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Synthesis of a C-linked hyaluronic acid disaccharide mimetic

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Abstract

The synthesis of a C-disaccharide that is designed as a mimetic for the repeating unit disaccharide of hyaluronic acid is described. The target compound was obtained via the SmI₂-promoted coupling reaction of the sulfone, 2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-1,2-dideoxy-1-pyridinylsulfonyl-β-D-glucopyranose (**6**), and the aldehyde, *p*-methoxyphenyl 2,3-di-*O*-benzyl-4-deoxy-4-*C*-formyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (**14**).

Keywords

C-glycosyl compounds; C-glycosides; C-disaccharide; Hyaluronic acid mimetic; Samarium diiodide

1. Introduction

Hyaluronic acid (hyaluronan, HA, Figure 1) is a polysaccharide of high molecular weight ($M_r > 10^6$) that is composed of a repeating disaccharide unit in which D-glucuronic acid is linked to the 3-position of 2-acetamido-2-deoxy-D-glucose (*N*-acetyl-D-glucosamine) i.e., [$\rightarrow 3$]-β-D-GlcNAc-(1 $\rightarrow$ 4)-β-D-GlcA-(1 $\rightarrow$)]_n. HA, which is synthesized in the plasma membrane and is associated with the complement of glycosaminoglycans (GAGs) located in the extracellular matrix, has a variety of functions in the human body. For example, it serves as the gelling agent of the vitreous body of the eye, is a component in the lubricants associated with the synovial fluid in joints, and is found in significant quantities in the placenta.^{1,2} A process that has come to the forefront in recent years concerns the role that HA plays in the metastasis of cancer: the binding of a migrating cancer cell's CD44 receptor to HA performs a critical role in the metastasis of certain cancers, especially the migration of melanoma cells to the lung.³ Several lines of evidence further implicate that this CD44–HA interaction facilitates cell movement in cancer cells during metastasis.^{4–6}

As a part of an ongoing project, a goal was to synthesize a “C-disaccharide” that would be a mimetic for the repeating unit of HA and would be totally resistant, due to the interresidue C–C linkages, to enzymes that degrade the natural polymer. Further objectives are to study its conformation and incorporate it into a synthetic oligosaccharide in such a way that the oligomer would be resistant to enzymes that degrade HA. Herein is presented a total synthesis of the target C-disaccharide as its *p*-methoxyphenyl glycoside.

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2. Results and discussion

2.1 Synthetic approaches

Approaches to C-linked disaccharides (C-glycosylic compounds, often referred to as “C-glycosides”) are varied;^{7,8} however, the success in any C-glycosylic coupling depends on the peculiar reactivities of the sugar units (i.e., whether primary or secondary carbon atoms are targeted in the glycosyl acceptor), as well as the stabilities of the protecting groups involved and their influence on the reactivity of both the glycosyl donor and acceptor. For our purposes, several processes were attempted in this laboratory,^{9–11} among them the Henry coupling advocated by Martin and co-workers,^{12,13} the olefin metathesis method of Postema and coworkers,^{14,15} as well as the dianion approach advocated by Kessler and co-workers.^{16,17} Of these, only the latter method, which had been developed for simple C-glycosyl–alkyl conjugates, gave good results with our specific compounds that have multiple functionality present; however, this rather harsh organometallic reaction limited the type of OH protection that could be employed, which limited future possibilities in construction of more complex C-glycosylic compounds. Another approach that involves the use of samarium diiodide-mediated coupling of a glycosyl sulfone (donor) with a C-formyl sugar (an aldehyde, the acceptor), as developed by Beau and co-workers for glucosamine derivatives^{18–22} and by Linhardt^{23, 24} and co-workers for the synthesis of sialic acid mimetics, was carried out and gave the most promising results. Using this SmI₂ strategy, the synthesis, which makes use of the glycosyl donor **6** and the acceptor **14**, was carried out as described in the following sections.

2.2 Synthesis of protected sulfone **6**

The synthesis of sulfone **6** was carried out as shown in Scheme 1. Thus, the reaction of glycosyl chloride **1** with K₂CO₃ and 2-mercaptopyridine in dry acetone at 50 °C gave the desired pyridinyl thioglycoside **2**.²⁵ In order to manipulate the protective groups, **2** was treated with NaOMe in 1:5 CH₂Cl₂–MeOH to afford the free-hydroxy compound **3** that was directly reacted with benzaldehyde and ZnCl₂ at room temperature for 16 h to give the 4,6-*O*-benzylidenated **4**.^{26,27} Treatment of **4** with *tert*-butylchlorodimethylsilane (TBDMSCl) in the presence of imidazole in DMF at room temperature overnight²⁸ gave compound **5**, which was readily converted to the corresponding protected sulfone **6** in 79% yield via treatment with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH₂Cl₂ at 0 °C.¹⁹ The β configuration for **6** was clearly indicated by the doublet for H-1 at δ 5.81 (*J*_{1,2} = 10.3 Hz.); furthermore, there was no resonance indicative of any α anomer.

2.3 Synthesis of protected aldehyde **14**

The synthesis of aldehyde **14** proceeded from known compound **7**²⁹ as shown in Scheme 2. Deacetylation of **7** with NaOMe in 1:5 CH₂Cl₂ and MeOH gave the corresponding tetraol **8** in nearly quantitative yield. Regioselective bis-protection of the 4-OH and 6-OH positions with a *p*-methoxybenzylidene group was accomplished via treatment of **8** with anisaldehyde dimethyl acetal (ADMA) in the presence of a catalytic amount of *p*-TsOH in dry CH₃CN to afford diol **9** as a precipitate in 84% yield.³⁰ The resulting diol **9** was then treated with NaH at 0 °C for 10 min, followed by addition of benzyl bromide in DMF, to give *O*-dibenzylated **10** in 95% yield. Regioselective reductive cleavage of the benzylidene ring of compound **10** was achieved via treatment with NaBH₃CN and CF₃CO₂H in the presence of 4A MS in DMF at room temperature for 10 h to render the 4-OH isomer **11** in 74% yield as the major product, along with the 6-OH isomer as a byproduct (21%, data not provided).³¹ Treatment of compound **11** with (CF₃SO)₂O in pyridine at 0 °C overnight gave the corresponding triflate **12** in nearly quantitative yield. Reaction of triflate **12** with Bu₄NCN in THF afforded the S_N2 product **13** in 63% yield. The major byproduct was the E2 elimination product, which is slightly less polar than the substitution product on TLC (data not provided). Reduction of compound **13** with DIBALH in THF at –78 °C, followed by treatment with 1.0 N H₃PO₄ at 0 °C, afforded

aldehyde **14** in 71% yield.^{32,33} Aldehyde **14** was definitively shown to be the equatorial isomer (D-gluco configuration) by the appearance of H-4 at δ 3.01 as a broad doublet of doublets (pseudo triplet) with $J_{3,4} \approx J_{4,5} = 10.2$ Hz.

2.4 Synthesis of the C-disaccharides

With sulfone **6** and aldehyde **14** in hand, the stage was set for the synthesis of C-disaccharides as shown in Scheme 3. Thus, treatment of sulfone **6** and aldehyde **14** with samarium diiodide (SmI_2) in THF at room temperature, following the general protocols of Beau and co-workers, 20,21 gave three disaccharides, **15a**, **15b** and **15c** as shown in Scheme 3. The β anomers **15a** and **15b** appeared as the high- and low-running zones on TLC, with the α anomer **15c** situated between them. All three of the disaccharides were easily identified by positive-ion ESI mass spectroscopy, which gave inter alia $[\text{M} + \text{H}]$, $[\text{M} + \text{Na}]$ and $[\text{M} + \text{K}]$ ions as expected (see Experimental section). The NMR spectra of the pure anomeric compounds were complex, even at 600 MHz, and did not lend themselves to complete assignments of all resonances. However, H-1^{II} for **15a** showed $J_{1,2}$ 8.4 Hz, which is indicative of the β anomer. Further corroboration of the β linkage for **15a** was provided by single-crystal X-ray diffraction analysis that showed the β -(1 $\rightarrow$ 4)-C-linkage and the configuration of the linking CHOH group, as shown in Figure 2. Thus **15a** is the β -(4aR)-isomer. Disaccharide **15b**, which showed $J_{1,2}$ 9.6 Hz, was also assigned the β linkage. Furthermore **15b**, after deoxygenation at the 4a position, gave the same disaccharide as that derived from **15a** (as described in the section which follows). Both **15a** and **15b** gave large, negative optical rotations (-41.2 and -97.1 , respectively). Disaccharide **15c** was assigned as the α anomer, as the deoxygenated derivative of **15c** is different from that derived from either **15a** or **15b**. From the appearance of the H-1^I and H-1^{II} signals and other resonances in the ¹H NMR spectrum of **15c**, a single epimer at H-4a was indicated; however, little support for firm epimeric and anomeric assignments was otherwise afforded by either the NMR spectra or optical rotations (see data in Experimental section). The structural relationship of **15c** to the β anomers **15a** and **15b** was established chemically as described in the following section.

Conversion of the presumed α isomer **15c** to the β isomers (**15a** and **15b**) was achieved via a series of reactions as shown in Scheme 4. Compound **15c** was oxidized to the corresponding α ketone **16** (H-1^{II}, $J_{1,2}$ 6.0 Hz) with pyridinium chlorochromate (PCC) in CH_2Cl_2 , and subsequent isomerization of the resulting α ketone to the β ketone **17** (H-1^{II}, $J_{1,2}$ 10.8 Hz) was cleanly effected with NaOMe in MeOH. The yield of the β anomer was 36%, with 50% recovery of starting material **16**. No side products from elimination reactions or epimerization at the C-4 carbon were observed. Reduction of the β ketone **17** to a ~1:3 mixture of **15a** and **15b** was carried out with NaBH_4 in EtOH, which served to increase the amounts of these compounds that were required for synthesis of the targeted disaccharide.

Deoxygenation at the 4a-position was achieved according to the procedure of Barton and McCombie,³⁴ as modified by Dietrich and Schmidt (Scheme 5).³⁵ Thus treatment of **15a** or **15b** with NaH in the presence of imidazole in THF at room temperature, followed by addition of CS_2 and then MeI after 40 min, afforded thionocarbonate **18a** or **18b** in 54% or 50% yield, respectively. The modest yields of these compounds are most likely due to their limited stability to column chromatography. Treatment of **18a** or **18b** with Bu_3SnH and azoisobutyronitrile (AIBN) in refluxing toluene afforded the desired C-linked disaccharide **19** in 91% yield, which after removal of the *tert*-butyldimethylsilyl (TBDMS) group with Bu_4NF (TBAF) in THF,²⁸ gave disaccharide **20** in 93% yield. The disaccharide showed the expected $[\text{M} + \text{H}]$, $[\text{M} + \text{NH}_4]$, $[\text{M} + \text{Na}]$ and $[\text{M} + \text{K}]$ peaks in the positive-ion ESIMS. The NMR spectra, in general, supported the assigned structure; however, while the ¹H NMR spectrum showed a distinct signal for H-1^I, H-1^{II} was hopelessly buried in an envelope of signals at δ 3.47–3.34, which prevented firm confirmation of the β linkage, although the β assignment is not in doubt,

beginning with the series of reactions from **15a**. Disaccharide **20** will also serve as an acceptor in the synthesis of C-/O-linked HA tetrasaccharide mimetics (details to be published).

Following removal of the *p*-methoxybenzyl (PMB) group on **20** with DDQ,³⁶ the resulting primary hydroxyl group was selectively oxidized to the corresponding carboxylic (uronic) acid with 5% aq NaClO in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).³⁷ Debenzylation with Pearlman's catalyst (1 atm) afforded the target C-disaccharide **21**. The structure of **21** was supported by the negative-ion HRESIMS that showed the expected ion for [M – H]. In the ¹H NMR spectrum H-1^{II} appeared as a complex multiplet at δ 3.26–3.21, and resonances for H-6, 6a^I of **20** disappeared and were replaced by a ¹³C resonance at δ 174.3, which is indicative of a carboxylic acid.³⁷ The other resonances were supportive of the structure.

2.5 Conclusions

The target C-linked disaccharide that constitutes the repeat unit of HA was synthesized as its *p*-methoxyphenyl glycoside using SmI₂-mediated coupling of the sugar units. Extension of this methodology to higher oligosaccharides that incorporate the C/O linked sugars, as well as extensive biological studies of these synthetic HA mimetics, are underway.

3. Experimental Section

3.1 General methods

¹H (250 MHz, 300 MHz, and 600 MHz) and ¹³C (62.5 MHz, 75 MHz, and 150 MHz) NMR spectra were recorded at 25 °C as designated. Chemical shifts are expressed in δ units (ppm) and were measured relative to an internal standard of TMS for ¹H, and relative to the signal for CDCl₃ (δ 77.0) or DMSO-*d*₆ (δ 39.5) for ¹³C, unless otherwise stated. Apparent, first-order multiplicities are indicated by s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet, and m, multiplet. All assignments were confirmed with the aid of two-dimensional experiments (gCOSY, HSQC, HMBC and TOCSY as needed) at 600 MHz. Sugar units are numbered analogously to O-glycosides using the Whelan system (Rule 2-Carb-37.2)³⁸ where “I” designates the reducing end unit, “II” the next unit, etc.; NMR resonances are indicated by the appropriate superscript. Nomenclature follows the use of the “carba” designation for C replacement of O in sugar units (Rule 2-Carb-37.5).³⁸ Electrospray-ionization mass spectrometry (ESIMS) was carried out at low resolution using a Micromass Quattro-II triple quadrupole instrument operating in the positive-ion mode; the HRESIMS measurement (negative-ion) was made on an Applied Biosystems QSTAR XL quadrupole instrument. Column chromatography was performed on 60 Å (63–200 mm, termed “coarse”) silica gel (Sorbent Technologies, Atlanta, Ga), and fractions were monitored by TLC on Silica Gel UV₂₅₄ [0.2-mm aluminum-backed plates (Sorbent Technologies)] by detection with 254-nm UV light and then spray-heat development using a *p*-anisaldehyde-sulfuric acid reagent.³⁹ Melting points were measured with a capillary melting point apparatus, and optical rotations were carried out at the sodium D line in a 1-dm cell at 20 °C; units are (degrees·mL)/(g·dm). Microanalyses were carried out by Atlantic Microlabs, Inc., Atlanta, GA.

3.2 2-Pyridinyl 2-acetamido-4,6-O-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (**4**)

To a solution of compound **2**²⁵ (20.0 g, 45.5 mmol) in MeOH (150 mL) and CH₂Cl₂ (30 mL) was added NaOMe (25% in MeOH, 1.0 mL). The reaction was stirred at room temperature for 1 h, after which time 1 mL of satd NH₄Cl solution was added, and the solvent was evaporated to afford compound **3** (13.6 g, 43.2 mmol, 95%) as a white amorphous solid that was used directly in the next step; mp 154–156 °C; [α]_D +9.5 (c 1.0, DMSO). Compound **3** (16.0 g, 51.0 mmol) was stirred with dry ZnCl₂ (14 g, 0.10 mol) in benzaldehyde (100 mL) at room temperature for 16 h, after which time the reaction was quenched with water (250 mL). The

suspension was filtered, and the solid was sequentially washed with EtOAc and MeOH to afford compound **4** as a white amorphous solid (16.3 g, 40.5 mmol, 80%). TLC (10:1 CHCl₃–MeOH): *R*_f 0.4; mp 164–166 °C; [α]_D +4.6 (*c* 0.5, DMSO); ¹H NMR (250 MHz, DMSO-*d*₆): δ 8.43–7.12 (m, 4 H, ArH), 7.47–7.32 (m, 5 H, ArH), 5.62 (s, 1 H, PhCH), 5.54 (d, 1 H, H-1, *J*_{1,2} = 10.5 Hz), 5.46 (d, 1 H, NH), 4.19–4.17 (m, 1 H, H-6), 3.85 (dd, 1 H, H-2), 3.74–3.63 (m, 2 H, H-3, H-4), 3.59–3.48 (m, 2 H, H-6, H-5), 3.16 (d, 1 H, OH), 1.80 (s, 3 H, CH₃CO); ¹³C NMR (62.5 MHz, DMSO-*d*₆): δ 169.2, 157.2, 149.4, 137.7, 137.2, 128.9, 128.0, 126.4, 122.0, 120.5, 100.7, 83.3, 81.0, 71.7, 70.2, 67.6, 54.0, 23.0; ESIMS (positive-ion): *m/z* 403.1 [M + H], 425.1 [M + Na], 441.1 [M + K]. Anal. Calcd for C₂₀H₂₂N₂O₅S·0.16CH₂Cl₂ (416.06): C, 58.20; H, 5.41; N, 6.73. Found: C, 58.19; H, 5.56; N, 6.50. CH₂Cl₂ complexed with **4** was confirmed by NMR spectroscopy.

3.3 2-Pyridinyl 2-acetamido-4,6-O-benzylidene-3-O-*tert*-butyldimethylsilyl-2-deoxy-1-thio- β -D-glucopyranoside (**5**)

To a solution of compound **4** (16.30 g, 40.54 mmol) and imidazole (6.25 g, 96.0 mmol) in dry DMF was added *tert*-butylchlorodimethylsilane (10.4 g, 69.0 mmol) at 0 °C. The reaction was allowed to stir and warm to room temperature over 15 h, after which time it was quenched with water, washed with satd NaHCO₃ and extracted with CH₂Cl₂. The organic phase was dried with anhyd Na₂SO₄ and then evaporated to dryness. The residue was submitted to silica gel column chromatography (2.5:1 to 1:1 hexanes–EtOAc) to yield compound **5** as a pale-yellow solid (16.3 g, 31.6 mmol, 78%). TLC (1:2 hexanes–EtOAc): *R*_f 0.5; mp 210–212 °C; [α]_D +4.3 (*c* 1.0, CH₂Cl₂); ¹H NMR (250 MHz, CDCl₃): δ 8.44–7.03 (m, 4 H, ArH), 7.55–7.34 (m, 5 H, ArH), 5.98 (d, 1 H, NH), 5.85 (d, 1 H, H-1, *J*_{1,2} = 10.6 Hz), 5.51 (s, 1 H, PhCH), 4.31 (dd, 1 H, H-6), 4.20–3.96 (m, 2 H, H-2, H-3), 3.82–3.48 (m, 3 H, H-6, H-5, H-4), 1.91 (s, 3 H, CH₃CO), 0.82 (s, 9 H, C(CH₃)₃), 0.05 (s, 3 H, SiCH₃), –0.02 (s, 3 H, SiCH₃); ¹³C NMR (62.5 MHz, CDCl₃): δ 170.1, 156.6, 149.4, 137.2, 136.6, 129.0, 128.1, 126.3, 123.5, 120.6, 101.8, 83.2, 82.1, 74.0, 70.8, 68.7, 56.2, 25.6, 23.5, 18.1, –4.1, –5.0; ESIMS (positive-ion): *m/z* 517.2 [M + H], 539.2 [M + Na], 555.2 [M + K]. Anal. Calcd for C₂₆H₃₆N₂O₅SSi (516.74): C, 60.43; H, 7.02; N, 5.42. Found: C, 60.41; H, 6.83; N, 5.36.

3.4 2-Acetamido-4,6-O-benzylidene-3-O-*tert*-butyldimethylsilyl-1,2-dideoxy-1-pyridinylsulfonyl- β -D-glucopyranose (**6**)

To a stirred solution of compound **5** (16.3 g, 31.6 mmol) in CH₂Cl₂ (200 mL) was added *m*-CPBA (50–60%, 33.0 g) at 0 °C. The reaction was allowed to stir and warm to room temperature over 1.5 h, after which time the reaction mixture was diluted with CH₂Cl₂, washed consecutively with satd Na₂S₂O₃, satd Na₂CO₃ and brine, and extracted with CH₂Cl₂. The organic phase was dried with anhyd Na₂SO₄ and then concentrated to dryness. The residue was submitted to silica gel column chromatography (1:1 hexanes–EtOAc) to give compound **6** as a white amorphous solid (13.9 g, 25.4 mmol, 79%). TLC (1:2 hexanes–EtOAc): *R*_f 0.4; mp 162–164 °C; [α]_D –34.8 (*c* 1.0, CH₂Cl₂); ¹H NMR (250 MHz, CDCl₃): δ 8.85 (d, 1 H, ArH), 8.16 (d, 1 H, ArH), 8.02 (t, 1 H, ArH), 7.62 (t, 1 H, ArH), 7.50–7.39 (m, 5 H, ArH), 6.84 (d, 1 H, NH), 5.81 (d, 1 H, H-1, *J*_{1,2} = 10.3 Hz), 4.72–4.61 (m, 1 H, H-6), 4.12–4.02 (m, 2 H, H-2, H-3), 3.69–3.48 (m, 3 H, H-6, H-5, H-4), 2.06 (s, 3 H, CH₃CO), 0.09 (s, 9 H, C(CH₃)₃), 0.06 (s, 3 H, SiCH₃), –0.01 (s, 3 H, SiCH₃); ¹³C NMR (62.5 MHz, CDCl₃): δ 171.0, 155.1, 150.2, 137.8, 136.8, 128.9, 127.9, 127.6, 126.1, 124.2, 101.7, 86.1, 81.6, 71.0, 70.1, 67.9, 53.5, 25.6, 23.5, 17.9, –4.4, –5.1; ESIMS (positive-ion): *m/z* 549.0 [M + H], 571.0 [M + Na], 587.0 [M + K]. Anal. Calcd for C₂₆H₃₆N₂O₇SSi (548.74): C, 56.91; H, 6.61; N, 5.11. Found: C, 56.72; H, 6.60; N, 4.96.

3.5 *p*-Methoxyphenyl 4,6-*O*-*p*-methoxybenzylidene- β -D-galactopyranoside (9)

To a solution of compound **7**⁴⁰ (20.5 g, 45.4 mmol) in dry CH₂Cl₂ (50 mL) and dry MeOH (250 mL) was added NaOMe (25% in MeOH, 0.25 mL). The reaction was stirred at room temperature for 1 h, after which time the reaction was quenched with Dowex 50 $\times$ 2–100 (H⁺ form). The suspension was filtered and evaporated to afford **8** as a white amorphous solid (12.7 g, 44.0 mmol, 97%), which was used in the next step without characterization. TLC (9:1 CH₂Cl₂–MeOH): *R*_f 0.1; mp 158–160 °C; [α]_D –35.7 (*c* 1.1, H₂O). To a suspension of **8** (11.0 g, 38.5 mmol) in dry CH₃CN (250 mL) were added anisaldehyde dimethyl acetal (ADMA, 69.0 mL, 0.40 mol) and *p*-toluenesulfonic acid (0.75 g, 3.9 mmol, 0.1 equiv). The solution was stirred at room temperature for about 4 h. After this time the reaction was quenched with Et₃N. The suspension was filtered, and the solid was sequentially washed with EtOAc and hexanes to afford compound **9** as a white amorphous solid (13.1 g, 32.2 mmol, 84%). TLC (9:1 CH₂Cl₂–MeOH): *R*_f 0.5; mp 224–226 °C; [α]_D –74.9 (*c* 1.0, DMSO); ¹H NMR (250 MHz, DMSO-*d*₆): δ 7.37 (d, 2 H, ArH), 7.01 (d, 2 H, ArH), 6.91 (d, 2 H, ArH), 6.86 (d, 2 H, ArH), 5.51 (s, 1 H, CH₃OCH), 5.26 (d, 1 H, H-2), 5.02 (d, 1 H, H-3), 4.83 (d, 1 H, H-1, *J*_{1,2} = 6.5 Hz), 4.10 (s, 1 H, H-4), 4.02 (s, 2 H, H-6), 3.74 (s, 3 H, OCH₃), 3.70 (s, 3 H, OCH₃), 3.67 (s, 1 H, H-5), 3.58 (m, 1 H, OH); ¹³C NMR (62.5 MHz, DMSO-*d*₆): δ 159.4, 154.3, 151.3, 131.0, 127.5, 117.6, 114.4, 113.2, 101.5, 99.7, 75.8, 71.7, 69.7, 68.4, 66.0, 55.3, 55.1; ESIMS (positive-ion): *m/z* 404.7 [M + H], 426.7 [M + Na], 442.6 [M + K]. Anal. Calcd for C₂₁H₂₄O₈ (404.72): C, 62.37; H, 5.98. Found: C, 62.30; H, 5.99.

3.6 *p*-Methoxyphenyl 2,3-di-*O*-benzyl-4,6-*O*-*p*-methoxybenzylidene- β -D-galactopyranoside (10)

To a solution of diol **9** (7.35 g, 18.1 mmol) in dry DMF (40 mL) was added NaH (60% in mineral oil, 2.17 g, 54.3 mmol) at 0 °C. The reaction was stirred at 0 °C for 10 min, and then BnBr (8.49 mL, 72.4 mmol) was added dropwise. The reaction was allowed to stir and warm to room temperature over 10 h, after which time it was quenched with water and extracted with CH₂Cl₂. The organic phase was dried with anhyd Na₂SO₄ and then concentrated to dryness. The residue was submitted to silica gel column chromatography (3:1 to 2:1 hexanes–EtOAc) to give compound **10** as a white amorphous solid (10.0 g, 17.1 mmol, 95%). TLC (1:1 hexanes–EtOAc): *R*_f 0.5; mp 167–169 °C; [α]_D –6.3 (*c* 1.0, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 7.49 (d, 2 H, ArH), 7.40–7.25 (m, 10 H, ArH), 7.06 (d, 2 H, ArH), 6.90 (d, 2 H, ArH), 6.80 (d, 2 H, ArH), 5.47 (s, 1 H, MeOPhCH), 5.00 (d, 1 H, H-1, *J*_{1,2} = 10.7 Hz), 4.86 (m, 2 H, H-2, H-3), 4.78 (s, 2 H, ArCH₂O), 4.31 (d, 1 H, ArCH₂O), 4.15–3.99 (m, 3 H, H-6, H-4, ArCH₂O), 3.81 (s, 3 H, OCH₃), 3.77 (s, 3 H, OCH₃), 3.61 (dd, 1 H, H-5), 3.39 (s, 1 H, H-6); ¹³C NMR (62.5 MHz, CDCl₃): δ 160.0, 155.2, 151.6, 138.6, 138.3, 130.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.5, 118.9, 114.4, 113.4, 103.1, 101.2, 79.1, 78.1, 75.4, 73.6, 71.9, 69.0, 66.4, 55.6, 55.2; ESIMS (positive-ion): *m/z* 585.2 [M + H], 607.2 [M + Na], 623.2 [M + K]. Anal. Calcd for C₃₅H₃₆O₈ (584.67): C, 71.90; H, 6.21. Found: C, 71.84; H, 6.30.

3.7 *p*-Methoxyphenyl 2,3-di-*O*-benzyl-6-*O*-*p*-methoxybenzyl- β -D-galactopyranoside (11)

A suspension of compound **10** (0.900 g, 1.54 mmol), NaBH₃CN (0.390 g, 6.16 mmol) and 4 Å MS (0.41 g) in dry DMF (20 mL) was stirred at 0 °C for 15 min, and then a solution of CF₃CO₂H (0.95 mL, 12.3 mmol) in dry DMF (3 mL) was added dropwise. The reaction was allowed to stir and warm to room temperature over 10 h, after which time the mixture was filtered through a bed of Celite, washed with satd NaHCO₃, and extracted with CH₂Cl₂. The organic phase was dried with anhyd Na₂SO₄ and then concentrated to dryness. The residue was submitted to silica gel column chromatography (4:1 to 3.5:1 hexanes–EtOAc) to give compound **11** as colorless crystals (0.670 g, 1.14 mmol, 74%). TLC (2:1 hexanes–EtOAc): *R*_f 0.5; mp 93–95 °C; [α]_D –6.2 (*c* 1.0, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 7.38–7.22 (m, 12 H, ArH), 7.03 (d, 2 H, ArH), 6.85 (d, 2 H, ArH), 6.80 (d, 2 H, ArH), 5.01 (d, 1 H,

ArCH₂O), 4.84 (d, 1 H, H-1, $J_{1,2} = 7.5$ Hz), 4.81 (d, 1 H, ArCH₂O), 4.74 (s, 2 H, ArCH₂O), 4.50 (s, 2 H, ArCH₂O), 4.05 (d, 1 H, H-6), 3.91 (dd, 1 H, H-2), 3.80 (s, 3 H, OCH₃), 3.74 (s, 3 H, OCH₃), ~3.7 (m, 1 H, H-6a), 3.63 (dd, 1 H, H-3), 3.56 (m, 1 H, H-5), 2.56 (s, 1 H, OH); ¹³C NMR (62.5 MHz, CDCl₃): δ 159.3, 155.2, 151.5, 138.4, 137.8, 130.1, 129.4, 128.5, 128.3, 128.1, 127.9, 127.8, 127.7, 118.6, 114.5, 113.8, 102.9, 80.6, 78.7, 75.3, 73.5, 73.4, 72.5, 68.9, 66.8, 55.6, 55.2; ESIMS (positive-ion): m/z 609.3 [M + Na], 625.2 [M + K]. Anal. Calcd for C₃₅H₃₈O₈ (586.69): C, 71.65; H, 6.53. Found: C, 71.54; H, 6.60.

3.8 *p*-Methoxyphenyl 2,3-di-*O*-benzyl-4-*C*-cyano-4-deoxy-6-*O*-*p*-methoxybenzyl-β-*D*-glucopyranoside (**13**)

To a solution of compound **11** (10.0 g, 17.06 mmol) in dry CH₂Cl₂ (80 mL) and pyridine (3.5 mL, 43.3 mmol) was added trifluoromethanesulfonic anhydride (3.5 mL, 21.3 mmol) dropwise at 0 °C. The reaction was stirred at 0 °C for 10 h, after which time it was concentrated and passed through a short plug of silica gel (3:1 hexanes–EtOAc) to give triflate **12** as an unstable, pale-yellow syrup that was used in the next step without characterization. TLC (2:1 hexanes–EtOAc): R_f 0.72. To a solution of triflate **12** (12.26 g, 17.06 mmol) in dry THF (40 mL) was added Bu₄NCN (50 mL, 0.44 M in THF, 1.2 equiv) dropwise at –45 °C. The solution was allowed to stir and warm to room temperature over 4 h, at which time TLC (3:1 hexanes–EtOAc) showed complete consumption of starting material and formation of two main spots. The reaction was concentrated to dryness, and the residue was subjected to silica gel column chromatography (7:1 to 5.5:1 hexanes–EtOAc) to afford compound **13** as a yellow syrup (6.40 g, 10.75 mmol, 63%). TLC (3:1 hexanes–EtOAc): R_f 0.4; $[\alpha]_D -19.1$ (c 1.0, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 7.34–7.20 (m, 12 H, ArH), 6.99 (d, 2 H, ArH), 6.83 (d, 2 H, ArH), 6.79 (d, 2 H, ArH), 5.01 (d, 1 H, ArCH₂O), 4.87 (s, 2 H, ArCH₂O), 4.85 (d, 1 H, H-1, $J_{1,2} = 7.5$ Hz), 4.78 (d, 1 H, ArCH₂O), 4.47 (dd, 2 H, ArCH₂O), 3.71 (s, 3 H, OCH₃), 3.69 (s, 3 H, OCH₃), 3.78–3.64 (m, 4 H, H-2, H-5, H-6), 3.55 (t, 1 H, H-3), 2.98 (t, 1 H, H-4); ¹³C NMR (62.5 MHz, CDCl₃): δ 158.4, 154.6, 150.2, 136.9, 136.4, 128.7, 128.4, 127.5, 127.4, 127.2, 127.1, 127.0, 117.6, 116.6, 113.7, 112.9, 101.9, 80.5, 78.4, 74.9, 74.2, 72.5, 71.4, 68.2, 54.6, 54.3, 35.0; ESIMS (positive-ion): m/z 618.2 [M + Na], 634.2 [M + K]. Anal. Calcd for C₃₆H₃₇NO₇ (595.70): C, 72.59; H, 6.26; N, 2.35. Found: C, 72.59; H, 6.45; N, 2.24.

3.9 *p*-Methoxyphenyl 2,3-di-*O*-benzyl-4-deoxy-4-*C*-formyl-6-*O*-*p*-methoxybenzyl-β-*D*-glucopyranoside (**14**)

To a solution of compound **13** (1.06 g, 1.78 mmol) in dry THF (25 mL) was added Bu₂AlH [DIBALH (Aldrich), 7.11 mL, 1.5 M in toluene, 6 equiv] at –78 °C. The reaction was allowed to stir and warm to room temperature over 10 h, after which time it was quenched with EtOAc, and the solution was stirred with 1.0 N H₃PO₄ (10 mL) for another 30 min at 0 °C. The mixture was then neutralized with satd NaHCO₃, filtered through a bed of Celite and extracted with CH₂Cl₂. The organic phase was dried with anhyd Na₂SO₄ and then concentrated to dryness. The residue was adsorbed onto a short plug of silica gel and eluted (3.5:1 hexanes–EtOAc) to give compound **14** as a pale-yellow syrup (0.76 g, 1.26 mmol, 71%). TLC (3:1 hexanes–EtOAc): R_f 0.3; $[\alpha]_D -31.7$ (c 0.5, CH₂Cl₂); ¹H NMR (250 MHz, CDCl₃): δ 9.65 (d, 1 H, CHO), 7.33–7.16 (m, 12 H, ArH), 6.99 (d, 2 H, ArH), 6.83 (d, 2 H, ArH), 6.80 (d, 2 H, ArH), 5.05 (d, 1 H, ArCH₂O), 4.84 (m, 3 H, ArCH₂O, H-1, $J_{1,2} = 10.0$ Hz), 4.56 (d, 1 H, ArCH₂O), 4.40 (dd, 2 H, ArCH₂O), 4.00 (dd, 1 H, H-3), 3.74 (s, 3 H, OCH₃), 3.72 (s, 3 H, OCH₃), 3.81–3.67 (m, 2 H, H-5, H-3), 3.58 (m, 2 H, H-6), 3.01 (dd, 1 H, $J = 10.2$ Hz, H-4); ¹³C NMR (62.5 MHz, CDCl₃): δ 200.1, 159.4, 155.5, 151.4, 138.3, 138.0, 129.8, 129.5, 128.5, 128.5, 128.3, 128.1, 127.9, 118.5, 114.7, 113.9, 102.8, 82.6, 78.8, 75.2, 75.1, 73.2, 72.1, 70.3, 57.3, 55.7, 55.3; ESIMS (positive-ion): m/z 621.1 [M + Na], 637.2 [M + K]. Anal. Calcd for C₃₆H₃₈O₈ (598.70): C, 72.22; H, 6.40. Found: C, 72.44; H, 6.28.

3.10 Samarium diiodide-promoted coupling reaction: Synthesis of 15a–c

To a stirred solution of sulfone **6** (2.90 g, 5.3 mmol) and aldehyde **14** (2.50 g, 4.2 mmol) in THF (50 mL) was added a solution of SmI_2 (Aldrich) in dry THF (0.1 M, 150 mL, 15 mmol) under N_2 . The reaction was stirred at room temperature for 1 h, after which time it was quenched with satd NH_4Cl and extracted with CH_2Cl_2 . The organic phase was dried with anhyd Na_2SO_4 , and then evaporated to dryness. The residue was submitted to silica gel column chromatography (3:1 to 1:1 hexanes–EtOAc) to afford **15a** (845 mg, 0.84 mmol, 20%), **15b** (630 mg, 0.63 mmol, 15%) and **15c** (1.25 g, 1.24 mmol, 30%) as white amorphous solids. Physicochemical data for **15a–c** are provided in the paragraphs that follow.

3.10.1 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-(4a*R*)-2,3-di-*O*-benzyl-4a-hydroxy-6-*O*-*p*-methoxybenzyl-4a-carba- β -D-glucopyranoside (15a**)**—TLC (2:1 hexanes–EtOAc): R_f 0.5; mp 176–178 °C; $[\alpha]_D^{25}$ –41.2 (*c* 0.5, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3): δ 7.51–7.19 (m, 17 H, ArH), 7.07 (d, 2 H, ArH), 6.84 (d, 2 H, ArH), 6.75 (d, 2 H, ArH), 5.44 (s, 1 H, PhCH), 5.07 (d, 1 H, ArCH_2O), 4.99 (d, 1 H, ArCH_2O), 4.99 (d, 1 H, NH), 4.91 (d, 1 H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.80 (d, 1 H, ArCH_2O), 4.59 (d, 1 H, ArCH_2O), 4.45 (dd, 2 H, ArCH_2O), 4.21 (dd, 1 H, H-6^{II}), 4.02 (s, 1 H, CH-OH), 3.97 (dd, 1 H, H-6^I), 3.91–3.83 (m, 2 H, H-5^I, H-2^{II}), 3.80–3.76 (m, 3 H, H-2^I, H-3^I, CH-OH), 3.78 (s, 3 H, CH_3O), 3.76 (s, 3 H, CH_3O), 3.62–3.57 (m, 2 H, H-6^I, H-6^{II}), 3.43–3.36 (m, 2 H, H-4^{II}, H-1^{II}, $J_{1,2} = 8.4$ Hz), 3.29–3.21 (m, 2 H, H-3^{II}, H-5^{II}), 2.32–2.26 (m, 1 H, H-4^I), 1.76 (s, 3 H, CH_3CO), 0.77 (s, 9 H, $\text{C}(\text{CH}_3)_3$), –0.05 (s, 3 H, SiCH_3), –0.08 (s, 3 H, SiCH_3); ^{13}C NMR (62.5 MHz, CDCl_3): δ 171.2, 158.9, 155.0, 151.5, 138.8, 138.1, 137.1, 130.8, 129.8, 129.0, 128.6, 128.4, 128.1, 127.8, 127.7, 126.2, 118.2, 114.5, 113.6, 102.7, 101.8, 83.1, 82.0, 78.5, 78.4, 74.6, 74.2, 73.7, 73.5, 72.8, 71.4, 70.5, 68.6, 67.3, 55.5, 55.1, 53.5, 46.0, 25.6, 23.2, 18.0, –4.0, –4.9; ESIMS (positive-ion): m/z 1028.4 [$\text{M} + \text{Na}$], 1044.5 [$\text{M} + \text{K}$]. Anal. Calcd for $\text{C}_{57}\text{H}_{71}\text{NO}_{13}\text{Si}$ (1006.28): C, 68.04; H, 7.11; N, 1.39. Found: C, 67.76; H, 7.22; N, 1.34.

3.10.2 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-(4a*S*)-2,3-di-*O*-benzyl-4a-hydroxy-6-*O*-*p*-methoxybenzyl-4a-carba- β -D-glucopyranoside (15b**)**—TLC (1:2 hexanes–EtOAc): R_f 0.2; mp 90–92 °C; $[\alpha]_D^{25}$ –97.1 (*c* 0.5, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3): δ 7.47–7.24 (m, 17 H, ArH), 7.04 (d, 2 H, ArH), 6.87 (d, 2 H, ArH), 6.79 (d, 2 H, ArH), 5.40 (s, 1 H, PhCH), 5.09 (d, 1 H, ArCH_2O), 5.03 (d, 1 H, ArCH_2O), 4.99 (d, 1 H, NH), 4.94 (d, 1 H, H-1^I, $J_{1,2} = 6.6$ Hz), 4.77 (d, 1 H, ArCH_2O), 4.65 (d, 1 H, ArCH_2O), 4.50 (d, 1 H, ArCH_2O), 4.43 (d, 1 H, ArCH_2O), 4.17 (dd, 1 H, H-6^{II}), 3.88–3.74 (m, 5 H, H-5^I, H-3^{II}, H-2^I, CH-OH, H-3^I), 3.78 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.72 (dd, 1 H, H-6^I), 3.61 (dd, 1 H, H-6^I), 3.58–3.52 (m, 2 H, H-6^{II}, H-1^{II}, $J_{1,2} = 9.6$ Hz), 3.48 (dd, 1 H, H-2^{II}), 3.28 (t, 1 H, H-4^{II}), 3.26–3.21 (m, 1 H, H-5^{II}), 2.25–2.08 (m, 1 H, H-4^I), 1.89 (s, 3 H, CH_3CO), 0.08 (s, 9 H, $\text{C}(\text{CH}_3)_3$), –0.03 (s, 3 H, SiCH_3), –0.07 (s, 3 H, SiCH_3); ^{13}C NMR (62.5 MHz, CDCl_3): δ 170.8, 159.3, 155.1, 151.4, 138.5, 138.0, 137.2, 130.0, 129.7, 129.0, 128.7, 128.4, 128.1, 128.1, 127.8, 127.7, 126.3, 126.2, 114.5, 113.8, 102.8, 101.7, 83.2, 82.2, 79.5, 78.7, 74.4, 73.1, 72.9, 71.5, 71.5, 69.6, 68.6, 56.9, 55.6, 55.2, 45.3, 25.7, 23.5, 18.1, –4.1, –5.0; ESIMS (positive-ion): m/z 1006.4 [$\text{M} + \text{H}$], 1028.5 [$\text{M} + \text{Na}$], 1044.6 [$\text{M} + \text{K}$]. Anal. Calcd for $\text{C}_{57}\text{H}_{71}\text{NO}_{13}\text{Si}$ (1006.28): C, 68.04; H, 7.11; N, 1.39. Found: C, 67.74; H, 6.95; N, 1.38.

3.10.3 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-2,3-di-*O*-benzyl-4a-hydroxy-6-*O*-*p*-methoxybenzyl-4a-carba- β -D-glucopyranoside (15c**)**—TLC (2:1 hexanes–EtOAc): R_f 0.4; mp 96–98 °C; $[\alpha]_D^{25}$ –2.9 (*c* 0.1, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3): δ 7.47–7.26 (m, 15 H, ArH), 7.21 (d, 2 H, ArH), 7.00 (d, 2 H, ArH), 6.84 (d, 2 H, ArH), 6.81 (d, 2 H, ArH), 6.10 (d, 1 H, NH), 5.44 (s, 1 H, PhCH), 5.11 (d, 1 H, ArCH_2O), 5.05

(d, 1 H, ArCH₂O), 4.93 (d, 1 H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.75 (d, 1 H, ArCH₂O), 4.74 (d, 1 H, ArCH₂O), 4.46 (d, 1 H, ArCH₂O), 4.35 (d, 1 H, ArCH₂O), 4.27 (m, 1 H, H-2^{II}), 4.12 (dd, 1 H, H-6^{II}), 4.02 (m, 1 H, H-4^{II}), 3.95 (m, 2 H, H-3^I, H-3^{II}), 3.84–3.71 (m, 4 H, H-6^I, H-5^I, H-1^{II}, CH-OH), 3.78 (s, 3 H, CH₃O), 3.78 (s, 3 H, CH₃O), 3.68 (t, 1 H, H-2^I), 3.65–3.61 (m, 1 H, H-6^I), 3.56 (t, 1 H, H-6^{II}), 3.50–3.40 (m, 1 H, H-5^{II}), 2.05–1.98 (m, 1 H, H-4^I), 1.86 (s, 3 H, CH₃CO), 0.75 (s, 9 H, C(CH₃)₃), –0.08 (s, 3 H, SiCH₃), –0.13 (s, 3 H, SiCH₃); ¹³C NMR (62.5 MHz, CDCl₃): δ 169.7, 159.1, 155.1, 150.9, 137.5, 137.3, 137.1, 129.6, 129.0, 128.8, 128.6, 128.3, 128.1, 128.1, 128.0, 127.7, 127.7, 126.1, 118.2, 114.4, 113.5, 102.5, 101.6, 83.0, 82.7, 80.0, 75.2, 74.3, 73.5, 73.2, 71.9, 71.4, 71.3, 69.1, 67.6, 65.4, 55.6, 55.2, 54.5, 48.3, 25.7, 23.4, 18.0, –4.0, –4.9; ESIMS (positive-ion): m/z 1006.2 [M + H], 1023.2 [M + NH₄], 1028.2 [M + Na], 1044.2 [M + K]. Anal. Calcd for C₅₇H₇₁NO₁₃Si (1006.28): C, 68.04; H, 7.11; N, 1.39. Found: C, 67.79; H, 7.03; N, 1.47.

3.11 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethyl-silyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-2,3-di-*O*-benzyl-4a-oxo-6-*O*-*p*-methoxybenzyl-4a-carba- β -D-glucopyranoside (16)

To a solution of compound **15c** (640 mg, 0.636 mmol) in dry CH₂Cl₂ (15 mL) was added PCC (1.35 g, 6.26 mmol, ~10 equiv). The reaction was stirred for 12 h, after which time it was concentrated to dryness, and the residue was submitted to silica gel column chromatography (3:1 to 2:1 hexanes–EtOAc) to yield **16** as a white solid (420 mg, 0.418 mmol, 66%). TLC (2:1 hexanes–EtOAc): R_f 0.5; mp 68–69 °C; $[\alpha]_D -10.6$ (c 0.5, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃): δ 7.46–7.43 (m, 2 H, ArH), 7.36–7.26 (m, 11 H, ArH), 7.21 (d, 2 H, ArH), 7.16 (d, 2 H, ArH), 7.00 (d, 2 H, ArH), 6.82 (d, 2 H, ArH), 6.80 (d, 2 H, ArH), 6.05 (d, 1 H, NH), 5.46 (s, 1 H, PhCH), 5.07 (d, 1 H, ArCH₂O), 4.95 (d, 1 H, ArCH₂O), 4.92 (d, 1 H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.75 (d, 1 H, ArCH₂O), 4.61 (d, 1 H, H-1^{II}, $J_{1,2} = 6.0$ Hz), 4.52–4.45 (m, 3 H, ArCH₂O, H-2^{II}), 4.20 (dd, 1 H, H-6^{II}), 3.89–3.84 (m, 2 H, ArCH₂O, H-3^I), 3.82–3.71 (m, 3 H, H-3^{II}, H-5^I, H-2^I), 3.78 (s, 3 H, CH₃O), 3.76 (s, 3 H, CH₃O), 3.68–3.65 (m, 1 H, H-5^I), 3.62–3.50 (m, 4 H, H-6^{II}, H-6^I, H-6^I, H-4^I), 3.45 (t, 1 H, H-4^{II}), 1.79 (s, 3 H, COCH₃), 0.77 (s, 9 H, C(CH₃)₃), –0.06 (s, 3 H, CH₃Si), –0.08 (s, 3 H, CH₃Si); ¹³C NMR (62.5 MHz, CDCl₃): δ 211.9, 169.1, 159.0, 155.3, 151.0, 137.6, 137.0, 136.8, 129.4, 129.1, 128.8, 128.5, 128.3, 128.0, 127.8, 127.7, 127.5, 126.1, 118.4, 114.4, 113.6, 102.7, 101.6, 82.6, 82.5, 81.2, 80.2, 75.2, 74.6, 73.0, 72.9, 70.7, 69.1, 68.6, 67.8, 55.4, 54.9, 52.5, 51.6, 25.4, 23.2, 17.8, –4.2, –5.1; ESIMS: m/z 1026.6 [M + Na], 1042.5 [M + K]. Anal. Calcd for C₅₇H₆₉NO₁₃Si: C, 68.17; H, 6.93; N, 1.39. Found: C, 68.16; H, 6.89; N, 1.44.

3.12 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethyl-silyl-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-2,3-di-*O*-benzyl-4a-oxo-6-*O*-*p*-methoxybenzyl-4a-carba- β -D-glucopyranoside (17)

To a solution of compound **16** (250 mg, 0.244 mmol) in MeOH (5 mL) was added NaOMe (0.75 mmol, 3 equiv). The reaction was stirred at room temperature for 2 h, after which time it was neutralized with Dowex 50W $\times$ 2 (H⁺) and concentrated to dryness. The residue was submitted to silica gel column chromatography (3:1 to 2:1 hexanes–EtOAc) to give starting material **16** (125 mg, 50%) and product **17** as a white solid (89 mg, 36%). TLC (2:1 hexanes–EtOAc): R_f 0.4; mp 94–95 °C; $[\alpha]_D +0.2$ (c 0.5, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃): δ 7.45–7.43 (m, 2 H, ArH), 7.38–7.25 (m, 13 H, ArH), 7.17 (d, 2 H, ArH), 7.02 (d, 2 H, ArH), 6.85 (d, 2 H, ArH), 6.81 (d, 2 H, ArH), 5.44 (s, 1 H, PhCH), 5.09 (d, 1 H, ArCH₂O), 5.05 (d, 1 H, ArCH₂O), 4.95 (d, 1 H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.81 (d, 1 H, ArCH₂O), 4.65–4.62 (m, 2 H, H-1^{II}, $J_{1,2} = 10.8$ Hz, NH), 4.56 (t, 1 H, H-3^{II}), 4.47 (d, 1 H, ArCH₂O), 4.38 (dd, 2 H, ArCH₂O), 4.15 (dd, 1 H, H-6^{II}), 4.06 (dd, 1 H, H-3^I), 3.78 (s, 3 H, CH₃O), 3.78 (s, 3 H, CH₃O), 3.76–3.70 (m, 2 H, H-5^I, H-2^I), 3.63 (t, 1 H, H-6^{II}), 3.49–3.41 (m, 4 H, H-4^I, H-5^{II}, H-6^I), 3.29 (t, 1 H, H-4^{II}), 2.81–2.76 (m, 1 H, H-2^{II}), 1.64 (s, 3 H, COCH₃), 0.76 (s, 9 H, C(CH₃)₃), –0.12 (s, 3 H, SiCH₃), –0.16 (s, 3 H, SiCH₃); ¹³C NMR (62.5 MHz, CDCl₃): δ 204.8,

170.3, 159.2, 155.3, 151.2, 138.4, 137.8, 137.1, 129.6, 129.2, 129.0, 128.8, 128.4, 128.2, 128.0, 128.0, 127.8, 126.7, 126.3, 118.2, 114.5, 113.8, 102.9, 101.9, 82.7, 82.5, 80.6, 79.4, 75.2, 74.6, 74.1, 72.9, 70.5, 70.1, 69.3, 68.4, 55.6, 55.5, 55.2, 51.5, 25.8, 23.6, 18.1, -4.5, -5.0; ESIMS: m/z 1026.6 [M + Na], 1042.5 [M + K]. Anal. Calcd for $C_{57}H_{69}NO_{13}Si$: C, 68.17; H, 6.93; N, 1.39. Found: C, 68.09; H, 6.90; N, 1.45.

3.13 Reduction of 17 to 15a and 15b

To a solution of 17 (120 mg, 0.117 mmol) in abs EtOH (10 mL) was added $NaBH_4$ (15 mg). The reaction was stirred for 4 h, after which time 1 M HCl was added, and the mixture was diluted with wet CH_2Cl_2 (20 mL), poured into water (50 mL), and extracted with CH_2Cl_2 . The organic phase was dried with anhyd Na_2SO_4 and evaporated to dryness. The residue was submitted to silica gel column chromatography to yield **15a** (25.0 mg, 0.024 mmol, 21%) and **15b** (75.0 mg, 0.075 mmol, 62%) as white solids. The physicochemical and spectral data for these compounds matched those of **15a** and **15b** synthesized using SmI_2 as the promoter.

3.14 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethyl-silyl-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-(4a*R*)-2,3-di-*O*-benzyl-4a-*O*-methylthiothiocarbonyl-6-*O*-*p*-methoxybenzyl-4a-carba- β -D-glucopyranoside (**18a**)

To a solution of compound **15a** (1.90 g, 1.68 mmol) and imidazole (10 mg, 0.15 mmol) in dry THF (15 mL) was added NaH (60% in mineral oil, 135 mg, 3.38 mmol). The reaction was stirred for 30 min, after which time CS_2 (1.74 mL, 3.78 mmol) was added. MeI (0.42 mL, 6.72 mmol) was then added after another 40 min. The mixture was stirred for 40 min, after which time it was quenched with wet CH_2Cl_2 (20 mL), poured into water (50 mL), and extracted with CH_2Cl_2 . The organic phase was dried with anhyd Na_2SO_4 and then evaporated to dryness. The residue was submitted to silica gel column chromatography (3:1 to 2:1 hexanes–EtOAc) to yield compound **18a** as a white amorphous solid (1.01 g, 0.91 mmol, 54%). TLC (2:1 hexanes–EtOAc): R_f 0.5; mp 85–87 °C; $[\alpha]_D -4.3$ (c 0.1, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 7.46–7.23 (m, 17 H, ArH), 7.06 (d, 2 H, ArH), 6.85 (d, 2 H, ArH), 6.74 (d, 2 H, ArH), 6.33 (m, 1 H, CHOC=S), 5.44 (s, 1 H, PhCH), 5.09 (d, 1 H, $ArCH_2O$), 5.08 (d, 1 H, $ArCH_2O$), 4.86 (d, 1 H, $H-1^I$, $J_{1,2} = 7.8$ Hz), 4.75 (d, 1 H, $ArCH_2O$), 4.67 (d, 1 H, $ArCH_2O$), 4.51 (d, 1 H, $ArCH_2O$), 4.42 (d, 1 H, $ArCH_2O$), 4.23 (dd, 1 H, $H-6^{II}$), 4.00–3.95 (m, 2 H, $H-6^I$, $H-5^I$), 3.80–3.74 (m, 1 H, $H-2^I$), 3.77 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.66–3.32 (m, 8 H, $H-3^I$, $H-6^{II}$, $H-6^I$, $H-3^{II}$, $H-2^{II}$, $H-1^{II}$, $H-5^{II}$, $H-4^{II}$), 2.72–2.52 (m, 1 H, $H-4^I$), 2.55 (s, 3 H, SCH_3), 1.49 (s, 3 H, CH_3CO), 0.77 (s, 9 H, $C(CH_3)_3$), -0.08 (s, 3 H, $SiCH_3$), -0.09 (s, 3 H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 216.3, 169.7, 158.9, 155.1, 151.5, 139.0, 138.0, 137.1, 130.8, 129.0, 128.3, 128.0, 127.7, 127.4, 127.3, 126.3, 118.3, 114.4, 113.5, 102.9, 101.9, 83.4, 82.3, 78.9, 75.5, 74.5, 74.3, 73.4, 72.9, 71.8, 71.0, 70.6, 68.5, 55.5, 55.1, 54.5, 44.9, 25.6, 23.3, 19.4, 18.0, -4.2, -5.1; ESIMS (positive-ion): m/z 1096.4 [M + H], 1118.5 [M + Na], 1134.6 [M + K]. Anal. Calcd for $C_{59}H_{73}NO_{13}S_2Si$ (1096.45): C, 64.63; H, 6.71; N, 1.28. Found: C, 64.58; H, 6.71; N, 1.26.

3.15 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethyl-silyl-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-(4a*S*)-2,3-di-*O*-benzyl-4a-*O*-methylthiothiocarbonyl-6-*O*-*p*-methoxybenzyl-4a-carba- β -D-glucopyranoside (**18b**)

Compound **18b** was synthesized from **15b** using the same procedure as that for **18a**. (50% yield). TLC (2:1 hexanes–EtOAc): R_f 0.45; mp 80–82 °C; $[\alpha]_D -9.0$ (c 0.5, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$): δ 7.46–7.23 (m, 17 H, ArH), 7.11 (d, 2 H, ArH), 6.85 (d, 2 H, ArH), 6.75 (d, 2 H, ArH), 6.42 (m, 1 H, CHOC=S), 5.37 (s, 1 H, PhCH), 5.32 (d, 1 H, $ArCH_2O$), 5.05 (d, 1 H, $ArCH_2O$), 5.00 (d, 1 H, NH), 4.93 (d, 1 H, $H-1^I$, $J_{1,2} = 7.2$ Hz), 4.78 (dd, 2 H, $ArCH_2O$), 4.58 (t, 1 H, $H-4^{II}$), 4.48 (dd, 2 H, $ArCH_2O$), 4.43 (d, 1 H, $H-1^{II}$, $J_{1,2} = 10.8$ Hz), 4.14 (d, 1 H, $H-6^{II}$), 4.02 (d, 1 H, $H-6^I$), 3.77 (s, 3 H, CH_3O), 3.76 (s, 3 H, CH_3O), 3.79–3.73 (m, 3 H,

H-3^{II}, H-2^I, H-3^I), 3.49–3.43 (m, 4 H, H-5^I, H-1^{II}, H-6^{II}, H-6^I), 3.19 (t, 1 H, H-5^{II}), 2.73 (m, 1 H, H-2^{II}), 2.55 (s, 3 H, SCH₃), 2.21 (t, 1 H, H-4^I), 1.33 (s, 3 H, CH₃CO), 0.79 (s, 9 H, C(CH₃)₃), −0.11 (s, 3 H, SiCH₃), −0.14 (s, 3 H, SiCH₃); ¹³C NMR (62.5 MHz, CDCl₃): δ 216.7, 170.2, 159.1, 155.0, 151.5, 138.8, 137.8, 137.2, 130.6, 129.2, 129.1, 128.9, 128.3, 128.2, 128.0, 127.8, 126.3, 126.2, 118.0, 114.5, 113.7, 102.7, 101.8, 83.1, 82.5, 80.4, 79.1, 76.8, 75.0, 74.3, 73.9, 73.0, 72.3, 69.7, 68.9, 68.3, 56.9, 55.5, 55.1, 42.2, 25.6, 23.4, 19.0, 18.1, −4.3, −5.1; ESIMS (positive-ion): *m/z* 1118.1 [M + Na], 1134.1 [M + K]. Anal. Calcd for C₅₉H₇₃NO₁₃S₂Si (1096.45): C, 64.63; H, 6.71; N, 1.28. Found: C, 64.39; H, 6.86; N, 1.22.

3.16 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethyl-silyl-2-deoxy-β-D-glucopyranosyl)-(1→4a)-2,3-di-*O*-benzyl-6-*O*-*p*-methoxybenzyl-4a-carba-β-D-glucopyranoside (19)

To a refluxing solution of Bu₃SnH (1.33 mL, 5.0 mmol) in dry toluene (10 mL) was added dropwise a solution of compound **18a** or **18b** (1.00 g, 0.91 mmol) and AIBN (11 mg) in dry toluene (10 mL). The reaction was stirred for 30 min, and then the reaction mixture was extracted with CH₂Cl₂. The organic phase was dried with anhyd Na₂SO₄ and concentrated to dryness. The residue was submitted to silica gel column chromatography (2:1 hexanes–EtOAc) to yield compound **19** as a white amorphous solid (820 mg, 0.83 mmol, 91%). TLC (2:1 hexanes–EtOAc): *R*_f 0.3; mp 67–69 °C; [α]_D −21.3 (*c* 0.5, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃): δ 7.47–7.25 (m, 20 H, ArH), 7.04 (d, 2 H, ArH), 6.89 (d, 2 H, ArH), 6.80 (d, 2 H, ArH), 5.44 (s, 1 H, PhCH), 5.08 (d, 1 H, ArCH₂O), 5.02 (d, 1 H, ArCH₂O), 4.84 (d, 1 H, H-1^I, *J*_{1,2} = 7.8 Hz), 4.79 (d, 1 H, ArCH₂O), 4.60 (d, 1 H, ArCH₂O), 4.57 (d, 1 H, NH), 4.51 (d, 1 H, ArCH₂O), 4.44 (d, 1 H, ArCH₂O), 4.19 (dd, 1 H, H-6^{II}), 3.79 (s, 3 H, OCH₃), 3.77 (s, 3 H, OCH₃), 3.74–3.68 (m, 3 H, H-6^I, H-2^I, H-3^{II}), 3.60–3.50 (m, 4 H, H-6^I, H-6^{II}, H-2^{II}, H-3^I), 3.50–3.44 (m, 2 H, H-5^I, H-4^{II}), 3.34–3.28 (m, 1 H, H-1^{II}, *J*_{1,2} = 8.4 Hz), 3.25–3.20 (m, 1 H, H-5^{II}), 2.12–2.05 (m, 1 H, H-4^I), 1.73 (m, 1 H, CH₂), 1.67 (s, 3 H, CH₃CO), 1.61 (dd, 1 H, CH₂), 0.77 (s, 9 H, C(CH₃)₃), −0.03 (s, 3 H, SiCH₃), −0.08 (s, 3 H, SiCH₃); ¹³C NMR (62.5 MHz, CDCl₃): δ 169.5, 159.1, 155.1, 151.5, 139.1, 138.1, 137.1, 130.2, 129.5, 128.9, 128.4, 128.3, 128.1, 128.0, 127.5, 126.2, 118.3, 114.4, 113.7, 103.0, 101.7, 83.2, 82.4, 80.7, 75.8, 74.5, 73.8, 73.3, 73.0, 70.0, 68.7, 57.0, 55.4, 55.1, 39.8, 28.8, 25.5, 23.3, 17.9, −4.1, −5.1; ESIMS (positive-ion): *m/z* 1012.4 [M + Na], 1028.5 [M + K]. Anal. Calcd for C₅₇H₇₁NO₁₂Si (990.28): C, 69.13; H, 7.23; N, 1.41. Found: C, 68.57; H, 7.28; N, 1.34.

3.17 *p*-Methoxyphenyl C-(2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosyl)-(1→4a)-2,3-di-*O*-benzyl-6-*O*-*p*-methoxybenzyl-4a-carba-β-D-glucopyranoside (20)

To a solution of compound **19** (1.22 g, 1.23 mmol) in dry THF (20 mL) was added Bu₄NF (1.35 mL, 1.0 M in THF, 1.1 equiv). The reaction was stirred at room temperature for 1.5 h, after which time it was quenched with water, and the mixture was extracted with CH₂Cl₂. The organic phase was dried with anhyd Na₂SO₄ and evaporated to dryness. The residue was submitted to silica gel column chromatography (50:1 CH₂Cl₂–MeOH) to give compound **20** as a white amorphous solid (1.00 g, 1.14 mmol, 93%). TLC (10:1 CH₂Cl₂–MeOH): *R*_f 0.5; mp 234–236 °C; [α]_D −36.7 (*c* 0.5, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃): δ 7.53–7.24 (m, 15 H, ArH), 7.21 (d, 2 H, ArH), 7.04 (d, 2 H, ArH), 6.82 (dd, 4 H, ArH), 6.67 (d, 1 H, NH), 5.52 (s, 1 H, PhCH), 5.16 (d, 1 H, ArCH₂O), 5.11 (d, 1 H, ArCH₂O), 4.90 (d, 1 H, H-1^I, *J*_{1,2} = 7.8 Hz), 4.89 (d, 1 H, ArCH₂O), 4.60 (d, 1 H, ArCH₂O), 4.48 (s, 2 H, ArCH₂O), 4.29–4.24 (m, 1 H, H-6^I), 4.16–4.13 (dd, 1 H, H-6^{II}), 3.90–3.87 (m, 1 H, H-5^I), 3.79 (s, 3 H, OCH₃), 3.78 (s, 3 H, OCH₃), 3.70–3.67 (m, 2 H, H-2^I, H-3^{II}), 3.64–3.60 (m, 1 H, H-6^I), 3.54 (dd, 1 H, H-3^I), 3.47–3.34 (m, 5 H, H-6^{II}, H-5^{II}, H-1^{II}, H-2^{II}, H-4^{II}), 2.04–1.98 (m, 1 H, H-4^I), 1.81–1.76 (m, 1 H, CH₂), 1.57 (s, 3 H, COCH₃), 1.39–1.36 (m, 1 H, CH₂); ¹³C NMR (62.5 MHz, CDCl₃): δ 171.4, 159.2, 155.3, 151.3, 137.9, 137.2, 136.8, 129.8, 129.4, 129.3, 129.1, 129.0, 128.8, 128.5, 128.3, 128.2, 127.9, 126.3, 118.4, 114.5, 113.7, 102.9, 101.7, 83.1, 83.0, 82.7, 76.8, 74.5, 74.0, 73.2, 70.1, 69.1, 69.0, 64.8, 55.6, 55.2, 53.5, 41.6, 28.9, 22.5; ESIMS (positive-

ion): m/z 876.3 [M + H], 893.3 [M + NH₄], 898.2 [M + Na], 914.3 [M + K]. Anal. Calcd for C₅₁H₅₇NO₁₂ (876.01): C, 69.93; H, 6.56; N, 1.60. Found: C, 69.86; H, 6.66; N, 1.67.

3.18 *p*-Methoxyphenyl C-(2-acetamido-2-deoxy- β -D-glucopyranosyl)-(1 $\rightarrow$ 4a)-4a-carba- β -D-glucopyranosiduronic acid (21)

To a solution of compound **20** (505 mg, 0.58 mmol) in CH₂Cl₂ (20 mL) and H₂O (1 mL) was added DDQ (308 mg, 1.1 equiv). The reaction was stirred at room temperature for 1.5 h, after which time the mixture was washed with satd NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried with anhyd Na₂SO₄ and evaporated to dryness. To a solution of the resulting white solid in CH₂Cl₂ (6 mL) and H₂O (1 mL) were added sequentially NaBr (2.66 mg), Bu₄NBr (2.66 mg), TEMPO (2.66 mg), a satd NaHCO₃ solution (1.33 mL), and a 5% solution of NaOCl (1.73 mL) at 0 °C. After 2 h the reaction was quenched with MeOH (1.5 mL), neutralized with 1 M HCl, and extracted with CH₂Cl₂. The combined organic extracts were dried with anhyd MgSO₄ and then concentrated to dryness. To a solution of the residue in 20:1 EtOAc and MeOH (10 mL) was added Pd(OH)₂/C (20%, 50 mg), and the reaction was stirred in an H₂ atmosphere (1 atm) for 60 h at room temperature. At the end of this time the reaction mixture was filtered through Celite and concentrated to dryness. The residue was submitted to silica gel chromatography (20:1:1 CH₂Cl₂–MeOH–AcOH) to give compound **21** as a white solid (61 mg, 0.12 mmol, 21%). ¹H NMR (600 MHz, CD₃OD): δ 7.07 (d, 2 H, ArH), 6.82 (d, 2 H, ArH), 4.73 (d, 1 H, H-1^I, $J_{1,2}$ = 7.8 Hz), 3.90–3.82 (m, 2 H, H-6^{II}, H-5^I), 3.73 (s, 3 H, OCH₃), 3.61–3.56 (m, 1 H, H-6^{II}), 3.56–3.50 (dd, 1 H, H-4^{II}), 3.46 (t, 1 H, H-2^I), 3.40–3.27 (m, 4 H, H-3^I, H-2^{II}, H-5^{II}, H-3^{II}), 3.26–3.21 (m, 1 H, H-1^{II}), 2.03–1.92 (m, 1 H, H-4^I), 1.99 (s, 3 H, COCH₃), 1.81–1.72 (m, 1 H, CH₂), 1.68–1.56 (m, 1 H, CH₂). ¹³C NMR (62.5 MHz, CD₃OD): δ 174.3, 156.5, 153.0, 119.4, 115.5, 103.5, 81.3, 77.5, 77.2, 76.1, 75.1, 72.3, 63.0, 57.2, 56.2, 43.0, 30.0, 23.1. ESIMS (negative-ion): Calcd for C₂₂H₃₁NO₁₂ 501.1846; Found: 501.1840 [M]; 500.1773 ([M – H] (calcd 500.1768).

Supplementary Material

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Figure 1.
Hyaluronic acid (hyaluronan, HA).

Figure 2.
ORTEP depiction of compound **15a**.

Scheme 1. Synthesis of the C-glycosyl donor, protected sulfone **6**.

Scheme 2.
Synthesis of C-glycosyl acceptor, aldehyde **14**.

Scheme 3.
SmI₂-promoted coupling reaction.

Scheme 4.
Conversion of **15c** to **15a** and **15b**.

Scheme 5.
Synthesis of the C-disaccharide.