

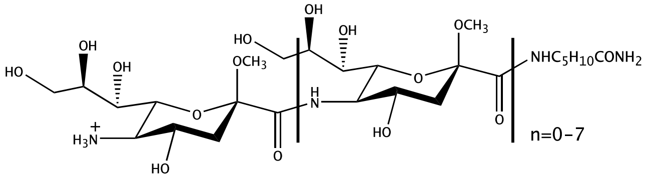
1. Introduction

The design and synthesis of artificial peptides as molecular scaffolds is a continually growing field of research.[1] Much of the synthetic work in this area has focused on employing solid-phase peptide synthesis in the construction of oligomeric materials derived from α-, β-, or γ-amino acids.[2] These materials often adopt stable secondary structures reminiscent of naturally occurring peptides, which undoubtedly contribute to their biological activities. Carbohydrates have also been incorporated into novel structural motifs,[3] and here again amide bond formation between monomeric subunits is the most commonly employed synthetic strategy.



***N*-Acetylneuraminic acid (Neu5Ac)**

Until recently, we focused our studies on the synthesis of compounds containing analogs of neuraminic acid (Neu),[4] which is a naturally occurring sugar amino acid (a 5-amino-3,5-dideoxynonulosonic acid). The most abundant form of neuraminic acid is *N*-acetylneuraminic acid (Neu5Ac), which is commercially available. It can also be prepared in a simple enzymatic reaction.[5] We felt that Neu would be an ideal candidate for incorporation into oligomeric materials because of the hydroxylated C-6 side chain. We anticipated this functionality would increase water solubility relative to other pyranose sugars that were known to precipitate when more than four monomer subunits were incorporated.[6] In order to incorporate Neu into to solid-phase peptide synthesis, we developed methodologies for converting Neu into several different *N*-fluoren-9-ylmethoxycarbonylneuraminc acid analogs,[7] and indeed, Neu homooligomers derived from these subunits demonstrated desirable solubility profiles.[8]



Neuraminic acid homooligomers

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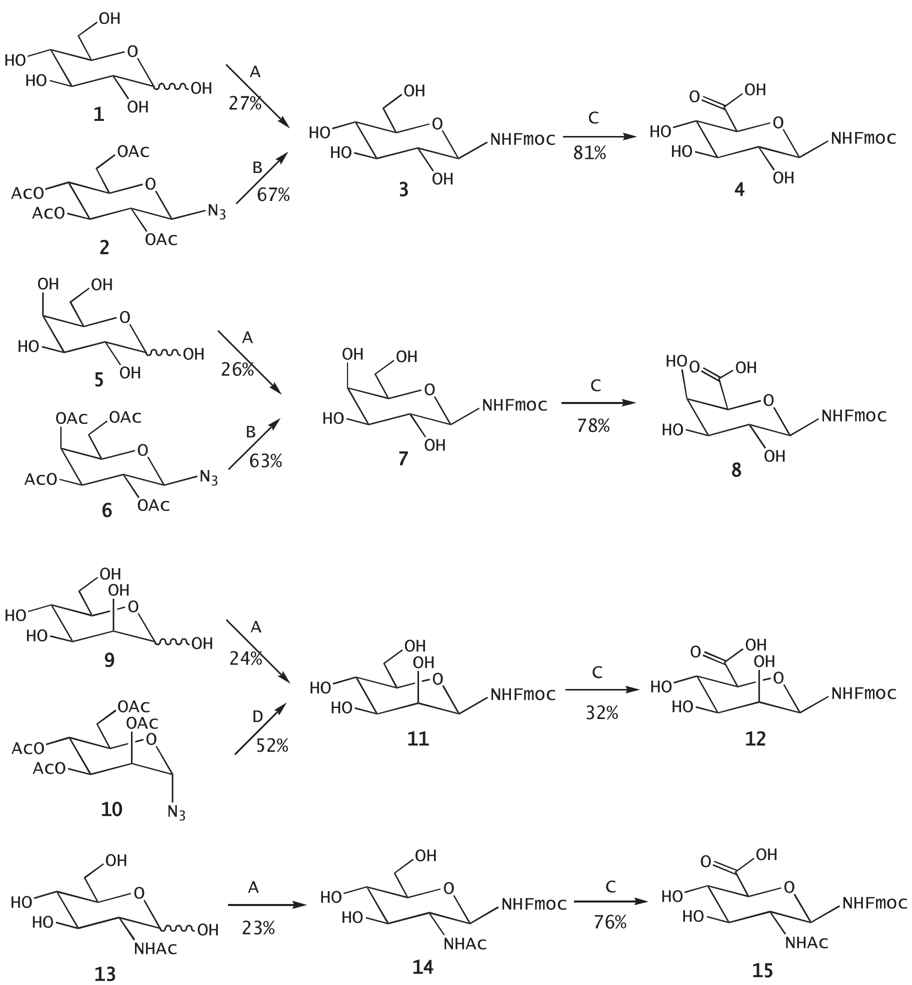
While our studies centering on synthetic and structural studies of amide-linked homooligomeric neuraminic acids have revealed important factors governing conformational stability, we are currently not able to rationally design compounds with desirable biological activity. To address this important issue, we have initiated combinatorial studies to complement our rational design investigations. The advent of combinatorial chemistry and the ability to make libraries of compounds, which are only limited in size by building block variation, have prompted us to develop routes to more diverse sugar amino acid building blocks. Reported herein are facile and efficient methods for the synthesis of *N*-(fluoren-9-ylmethoxycarbonyl)glycopyranosylamine uronic acids.

2. Results and discussion

Our investigations began with the conversion of D-glucopyranose (**1**), D-galactopyranose (**5**) and D-mannopyranose (**9**) to the corresponding *N*-fluoren-9-ylmethoxycarbonyl (Fmoc) glycosyl amines (Scheme 1). Two routes were explored: method A involved direct conversion of the unprotected pyranoses, while method B employed per-*O*-acetylated glycosyl azides **2**, **6**, and **10** as the starting materials.[9] The free pyranoses were first reacted with ammonium hydrogen carbonate (NH_4HCO_3) in water to form the corresponding glycosyl amines,[10] which were directly reacted with fluoren-9-ylmethoxycarbonyl-*O*-succinimide (Fmoc-OSu) in pyridine to give the desired Fmoc-protected amines **3**, **7**, and **11**.[11] Purified yields for the combined reactions ranged from 24% to 27%. Higher yields were obtained when beginning with protected glycosyl azides, which were first deacetylated using sodium methoxide in MeOH and subsequently subjected to hydrogenolysis. The resulting crude glycosyl amines were further reacted to give **3**, **7**, and **11** in 67%, 63%, and 52% purified yields, respectively, for the three-step reaction sequence. The next task was to selectively oxidize the C-6 hydroxyl of the Fmoc-protected glycosyl amine intermediates, and this was accomplished by TEMPO-catalyzed sodium hypochlorite oxidation with careful pH control.[12]



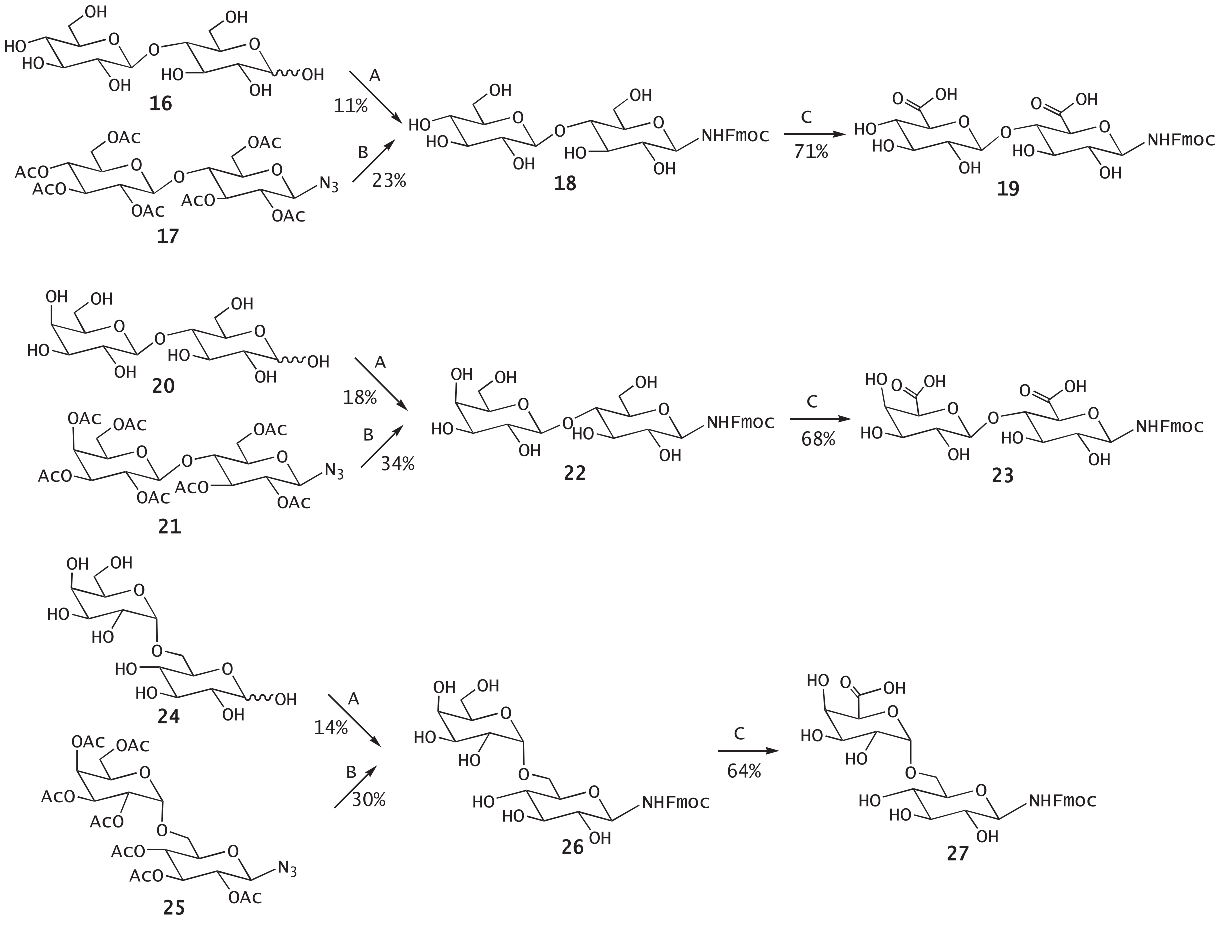
Scheme 1. (A) Aq NH_4HCO_3; Fmoc-OSu, pyridine. (B) NaOMe, MeOH; 10% Pd/C, H_2MeOH; Fmoc-OSu, pyridine. (C) TEMPO, NaOCl, KBr, $NaHCO_3$, THF, H_2O. (D) NaOMe, H_2MeOH; Raney nickel, MeOH; Fmoc-OSu, pyridine.

The oxidation went smoothly for the gluco- and galactopyranosyl sugars (**3** and **7**); however, conversion of β-D-*N*-(fluoren-9-ylmethoxycarbonyl)mannopyranosylamine (**11**) was much less efficient. Poor yields in mannosyl oxidations have been reported by others as well, and are presumably due to stereoelectronic factors imposed by the C-2 axial hydroxyl group.[13] In related studies, *N*-acetylglucosamine analog (**15**) was added to our library of monosaccharides by subjecting **13** to aminolysis and subsequent protection to provide **14**, which was efficiently oxidized to the corresponding glucuronic acid in 76% yield.

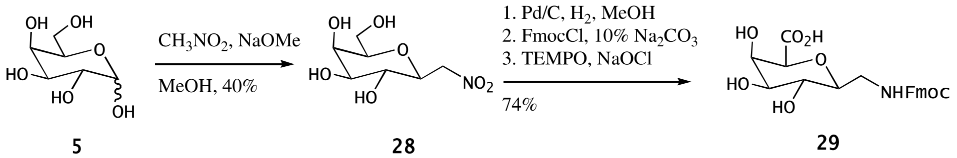
As shown in Scheme 2, disaccharide-derived compounds were accessed using the same methods as those described for the monosaccharides; however, the yields when using method B showed no improvement relative to method A. And since this route accommodates multigram reaction scales beginning with commercially available disaccharides, it is clearly the method of choice for preparing **18**, **22**, and **26**. Subsequent oxidation of the *N*-fluoren-9-ylmethoxycarbonyl disaccharides proceeded smoothly yielding **19**, **23**, and **27** in 71%, 68%, and 64% purified yields, respectively.

The synthesis of β-D-glucopyranosyl-*N*-(fluoren-9-ylmethoxycarbonyl)methane was previously reported by von Roedern and Kessler,[14] and simple extension of this protocol enabled the preparation of the galactosyl analog **29** (Scheme 3). In the event, β-D-galactopyranosyl nitromethane (**28**) was prepared via aldol condensation, followed by acid-catalyzed intramolecular ring closure.[15] Reduction of the nitro compound with hydrogen using 10% Pd/C, protection of the resulting amine with Fmoc-Cl, and TEMPO oxidation afforded **29** in 74% yield for the three-step sequence.

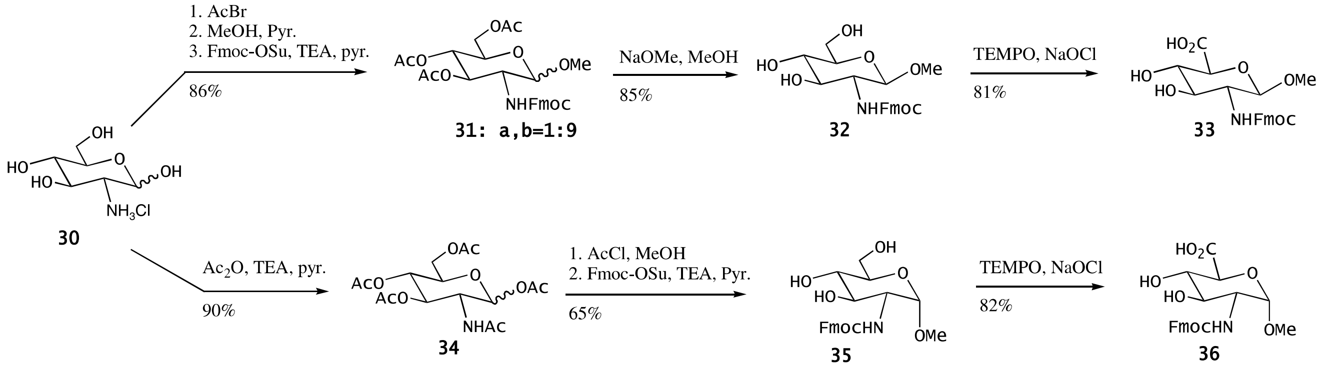
In the 1950s Fodor, and Paulsen and co-workers, independently reported the synthesis 2-*N*-benzyloxycarbonyl-2-amido-2-deoxyglycuronic acids as intermediates en route to naturally occurring sugar amino acid conjugates.[16] We found that similar strategies could be employed in the synthesis of Fmoc-protected analogs (Scheme 4). Accordingly, the HCl salt of D-glucosamine was reacted with AcBr to yield 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide,[17] which was treated with MeOH in pyridine to obtain a mixture of methyl α,β-D-glucosides (1:9). The mixture was protected with Fmoc-OSu, after which the α,β-anomers



Scheme 2. (A) Aq NH_4HCO_3; Fmoc-OSu, pyridine. (B) NaOMe, MeOH; 10% Pd/C, H_2MeOH; Fmoc-OSu, pyridine. (C) TEMPO, NaOCl, KBr, $NaHCO_3$, THF, H_2O.



Scheme 3.



Scheme 4.

were separated to provide **31a**,**b** in 86% combined yield. The β-anomer **31b** was deacetylated with NaOMe to give **32** in 85% yield, and selective oxidation of the primary hydroxyl group with TEMPO gave **33** in 81% yield. The α-anomer (**36**) was most efficiently prepared from D-glucosamine pentaacetate, obtained upon treatment of **30** with Ac_2O. Acid-catalyzed methanolysis afforded methyl 2-amino-2-deoxy-α-D-glucopyranoside, which was protected to provide **35**[18] in 65% yield and finally oxidized to provide **36** (Scheme 4).

3. Conclusions

We have developed facile and efficient protocols for 10 *N*-(fluoren-9-ylmethoxycarbonyl)glycuronic amino acids that can be carried out on multigram scale. Beginning with readily available starting materials, amine functionalities can be introduced either through aminolysis or azide reduction. Subsequent protection of the amines occurs without incident, providing substrates for TEMPO oxidation in order to introduce the acid functionality. For the most part, the oxidation proceeds smoothly giving selective oxidation of the C-6 hydroxyl or bis-oxidation in the case of disaccharides possessing C-6 and C-6′ hydroxyl groups. The only problem encountered was in the oxidation of mannopyranosyl analogs, which are somewhat resistant to oxidation, apparently due to stereoelectronic effects posed by the C-2 axial hydroxyl group. Preparation of the compounds described herein is a prerequisite for the synthesis of diverse libraries of amide-linked oligomers in an effort to create unique structural motifs with important biological activities.

4. Experimental

4.1. General methods

All chemicals were used as supplied without further purification. Solvents (MeOH 99.8%, CH_2Cl_2 99.8%, benzene 99.8%) were purchased in anhydrous Sure/Seal^{TM} bottles from Aldrich, used without further purification, and stored under argon. Dowex 50W-X8 (200 mesh) acidic resin was purchased from Aldrich, washed copiously with MeOH, and used without further purification. NaOMe/MeOH (0.5 M) was purchased from Aldrich. Glass-backed EM Science TLC plates (Silica Gel 60 with a 254-nm fluorescent indicator) were purchased from VWR International, cut into 2 cm × 5 cm portions, used without further manipulation, and stored over desiccant. Developed TLC plates were visualized under a short-wave UV lamp, then stained with a cerium–molybdate solution and charred. Column chromatography was conducted using flash silica gel (32–63 μm) available from Scientific Adsorbents and solvents purchased from EM Science. NMR experiments (1D and 2D) were conducted on Bruker DRX500 MHz spectrometers at 298 K. Optical data were taken on a JASCO DIP-370 Digital Polarimeter. RP-HPLC preparative separations were carried out on a Vydac C18 column. Solvents: (A) H_2O+0.1% TFA and (B) CH_3OH with UV detection at 220 and 254 nm.

4.2. General procedure for the synthesis of *N*-(fluoren-9-ylmethoxycarbonyl)-β-D-glycopyranosylamines: method A

The saccharide (5 g) was dissolved in aq NH_4HCO_3 (200 mL) and stirred for 7 days at 30 °C. The reaction mixture was diluted with equal volumes of water, and NH_4HCO_3 was removed by concentration in vacuo (bath temperature 30 °C) to the original volume. This procedure was repeated five times. After lyophilization of the solution, the product was used directly in the next step. The glycopyranosylamine (~10 mmol) was suspended in pyridine (50 mL), Fmoc-OSu (10 mmol) was added, and the mixture was stirred overnight at room temperature. The solution was concentrated in vacuo. The residue was washed with water, CH_2Cl_2, and was purified by crystallization from MeOH or by column chromatography (silica gel, 8:1–4:1 CH_2Cl_2–CH_3OH).

4.3. Method B

2,3,4,6-Tetra-*O*-acetyl-α,β-D-glycopyranosyl azide[9] (5.0 mmol) was suspended in dry MeOH (20 mL). NaOMe (0.2 mL, 0.5 M) was added, and the mixture was stirred for approximately 30 min. Upon completion of the reaction as indicated by TLC, the solution was neutralized with Dowex-50 (H^+) resin, filtered, and concentrated to dryness. The glycosyl azide (500 mg) was dissolved in dry MeOH (20 mL), 10% Pd/C (wet, 40 mg) was added (Caution. Extreme fire hazard!). For mannose, Raney nickel (50 mg) was added, and the solution was bubbled with H_2 for 3–4 h. After completion, as indicated by TLC, the Pd/C was removed by filtration and the solution was concentrated to dryness. The glycopyranosylamine (2.5 mmol) was suspended in pyridine (20 mL), Fmoc-OSu (2.6 mmol) was added, and the mixture was stirred overnight at room temperature. The solution was concentrated in vacuo. The residue was washed with CH_2Cl_2, and the precipitate was purified by recrystallization from MeOH or by column chromatography (Silica gel, 8:1–4:1) CH_2Cl_2–CH_3OH).

4.4. General procedure for TEMPO oxidation

N-(Fluoren-9-ylmethoxycarbonyl)-β-D-glycopyranosylamine (0.5 mmol) was suspended in 1:1 THF–aq $NaHCO_3$ (12 mL), and TEMPO (0.1 mmol) and potassium bromide (0.15 mmol) were added. NaOCl (1.1 mL, 1.3 M) was added dropwise at 0 °C. After 1 h, additional amounts of NaOCl (0.6 mL) and TEMPO (0.05 mmol) were added. After TLC indicated the reaction was complete, the solution was extracted with Et_2O (2 × 10 mL). The aqueous layer was acidified with 2 N HCl to pH 1–2 and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to yield a residue that was purified by preparative HPLC.

4.5. *N*-(Fluoren-9-ylmethoxycarbonyl)-β-D-glucopyranylamine (3)

A white powder was obtained in 27% yield from **1** and 67% from **2**. ^1H NMR (CD_3OD, 500 MHz): δ 3.17 (t, *J* 9.0 Hz, 1H, H-2), 3.25 (m, 2H, H-4, H-5), 3.31 (t, *J* 9.0 Hz, 1H, H-3), 3.59 (dd, *J* 3.5, 11.5 Hz, 1H, H-6), 3.76 (d, *J* 11.5 Hz, 1H, H-6′), 4.16 (t, *J* 6.5 Hz, 1H, Fmoc-CH), 4.34 (m, 2H, Fmoc-CH_2), 4.63 (d, *J* 8.5Hz, 1H, H-1), 7.25 (app-t, 2H, Fmoc-Ar), 7.33 (app-t, 2H, Fmoc-Ar), 7.61 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.73 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 46.9 (Fmoc-CH), 61.1 (C-6), 66.2 (Fmoc-CH_2), 70.1, 72.2 (C-2), 77.6 (C-3), 78.5, 82.7 (C-1), 120.5, 125.7, 127.6, 128.2, 141.1, 144.0, 144.2, 156.6. ESIMS: calcd for $C_{12}H_{23}NO_7Na$ $[M+Na]^+$ 424.2, found 424.2.

4.6. *N*-(Fluoren-9-ylmethoxycarbonyl)-β-D-glucopyranosylamine uronic acid (4)

A white powder was obtained in 81% yield from **3**. $[\alpha]_D^{25}$ −5.0° (*c* 0.5, CH_3OH). ^1H NMR (DMSO, 500 MHz): δ 3.17 (t, *J* 8.5 Hz, 1H, H-2), 3.22 (t, *J* 8.5 Hz, 1H, H-3), 3.29 (t, *J* 8.5 Hz, 1H, H-4), 3.61 (d, *J* 8.5 Hz, 1H, H-5), 4.22–4.32 (m, 3H, Fmoc-CH, Fmoc-CH_2), 4.55 (d, *J* 8.5 Hz, 1H, H-1), 7.32 (app-t, 2H, Fmoc-Ar), 7.41 (app-t, 2H, Fmoc-Ar), 7.71 (m, 2H, Fmoc-Ar), 7.87 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 46.7 (Fmoc-CH), 66.0 (Fmoc-CH_2), 71.6 (C-2, C-4), 76.8 (C-3), 77.2 (C-5), 82.9 (C-1), 120.3, 125.4, 125.5, 127.4, 127.9, 140.9, 143.8, 144.0, 156.24, 170.5 (C-6). HRFABMS: calcd for $C_{12}H_{12}NO_8Na$ $[M+Na]^+$ 438.1159, found 438.1176.

4.7. *N*-(Fluoren-9-ylmethoxycarbonyl)-β-D-galactopyranosylamine (7)

A white powder was obtained in 26% yield from **5** and 63% from **6**. ^1H NMR (CD_3OD, 500 MHz): δ 3.42–3.50 (m, 3H, H-2, H-3, H-5), 3.62 (m, 2H, H-6, H-6′), 3.80 (br s, 1H, H-4), 4.15 (t, *J* 6.5 Hz, 1H, Fmoc-CH), 4.32 (m, 2H, Fmoc-CH_2), 4.59 (d, *J* 8.0 Hz, 1H, H-1), 7.23 (app-t, 2H, Fmoc-Ar), 7.31 (app-t, 2H, Fmoc-Ar), 7.60 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.71 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 46.2 (Fmoc-CH), 62.4 (C-6), 68.0 (Fmoc-CH_2), 70.3 (C-4), 71.1 (C-3), 75.7 (C-2), 78.0 (C-5), 84.2 (C-1), 121.0, 126.2, 128.2, 128.8, 142.6, 145.2, 158.8. ESIMS: calcd for $C_{21}H_{23}NO_7Na$ $[M+Na]^+$ 424.2, found 424.2.

4.8. *N*-(Fluoren-9-ylmethoxycarbonyl)-β-D-galactopyranosylamine uronic acid (8)

A white powder was obtained in 78% yield from **7**. $[\alpha]_D^{25}$ −2.7° (*c* 0.6, CH_3OH). ^{1}H NMR (DMSO, 500 MHz): δ 3.41–3.43 (m, 2H, H-2, H-3), 3.94 (1H, H-4), 4.09 (br s, 1H, H-5), 4.20–4.28 (m, 3H, Fmoc-CH, Fmoc-CH_2), 4.49 (d, *J* 8.0 Hz, 1H, H-1), 7.32 (app-t, 2H, Fmoc-Ar), 7.40 (app-t, 2H, Fmoc-Ar), 7.69 (m, 2H, Fmoc-Ar), 7.84 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 47.0 (Fmoc-CH), 66.6 (Fmoc-CH_2), 69.0, 70.4 (C-4), 73.9, 75.4 (C-5), 82.7 (C-1), 120.8, 125.9, 125.9, 127.9, 128.5, 141.3, 144.2, 144.3, 157.0, 170.7 (C-6). HRFABMS: calcd for $C_{12}H_{12}NO_8Na$ $[M+Na]^+$ 438.1159, found $[M+Na]^+$ 438.1178.

4.9. *N*-(Fluoren-9-ylmethoxycarbonyl)-β-D-mannopyranosylamine (11)

A white powder was obtained in 24% yield from **9** and 52% from **10**. ^{1}H NMR (DMSO, 500 MHz): δ 3.07 (m, 1H, H-5), 3.28–3.35 (m, 2H, H-3, H-4), 3.41 (m, 1H, H-6), 3.60–3.63 (m, 2H, H-2, H-6′), 4.20–4.33 (m, 3H, Fmoc-CH, Fmoc-CH_2), 4.76 (s, 1H, H-1), 7.31 (app-t, 2H, Fmoc-Ar), 7.39 (app-t, 2H, Fmoc-Ar), 7.66 (m, 2H, Fmoc-Ar), 7.83 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 47.0 (Fmoc-CH), 61.5 (C-6), 66.7, 66.9, 71.0 (C-2), 74.1, 78.9 (C-5), 80.2 (C-1), 120.7, 125.7, 127.9, 128.4, 141.3, 144.2, 144.2, 156.2. ESIMS: calcd for $C_{12}H_{23}NO_7Na$ $[M+Na]^+$ 424.2, found 424.2.

4.10. *N*-(Fluoren-9-ylmethoxycarbonyl)-β-D-mannopyranosylamine uronic acid (12)

A white powder was obtained with yield 32% from **11**. $[\alpha]_D^{25}$ −3.8° (*c* 0.6, CH_3OH). ^{1}H NMR (DMSO, 500 MHz): δ 3.40 (m, 1H, H-2), 3.56–3.65 (m, 3H, H-3, H-4, H-5), 4.20–4.31 (m, 3H, Fmoc-CH, Fmoc-CH_2), 4.85 (s, 1H, H-1), 7.31 (app-t, 2H, Fmoc-Ar), 7.39 (app-t, 2H, Fmoc-Ar), 7.67 (m, 2H, Fmoc-Ar), 7.84 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 46.9 (Fmoc-CH), 66.67 (Fmoc-CH_2), 68.1, 70.5, 73.5 (C-2), 77.7 (C-5), 80.7 (C-1), 120.6, 125.7, 125.8, 127.8, 128.4, 141.2, 144.1, 144.2, 156.0, 170.9 (C-6). HRFABMS: calcd for $C_{12}H_{12}NO_8Na$ $[M+Na]^+$ 438.1159, found $[M+Na]^+$ 438.1180.

4.11. 2-Acetamido-2-deoxy-*N*^{1}-(fluoren-9-ylmethoxycarbonyl)-β-D-glucopyranosylamine (14)

A white powder was obtained in 23% yield from **13**. ^{1}H NMR (DMSO, 500 MHz): δ 1.82 (s, 3H, NAc), 3.09–3.12 (m, 2H, H-4, H-5), 3.34 (t, *J* 8.0 Hz, 1H, H-3), 3.44 (dd, *J* 3.5 Hz, 11.5 Hz, 1H, H-6), 3.53 (t, *J* 8.0 Hz, 1H, H-2), 3.76 (d, *J* 11.5 Hz, 1H, H-6′), 4.10–4.30 (m, 3H, Fmoc-CH, Fmoc-CH_2), 4.62 (d, *J* 8.0 Hz, 1H, H-1), 7.30 (app-t, 2H, Fmoc-Ar), 7.39 (app-t, 2H, Fmoc-Ar), 7.61 (m, 2H, Fmoc-Ar), 7.84 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 23.3, 46.9 (Fmoc-CH), 54.9 (C-2), 61.3 (C-6), 66.8 (Fmoc-CH_2), 70.6 (C-4), 74.7 (C-3), 78.6 (C-5), 81.8 (C-1), 120.8, 125.8, 125.9, 127.9, 128.5, 141.3, 144.1, 144.2, 156.6, 171.9. ESIMS: calcd for $C_{23}H_{26}N_2O_7Na$ $[M+Na]^+$ 465.2, found 465.2.

4.12. 2-Acetamido-2-deoxy-*N*^{1}-(fluoren-9-ylmethoxycarbonyl)-β-D-glucopyranosylamine uronic acid (15)

A white powder was obtained in 76% yield from **14**. $[\alpha]_D^{25}$ +41.4° (*c* 0.2, CH_3OH). ^{1}H NMR (DMSO, 500 MHz): δ 1.82 (s, 3H, NAc), 3.33 (t, *J* 9.0 Hz, 1H, H-4), 3.39 (t, *J* 9.0 Hz, 1H, H-3), 3.57 (t, *J* 9.0 Hz, 1H, H-2), 3.62 (d, *J* 9.0 Hz, 1H, H-5), 4.15–4.27 (m, 3H, Fmoc-CH, Fmoc-CH_2), 4.71 (d, *J* 9.0 Hz, 1H, H-1), 7.30 (app-t, 2H, Fmoc-Ar), 7.40 (app-t, 2H, Fmoc-Ar), 7.61 (m, 2H, Fmoc-Ar), 7.84 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 22.9, 46.7 (Fmoc-CH), 54.4 (C-2), 66.3 (Fmoc-CH_2), 72.1 (C-4), 74.0 (C-3), 77.4 (C-5), 82.0 (C-1), 120.3, 125.4, 125.6, 127.3, 127.9, 141.0, 143.9, 156.1, 170.3, 170.7. HRFABMS: calcd for $C_{23}H_{24}N_2O_8Na$ $[M+Na]^+$ 479.1424, found 479.1417.

4.13. β-D-Glucopyranosyl-(1 → 4)-*N*-(fluoren-9-ylmethoxy carbonyl)-β-D-glucopyranosylamine (18)

A white powder was obtained in 11% yield from **16** and 23% from **17**. ^{1}H NMR (DMSO, 500 MHz): δ 2.98 (t, *J* 8.5 Hz, 1H, H-2′), 3.04 (t, *J* 8.5 Hz, 1H, H-3′), 3.13–3.21 (m, 4H, H-4′, H-2, H-3, H-5), 3.24–3.40 (m, 4H, H-4, H-5′, H-6″, H-6′), 3.56–3.70 (m, 3H, H-5, H-6, H-6′), 4.21–4.36 (m, 3H, H-1′, Fmoc-CH, Fmoc-CH_2), 4.52 (d, *J* 9.0 Hz, 1H, H-1), 7.33 (app-t, 2H, Fmoc-Ar), 7.42 (app-t, 2H, Fmoc-Ar), 7.72 (m, 2H, Fmoc-Ar), 7.88 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 46.7 (Fmoc-CH), 60.2 (C-6), 61.1 (C-6′), 65.9 (Fmoc-CH_2), 70.1 (C-3′), 71.67, 73.4 (C-2′), 75.8, 76.4, 76.4, 76.9, 80.3 (C-4), 82.4 (C-1), 103.2 (C-1′), 120.4, 125.4, 125.5, 127.4, 128.0, 140.9, 143.9, 144.1, 156.4. ESIMS: calcd for $C_{27}H_{33}NO_{12}Na$ $[M+Na]^+$ 586.2, found 586.3.

4.14. β-D-Glucuronyl-(1 → 4)-*N*-(fluoren-9-ylmethoxycarbonyl)-β-D-glucopyranosylamine uronic acid (19)

A white powder was obtained in 71% yield from **18**. $[\alpha]_D^{25}$ −7.9° (*c* 0.3, CH_3OH). ^{1}H NMR (CD_3OD, 500 MHz): δ 2.97 (t, *J* 8.5 Hz, 1H, H-2′), 3.24 (t, *J* 8.5 Hz, 1H, H-2), 3.28 (t, *J* 8.5 Hz, 1H, H-3′), 3.40 (t, *J* 8.5 Hz, 1H, H-4′), 3.48 (t, *J* 8.5 Hz, 1H, H-3), 3.63 (t, *J* 8.5 Hz, 1H, H-4), 3.78 (d, *J* 8.5 Hz, 1H, H-5′), 3.93 (d, *J* 8.5 Hz, 1H, H-5), 4.13 (t, *J* 7.0 Hz, 1H, Fmoc-CH), 4.29 (m, 2H, Fmoc-

CH_2), 4.38 (d, *J* 8.5 Hz, 1H, H-1′), 4.68 (d, *J* 8.5 Hz, 1H, H-1), 7.20 (app-t, 2H, Fmoc-Ar), 7.28 (app-t, 2H, Fmoc-Ar), 7.57 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.68 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 48.3 (Fmoc-CH), 68.2 (Fmoc-CH_2), 72.9, 73.0, 74.6 (C-2′), 76.1, 76.3, 76.8, 77.1, 81.9 (C-4), 84.0 (C-1), 104.4 (C-1′), 120.9, 126.3, 128.2, 128.8, 142.6, 145.2, 158.8, 171.8, 172.3. HRFABMS: calcd for $C_{27}H_{29}NO_{14}Na$ $[M+Na]^+$ 614.1477, found 614.1457.

4.15. β-D-Galactopyranosyl-(1 → 4)-*N*-(fluoren-9-yl-methoxycarbonyl)-β-D-glucopyranosylamine (22)

A white powder was obtained in 18% yield from **20** and 34% from **21**. ^{1}H NMR (DMSO, 500 MHz): δ 3.11 (t, *J* 9.0 Hz, 1H, H-2), 3.20–3.28 (m, 5H, H-2′, H-3′, H-3, H-4, H-5), 3.39–3.63 (m, 6H, H-4′, H-5′, H-6, H-6′, H-6″, H-6′), 4.14–4.28 (m, 4H, H-1′, Fmoc-CH, Fmoc-CH_2), 4.46 (d, *J* 9.0 Hz, 1H, H-1), 7.27 (app-t, 2H, Fmoc-Ar), 7.35 (app-t, 2H, Fmoc-Ar), 7.65 (m, 2H, Fmoc-Ar), 7.81 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 47.0 (Fmoc-CH), 60.5 (C-6), 60.9 (C-6′), 66.3 (Fmoc-CH_2), 68.6 (C-4′), 71.0 (C-2′), 71.9 (C-2), 73.4, 75.9 (2C), 76.6, 80.5, 82.5 (C-1), 104.1 (C-1′), 120.7, 125.7, 125.8, 127.8, 128.3, 141.2, 144.1, 144.3, 156.8. ESIMS: calcd for $C_{27}H_{33}NO_{12}Na$ $[M+Na]^+$ 586.2, found 586.2.

4.16. β-D-Galactopyranosyl-(1 → 4)-*N*-(fluoren-9-yl-methoxycarbonyl)-β-D-glucopyranosylamine uronic acid (23)

A white powder was obtained in 68% yield from **22**. $[\alpha]_D^{25}$ −12.0° (*c* 1.0, CH_3OH). ^{1}H NMR (CD_3OD, 500 MHz): δ 3.31 (t, *J* 9.0 Hz, 1H, H-2), 3.49 (m, 2H, H-2′, H-3′), 3.55 (t, *J* 9.0 Hz, 1H, H-3), 3.65 (t, *J* 9.0 Hz, 1H, H-4), 3.94 (d, *J* 9.0 Hz, 1H, H-5), 4.09 (s, 1H, H-4′), 4.15 (t, *J* 7.0 Hz, 1H, Fmoc-CH), 4.21 (s, 1H, H-5′), 4.29 (m, 2H, Fmoc-CH_2), 3.39–3.63 (m, 6H, H-4′, H-5′, H-6, H-6′, H-6″, H-6′), 4.30–4.33 (m, 3H, H-1′, Fmoc-CH_2), 4.72 (d, *J* 9.0 Hz, 1H, H-1), 7.22 (app-t, 2H, Fmoc-Ar), 7.30 (app-t, 2H, Fmoc-Ar), 7.59 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.70 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3 OD, 125 MHz): δ 48.3 (Fmoc-CH), 68.2 (Fmoc-CH_2), 71.1 (C-4′), 71.8 (C-2′), 73.0 (C-2), 74.1 (C-5′), 76.7 (C-5), 77.0 (C-3′), 82.3 (C-4), 83.8 (C-1), 104.6 (C-1′), 120.9, 126.2, 128.2, 128.8, 142.6, 145.2, 158.7, 171.6, 172.4. HRFABMS: calcd for $C_{27}H_{29}NO_{14}Na$ $[M+Na]^+$ 614.1477, found 614.1476.

4.17. α-D-Galactopyranosyl-(1 → 6)-*N*-(fluoren-9-ylmethoxycarbonyl)-β-D-glucopyranosylamine (26)

A white powder was obtained in 14% yield from **24** and 30% from **25**. ^{1}H NMR (CD_3OD, 500 MHz): δ 3.20 (t, *J* 9.0 Hz, 1H, H-2), 3.33 (m, 2H, H-3, H-4), 3.43 (m, 1H, H-5), 3.60–3.69 (m, 5H, H-2′, H-3′, H-6, H-6″, H-6′), 3.80–3.87 (m, 3H, H-4′, H-5′, H-6′), 4.14–4.36 (m, 3H, Fmoc-CH, Fmoc-CH_2), 4.63 (d, *J* 9.0 Hz, 1H, H-1), 4.80 (1H, H-1′), 7.25 (app-t, 2H, Fmoc-Ar), 7.32 (app-t, 2H, Fmoc-Ar), 7.60 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.72 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 48.2 (Fmoc-CH), 62.8 (C-6′), 67.6 (C-6), 68.0 (Fmoc-CH_2), 70.5, 71.2, 71.4, 71.6, 72.3, 73.6, 78.0, 79.0, 83.9 (C-1), 100.3 (C-1′), 120.9, 126.1, 128.2, 128.8, 142.6, 145.2, 158.7. ESIMS: calcd for $C_{27}H_{33}NO_{12}Na$ $[M+Na]^+$ 586.2, found 586.2.

4.18. α-D-Galactopyranosyluronic acid-(1 → 6)-*N*-(fluoren-9-ylmethoxycarbonyl)-β-D-glucopyranosylamine (27)

A white powder was obtained with yield 64% from **26**. $[\alpha]_D^{25}$ −40.1° (*c* 0.7, CH_3OH). ^{1}H NMR (DMSO, 500 MHz): δ 3.11 (m, 2H, H-2, H-4), 3.19 (t, *J* 9.0 Hz, 1H, H-3), 3.29 (m, 1H, H-5), 3.51–3.63 (m, 4H, H-2′, H-3′, H-6, H-6′), 3.99 (s, 1H, H-5′), 4.21–4.34 (m, 4H, H-4′, Fmoc-CH, Fmoc-CH_2), 4.46 (d, *J* 9.0 Hz, 1H, H-1), 4.72 (d, *J* 2.5 Hz, 1H, H-1′), 7.32 (app-t, 2H, Fmoc-Ar), 7.40 (app-t, 2H, Fmoc-Ar), 7.68 (m, 2H, Fmoc-Ar), 7.85 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (DMSO, 125 MHz): δ 47.0 (Fmoc-CH), 66.5 (Fmoc-CH_2), 66.6 (C-6), 68.1, 69.2, 70.1, 70.6, 70.7, 72.2, 76.6 (C-5), 77.7 (C-3), 82.9 (C-1), 98.8 (C-1′), 120.7, 125.8, 125.9, 127.8, 128.4, 141.2, 141.2, 144.2, 144.4, 156.7, 171.1. HRFABMS: calcd for $C_{27}H_{31}NO_{13}Na$ $[M+Na]^+$ 600.1684, found 600.1711.

4.19. *N*-(Fluoren-9-ylmethoxycarbonyl)-*C*-(β-D-galactopyranosyluronic acid)methylamine

A white powder was obtained in 30% over yield from **5**. ^{1}H NMR (CD_3OD, 500 MHz): δ 3.17 (m, 1H, H-1), 3.22 (m, 1H, CH_2), 3.41 (t, *J* 9.0 Hz, 1H, H-2), 3.46 (dd, *J* 3.5, 9.0 Hz, 1H, H-3), 3.63 (m, 1H, CH_2), 4.11–4.16 (m, 3H, H-4, H-5, Fmoc-CH), 4.31 (m, 2H, Fmoc-CH_2), 7.16 (app-t, 2H, Fmoc-Ar), 7.24 (app-t, 2H, Fmoc-Ar), 7.51 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.64 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 43.0 (CH_2), 48.4 (Fmoc-CH), 67.7 (Fmoc-CH_2), 69.3 (C-2), 71.7 (C-4), 75.5 (C-3), 78.6 (C-5), 80.3 (C-1), 120.9, 126.2, 128.1, 128.7, 142.6, 145.3, 145.3, 159.1, 173.0 (C-6). HRFABMS: calcd for $C_{22}H_{22}NO_8Na_2$ $[M+2Na-H]^+$ 474.1135, found 474.1184.

4.20. Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(fluoren-9-yl-methoxycarbonylamino)-α,β-D-glucopyranoside (31a,b)

AcBr (20 mL) was slowly added to D-glucosamine hydrochloride (3 g, 13.9 mmol) under argon. The flask was tightly sealed and stirred overnight at room temperature. The α-glucosyl bromide crystallized out of solution, the excess AcBr was removed by filtration, and the residue was washed with anhyd benzene. MeOH (50 mL) and pyridine (10 mL) were added to the α-glucosyl bromide with stirring for 1 h at room temperature. The solution was concentrated in vacuo, and the residue was dissolved in pyridine (50 mL) and Et_3N (3.8 mL, 25.8 mmol). Fmoc-OSu (5.6 g, 16.6 mmol) was added to the solution, and the mixture was stirred overnight. The solution was concentrated in vacuo to afford a residue that was dissolved in CH_2Cl_2 (200 mL). The solution was washed with water, aq $NaHCO_3$, brine, and dried (Na_2SO_4). The resulting methyl α,β-D-glucosides were separated by column chromatography to give **31a** and **31b** in 86% over all yield (α:β 1:9). **31a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.96, 2.02, 2.10 (3s, 9H, 3OAc), 3.42 (s, 3H, OCH_3), 3.93 (m, 1H, H-5), 4.05–4.12 (m, 2H, H-2, H-6), 4.19 (t, *J* 7.0 Hz, 1H, Fmoc-CH), 4.24–4.31 (m, 2H, H-6′, Fmoc-CH_2), 4.43 (m, 1H, Fmoc-CH_2), 4.75 (d, *J* 3.5 Hz, 1H, H-1), 5.05 (d, *J* 9.5 Hz, 1H, NH), 5.10 (d, *J* 10.0 Hz, 1H, H-4), 5.24 (d, *J* 10.0 Hz, 1H, H-3), (4.55 (br s, 1H, H-1), 5.07 (br s, 1H, H-4), 5.22 (br s, 1H, NH), 7.31 (app-t, 2H, Fmoc-Ar), 7.40 (app-t, 2H, Fmoc-Ar), 7.56 (m, 2H, Fmoc-Ar), 7.76 (d, J 7.3 Hz, 2H, Fmoc-Ar). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.8, 20.9, 47.2 (Fmoc-CH), 53.9 (C-2), 55.7 (OCH_3), 62.2 (C-6), 66.3 (Fmoc-CH_2), 67.6 (C-5), 68.4 (C-4), 71.3 (C-3), 98.7 (C-1), 120.2, 120.19, 125.2, 125.2, 127.2, 127.9, 141.5, 143.8, 143.9, 155.9, 169.3, 169.6, 170.9. HRFABMS: calcd for $C_{28}H_{31}NO_{10}Na$ $[M+Na]^+$ 564.1837, found: 564.1856. **31b:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.98, 2.01, 2.08 (3s, 9H, 3OAc), 3.49 (s, 3H, OCH_3), 3.63 (br s, 1H, H-2), 3.70 (br s, 1H, H-5), 4.11–4.35 (m, 5H, H-6, H-6′, Fmoc-CH, Fmoc-CH_2), 4.55 (br s, 1H, H-1), 5.07 (br s, 1H, H-4), 5.22 (br s, 1H, NH), 5.32 (br s, 1H, H-3), 7.27 (m, 2H, Fmoc-Ar), 7.37 (app-t, 2H, Fmoc-Ar), 7.54 (m, 2H, Fmoc-Ar), 7.74 (d, *J* 7.3 Hz, 2H, Fmoc-Ar). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.6, 20.7, 46.9 (Fmoc-CH), 55.9 (C-2), 57.0 (OCH_3), 62.0 (C-6), 66.8 (Fmoc-CH_2), 68.6 (C-4), 71.6 (C-5), 72.0 (C-3), 101.7 (C-1), 119.9, 124.9, 126.9, 127.6, 141.2, 143.6, 143.8, 155.7, 169.4, 170.7. HRFABMS: calcd for $C_{28}H_{31}NO_{10}Na$ $[M+Na]^+$ 564.1837, found 564.1867.

4.21. Methyl 2-deoxy-2-(fluoren-9-ylmethoxycarbonylamino)-β-D-glucopyranoside (32)

To a solution of **31b** (400 mg, 0.74 mmol) in dry MeOH (50 mL) was added 0.5 M NaOMe (0.1 mL, 0.05 mmol, pH < 9), and the reaction was stirred for 20 min. The methanolic solution was acidified with Dowex-50 (H^+) resin and evaporated to dryness. Purification of the residue by column chromatography afforded **32** in 85% yield. ^{1}H NMR (CD_3 OD, 500 MHz): δ 3.13–3.23 (m, 3H, H-2, H-4, H-5), 3.30 (t, *J* 8.0 Hz, 1H, H-3), 3.35 (s, 3H, OCH_3), 3.54 (dd, *J* 5.5, 12.0 Hz, 1H, H-6), 3.73 (d, *J* 12.0 Hz, 1H, H-6′), 4.16–4.23 (m, 3H, H-1, Fmoc-CH, Fmoc-CH_2), 4.28 (m, 1H, Fmoc-CH_2), 7.25 (app-t, 2H, Fmoc-Ar), 7.33 (app-t, 2H, Fmoc-Ar), 7.62 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.75 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 48.0 (Fmoc-CH), 56.2 (OCH_3), 57.8 (C-2), 61.7 (C-6), 66.2 (Fmoc-CH_2), 71.3 (C-4), 74.9 (C-3), 77.1 (C-5), 102.9 (C-1), 120.20, 125.6, 127.4, 128.0, 141.5, 144.5, 144.5, 157.4. HRFABMS: calcd for $C_{22}H_{25}NO_7Na$ $[M+Na]^+$ 438.1522, found 438.1547.

4.22. Methyl 2-deoxy-2-(fluoren-9-ylmethoxycarbonylamino)-β-D-glucopyranosiduronic acid (33)

A white powder was obtained in 81% yield from **32**. ^{1}H NMR (CD_3OD) δ 3.28–3.37 (m, 5H, H-2, H-3, OCH_3), 3.45 (t, *J* 8.5 Hz, 1H, H-4), 3.65 (d, *J* 8.5 Hz, 1H, H-5), 4.11 (t, *J* 7.0 Hz, 1H, Fmoc-CH), 4.17–4.27 (m, 3H, H-1, Fmoc-CH_2), 7.19 (app-t, 2H, Fmoc-Ar), 7.27 (app-t, 2H, Fmoc-Ar), 7.55 (d, *J* 7.5 Hz, 2H, Fmoc-Ar), 7.67 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 48.37 (Fmoc-CH), 57.46 (OCH_3), 58.60 (C-2), 67.83 (Fmoc-CH_2), 73.65 (C-4), 75.38 (C-3), 76.71 (C-5), 104.30 (C-1), 120.90, 126.24, 126.30, 128.14, 128.75, 142.58, 145.36, 158.99, 172.37 (C-6). HRFABMS: calcd for $C_{22}H_{23}NO_8Na$ $[M+Na]^+$ 452.1315, found 452.1332.

4.23. Methyl 2-deoxy-2-(fluoren-9-ylmethoxycarbonylamino)-α-D-glucopyranoside (35)

2-Amino-2-deoxy-D-glucose (D-glucosamine) was acetylated using Ac_2O, Et_3N, and pyridine to produce 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α,β-D-glucopyranose (α,β-glucosamine pentaacetate, **34**) in 90% yield. Glucosamine pentaacetate **34** (1 g, 2.6 mmol) in AcCl (6.0 mL, 84.1 mmol) and dry MeOH (60 mL) was refluxed 14 h to afford methyl 2-amino-2-deoxy-α-glucopyranoside (415 mg, 70%).[18] Methyl 2-amino-2-deoxy-α-glucopyranoside (300 mg, 1.3 mmol) in Et_3N (0.4 mL (2.6 mmol), Fmoc-OSu (525 mg (1.6 mmol), and pyridine (30 mL) were stirred overnight. The solution was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with water, aq $NaHCO_3$, brine, and dried (Na_2SO_4). The residue was purified by column chromatography to provide **35** in 92% yield. ^{1}H NMR (CD_3OD, 500 MHz): δ 3.26 (m, 1H, H-5), 3.29 (s, 3H, OCH_3), 3.45 (m, 1H, H-4), 3.52 (m, 2H, H-2, H-3), 3.58–3.75 (m, 2H, H-6, H-6′), 4.14 (t, *J* 7.0 Hz, H-1, Fmoc-CH), 4.27 (m, 2H, Fmoc-CH_2), 4.58 (s, 1H, H-1), 7.22 (app-t, 2H, Fmoc-Ar), 7.30 (app-t, 2H, Fmoc-Ar), 7.58 (m, 2H, Fmoc-Ar), 7.70 (d, *J* 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 48.4 (Fmoc-CH), 55.6 (OCH_3), 57.2 (C-2), 62.8 (C-6), 67.9 (Fmoc-CH_2), 72.3 (C-5), 73.0 (C-3), 73.7 (C-4), 100.2 (C-1), 120.9, 126.2, 128.2, 128.8, 142.6, 145.2, 145.4, 158.9. HRFABMS: calcd for $C_{22}H_{25}NO_7Na$ $[M+Na]^+$ 438.1522, found: 438.1534.

4.24. Methyl 2-deoxy-2-(fluoren-9-ylmethoxycarbonylamino)-α-D-glucopyranosiduronic acid (36)

A white powder was obtained in 82% yield from **35**. ^{1}H NMR (CD_3OD, 500 MHz): δ 3.28 (s, 3H, OCH_3), 3.46 (t, J 8.0 Hz, 1H, H-4), 3.51 (t, J 8.0 Hz, 1H, H-3), 3.56 (dd, J 2.5, 8.0 Hz, 1H, H-2), 3.89 (d, J 8.0 Hz, 1H, H-5), 4.11 (t, J 7.0 Hz, 1H, Fmoc-CH), 4.24 (m, 2H, Fmoc-CH_2), 4.59 (d, J 2.5 Hz, 1H, H-1), 7.12 (app-t, 2H, Fmoc-Ar), 7.27 (app-t, 2H, Fmoc-Ar), 7.55 (m, 2H, Fmoc-Ar), 7.67 (d, J 7.5 Hz, 2H, Fmoc-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 48.4 (Fmoc-CH), 56.01 (OCH_3), 58.8 (C-2), 67.9 (Fmoc-CH_2), 72.5 (C-3), 72.7 (C-5), 73.7 (C-4), 100.7 (C-1), 120.9, 126.24 126.3, 128.2, 128.8, 142.6, 145.2, 145.4, 158.9, 173.1 (C-6). HRFABMS: calcd for $C_{22}H_{23}NO_8Na$ $[M+Na]^+$ 452.1315, found 452.1338.

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