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Toward synthesis of the regular sequence of heparin: synthesis of two tetrasaccharide precursors

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Abstract—Two fully protected tetrasaccharides, which represent precursors for the synthesis of the regular sequence of heparin, were synthesized via coupling of a pair of disaccharide trichloroacetimidates with a thioglycoside and a glucosamine derivative, respectively, in a sequential manner.

Keywords: Heparin; Synthesis; Glycosylation; Thioglycoside; L-Idopyranuronic acid; One pot

1. Introduction

The structure of heparin is composed of a repetitive disaccharide in which a uronic acid is β-(1→4)-linked to 2-amino-2-deoxy-α-D-glucopyranose (D-Glc*p*N). A number of structural variations of this disaccharide exist leading to tremendous microheterogeneity in the polysaccharide. Those structural variations include sulfonation of the hydroxyl groups, various substitutions (sulfonation, acetylation or none) of the amino group of the D-Glc*p*N residue and the alternating occurrence of L-idopyranosyluronic acid (L-Ido*p*A) and D-glucopyranosyluronic acid (D-Glc*p*A). Associated with its complex structure, heparin displays numerous biological activities via interaction with diverse proteins.[1] A few of these heparin-protein interactions have been shown to be sequence-specific by employing homogeneous heparin fragments as probes.[1,2] Chemical synthesis is therefore a powerful tool for obtaining these diverse heparin and heparin-like oligosaccharides. However, the synthesis of heparin oligosaccharides still remains as one of the most formidable tasks for carbohydrate chemists.[3] Among the difficulties posed by heparin oligosaccharide synthesis is a lack of highly efficient (1→4) glycosidic couplings (e.g., >90% yield) between D-Glc*p*A/L-Ido*p*A and D-Glc*p*N residues, which has rarely been achieved. In fact, the well-developed one-pot sequential glycosylation strategy[4] has never been used for the synthesis of heparin oligosaccharides, although a sequential glycosylation protocol has been reported.[5] Using the regular sequence of heparin as a target, we set out to examine the combined use of two orthogonal classes of glycosyl donors, glycosyl trichloroacetimidates and thioglycosides, in a sequential glycosylation approach for the synthesis of heparin oligosaccharides.[6]

2. Results and discussion

Adopting the common protecting-group strategy for heparin synthesis,[3] we envisioned tetrasaccharides **1** as precursors to the regular sequence of heparin (Scheme 1). In this approach, benzyl groups were used as a permanent protecting group, acetyl/benzoyl groups were used for protection of the hydroxyl groups destined for sulfonation and an azide as the precursor to the 2-amino group of the D-Glc*p*N residues. In addition, a levulinoyl group at the 4-hydroxyl group of the nonreducing end residue would enable further elongation

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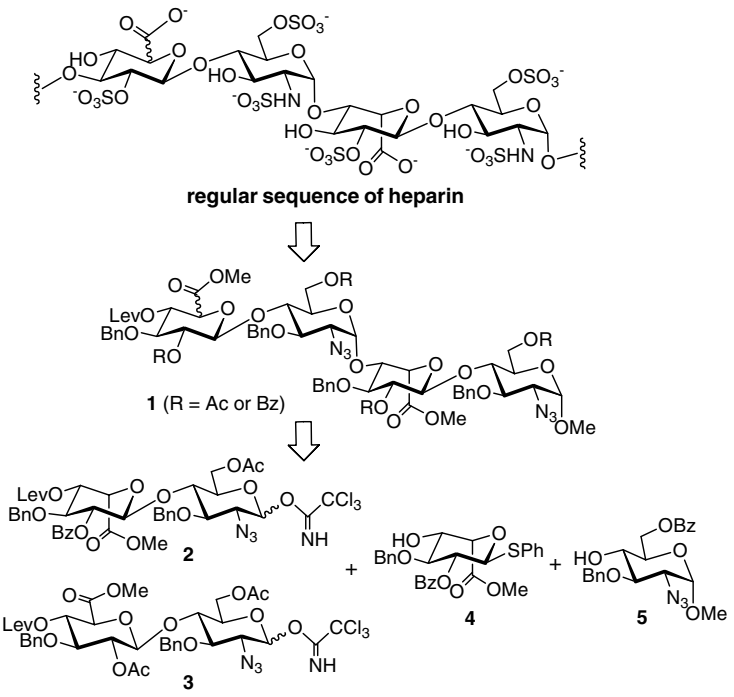
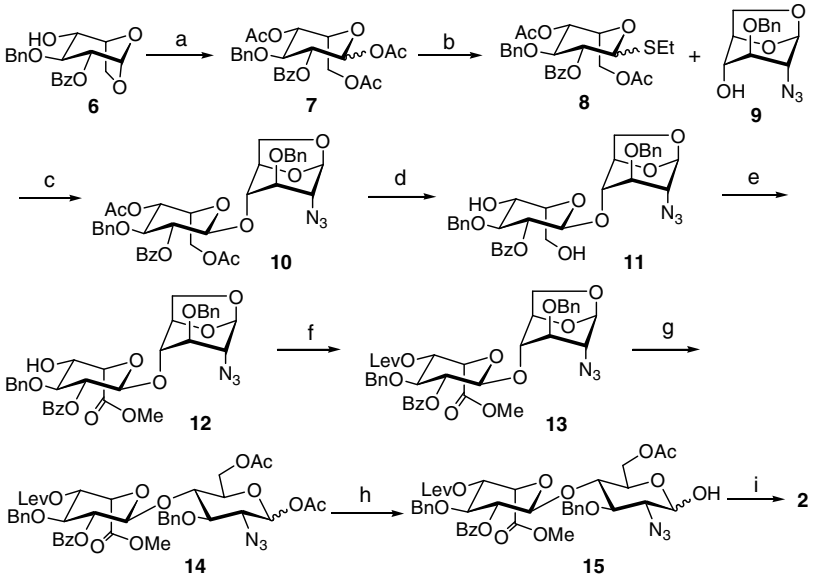


Scheme 1. Retrosynthesis for tetrasaccharides **1**.

upon selective removal. To test a sequential glycosylation protocol for the synthesis of the tetrasaccharides **1**, we attempted to employ trichloroacetimidate **2/3**, thioglycoside **4**,[5,7] and glucosamine derivative **5**[8] as building blocks.

Disaccharide trichloroacetimidate **2** was prepared as shown in Scheme 2. Thus, 1,6-anhydro-2-*O*-benzoyl-3-*O*-benzyl-β-L-idopyranoside **6**, a versatile L-idose building block recently developed by Hung and co-workers,[8] was subjected to acetolysis in the presence of a catalytic amount of TMSOTf, affording triacetate **7**[9] (89%), which was converted readily into ethyl thioglycoside **8** (91%, α/β, 3:2 from ^{1}H NMR) in the presence of EtSH and $BF_3{\cdot}Et_2O$. Coupling of **8** with 1,6-anhydro-2-azido-



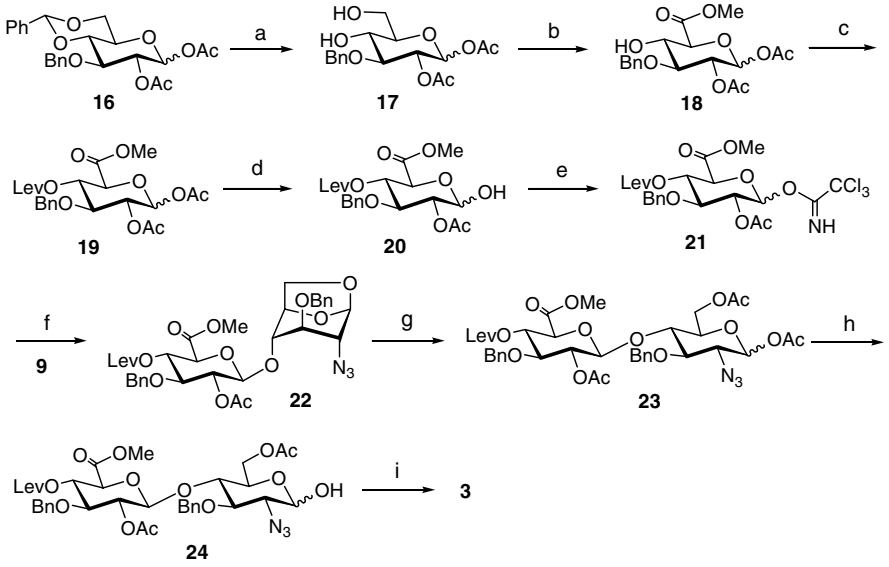
Scheme 2. Synthesis of the disaccharide trichloroacetimidate **2**. Reagents and conditions: (a) TMSOTf, Ac_2O, CH_2Cl_2, 0 °C, 89%; (b) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 91%; (c) AgOTf, NIS, 4 Å MS, toluene, 0 °C→rt, 95%; (d) 0.1 M HCl/methanol, rt, 88%; (e) (i) TEMPO, $Ca(ClO)_2$, $NaHCO_3$–KBr–^{t}Bu$_4$NBr, CH_2Cl_2/H_2O, 0 °C; (ii) CH_2N_2, THF, rt, 84%; (f) Levulinic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 92%; (g) TMSOTf, Ac_2O, CH_2Cl_2, 0 °C, 88%; (h) NH_3, THF/methanol (7:3), 0 °C, 77%; (i) CCl_3CN, K_2CO_3, CH_2Cl_2, 0 °C–rt, 95%.

3-*O*-benzyl-2-deoxy-β-D-glucopyranoside **9**[10] under the action of NIS/AgOTf provided the α-linked disaccharide **10** in an excellent 95% yield. The 4,6-*O*-acetyl groups in **10** were then selectively removed with HCl in methanol (0.1 M) to give diol **11**[11] (88%). Subjection of **11** to the modified TEMPO oxidation protocol with addition of solid $Ca(ClO)_2$ as the co-oxidant and subsequent methyl ester formation with CH_2N_2,[12] provided the desired α-L-Ido*p*A-(1→4)-D-Glc*p*N disaccharide **12**[12] in a satisfactory 84% yield. The remaining 4′-hydroxyl group was protected with levulinoyl ester giving **13** (92%), which was then subjected to acetolysis to provide 1,6-diacetate **14**[13] (88%). Selective removal of the anomeric acetyl group (77%) followed by addition with CCl_3CN led to the desired trichloroacetimidate **2** (95%).

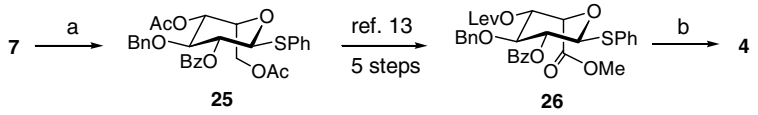
Disaccharide trichloroacetimidate **3** was synthesized starting from 1,2-di-*O*-acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside **16**[14] (Scheme 3). Selective removal of the 4,6-*O*-benzylidene group in **16** with 80% HOAc gave diol **17** (79%), which was subjected to TEMPO oxidation and methylation under similar conditions for **11**→**12** to provide methyl uronate **18** in a good 70% yield. Blocking the remaining 4-hydroxyl group as a levulinate ester, followed by selective removal of the anomeric acetyl group (with Bu_2SnO in methanol)[15] and subsequent reaction of the resulting lactol with CCl_3CN and DBU led to trichloroacetimidate **21**. Coupling of **21** with **9** in the presence of TMSOTf afforded the desired D-Glc*p*A-β-(1→4)-D-Glc*p*N disaccharide **22** in good (70%) yield. In this reaction, the corresponding orthoester was initially formed (as indicated by TLC and ^1H NMR analysis), which was gradually transformed into the glycoside (**22**) upon continued stirring of the mixture at room temperature overnight. Acetolysis of 1,6-anhydride **22** was achieved with 1:5 CF_3COOH/Ac_2O and the same transformations used to convert **14** into **2** were applied for the conversion of acetate **23** into trichloroacetimidate **3**.

Phenyl thioglycoside **4**[5,7] was prepared by adopting, for the most part, transformations previously reported in the literature (Scheme 4).[13] In contrast to the conversion of idose acetate **7** to ethyl thioglycoside **8** (above), where an α/β mixture was produced, treatment of **7** with PhSH and $BF_3{\cdot}Et_2O$ under similar conditions provided only the α anomer of the phenyl thioglycoside **25** (89%).

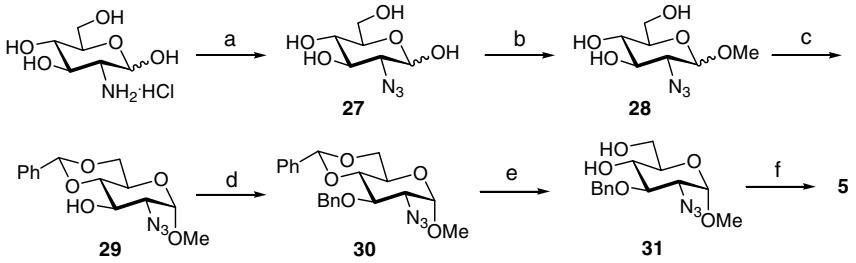
The 2-azidoglucoside **5**[8] was synthesized from D-glucosamine hydrochloride in six steps (Scheme 5). Thus, the crude diazo transfer product **27**[16] was treated with 10% HCl in methanol and the resulting methyl glycoside **28**[17] was subsequently subjected to 4,6-*O*-benzylidene



Scheme 3. Synthesis of the disaccharide trichloroacetimidate **3**. Reagents and conditions: (a) 80% HOAc/H_2O, 70 °C, 79%; (b) (i) TEMPO, $Ca(ClO)_2$, $NaHCO_3$–KBr–$^tBu_4NBr$, CH_2Cl_2/H_2O, 0 °C; (ii) CH_2N_2, THF, rt, 70%; (c) Levulinic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 95%; (d) Bu_2SnO, methanol, 55 °C, 87%; (e) CCl_3CN, DBU, CH_2Cl_2, rt, 93%; (f) TMSOTf, 4 Å MS, CH_2Cl_2, rt, 70%; (g) CF_3COOH/Ac_2O (1:5), 0 °C, 96%; (h) NH_3, THF/methanol (7:3), 0 °C, 92%; (i) CCl_3CN, K_2CO_3, CH_2Cl_2, rt, 92%.



Scheme 4. Synthesis of IdoA thioglycoside **4**. Reagents and conditions: (a) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 89%; (b) $H_2NNH_2{\cdot}HOAc$, CH_2Cl_2, rt, 90%.



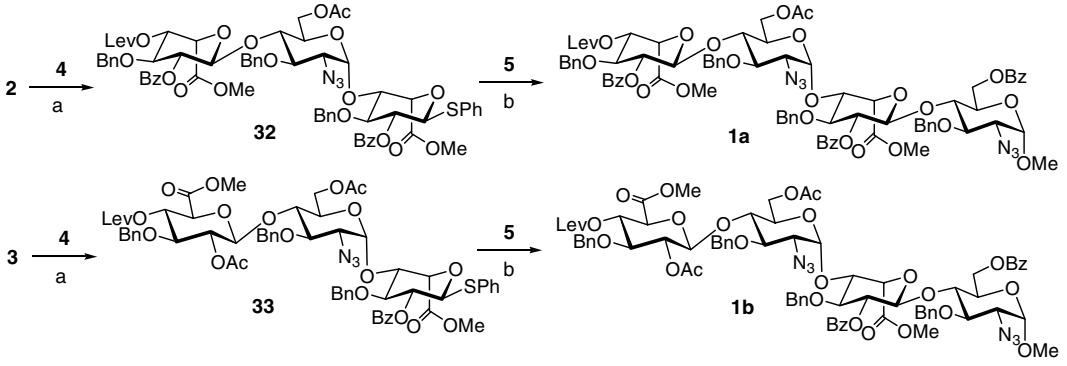
Scheme 5. Synthesis of glucosamine derivative **5**. Reagents and conditions: (a) TfN_3, NaOMe/MeOH, DMAP, rt; (b) 10% HCl/methanol, reflux; (c) *p*-TsOH, $PhCH(OMe)_2$, DMF, 40 °C, 51% (three steps for **29**); (d) NaH, BnBr, THF, rt, 85%; (e) 80% $HOAc/H_2O$, 70 °C, 71%; (f) BzCl, pyridine, CH_2Cl_2, 0 °C, 96%.

formation. The desired α-anomer **29**[17,18] was isolated in 51% yield via column chromatography and the corresponding β-anomer was also obtained in 20% yield. Protection of the remaining 3-hydroxyl group as a benzyl ether followed by removal of the 4,6-*O*-benzylidene acetal[13] and selective protection of the resulting 6-hydroxyl group as a benzoate ester[8] furnished the desired compound **5**.

With all of the building blocks **2**–**5** available, we examined the final glycosidic coupling to elaborate the target tetrasaccharides **1a** and **1b** (Scheme 6). Coupling between trichloroacetimidate **2** and thioglycoside **4** was found to be problematic,[19] leading unavoidably to complex mixtures under a variety of conditions. A modest 56% yield of the desired trisaccharide **32** was obtained under the promotion of TMSOTf in toluene at −78 °C. Promotion with TBSOTf, $Zn(OTf)_2$ or $BF_3{\cdot}Et_2O$, in CH_2Cl_2 or Et_2O, and at varying temperatures did not improve the yield of the coupling product (**32**). In comparison, coupling between imidate **3** and thioglycoside **4** led to fewer by-products; up to a 70% yield of the corresponding trisaccharide **33** was obtained under the same conditions leading to a 56% yield of **32** (from **2**+**4**). The α-stereochemistry of nascent glycosidic linkages in **32** and **33** was established by the resonances of the C-1′ signals, which were appeared at 97.8 and 99.7 ppm, respectively.[20,21] Recently, thioglycosides of the idouronate type were found by van der Marel and co-workers[5] to be effective glycosyl donors under the action of BSP (1-benzenesulfinyl-piperidine)/Tf_2O, a powerful promoter system developed by Crich et al.[22] In our hands, after failing to couple thioglycoside **32** with sugar alcohol **5** under the promotion of NIS/AgOTf (or TfOH, no reaction took place at all), we found independently that BSP/Tf_2O could promote this coupling reaction effectively, furnishing the desired tetrasaccharide **1a** in an impressive 87% yield. Coupling of thioglycoside **33** with **5** under similar conditions gave **1b** in 79% yield.

It should be noted that a successful one-pot procedure for the coupling of imidate **2**/**3**, thioglycoside **4**, and sugar alcohol **5** (and related derivatives for the synthesis of heparin oligosaccharides) still waits for improvement in the efficiency of each coupling step. Nevertheless, we examined a one-pot procedure for sequential coupling of **2**/**3**, **4**, and **5** adopting the present coupling conditions. Thus, treatment of imidate **2**/**3** (1.2 equiv) with thioglycoside **4** (1.0 equiv) in the presence of TMSOTf (0.05 equiv) in CH_2Cl_2 under argon (−78 °C to rt) followed by subsequent addition of BSP (1.2 equiv), Tf_2O (1.2 equiv, at −60 °C), and **5** in CH_2Cl_2 (2.0 equiv, at −40 °C) afforded the desired tetrasaccharides **1a** and **1b** in a low 10% and 17% isolated yield, respectively.

In summary, tetrasaccharides **1a** and **1b** are synthesized via coupling of trichloroacetimidate **2**/**3**,



Scheme 6. Sequential glycosylation for the synthesis of tetrasaccharides **1a** and **1b**. Reagents and conditions: (a) TMSOTf, 4 Å MS, toluene, −78 °C, 56% for **32**; 70% for **33**; (b) BSP, Tf_2O, CH_2Cl_2, −60 °C, 30 min, then −40 °C, **5**, 15 min, →rt, 87% for **1a**, 79% for **1b**.

thioglycoside **4**, and glucosamine derivative **5** in a sequential manner. A successful one-pot procedure requires further improvement of the efficiency of each coupling steps, especially of the one between the 2-azidoglucopyranosyl imidates (e.g., **2**/**3**) and the idopyranosyluronate thioglycosides (e.g., **4**). It should be mentioned that a tetrasaccharide similar to **1a** en route to heparin fragments has been prepared by Sinaÿ and co-workers employing a convergent 2+2 coupling approach.[21] In addition, the present preparation of the useful building blocks **2**–**5** employs routine transformations but in new sequences.

3. Experimental

3.1. General methods[23]

3.1.1. 1,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-3-*O*-benzyl-L-idopyranose (7). To a cooled solution of 1,6-anhydride **6**[8] (366 mg, 1.03 mmol) in dry CH_2Cl_2 (5 mL) and Ac_2O (2 mL) at 0 °C, TMSOTf (three drops) was added. After stirring for 10 min, the reaction was quenched by the addition of Et_3N (0.5 mL), and the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (4:1, petroleum ether/EtOAc) to give **7**[9] (456 mg, 89%) as a colorless syrup. A small amount of the mixture was separated for ^1H NMR measurement. Compound **7α**: $R_f = 0.79$ (petroleum ether/EtOAc 2:1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (m, 2H), 7.60 (t, 1H, $J = 7.5$ Hz), 7.46 (t, 2H, $J = 7.8$ Hz), 7.37–7.26 (m, 5H, ArH), 6.20 (d, 1H, $J = 1.2$ Hz, H-1), 5.30 (m, 1H, H-2), 4.93 (t, 1H, $J = 2.1$ Hz, H-4), 4.78 (d, 2H, $J = 12.3$ Hz, $PhCH_2$), 4.47 (m, 1H, H-5), 4.27 (m, 2H, H-6), 4.00 (t, 1H, $J = 3.0$ Hz, H-3), 2.07, 1.92 (s each, 3H each, Ac). Compound **7β**: $R_f = 0.82$ (2:1, petroleum ether/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (m, 2H), 7.59 (t, 1H, $J = 7.5$ Hz), 7.46 (t, 2H, $J = 7.8$ Hz), 7.37–7.26 (m, 5H, ArH), 6.22 (s, 1H, H-1), 5.21 (m, 1H, H-2), 4.99 (br, 1H, H-4), 4.81 (d, 2H, $J = 12.3$ Hz, $PhCH_2$), 4.61 (m, 1H, H-5), 4.31 (m, 2H, H-6), 3.90 (br, 1H, H-3), 2.09, 1.94 (s each, 3H each, Ac); IR: 2928, 1745, 1371, 1272, 1223, 1114, 1097, 1056, 715 cm^{-1}; ESIMS *m*/*z* calcd for $[C_{26}H_{28}O_{10}]Na^+$ 523.1575. Found: 523.1579.

3.1.2. Ethyl 4,6-di-*O*-acetyl-2-*O*-benzoyl-3-*O*-benzyl-1-thio-L-idopyranoside (8). To a solution of acetate **7** (281 mg, 0.56 mmol) and ethanethiol (0.063 mL, 0.84 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C, $BF_3{\cdot}Et_2O$ (0.028 mL, 0.21 mmol) was added. After stirring at rt for 5 h, a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was washed with water, dried over Na_2SO_4, and then filtered and concentrated. The residue was purified by silica gel column chromatography (4:1, petroleum ether/EtOAc) to provide **8** (262 mg, 91%) as a colorless syrup (α/β, 1.5:1). $R_f = 0.78$ (2:1, petroleum ether/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 8.18–8.07 (m, 2H), 7.57 (m, 1H), 7.47–7.32 (m, 7H, ArH), 5.44 (s, 0.4H), 5.27 (t, 0.4H, $J = 1.5$ Hz), 5.22 (m, 0.6H), 5.13 (d, 0.6H, $J = 1.8$ Hz), 4.92–4.68 (m, 4H), 4.25 (m, 2H), 3.97 (t, 0.6H, $J = 3.0$ Hz), 3.82 (m, 0.4H), 2.78 (m, 1.2H), 2.71–2.66 (m, 0.8H), 2.06 (s, 3H, Ac), 1.97 (s, 1.2H, Ac), 1.79 (s, 1.8H, Ac), 1.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.1, 165.5, 165.1, 137.2, 133.5, 130.0, 129.8, 129.5, 128.6, 128.4, 128.2, 127.9, 127.8, 82.6, 81.5, 73.0, 72.8, 72.7, 72.6, 72.0, 69.6, 69.0, 67.2, 66.0, 64.1, 62.8, 26.8, 26.0, 20.7, 20.6, 15.1, 15.0; IR: 2968, 2930, 1746, 1453, 1268, 1235, 1112, 1070, 1027, 713 cm^{-1}; ESIMS *m*/*z* calcd for $[C_{26}H_{30}O_8S]Na^+$: 525.1554. Found: 525.1561.

3.1.3. 4,6-Di-*O*-acetyl-2-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranosyl-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (10). A mixture of thioglycoside **8** (117 mg, 0.227 mmol), alcohol **9** (53 mg, 0.189 mmol), and freshly activated 4 Å MS (100 mg) in dry toluene (1.5 mL) was stirred under argon at rt for 30 min. The mixture was cooled in an ice bath and then NIS (65 mg, 0.28 mmol) and a solution of AgOTf in toluene (0.09 M, 0.4 mL) were added. The ice bath was removed and stirring continued for 1 h. The reaction was then quenched by the addition of Et_3N (0.2 mL). The mixture was filtered and concentrated under reduced pressure. Silica gel column chromatography (2:1, petroleum ether/EtOAc) of the residue provided **10** (129 mg, 95%) as a colorless syrup. $R_f = 0.62$ (2:1, petroleum ether/EtOAc); $[\alpha]_D^{19}$ −9.4 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.01–7.24 (m, 15H, ArH), 5.55 (s, 1H), 5.31 (d, 1H, $J = 3.3$ Hz), 5.27 (s, 1H), 4.95 (br, 1H), 4.89 (d, 1H, $J = 11.5$ Hz), 4.78 (d, 1H, $J = 4.8$ Hz), 4.73–4.57 (m, 4H), 4.51 (t, 1H, $J = 6.3$ Hz), 4.27–4.06 (m, 3H), 3.88 (br, 1H), 3.82–3.72 (m, 2H), 3.21 (br, 1H), 1.99, 1.97 (s each, 3H each, Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.9, 164.9, 137.3, 137.2, 133.5, 129.6, 129.2, 128.3, 127.7, 127.6, 127.5, 100.9, 95.0, 77.8, 73.0, 72.7, 72.0, 71.9, 71.8, 66.8, 66.3, 65.4, 64.0, 62.8, 60.3, 20.6, 20.6; IR: 2103, 1745, 1725, 1234, 1113, 1027, 714 cm^{-1}; ESIMS *m*/*z* calcd for $[C_{37}H_{39}N_3O_{12}]Na^+$: 740.2426. Found: 740.2428.

3.1.4. 2-*O*-Benzoyl-3-*O*-benzyl-α-L-idopyranosyl-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (11). A solution of **10** (1.154 g, 1.6 mmol) in 0.1 M HCl/CH_3OH (20 mL) was stirred at rt for 5 h. The mixture was neutralized with Et_3N, and then concentrated. The residue was purified by silica gel column chromatography (2:1:1, petroleum ether/EtOAc/CH_2Cl_2) to provide **11**[11] (900 mg, 88%) as a colorless syrup. $R_f = 0.11$ (2:1, petroleum ether/EtOAc).

3.1.5. Methyl (2-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranosyl)-uronate-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (12). The same procedure described for the preparation of methyl glucuronate **18** (from diol **17**) was employed for the preparation of **12** from **11**. Purification by silica gel column chromatography (3:1:1, petroleum ether/EtOAc/CH_2Cl_2) gave **12**[12] (84%) as a colorless syrup. $R_f = 0.34$ (2:1:1, petroleum ether/EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$ −22.1 (*c* 1.2, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 164.9, 137.3–127.7, 101.1, 96.3, 78.0, 75.0, 74.0, 73.1, 73.0, 72.0, 68.2, 68.0, 67.2, 65.7, 61.2, 52.3; IR: 3577, 3031, 2111, 1749, 1720, 1271, 1108, 714, 696 cm^{-1}; ESIMS *m*/*z* calcd for $[C_{34}H_{35}N_3O_{11}]Na^+$: 684.2164. Found: 684.2166.

3.1.6. Methyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosyl)uronate-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (13). The same procedure described for the preparation of levulinoyl ester **19** (from **18**) was employed for the preparation of **13** from **12**. Purification by silica gel column chromatography (2:1, petroleum ether/EtOAc) gave **13** (92%) as a colorless syrup. $R_f = 0.11$ (3:4:1, petroleum ether/toluene/acetone); $[\alpha]_D^{21}$ −11.8 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.05–7.20 (m, 15H), 5.50 (s, 1H), 5.38 (s, 1H), 5.25 (d, 2H, $J = 6.3$ Hz), 4.87 (d, 2H, $J = 11.1$ Hz), 4.74 (m, 2H), 4.55 (s, 2H), 4.01 (d, 1H, $J = 7.2$ Hz), 3.94 (s, 1H), 3.80 (m, 1H), 3.74 (s, 4H), 3.64 (t, 1H, $J = 3.3$ Hz), 3.24 (d, 1H, $J = 3.0$ Hz), 2.63 (m, 2H), 2.43 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 171.5, 168.5, 165.1, 137.2, 137.1, 133.6, 129.7, 129.2, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 101.1, 95.7, 77.8, 74.7, 73.2, 72.3, 71.9, 67.8, 66.5, 66.2, 65.7, 61.4, 52.5, 37.6, 29.6, 29.5, 27.8; IR: 2104, 1746, 1721, 1269, 1112, 1029 cm^{-1}; ESIMS *m*/*z* calcd for $[C_{39}H_{41}N_3O_{13}]Na^+$: 782.2532. Found: 782.2540.

3.1.7. Methyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosyl)uronate-(1→4)-1,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-D-glucopyranose (14). To a solution of 1,6-anhydride **13** (2.55 g, 3.35 mmol) in dry CH_2Cl_2 (10 mL) was added Ac_2O (10 mL). The mixture was cooled to 0 °C and TMSOTf (three drops) was added under argon. After stirring at 0 °C for 10 min, the reaction was quenched by the addition of Et_3N (1 mL). The resulting mixture was concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (4:1, petroleum ether/EtOAc) to provide **14**[13] (2.55 g, 88%) as a colorless syrup (α/β, 4:1). $R_f = 0.60$ (1:1, petroleum ether/EtOAc).

3.1.8. Methyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosyl)uronate-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-D-glucopyranose (15). Ammonia gas was bubbled through a solution of compound **14** (1.34 g, 1.56 mmol) in a mixture of THF/CH_3OH (7:3, 15 mL) at 0 °C for 20 min. The solvent was then concentrated under reduced pressure to give a residue that was purified by silica gel column chromatography (1:1, petroleum ether/EtOAc) to afford **15** (988 mg, 77%) as a colorless syrup (α/β, 4:1). $R_f = 0.21$ (2:1, petroleum ether/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.58 (m, 1H), 7.46–7.23 (m, 12H), 5.33 (d, 0.8H, $J = 2.1$ Hz), 5.31 (d, 0.2H, $J = 2.8$ Hz), 5.27 (t, 0.8H, $J = 3.3$ Hz), 5.20 (m, 1H), 5.14 (t, 0.8H, $J = 3.0$ Hz), 5.11 (t, 0.2H, $J = 3.0$ Hz), 5.01 (d, 0.2H, $J = 3.3$ Hz), 4.99 (d, 0.2H, $J = 3.0$ Hz), 4.83–4.67 (m, 4H), 4.58 (m, 0.8H), 4.46 (d, 0.8H, $J = 12.6$ Hz), 4.28 (m, 1H), 4.11 (d, 0.8H, $J = 9.6$ Hz), 4.01–3.79 (m, 3.2H), 3.49 (s, 0.8H), 3.47 (s, 3H), 3.43 (m, 1H), 3.33 (m, 0.8H), 2.68 (m, 2H), 2.48 (m, 2H), 2.12 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 171.6, 171.0, 170.9, 168.7, 165.3, 137.6, 137.4, 137.1, 133.6, 129.8, 129.0, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.3, 97.5, 96.3, 91.7, 81.0, 78.1, 74.9, 74.6, 74.3, 73.1, 72.8, 69.0, 68.2, 68.0, 67.3, 67.1, 67.0, 63.9, 62.1, 52.1, 37.5, 29.6, 27.7, 20.9, 20.8; IR: 3456, 2111, 1745, 1720, 1270, 1233, 1109, 1070 cm^{-1}; MALDIMS *m*/*z* calcd for $[C_{41}H_{45}N_3O_{15}]Na^+$: 842.2743. Found: 842.2781.

3.1.9. Methyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosyl)uronate-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-D-glucopyranosyl trichloroacetimidate (2). To a solution of compound **15** (269 mg, 0.33 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added anhydrous K_2CO_3 (114 mg, 0.82 mmol) followed by CCl_3CN (0.22 mL, 2.00 mmol). After stirring at rt for 30 min, the mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography (1:1, petroleum ether/EtOAc) providing **2** (306 mg, 95%, α/β, 2:7) as a colorless syrup. A small amount of the mixture was separated. Compound **2β**: $R_f = 0.68$ (1:1, petroleum ether/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.04 (m, 2H), 7.58 (m, 1H), 7.46–7.25 (m, 12H), 5.62 (d, 1H, $J = 8.7$ Hz), 5.30 (br, 1H), 5.21 (t, 1H, $J = 3.3$ Hz), 5.12 (br, 1H), 5.02 (d, 1H, $J = 3.0$ Hz), 4.78 (d, 2H, $J = 11.4$ Hz), 4.74 (s, 2H), 4.48 (d, 1H, $J = 12.2$ Hz), 4.32 (dd, 1H, $J = 4.2$, 12.2 Hz), 4.07 (t, 1H, $J = 9.6$ Hz), 3.94 (t, 1H, $J = 3.0$ Hz), 3.72 (t, 1H, $J = 8.7$ Hz), 3.64 (d, 1H, $J = 9.6$ Hz), 3.50 (s, 3H), 3.43 (t, 1H, $J = 9.0$ Hz), 2.67 (m, 2H), 2.48 (m, 2H), 2.12, 2.05 (s each, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 171.6, 170.4, 168.5, 165.2, 160.8, 137.4, 137.1, 133.5, 129.7, 129.0, 128.4, 128.2, 128.0, 127.9, 127.5, 97.5, 96.5, 90.2, 81.0, 74.9, 73.9, 72.9, 72.8, 67.9, 67.8, 66.9, 65.5, 61.7, 52.1, 37.5, 29.6, 27.7, 20.8. Compound **2α**: $R_f = 0.52$ (1:1, petroleum ether/EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.10 (m, 2H), 7.57 (m, 1H), 7.49–7.18 (m, 12H), 5.56 (d, 1H, $J = 7.8$ Hz), 5.29 (s, 1H), 5.26 (br, 1H), 5.20 (br, 1H), 4.85 (d, 2H, $J = 10.8$ Hz), 4.72 (d,

2H, $J = 11.7$ Hz), 4.62 (m, 2H), 4.37 (m, 1H), 3.99 (t, 1H, $J = 2.7$ Hz), 3.93 (d, 1H, $J = 9.6$ Hz), 3.79 (s, 3H), 3.65 (m, 2H), 3.50 (t, 1H, $J = 9.0$ Hz), 2.55 (m, 2H), 2.34 (m, 2H), 2.06, 2.03 (s each, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 171.6, 170.4, 168.5, 165.2, 160.4, 137.3, 137.0, 133.5, 129.8, 129.0, 128.4, 128.1, 128.0, 127.6, 127.4, 97.6, 94.3, 90.7, 78.4, 77.4, 74.8, 74.1, 72.9, 72.7, 71.8, 68.0, 67.8, 67.2, 63.0, 61.6, 52.1, 37.5, 29.6, 27.7, 20.8; IR: 2114, 1744, 1722, 1677, 1272, 1070 cm^{-1}; ESIMS *m/z* calcd for $[C_{43}H_{45}Cl_3N_4O_{15}]Na^+$: 985.1839. Found 985.1838.

3.1.10. 1,2-di-*O*-acetyl-3-*O*-benzyl-D-glucopyranose (17). A solution of compound **16** (2.61 g, 5.9 mmol) in 80% aqueous HOAc (30 mL) was heated at 70 °C for 6 h and then concentrated. The residue was purified by silica gel column chromatography (2:1, petroleum ether/EtOAc) providing **17** (1.64 g, 79%, α/β, 1:1) as a colorless syrup. $R_f = 0.35$ (2:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 6.27 (d, 0.5H, $J = 3.6$ Hz), 5.61 (d, 0.5H, $J = 8.1$ Hz), 5.05 (t, 0.5H, $J = 8.7$ Hz), 4.97 (dd, 0.5H, $J = 3.3$, 9.3 Hz), 4.82 (m, 1.5H), 4.72 (m, 0.5H), 3.97 (br, 0.5H), 3.82 (m, 4H), 3.59 (t, 0.5H, $J = 9.0$ Hz), 3.46 (m, 0.5H), 3.20 (br, 1H), 2.13 (s, 1.5H), 2.06 (s, 1.5H), 1.96 (s, 1.5H), 1.95 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.5, 169.4, 138.2, 137.9, 128.5, 128.3, 127.7, 127.6, 127.4, 92.0, 89.7, 82.0, 79.2, 76.2, 75.0, 74.6, 73.8, 71.6, 71.4, 69.6, 69.1, 61.2, 61.1, 20.8, 20.7, 20.6, 20.5; IR: 3448, 1751, 1240, 1059 cm^{-1}; ESIMS *m/z* calcd for $[C_{17}H_{22}O_8]Na^+$: 377.1207. Found: 377.1212.

3.1.11. Methyl (1,2-di-*O*-acetyl-3-*O*-benzyl-D-glucopyranosyl)uronate (18). To a solution of diol **17** (6.951 g, 19.6 mmol) in CH_2Cl_2 (30 mL) containing TEMPO (76 mg, 0.02 equiv) was added a solution of saturated aqueous $NaHCO_3$ (20 mL) containing KBr (1.077 g, 0.5 equiv) and $^tBu_4NBr$ (451 mg, 0.07 equiv). The mixture was cooled to 0 °C, and then $Ca(ClO)_2$ (8.512 g, 3.0 equiv) was added slowly in portions under vigorous stirring. After TLC indicated complete conversion of the starting material, the reaction was quenched by the addition of a saturated solution of NaCl (20 mL) and $NaHSO_3$ (7.66 g, 3 equiv). After further stirring for 5 min, HOAc was added to adjust the final pH value of the mixture to pH 3. The resulting mixture was diluted with EtOAc (50 mL). The organic phase was separated and the remaining aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried with Na_2SO_4, and then filtered and concentrated in vacuo to yield the corresponding crude glucuronic acid, which was used without further purification. The crude glucuronic acid was dissolved in THF (30 mL) and treated with CH_2N_2 in ether at rt. After complete disappearance of the glucuronic acid, the mixture was concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc/CH_2Cl_2 3:1:1 to 2:1:1, then CH_2Cl_2/acetone 23:1) to provide **18** (5.25 g, 70%, α/β, 1:1) as a colorless syrup. $R_f = 0.30$ (2:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 6.33 (d, 0.5H, $J = 3.3$ Hz), 5.65 (d, 0.5H, $J = 7.5$ Hz), 5.07 (t, 0.5H, $J = 8.7$ Hz), 5.01 (dd, 0.5H, $J = 3.3$, 9.6 Hz), 4.87 (d, 0.5H, $J = 11.7$ Hz), 4.84 (d, 0.5H, $J = 12.0$ Hz), 4.74 (d, 0.5H, $J = 11.7$ Hz), 4.70 (d, 0.5H, $J = 12.0$ Hz), 4.29 (d, 0.5H, $J = 9.6$ Hz), 3.91 (m, 1.5H), 3.78 (s, 1.5H), 3.77 (s, 1.5H), 3.62 (m, 1.5H), 2.14 (s, 1.5H), 2.06 (s, 1.5H), 1.96 (s, 1.5H), 1.91 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 169.3, 169.2, 169.0, 168.8, 168.6, 138.0, 137.7, 128.2, 127.6, 127.5, 127.3, 91.6, 89.2, 80.6, 78.0, 74.9, 74.6, 74.4, 72.4, 71.4, 71.2, 70.8, 70.4, 52.6, 20.6, 20.5, 20.4, 20.3; IR: 3498, 1752, 1239, 1216, 1052 cm^{-1}; ESIMS *m/z* calcd for $[C_{18}H_{22}O_9]Na^+$: 405.1156, found: 405.1151. Anal. Calcd for $C_{18}H_{22}O_9$: C, 56.54; H, 5.80. Found: C, 56.19; H, 5.90.

3.1.12. Methyl (1,2-di-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-D-glucopyranosyl)uronate (19). A mixture of DCC (4.27 g, 20.6 mmol) and DMAP (173 mg, 1.37 mmol) in dry CH_2Cl_2 (5 mL) was added to a solution of compound **18** (5.25 g, 13.7 mmol) and levulinic acid (2.14 mL, 20.6 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under argon. After stirring overnight, the precipitate was removed by filtration through Celite and washed with CH_2Cl_2. The solution was concentrated in vacuo and the residue was purified by silica gel column chromatography (2:1, petroleum ether/EtOAc) to afford **19** (6.26 g, 95%, α/β, 3:7) as a colorless syrup. $R_f = 0.16$ (3:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.23 (m, 5H), 6.35 (d, 0.7H, $J = 3.3$ Hz), 5.67 (d, 0.3H, $J = 7.5$ Hz), 5.23–5.10 (m, 1.3H), 5.08 (dd, 0.7H, $J = 3.9$, 13.5 Hz), 4.68 (m, 1.7H), 4.61 (m, 0.3H), 4.32 (d, 0.7H, $J = 9.6$ Hz), 4.09 (d, 0.3H, $J = 9.6$ Hz), 3.98 (t, 0.7H, $J = 9.3$ Hz), 3.80 (t, 0.3H, $J = 8.7$ Hz), 3.68 (s, 2.1H), 3.67 (s, 0.9H), 2.69 (m, 2H), 2.52 (m, 2H), 2.16 (s, 2.1H), 2.15 (s, 2.1H), 2.13 (s, 0.9H), 2.06 (s, 0.9H), 1.96 (s, 2.1H), 1.94 (s, 0.9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 176.6, 171.3, 169.4, 169.0, 168.9, 168.4, 167.5, 167.2, 137.7, 137.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 91.3, 88.9, 78.6, 76.1, 74.8, 74.1, 73.0, 70.8, 70.6, 70.5, 70.4, 52.9, 37.6, 37.4, 29.7, 27.5, 20.7, 20.5, 20.4; IR: 1747, 1719, 1213 cm^{-1}; ESIMS *m/z* calcd for $[C_{23}H_{28}O_{11}]Na^+$: 503.1524. Found: 503.1526.

3.1.13. Methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-D-glucopyranosyl)uronate (20). To a solution of **19** (848 mg, 1.76 mmol) in dry MeOH (8 mL) was added Bu_2SnO (100 mg, 0.40 mmol). The mixture was stirred at 55 °C until the starting material disappeared and then was filtered and concentrated in vacuo. Silica gel column chromatography of the residue (2:1, petroleum ether/

EtOAc) provided **20** (672 mg, 87%) as a colorless syrup. $R_f = 0.17$ (1:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) (data for β anomer): δ 7.35–7.25 (m, 5H), 5.49 (d, 1H, $J = 3.3$ Hz), 5.14 (t, 1H, $J = 9.3$ Hz), 4.87 (dd, 1H, $J = 3.6$, 9.3 Hz), 4.69 (s, 2H), 4.51 (d, 1H, $J = 9.6$ Hz), 4.09 (t, 1H, $J = 9.0$ Hz), 3.69 (s, 3H), 2.70 (m, 2H), 2.47 (m, 2H), 2.17 (s, 3H), 2.05 (s, 3H); ^{1}H NMR (data for α anomer): δ 7.35–7.25 (m, 5H), 5.69 (d, 1H, $J = 7.8$ Hz), 5.20 (m, 1H), 4.94 (t, 1H, $J = 8.7$ Hz), 4.66 (d, 2H, $J = 12.0$ Hz), 4.01 (d, 1H, $J = 9.6$ Hz), 3.78 (m, 1H), 3.70 (s, 1H), 2.65 (m, 2H), 2.46 (m, 2H), 2.16 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 206.3, 171.5, 171.4, 170.5, 170.2, 168.9, 168.0, 137.9, 137.5, 128.3, 128.2, 127.7, 127.6, 127.5, 95.3, 89.9, 78.7, 76.0, 74.7, 74.2, 74.1, 73.9, 72.8, 72.4, 72.3, 71.0, 70.9, 70.6, 68.3, 52.8, 52.7, 37.4, 29.7, 29.5, 27.8, 27.5, 20.7, 20.5; IR: 3448, 1749, 1721, 1236, 1158, 1071 cm^{-1}; ESIMS *m/z* calcd for $[C_{21}H_{26}O_{10}]Na^+$: 461.1418. Found: 461.1421. Anal. Calcd for $C_{21}H_{26}O_{10}$: C, 57.53; H, 5.98. Found: C, 57.37; H, 6.12.

3.1.14. Methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-D-glucopyranosyl)uronate trichloroacetimidate (21). To a solution of compound **20** (1.991 g, 4.54 mmol) in dry CH_2Cl_2 (20 mL) in an ice bath was added CCl_3CN (2.51 mL, 25.0 mmol) followed by addition of DBU (three drops). The mixture was stirred at rt until TLC showed the reaction was complete. The mixture was then concentrated to give a residue that was purified by silica gel column chromatography (1:1, petroleum ether/EtOAc) to afford **21** (2.46 g, 93%) as a colorless syrup. $R_f = 0.67$ (1:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) (data for α anomer): δ 8.68 (s, 1H), 7.36–7.27 (m, 5H), 6.61 (d, 1H, $J = 3.3$ Hz), 5.25 (t, 1H, $J = 9.3$ Hz), 5.10 (dd, 1H, $J_1 = 3.6$, 9.6 Hz), 4.73 (d, 2H, $J = 11.4$ Hz), 4.40 (d, 1H, $J = 9.9$ Hz), 4.12 (t, 1H, $J_1 = 9.3$ Hz, $J_2 = 9.9$ Hz), 3.72 (s, 3H), 2.72 (m, 2H), 2.54 (m, 2H), 2.18 (s, 3H), 1.96 (s, 3H); ^{1}H NMR (data for β anomer): δ 8.70 (s, 1H), 7.38–7.27 (m, 5H), 5.85 (d, 1H, $J = 7.2$ Hz), 5.36 (m, 2H), 4.69 (d, 2H, $J = 12.0$), 4.18 (d, 1H, $J = 9.3$ Hz), 3.84 (t, 1H, $J = 8.7$ Hz), 3.72 (s, 3H), 2.72 (m, 2H), 2.55 (m, 2H), 2.18 (s, 3H), 1.97 (s, 3H); ESI-MS: 604.2 [M+Na$^+$].

3.1.15. Methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)uronate-(1→4)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (22). A mixture of glycosyl imidate **21** (2.478 g, 4.25 mmol), sugar alcohol **9** (907 mg, 3.27 mmol), and freshly activated 4 Å molecular sieves (500 mg) in dry CH_2Cl_2 (20 mL) was stirred at rt under argon for 30 min. Then TMSOTf (0.06 mL, 0.327 mmol) was added dropwise. After stirring overnight at rt, the reaction was quenched by the addition of Et_3N (0.5 mL). The mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was subjected to silica gel column chromatography (4:1, petroleum ether/EtOAc) to provide disaccharide **22** (1.63 g, 70%) as a colorless syrup. $R_f = 0.20$ (2:1, petroleum ether/EtOAc); $[\alpha]_D^{19}$ −3.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.24 (m, 10H), 5.44 (s, 1H), 5.26 (t, 1H, $J = 9.3$ Hz), 5.11 (dd, 1H, $J = 7.5$, 9.0 Hz), 4.74 (d, 1H, $J = 7.5$ Hz), 4.70–4.59 (m, 5H), 4.07 (dd, 1H, $J = 0.9$, 7.5 Hz), 3.95 (d, 1H, $J = 9.9$ Hz), 3.86 (br, 1H), 3.75 (m, 3H), 3.71 (s, 3H), 3.23 (s, 1H), 2.68 (m, 2H), 2.48 (m, 2H), 2.17 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 171.3, 169.1, 167.3, 137.6, 137.3, 128.4, 128.3, 127.9, 127.8, 127.7, 100.6, 98.6, 79.0, 77.4, 74.7, 73.7, 73.2, 72.7, 72.5, 71.7, 70.9, 65.0, 59.6, 52.8, 37.5, 29.8, 29.6, 27.6, 20.7; IR: 2109, 1755, 1742, 1720, 1154, 742 cm^{-1}; ESIMS *m/z* calcd for $[C_{34}H_{39}N_3O_{13}]Na^+$: 720.2375. Found: 720.2371.

3.1.16. Methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)uronate-(1→4)-1,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-D-glucopyranose (23). Compound **22** (43 mg, 0.06 mmol) was dissolved in Ac_2O (0.7 mL) and cooled in an ice bath. Then a mixture of CF_3COOH/Ac_2O (1:5, 0.9 mL) was added. After stirring for 10 min, the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (1:1, petroleum ether/EtOAc) to afford **23** (47 mg, 96%) as a colorless syrup. $R_f = 0.32$ (1:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) (data for α anomer): δ 7.42–7.23 (m, 10H), 6.17 (d, 1H, $J = 3.6$ Hz), 5.20 (m, 2H), 4.72 (d, 2H, $J = 11.4$ Hz), 4.58 (d, 2H, $J = 10.2$ Hz), 4.35 (dd, 1H, $J = 0.6$, 12.1 Hz), 4.15 (dd, 1H, $J = 5.1$, 12.3 Hz), 3.85 (m, 4H), 3.70 (t, 1H, $J = 9.0$ Hz), 3.52 (m, 1H), 3.49 (s, 3H), 2.67 (m, 2H), 2.48 (m, 2H), 2.17 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.9, 171.3, 170.4, 169.1, 168.8, 167.0, 138.1, 137.5, 128.4, 128.2, 127.8, 127.7, 127.5, 127.4, 101.0, 90.1, 79.5, 78.2, 77.8, 75.3, 74.2, 72.9, 72.4, 71.1, 70.7, 62.2, 61.6, 52.7, 37.5, 29.8, 27.6, 21.0, 20.8, 20.7; IR: 2117, 1765, 1746, 1720, 1240, 1219 cm^{-1}; ESI-MS: 817.4 [M+NH$_4$]$^+$. Anal. Calcd for $C_{38}H_{45}N_3O_{16}$: C, 57.07; H, 5.67; N, 5.25. Found: C, 57.24; H, 5.81; N, 4.91.

3.1.17. Methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)uronate-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-D-glucopyranose (24). The same procedure employed for the preparation of lactol **15** (from acetate **14**) was employed for the preparation of **24** from **23**. Purification by silica gel column chromatography (1:1, petroleum ether/EtOAc) afforded **24** (92%, α/β, 1:1) as a colorless syrup. $R_f = 0.29$ (1:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.23 (m, 10H), 5.24 (t, 0.5H, $J = 3.0$ Hz), 5.20 (m, 0.5H), 5.19 (s, 0.5H), 5.15 (t, 0.5H, $J = 3.0$ Hz), 5.11 (s, 0.5H), 5.09–5.00 (m, 1.5H), 4.82 (s, 0.5H), 4.78 (s,

0.5H), 4.72 (d, 0.5H, $J = 13.2$ Hz), 4.66 (s, 1H), 4.57 (m, 2H), 4.42 (m, 1H), 4.17–4.05 (m, 1H), 3.97 (t, 0.5H, $J = 8.4$, 9.9 Hz), 3.81–3.66 (m, 4H), 3.51 (s, 1.5H), 3.49 (s, 1.5H), 3.45 (m, 1H), 3.34 (t, 0.5H, $J = 8.1$ Hz), 3.33 (t, 0.5H, $J = 10.5$ Hz), 2.66 (m, 2H), 2.48 (m, 2H), 2.15 (s, 3H), 2.10 (s, 1.5H), 2.08 (s, 1.5H), 1.98 (s, 1.5H), 1.95 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 171.3, 170.7, 169.2, 167.2, 138.2, 137.6, 137.5, 128.4, 128.2, 127.8, 127.7, 127.7, 127.5, 127.3, 100.9, 95.9, 91.7, 80.8, 79.5, 78.5, 78.1, 77.7, 75.0, 74.9, 74.2, 72.8, 72.7, 72.6, 72.4, 71.1, 68.4, 67.1, 63.5, 62.3, 52.7, 37.5, 29.7, 29.6, 27.5, 20.9, 20.8, 20.6; IR: 3443, 2116, 1766, 1744, 1702, 1235, 1031 cm^{-1}; ESIMS m/z calcd for $[C_{36}H_{43}N_3O_{15}]Na^+$: 780.2586. Found: 780.2587.

3.1.18. Methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)uronate-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-D-glucopyranosyl trichloroacetimidate (3). The same procedure described for the preparation of trichloroacetimidate **21** (from lactol **20**) was employed for the preparation of **3** from **24**. Purification by silica gel column chromatography (1:1, petroleum ether/EtOAc) afforded **3** (92%) as a colorless syrup. $R_f = 0.41$ (1:1, petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) (data for α anomer): δ 8.73 (s, 1H), 7.42–7.24 (m, 10H), 6.34 (d, 1H, $J = 3.6$ Hz), 5.21 (m, 2H), 5.09 (t, 1H, $J = 9.6$ Hz), 4.77 (d, 1H, $J =$ 11.4 Hz), 4.69 (d, 1H, $J = 11.7$ Hz), 4.59 (m, 2H), 4.39 (dd, 1H, $J = 2.1$, 12.3 Hz), 4.18 (dd, 1H, $J = 4.2$, 12.3 Hz), 4.01–3.80 (m, 3H), 3.72 (dd, 1H, $J = 6.6$, 11.7 Hz), 3.62 (dd, 1H, $J = 3.6$, 9.9 Hz), 3.54 (s, 1H), 3.51 (s, 3H), 2.67 (m, 2H), 2.53 (m, 2H), 2.16, 2.10, 1.99 (s each, 3H each); IR: 2115, 1751, 1720, 1677, 1229, 1151, 1068, 1029 cm^{-1}; ESIMS m/z calcd for $[C_{38}H_{43}Cl_3N_4O_{15}]Na^+$: 923.1683. Found: 923.1679.

3.1.19. Phenyl 4,6-di-*O*-acetyl-2-*O*-benzoyl-3-*O*-benzyl-1-thio-α-L-idopyranoside (25). To a solution of **7**[9] (5.77 g, 11.5 mmol) and thiophenol (1.414 mL, 13.8 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.3 mL, 2.3 mmol). After stirring at rt for 5 h, the mixture was treated with a saturated aqueous solution of $NaHCO_3$. The organic layer was washed with water, dried over Na_2SO_4, and then filtered and concentrated. The residue was subjected to silica gel column chromatography (6:1, petroleum ether/EtOAc), affording **25** (5.65 g, 89%) as a colorless syrup. $R_f = 0.53$ (3:1, petroleum ether/EtOAc); $[\alpha]_D^{20}$ −79.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–7.29 (m, 15H), 5.64 (s, 1H), 5.47 (m, 1H), 5.12 (m, 1H), 4.99 (m, 1H), 4.94 (d, 1H, $J = 12.0$ Hz), 4.77 (d, 1H, $J = 12.0$ Hz), 4.28 (m, 2H), 3.92 (m, 1H), 2.06, 1.97 (s each, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.0, 165.0, 137.0, 135.7, 133.6, 131.7, 129.7, 129.3, 128.9, 128.4, 127.9, 127.6, 127.5, 86.0, 72.6, 71.6, 68.7, 66.9, 64.5, 62.9, 20.7, 20.7; IR: 1745, 1722, 1269, 1230, 1111, 1068 cm^{-1}; ESIMS m/z calcd for $[C_{30}H_3O_8S]Na^+$: 573.1554. Found: 573.1552.

3.1.20. Methyl (phenyl 2-*O*-benzoyl-3-*O*-benzyl-1-thio-α-L-idopyranoside)uronate (4). To a solution of **26** (951 mg, 1.61 mmol) in dry CH_2Cl_2 (15 mL) was added a solution of hydrazine acetate (297 mg, 3.23 mmol) in MeOH (10 mL). After stirring at rt for 1 h, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (2:1, petroleum ether/EtOAc) to afford **4**[5,7] (725 mg, 90%) as a colorless syrup. $R_f = 0.61$ (2:1, petroleum ether/EtOAc).

3.1.21. Methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (29). Crude **27**, prepared from D-glucosamine hydrochloride (0.5 g, 2.3 mmol),[16] was dissolved in 10% HCl/CH_3OH (25 mL), and the reaction temperature was then raised to 90 °C. When TLC showed that the reaction was complete, the mixture was concentrated and the residue was dissolved in CH_3OH (30 mL) and treated with $NaHCO_3$ until the pH was neutral. The mixture was filtered and concentrated to give the crude methyl glycoside **28**[17] (1.5 g). Crude **28** was dissolved in DMF (10 mL) and *p*-TsOH (20 mg) and benzaldehyde dimethyl acetal (0.8 mL) were added. After stirring at 40 °C under reduced pressure for 10 h, the mixture was concentrated in vacuo. The obtained anomers (α/β, 6:4) were purified by silica gel column chromatography (petroleum ether/EtOAc 10:1 to 4:1) affording the α anomer **29**[18] (346 mg, 51%) as a white solid. $R_f = 0.85$ (3:1, petroleum ether/EtOAc).

3.1.22. Methyl 2-azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside (5). To a cooled (0 °C) solution of **29** (575 mg, 1.95 mol) in dry THF (10 mL), NaH (60% dispersion in mineral oil, 114 mg, 2.92 mmol) was added. After the mixture had been stirred for 1 h, benzyl bromide (0.3 mL, 2.53 mmol) was added. Stirring continued at rt for 24 h, and then CH_3OH (0.5 mL) was added. The resulting mixture was filtered through a pad of Celite and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (5:1, petroleum ether/EtOAc) to afford **30**[13] (640 mg, 85%) as a white solid. $R_f = 0.82$ (2:1, petroleum ether/EtOAc). Compound **30** (425 mg, 1.10 mmol) was converted into diol **31** (234 mg, 71%) accordingly.[13] $R_f = 0.12$ (2:1, petroleum ether/EtOAc). Compound **31** (215 mg, 0.74 mmol) was dissolved in CH_2Cl_2 (3 mL), and pyridine (0.18 mL, 2.23 mmol) and benzoyl chloride (0.12 mL, 1.12 mmol) were added consecutively at 0 °C under argon. After stirring at 0 °C for 30 min, the reaction was quenched by the addition of CH_3OH (0.2 mL) and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (5:1, petroleum ether/EtOAc) to provide **5**[8]

(280 mg, 96%) as a colorless syrup. $R_f = 0.3$ (5:1, petroleum ether/EtOAc); $[\alpha]_D^{20}$ +60.5 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.06–7.32 (m, 10H, ArH), 4.94 and 4.83 (AB, 2H, $J = 10.8$ Hz, CH_2Ph), 4.83 (d, 1H, $J = 3.6$ Hz, H-1), 4.77 (dd, 1H, $J = 12.0$, 3.9 Hz, H-6a), 4.47 (dd, 1H, $J = 12.0$, 1.8 Hz, H-6b), 3.91–3.83 (m, 2H), 3.62–3.54 (m, 1H, H-4), 3.46 (s, 3H, OMe), 3.37 (m, 1H, H-2), 2.83 (d, 1H, OH); IR: 3375, 2113, 1696, 1110, 837 cm^{-1}; ESIMS *m/z* calcd for $[C_{21}H_{23}N_3O_6]Na^+$: 436.1479. Found: 436.1483.

3.1.23. Phenyl [methyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosyl)uronate]-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1→4)-(2-*O*-benzoyl-3-*O*-benzyl-1-thio-α-L-idopyranoside)uronate (32). A mixture of trichloroacetimidate **2** (257 mg, 0.27 mmol) and thioglycoside **4** (95 mg, 0.19 mmol) in dry toluene (6 mL) was stirred in the presence of freshly activated powdered 4 Å molecular sieves (100 mg) for 30 min at rt under argon. After cooling to −78 °C, TMSOTf (0.19 mL, 0.05 M) was added dropwise. The reaction was stirred at −78 °C until TLC indicated complete conversion of the donor **2** and then was quenched by the addition of Et_3N (0.2 mL). The resulting mixture was filtered through a pad of Celite and concentrated. The residue was purified by silica gel column chromatography (2:1, petroleum ether/EtOAc) to provide trisaccharide **32** (125 mg, 56%) as a colorless syrup. $R_f = 0.67$ (1:1, petroleum ether/EtOAc); $[\alpha]_D^{20}$ −41.3 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.07–7.04 (m, 30H), 5.75 (s, 1H), 5.32 (s, 1H), 5.30 (d, 1H, $J = 1.8$ Hz), 5.26 (d, 1H, $J = 3.3$ Hz), 5.15 (t, 1H, $J =$ 3.7 Hz), 5.06 (t, 1H, $J = 3.6$ Hz), 4.93 (d, 1H, $J = 11.7$ Hz), 4.78–4.67 (m, 4H), 4.58 (d, 1H, $J = 3.6$ Hz), 4.30 (s, 2H), 4.24 (d, 1H, $J = 10.5$ Hz), 4.15 (br, 1H), 3.96 (br, 1H), 3.87–3.74 (m, 3H), 3.67 (d, 1H, $J = 10.2$ Hz), 3.61 (s, 3H), 3.48 (s, 3H), 3.35 (t, 1H, $J = 9.1$ Hz), 3.22 (dd, 1H, $J = 3.6$, 10.5 Hz), 2.61 (m, 2H), 2.47 (m, 2H), 2.08, 2.01 (s each, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 171.5, 170.7, 169.2, 168.8, 165.6, 165.0, 137.4, 137.2, 137.0, 135.2, 133.5, 133.4, 131.2, 129.9, 129.8, 129.5, 129.1, 129.0, 128.6, 128.5, 128.1, 128.0, 127.8, 127.5, 127.4, 99.4, 97.8, 86.7, 78.5, 76.3, 75.1, 74.4, 74.2, 73.3, 72.7, 71.6, 69.9, 69.5, 69.3, 68.5, 68.3, 68.1, 63.7, 61.6, 52.2, 52.0, 37.6, 29.7, 27.7, 20.7; IR: 2925, 2111, 1741, 1720, 1269, 1110, 1071, 1027, 713 cm^{-1}; ESIMS *m/z* calcd for $[C_{68}H_{69}N_3O_{21}S]Na^+$: 1318.4036. Found: 1318.4039.

3.1.24. Phenyl [methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)uronate]-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-(2-*O*-benzoyl-3-*O*-benzyl-1-thio-α-L-idopyranoside)uronate (33). The same procedure described for the preparation of trisaccharide **32** was employed for the synthesis of **33**. Thus, treatment of trichloroacetimidate **3** (130 mg, 0.14 mmol) with thioglycoside **4** (57 mg, 0.12 mmol) after purification by silica gel column chromatography (2:1, petroleum ether/EtOAc), afforded **33** (99 mg, 70%) as a colorless syrup. $R_f = 0.44$ (1:1, petroleum ether/EtOAc); $[\alpha]_D^{20}$ −27.7 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.12–7.15 (m, 25H), 5.79 (s, 1H), 5.42 (s, 1H), 5.34 (d, 1H, $J = 1.5$ Hz), 5.25 (t, 1H, $J = 9.3$ Hz), 5.14 (t, 1H, $J = 8.7$ Hz), 4.98 (d, 1H, $J = 11.7$ Hz), 4.80–4.51 (m, 7H), 4.20 (m, 2H), 4.09 (s, 1H), 3.95 (d, 1H, $J = 9.9$ Hz), 3.84 (d, 1H, $J = 10.2$ Hz), 3.82 (s, 3H), 3.73 (m, 2H), 3.58 (d, 1H, $J = 10.8$ Hz), 3.43 (s, 4H), 3.17 (dd, 1H, $J = 3.6$, 10.2 Hz), 2.69 (m, 2H), 2.45 (m, 2H), 2.10, 2.03, 2.00 (s each, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 171.2, 170.3, 169.2, 169.0, 167.0, 165.6, 138.2, 137.7, 137.1, 135.0, 133.7, 131.8, 130.0, 129.3, 129.0, 128.8, 128.4, 128.0, 127.8, 127.7, 127.6, 127.5, 127.1, 100.9, 99.7, 86.9, 79.8, 78.0, 77.9, 77.4, 74.9, 74.3, 73.3, 72.8, 72.6, 72.4, 71.3, 69.8, 69.2, 68.4, 63.2, 61.5, 52.6, 52.4, 37.6, 29.7, 27.7, 22.6, 20.9, 20.7; IR: 2925, 2112, 1753, 1720, 1223, 1149, 1071, 1029, 745 cm^{-1}; MALDIMS *m/z* calcd for $[C_{63}H_{67}N_3O_{21}S]Na^+$: 1256.3880. Found: 1256.3843.

3.1.25. Methyl [methyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosyl)uronate]-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→4)-methyl (2-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranosyl)uronate-(1→4)-2-azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside (1a). A solution of trisaccharide thioglycoside **32** (37 mg, 0.029 mmol) and BSP (8 mg, 0.04 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 30 min over freshly activated powdered 3 Å molecular sieves (100 mg). The mixture was cooled to −60 °C, and Tf_2O (5 μL, 0.037 mmol) was added. The temperature was raised to −40 °C and stirring continued for 15 min. Then a solution of the monosaccharide alcohol **5** (30 mg, 0.057 mmol) in dry CH_2Cl_2 (0.5 mL) was added and the resulting mixture was allowed to warm slowly to rt. The reaction was quenched by the addition of Et_3N (0.05 mL) and the mixture filtered through a pad of Celite. The filtrate was concentrated and purified by silica gel column chromatography (2:1, petroleum ether/EtOAc) affording **1a** (39 mg, 87%) as a colorless syrup. $R_f = 0.45$ (2:1, petroleum ether/EtOAc); $[\alpha]_D^{20}$ 20.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.07–7.16 (m, 35H), 5.56 (d, 1H, $J = 4.2$ Hz), 5.30 (d, 1H, $J = 3.6$ Hz), 5.19 (m, 2H), 5.12 (t, 1H, $J = 3.6$ Hz), 4.91 (d, 1H, $J = 10.5$ Hz), 4.83 (m, 2H), 4.79–4.72 (m, 7H), 4.69 (d, 1H, $J = 4.2$ Hz), 4.61 (dd, 1H, $J = 4.2$, 12.0 Hz), 4.54–4.43 (m, 2H), 4.29 (br, 2H), 4.17–4.11 (m, 2H), 4.03–3.71 (m, 7H), 3.51 (s, 3H), 3.50–3.42 (m, 3H), 3.39 (s, 3H), 3.33 (s, 4H), 3.32 (s, 1H), 3.28 (dd, 1H, $J = 3.6$, 10.2 Hz), 2.12, 2.07 (s each, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7, 171.6, 170.6, 169.2, 168.8, 166.0, 165.4, 165.1, 137.8, 137.5, 137.3, 137.2, 133.6, 133.4, 133.0, 129.8, 129.2, 129.1, 128.6, 128.5, 128.3,

128.1, 127.9, 127.8, 127.6, 127.4, 98.4, 98.3, 98.2, 97.7, 78.5, 78.3, 76.2, 75.1, 75.0, 74.6, 74.4, 74.1, 73.6, 73.3, 70.5, 70.1, 69.8, 69.4, 69.1, 68.4, 68.0, 63.5, 63.4, 62.7, 61.7, 55.4, 52.1, 51.7, 37.6, 29.6, 27.7, 20.8; IR: 2925, 2110, 1741, 1722, 1270, 1110, 1070, 1027, 713 cm^{-1}; ESIMS *m/z* calcd for $[C_{83}H_{86}N_6O_{27}]Na^+$: 1621.5433. Found: 1621.5438.

3.1.26. Methyl [methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)uronate]-(1→4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucopyranosyl-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranosyl)uronate-(1→4)-2-azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside (1b). The same procedure described for the preparation of tetrasaccharide **1a** was employed for the synthesis of **1b**. Thus, reaction of thioglycoside **33** (43 mg, 0.035 mmol) with alcohol **5** (36 mg, 0.087 mmol) after purification by silica gel column chromatography (2:1, petroleum ether/EtOAc) afforded **1b** (42 mg, 79%) as a colorless syrup. $R_f = 0.15$ (2:1, petroleum ether/EtOAc); $[\alpha]_D^{20}$ 26.9 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (m, 4H), 7.44–7.24 (m, 26H), 5.62 (d, 1H, $J = 4.7$ Hz), 5.23 (m, 2H), 5.10 (t, 1H, $J = 8.1$ Hz), 4.94–4.88 (m, 3H), 4.77–4.70 (m, 5H), 4.68–4.59 (m, 4H), 4.50 (t, 1H, $J = 7.9$ Hz), 4.47–4.39 (m, 2H), 4.21–4.09 (m, 3H), 4.01 (m, 2H), 3.89–3.82 (m, 5H), 3.72 (m, 2H), 3.50 (m, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 3.43 (dd, 1H, $J = 3.6$, 10.2 Hz), 3.38 (s, 3H), 3.19 (dd, 1H), 2.67 (m, 2H), 2.48 (m, 2H), 2.15, 2.06, 1.95 (s each, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 171.2, 170.3, 169.4, 168.9, 167.0, 166.0, 165.3, 138.1, 137.7, 129.9, 129.8, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 100.8, 98.7, 98.4, 98.3, 79.7, 78.5, 77.7, 77.3, 75.2, 75.1, 74.8, 74.3, 73.2, 72.4, 71.3, 69.2, 63.5, 55.4, 52.6, 52.0, 37.6, 29.7, 27.7, 20.8, 20.6; IR: 2927, 2111, 1749, 1722, 1272, 1224, 1149, 1110, 1070, 1029, 714 cm^{-1}; ESI-MS: 1559.7 [M+Na^+]; ESIMS *m/z* calcd for $[C_{78}H_{84}N_6O_{27}]Na^+$: 1559.5277. Found: 1559.5281.

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