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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 SmI_2-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, Fig. 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), that is, $[\rightarrow 3)$-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]

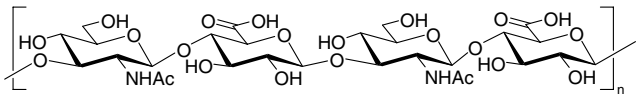

Figure 1. Hyaluronic acid (hyaluronan, HA).

As a part of an ongoing project, the 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–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.

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

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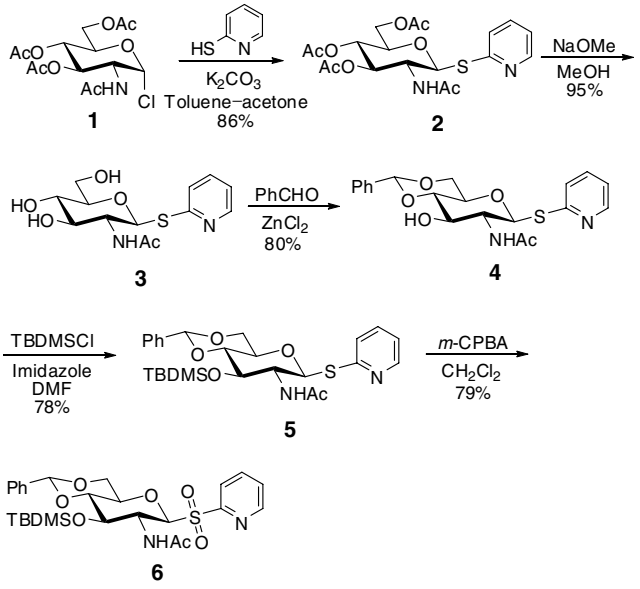
targeted in the glycosyl acceptor), as well as the stabilities of the protecting groups involved and their influence on the reactivity of both the glycosyl donor and acceptor. For our purposes, several processes were attempted in this laboratory,[9–11] among them the Henry coupling advocated by Martin and Lei,[12,13] the olefin metathesis method of Postema and co-workers,[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 functionalities 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 and co-workers[23,24] for the synthesis of sialic acid mimetics, was carried out and gave the most promising results. Using this SmI_2 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

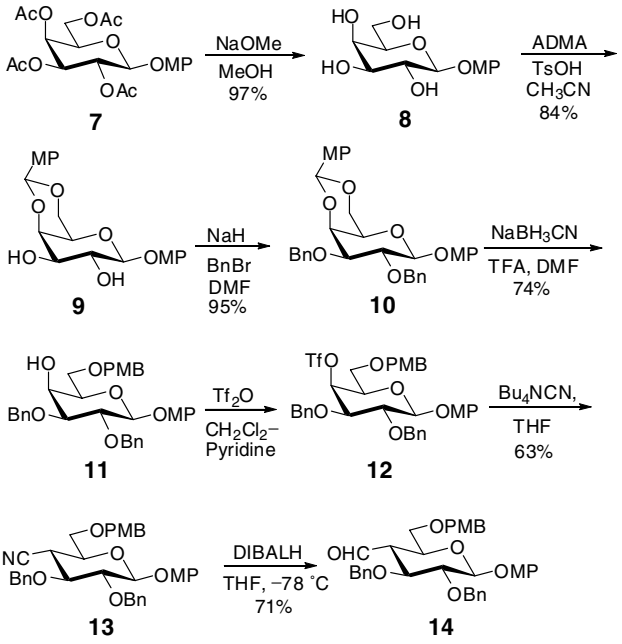
The synthesis of sulfone **6** was carried out as shown in Scheme 1. Thus, the reaction of glycosyl chloride **1** with K_2CO_3 and 2-mercaptopyridine in dry acetone at 50 °C gave the desired pyridinyl thioglycoside **2**.[25] In order to manipulate the protective groups, **2** was treated with NaOMe in 1:5 CH_2Cl_2–MeOH to afford the free-hydroxy compound **3** that was directly reacted with benzaldehyde and $ZnCl_2$ 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 overnight[28] 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 CH_2Cl_2 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.



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

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 CH_2Cl_2 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 CH_3CN 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 $NaBH_3CN$ and CF_3CO_2H in the presence of 4 Å MS in DMF at room temperature for 10 h to render 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

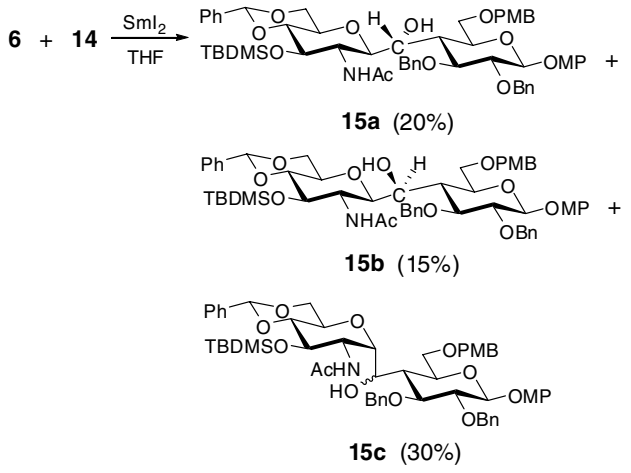


Scheme 2. Synthesis of *C*-glycosyl acceptor, aldehyde **14**.

$(CF_3SO)_2O$ in pyridine at 0 °C overnight gave the corresponding triflate **12** in nearly quantitative yield. Reaction of triflate **12** with Bu_4NCN 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 H_3PO_4 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 α anomer **15c** situated between them. All three of the disaccharides were easily identified by positive-ion ESI mass spectroscopy, which gave inter alia [M+H], [M+Na], and [M+K] ions as expected (see Section 3). 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→4)-C-linkage and the configuration of the linking CHOH group, as shown in Figure 2. Thus **15a** is the β-(4a*R*)-isomer. Disaccharide **15b**, which showed $J_{1,2}$ 9.6 Hz, was also assigned the β-linkage. Furthermore



Scheme 3. SmI_2-promoted coupling reaction.

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 ^{1}H 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 Section 3). 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 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 [M+H], [M+NH_4], [M+Na], and [M+K] peaks in the positive-ion ESIMS. The NMR spectra, in general, supported the assigned structure; however, while the ^{1}H 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).

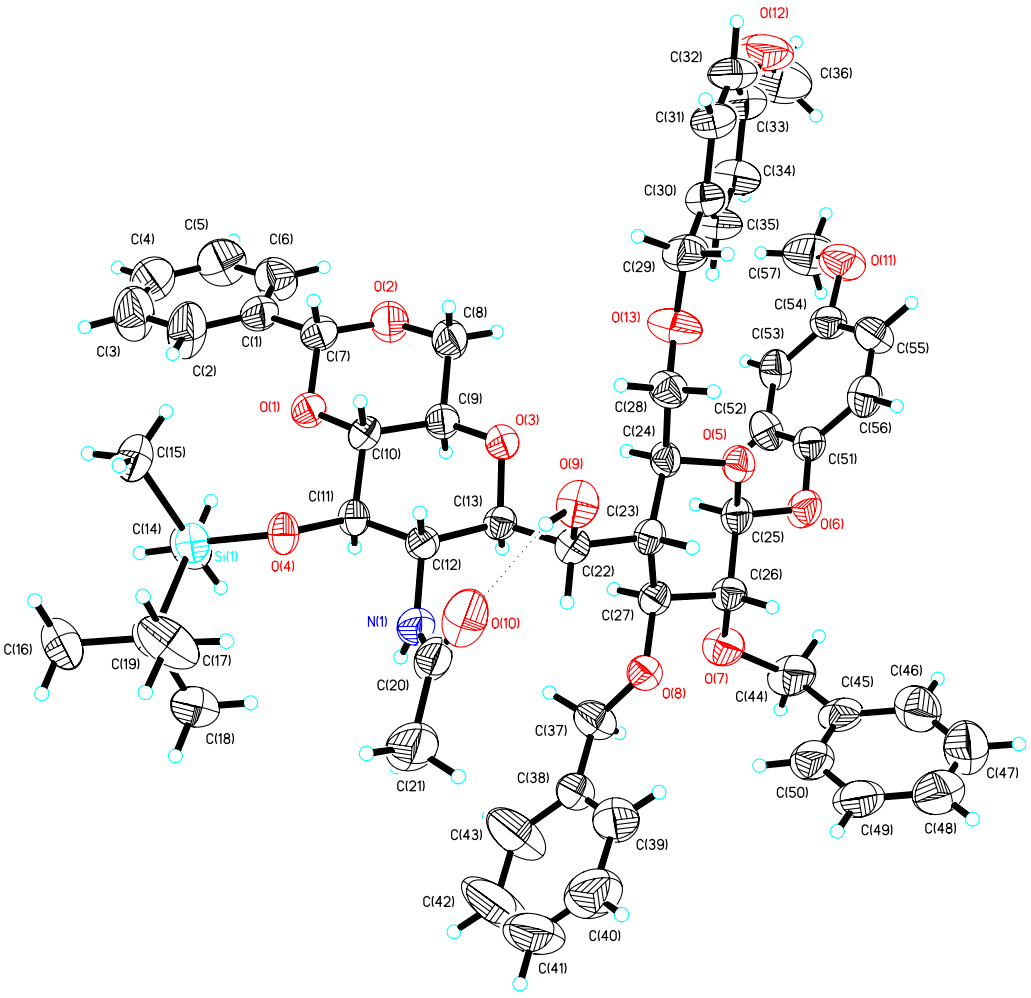
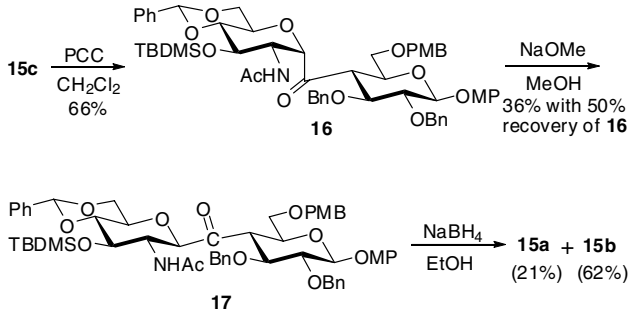


Figure 2. ORTEP depiction of compound **15a**.



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

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 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 ^{1}H 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 ^{13}C resonance at δ 174.3, which is indicative of a carboxylic acid.[37] The other resonances were supportive of the structure.

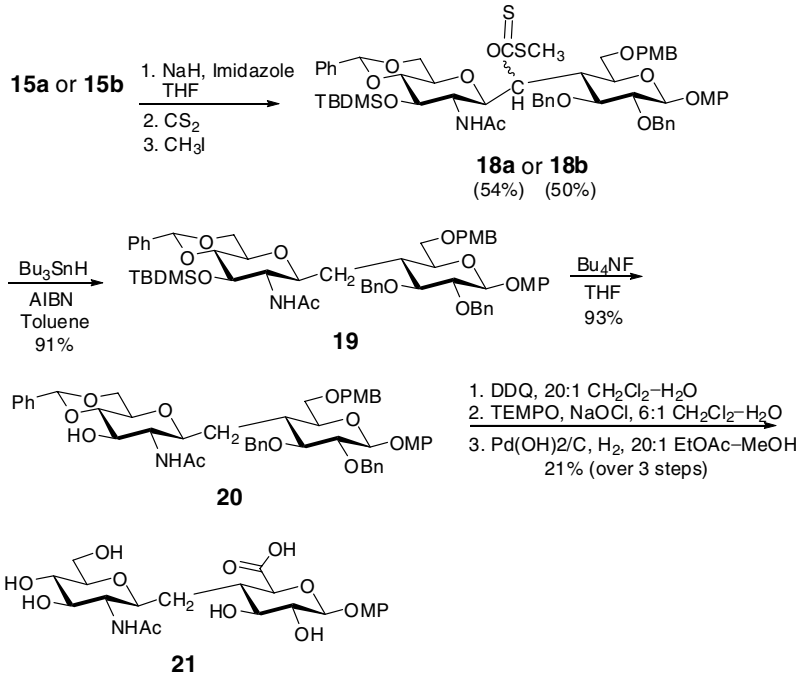
2.5. Conclusions

The target C-linked disaccharide that constitutes the repeat unit of HA was synthesized as its *p*-methoxyphenyl glycoside using SmI_2-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, is underway.

3. Experimental

3.1. General methods

^{1}H (250 MHz, 300 MHz, and 600 MHz) and ^{13}C (62.5 MHz, 75 MHz, and 150 MHz) NMR spectra were



Scheme 5. Synthesis of the C-disaccharide.

recorded at 25 °C as designated. Chemical shifts are expressed in δ units (parts per million) and were measured relative to an internal standard of TMS for ^{1}H, and relative to the signal for $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.5) for ^{13}C, 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 UV_{254} [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 CH_2Cl_2 (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 NH_4Cl 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; $[\alpha]_D$ +9.5 (*c* 1.0, DMSO). Compound **3** (16.0 g, 51.0 mmol) was stirred with dry $ZnCl_2$ (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 $CHCl_3$–MeOH): R_f 0.4; mp 164–166 °C; $[\alpha]_D$ +4.6 (*c* 0.5, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.43–7.12 (m, 4H, ArH), 7.47–7.32 (m, 5H, ArH), 5.62 (s, 1H, PhCH), 5.54 (d, 1H, H-1, $J_{1,2} = 10.5$ Hz), 5.46 (d, 1H, NH), 4.19–4.17 (m, 1H, H-6), 3.85 (dd, 1H, H-2), 3.74–3.63 (m, 2H, H-3, H-4), 3.59–3.48 (m, 2H, H-6, H-5), 3.16 (d, 1H, OH), 1.80 (s, 3H, CH_3CO); ^{13}C 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 $C_{20}H_{22}N_2O_5S\cdot 0.16CH_2Cl_2$ (416.06): C, 58.20; H, 5.41; N, 6.73. Found: C, 58.19; H, 5.56; N, 6.50. CH_2Cl_2 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 aq $NaHCO_3$, 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 (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; $[\alpha]_D$ +4.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.44–7.03 (m, 4H, ArH), 7.55–7.34 (m, 5H, ArH), 5.98 (d, 1H, NH), 5.85 (d, 1H, H-1, $J_{1,2} = 10.6$ Hz), 5.51 (s, 1H, PhCH), 4.31 (dd, 1H, H-6), 4.20–3.96 (m, 2H, H-2, H-3), 3.82–3.48 (m, 3H, H-6, H-5, H-4), 1.91 (s, 3H, CH_3CO), 0.82 (s, 9H, $C(CH_3)_3$), 0.05 (s, 3H, $SiCH_3$), −0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{26}H_{36}N_2O_5SSi$ (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 CH_2Cl_2 (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 CH_2Cl_2, washed consecutively with satd $Na_2S_2O_3$, satd Na_2CO_3 and brine, and extracted with CH_2Cl_2. The organic phase was dried with anhyd Na_2SO_4 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; $[\alpha]_D$ −34.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.85 (d, 1H, ArH), 8.16 (d, 1H, ArH), 8.02 (t, 1H, ArH), 7.62 (t, 1H, ArH), 7.50–7.39 (m, 5H, ArH), 6.84 (d, 1H, NH), 5.81 (d, 1H, H-1, $J_{1,2} = 10.3$ Hz), 4.72–4.61 (m, 1H, H-6), 4.12–4.02 (m, 2H, H-2, H-3), 3.69–3.48 (m, 3H, H-6, H-5, H-4), 2.06 (s, 3H, CH_3CO), 0.09 (s, 9H, $C(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), −0.01 (s, 3H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{26}H_{36}N_2O_7SSi$ (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 CH_2Cl_2 (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 × 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 CH_2Cl_2–MeOH): R_f 0.1; mp 158–160 °C; $[\alpha]_D$ −35.7 (*c* 1.1, H_2O). To a suspension of **8** (11.0 g, 38.5 mmol) in dry CH_3CN (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 Et_3N. 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 CH_2Cl_2–MeOH): R_f 0.5; mp 224–226 °C; $[\alpha]_D$ −74.9 (*c* 1.0, DMSO); ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.37 (d, 2H, ArH), 7.01 (d, 2H, ArH), 6.91 (d, 2H, ArH), 6.86 (d, 2H, ArH), 5.51 (s, 1H, CH_3OPhCH), 5.26 (d, 1H, H-2), 5.02 (d, 1H, H-3), 4.83 (d, 1H, H-1, $J_{1,2} = 6.5$ Hz), 4.10 (s, 1H, H-4), 4.02 (s, 2H, H-6), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.67 (s, 1H, H-5), 3.58 (m, 1H, OH); ^{13}C 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 $C_{21}H_{24}O_8$ (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 CH_2Cl_2. The organic phase was dried with anhyd Na_2SO_4 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; $[\alpha]_D$ −6.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.49 (d, 2H, ArH), 7.40–7.25 (m, 10H, ArH), 7.06 (d, 2H, ArH), 6.90 (d, 2H, ArH), 6.80 (d, 2H, ArH), 5.47 (s, 1H, MeOPhCH), 5.00 (d, 1H, H-1, $J_{1,2} = 10.7$ Hz), 4.86 (m, 2H, H-2, H-3), 4.78 (s, 2H, $ArCH_2O$), 4.31 (d, 1H, $ArCH_2O$), 4.15–3.99 (m, 3H, H-6, H-4, $ArCH_2O$), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.61 (dd, 1H, H-5), 3.39 (s, 1H, H-6); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{35}H_{36}O_8$ (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), $NaBH_3CN$ (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 CF_3CO_2H (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 aq $NaHCO_3$, and extracted with CH_2Cl_2. The organic phase was dried with anhyd Na_2SO_4 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; $[\alpha]_D$ −6.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.22 (m, 12H, ArH), 7.03 (d, 2H, ArH), 6.85 (d, 2H, ArH), 6.80 (d, 2H, ArH), 5.01 (d, 1H, $ArCH_2O$), 4.84 (d, 1H, H-1, $J_{1,2} = 7.5$ Hz), 4.81 (d, 1H, $ArCH_2O$), 4.74 (s, 2H, $ArCH_2O$), 4.50 (s, 2H, $ArCH_2O$), 4.05 (d, 1H, H-6), 3.91 (dd, 1H, H-2), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), ~3.7 (m, 1H, H-6a), 3.63 (dd, 1H, H-3), 3.56 (m, 1H, H-5), 2.56 (s, 1H, OH); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{35}H_{38}O_8$ (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 CH_2Cl_2 (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 nest 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 Bu_4NCN (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, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34–7.20 (m, 12H, ArH), 6.99 (d, 2H, ArH), 6.83 (d, 2H, ArH), 6.79 (d, 2H, ArH), 5.01 (d, 1H, $ArCH_2O$), 4.87 (s, 2H, $ArCH_2O$), 4.85 (d, 1H, H-1, $J_{1,2} = 7.5$ Hz), 4.78 (d, 1H, $ArCH_2O$), 4.47 (dd, 2H, $ArCH_2O$), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.78–3.64 (m, 4H, H-2, H-5, H-6), 3.55 (t, 1H, H-3), 2.98 (t, 1H, H-4); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{36}H_{37}NO_7$ (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 Bu_2AlH [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 H_3PO_4 (10 mL) for another 30 min at 0 °C. The mixture was then neutralized with satd aq $NaHCO_3$, filtered through a bed of Celite and extracted with CH_2Cl_2. The organic phase was dried with anhyd Na_2SO_4 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 com-

pound **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, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 9.65 (d, 1H, CHO), 7.33–7.16 (m, 12H, ArH), 6.99 (d, 2H, ArH), 6.83 (d, 2H, ArH), 6.80 (d, 2H, ArH), 5.05 (d, 1H, $ArCH_2O$), 4.84 (m, 3H, $ArCH_2O$, H-1, $J_{1,2} = 10.0$ Hz), 4.56 (d, 1H, $ArCH_2O$), 4.40 (dd, 2H, $ArCH_2O$), 4.00 (dd, 1H, H-3), 3.74 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.81–3.67 (m, 2H, H-5, H-3), 3.58 (m, 2H, H-6), 3.01 (dd, 1H, $J = 10.2$ Hz, H-4); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{36}H_{38}O_8$ (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→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; $[\alpha]_D$ −41.2 (*c* 0.5, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 7.51–7.19 (m, 17H, ArH), 7.07 (d, 2H, ArH), 6.84 (d, 2H, ArH), 6.75 (d, 2H, ArH), 5.44 (s, 1H, PhCH), 5.07 (d, 1H, $ArCH_2O$), 4.99 (d, 1H, $ArCH_2O$), 4.99 (d, 1H, NH), 4.91 (d, 1H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.80 (d, 1H, $ArCH_2O$), 4.59 (d, 1H, $ArCH_2O$), 4.45 (dd, 2H, $ArCH_2O$), 4.21 (dd, 1H, H-6^{II}), 4.02 (s, 1H, CH–O*H*), 3.97 (dd, 1H, H-6^I), 3.91–3.83 (m, 2H, H-5^I, H-2^{II}), 3.80–3.76 (m, 3H, H-2^I, H-3^I, C*H*–OH), 3.78 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 3.62–3.57 (m, 2H, H-6^I, H-6^{II}), 3.43–3.36 (m, 2H, H-4^{II}, H-1^{II}, $J_{1,2} = 8.4$ Hz), 3.29–3.21 (m, 2H, H-3^{II}, H-5^{II}), 2.32–2.26 (m, 1H, H-4^I), 1.76 (s, 3H, CH_3CO), 0.77 (s, 9H, $C(CH_3)_3$), −0.05 (s, 3H, $SiCH_3$), −0.08 (s, 3H, $SiCH_3$); ^{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 [M+Na], 1044.5 [M+K]. Anal. Calcd for $C_{57}H_{71}NO_{13}Si$ (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→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; $[\alpha]_D$ −97.1 (*c* 0.5, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 7.47–7.24 (m, 17H, ArH), 7.04 (d, 2H, ArH), 6.87 (d, 2H, ArH), 6.79 (d, 2H, ArH), 5.40 (s, 1H, PhCH), 5.09 (d, 1H, $ArCH_2O$), 5.03 (d, 1H, $ArCH_2O$), 4.99 (d, 1H, NH), 4.94 (d, 1H, H-1^I, $J_{1,2} = 6.6$ Hz), 4.77 (d, 1H, $ArCH_2O$), 4.65 (d, 1H, $ArCH_2O$), 4.50 (d, 1H, $ArCH_2O$), 4.43 (d, 1H, $ArCH_2O$), 4.17 (dd, 1H, H-6^{II}), 3.88–3.74 (m, 5H, H-5^I, H-3^{II}, H-2^I, CH–OH, H-3^I), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.72 (dd, 1H, H-6^I), 3.61 (dd, 1H, H-6^I), 3.58–3.52 (m, 2H, H-6^{II}, H-1^{II}, $J_{1,2} = 9.6$ Hz), 3.48 (dd, 1H, H-2^{II}), 3.28 (t, 1H, H-4^{II}), 3.26–3.21 (m, 1H, H-5^{II}), 2.25–2.08 (m, 1H, H-4^I), 1.89 (s, 3H, CH_3CO), 0.08 (s, 9H, $C(CH_3)_3$), −0.03 (s, 3H, $SiCH_3$), −0.07 (s, 3H, $SiCH_3$); ^{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 [M+H], 1028.5 [M+Na], 1044.6 [M+K]. Anal. Calcd for $C_{57}H_{71}NO_{13}Si$ (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→4a)-2,3-di-*O*-benzyl-4a-hydroxy-6-*O*-*p*-methoxybenzyl-4a-carba–D-glucopyranoside (15c). TLC (2:1 hexanes–EtOAc): R_f 0.4; mp 96–98 °C; $[\alpha]_D$ −2.9 (*c* 0.1, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 7.47–7.26 (m, 15H, ArH), 7.21 (d, 2H, ArH), 7.00 (d, 2H, ArH), 6.84 (d, 2H, ArH), 6.81 (d, 2H, ArH), 6.10 (d, 1H, NH), 5.44 (s, 1H, PhCH), 5.11 (d, 1H, $ArCH_2O$), 5.05 (d, 1H, $ArCH_2O$), 4.93 (d, 1H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.75 (d, 1H, $ArCH_2O$), 4.74 (d, 1H, $ArCH_2O$), 4.46 (d, 1H, $ArCH_2O$), 4.35 (d, 1H, $ArCH_2O$), 4.27 (m, 1H, H-2^{II}) 4.12 (dd, 1H, H-6^{II}), 4.02 (m, 1H, H-4^{II}), 3.95 (m, 2H, H-3^I, H-3^{II}), 3.84–3.71 (m, 4H, H-6^I, H-5^I, H-1^{II}, CH–OH), 3.78 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 3.68 (t, 1H, H-2^I), 3.65–3.61 (m, 1H, H-6^I), 3.56 (t, 1H, H-6^{II}), 3.50–3.40 (m, 1H, H-5^{II}), 2.05–1.98 (m, 1H, H-4^I), 1.86

(s, 3H, CH_3CO), 0.75 (s, 9H, $C(CH_3)_3$), −0.08 (s, 3H, $SiCH_3$), −0.13 (s, 3H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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+NH_4], 1028.2 [M+Na], 1044.2 [M+K]. Anal. Calcd for $C_{57}H_{71}NO_{13}Si$ (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*-butyldimethylsilyl-2-deoxy-α-D-glucopyranosyl)-(1→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 CH_2Cl_2 (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, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 7.46–7.43 (m, 2H, ArH), 7.36–7.26 (m, 11H, ArH), 7.21 (d, 2H, ArH), 7.16 (d, 2H, ArH), 7.00 (d, 2H, ArH), 6.82 (d, 2H, ArH), 6.80 (d, 2H, ArH), 6.05 (d, 1H, NH), 5.46 (s, 1H, PhCH), 5.07 (d, 1H, $ArCH_2O$), 4.95 (d, 1H, $ArCH_2O$), 4.92 (d, 1H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.75 (d, 1H, $ArCH_2O$), 4.61 (d, 1H, H-1^{II}, $J_{1,2} = 6.0$ Hz), 4.52–4.45 (m, 3H, $ArCH_2O$, H-2^{II}), 4.20 (dd, 1H, H-6^{II}), 3.89–3.84 (m, 2H, $ArCH_2O$, H-3^I), 3.82–3.71 (m, 3H, H-3^{II}, H-5^I, H-2^I), 3.78 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 3.68–3.65 (m, 1H, H-5^I), 3.62–3.50 (m, 4H, H-6^{II}, H-6^I, H-6^I, H-4^I), 3.45 (t, 1H, H-4^{II}), 1.79 (s, 3H, $COCH_3$), 0.77 (s, 9H, $C(CH_3)_3$), −0.06 (s, 3H, CH_3Si), −0.08 (s, 3H, CH_3Si); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{57}H_{69}NO_{13}Si$: 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*-butyldimethylsilyl-2-deoxy-β-D-glucopyranosyl)-(1→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 × 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, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 7.45–7.43 (m, 2H, ArH), 7.38–7.25 (m, 13H, ArH), 7.17 (d, 2H, ArH), 7.02 (d, 2H, ArH), 6.85 (d, 2H, ArH), 6.81 (d, 2H, ArH), 5.44 (s, 1H, PhCH), 5.09 (d, 1H, $ArCH_2O$), 5.05 (d, 1H, $ArCH_2O$), 4.95 (d, 1H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.81 (d, 1H, $ArCH_2O$), 4.65–4.62 (m, 2H, H-1^{II}, $J_{1,2} = 10.8$ Hz, NH), 4.56 (t, 1H, H-3^{II}), 4.47 (d, 1H, $ArCH_2O$), 4.38 (dd, 2H, $ArCH_2O$), 4.15 (dd, 1H, H-6^{II}), 4.06 (dd, 1H, H-3^I), 3.78 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 3.76–3.70 (m, 2H, H-5^I, H-2^I), 3.63 (t, 1H, H-6^{II}), 3.49–3.41 (m, 4H, H-4^I, H-5^{II}, H-6^I,), 3.29 (t, 1H, H-4^{II}), 2.81–2.76 (m, 1H, H-2^{II}), 1.64 (s, 3H, $COCH_3$), 0.76 (s, 9H, $C(CH_3)_3$), −0.12 (s, 3H, $SiCH_3$), −0.16 (s, 3H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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*-butyldimethylsilyl-2-deoxy-β-D-glucopyranosyl)-(1→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); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46–7.23 (m, 17H, ArH), 7.06 (d, 2H, ArH), 6.85 (d, 2H, ArH), 6.74 (d, 2H, ArH), 6.33 (m, 1H, CHOC=S), 5.44 (s, 1H, PhCH), 5.09 (d, 1H, $ArCH_2O$), 5.08 (d, 1H, $ArCH_2O$), 4.86 (d, 1H, H-1^I, $J_{1,2} = 7.8$ Hz), 4.75 (d, 1H, $ArCH_2O$), 4.67 (d, 1H, $ArCH_2O$), 4.51 (d, 1H, $ArCH_2O$), 4.42 (d, 1H, $ArCH_2O$), 4.23 (dd, 1H, H-6^{II}) 4.00–3.95 (m, 2H, H-6^I, H-5^I), 3.80–3.74 (m, 1H, H-2^I), 3.77 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.66–3.32 (m, 8H, 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, 1H, H-4^I), 2.55 (s, 3H, SCH_3), 1.49 (s, 3H, CH_3CO), 0.77 (s, 9H, $C(CH_3)_3$), −0.08 (s, 3H, $SiCH_3$), −0.09 (s, 3H, $SiCH_3$); ^{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*-butyldimethylsilyl-2-deoxy-β-D-glucopyranosyl)-(1→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); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46–7.23 (m, 17H, ArH), 7.11 (d, 2H, ArH), 6.85 (d, 2H, ArH), 6.75 (d, 2H, ArH), 6.42 (m, 1H, CHOC=S), 5.37 (s, 1H, PhCH), 5.32 (d, 1H, $ArCH_2O$), 5.05 (d, 1H, $ArCH_2O$), 5.00 (d, 1H, NH), 4.93 (d, 1H, H-1^I, $J_{1,2} = 7.2$ Hz), 4.78 (dd, 2H, $ArCH_2O$), 4.58 (t, 1H, H-4^{II}), 4.48 (dd, 2H, $ArCH_2O$), 4.43 (d, 1H, H-1^{II}, $J_{1,2} = 10.8$ Hz), 4.14 (d, 1H, H-6^{II}), 4.02 (d, 1H, H-6^I), 3.77 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 3.79–3.73 (m, 3H, H-3^{II}, H-2^I, H-3^I), 3.49–3.43 (m, 4H, H-5^I, H-1^{II}, H-6^{II}, H-6^I), 3.19 (t, 1H, H-5^{II}), 2.73 (m, 1H, H-2^{II}), 2.55 (s, 3H, SCH_3), 2.21 (t, 1H, H-4^I), 1.33 (s, 3H, CH_3CO), 0.79 (s, 9H, $C(CH_3)_3$), −0.11 (s, 3H, $SiCH_3$), −0.14 (s, 3H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{59}H_{73}NO_{13}S_2Si$ (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*-butyldimethylsilyl-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 Bu_3SnH (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 CH_2Cl_2. The organic phase was dried with anhyd Na_2SO_4 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; $[\alpha]_D$ −21.3 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47–7.25 (m, 20H, ArH), 7.04 (d, 2H, ArH), 6.89 (d, 2H, ArH), 6.80 (d, 2H, ArH), 5.44 (s, 1H, PhCH), 5.08 (d, 1H, $ArCH_2O$), 5.02 (d, 1H, $ArCH_2O$), 4.84 (d, 1H, H-1^I, $J_{1,2} = 7.8$ Hz), 4.79 (d, 1H, $ArCH_2O$), 4.60 (d, 1H, $ArCH_2O$), 4.57 (d, 1H, NH), 4.51 (d, 1H, $ArCH_2O$), 4.44 (d, 1H, $ArCH_2O$), 4.19 (dd, 1H, H-6^{II}), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.74–3.68 (m, 3H, H-6^I, H-2^I, H-3^{II}), 3.60–3.50 (m, 4H, H-6^I, H-6^{II}, H-2^{II}, H-3^I), 3.50–3.44 (m, 2H, H-5^I, H-4^{II}), 3.34–3.28 (m, 1H, H-1^{II}, $J_{1,2} = 8.4$ Hz), 3.25–3.20 (m, 1H, H-5^{II}), 2.12–2.05 (m, 1H, H-4^I), 1.73 (m, 1H, CH_2), 1.67 (s, 3H, CH_3CO), 1.61 (dd, 1H, CH_2), 0.77 (s, 9H, $C(CH_3)_3$), −0.03 (s, 3H, $SiCH_3$), −0.08 (s, 3H, $SiCH_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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 $C_{57}H_{71}NO_{12}Si$ (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 Bu_4NF (1.35 mL, 1.0 M in THF, 1.1 equiv). The reaction was stirred at room tem-

perature for 1.5 h, after which time it was quenched with water, and the mixture was 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 (50:1 CH_2Cl_2–MeOH) to give compound **20** as a white amorphous solid (1.00 g, 1.14 mmol, 93%). TLC (10:1 CH_2Cl_2–MeOH): R_f 0.5; mp 234–236 °C; $[\alpha]_D$ −36.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53–7.24 (m, 15H, ArH), 7.21 (d, 2H, ArH), 7.04 (d, 2H, ArH), 6.82 (dd, 4H, ArH), 6.67 (d, 1H, NH), 5.52 (s, 1H, PhCH), 5.16 (d, 1H, $ArCH_2O$), 5.11 (d, 1H, $ArCH_2O$), 4.90 (d, 1H, H-1^I, $J_{1,2} = 7.8$ Hz), 4.89 (d, 1H, $ArCH_2O$), 4.60 (d, 1H, $ArCH_2O$), 4.48 (s, 2H, $ArCH_2O$), 4.29–4.24 (m, 1H, H-6^I), 4.16–4.13 (dd, 1H, H-6^{II}), 3.90–3.87 (m, 1H, H-5^I), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.70–3.67 (m, 2H, H-2^I, H-3^{II}), 3.64–3.60 (m, 1H, H-6^I), 3.54 (dd, 1H, H-3^I), 3.47–3.34 (m, 5H, H-6^{II}, H-5^{II}, H-1^{II}, H-2^{II}, H-4^{II}), 2.04–1.98 (m, 1H, H-4^I), 1.81–1.76 (m, 1H, CH_2), 1.57 (s, 3H, $COCH_3$), 1.39–1.36 (m, 1H, CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$): 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+NH_4], 898.2 [M+Na], 914.3 [M+K]. Anal. Calcd for $C_{51}H_{57}NO_{12}$ (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→4a)-4a-carba-β-D-glucopyranosid-uronic acid (21)

To a solution of compound **20** (505 mg, 0.58 mmol) in CH_2Cl_2 (20 mL) and H_2O (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 aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhyd Na_2SO_4 and evaporated to dryness. To a solution of the resulting white solid in CH_2Cl_2 (6 mL) and H_2O (1 mL) were added sequentially NaBr (2.66 mg), Bu_4NBr (2.66 mg), TEMPO (2.66 mg), a satd aq $NaHCO_3$ 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 CH_2Cl_2. The combined organic extracts were dried with anhyd $MgSO_4$ 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 a H_2 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 CH_2Cl_2–MeOH–AcOH) to give compound **21** as a white solid (61 mg, 0.12 mmol, 21%). ^{1}H NMR (600 MHz, CD_3OD): δ 7.07 (d, 2H, ArH), 6.82 (d, 2H, ArH), 4.73 (d, 1H, H-1^I, $J_{1,2} = 7.8$ Hz), 3.90–3.82 (m, 2H, H-6^{II}, H-5^I), 3.73 (s, 3H, OCH_3), 3.61–3.56 (m, 1H, H-6^{II}), 3.56–3.50 (dd, 1H, H-4^{II}), 3.46 (t, 1H, H-2^I), 3.40–3.27 (m, 4H, H-3^I, H-2^{II}, H-5^{II}, H-3^{II}), 3.26–3.21 (m, 1H, H-1^{II}), 2.03–1.92 (m, 1H, H-4^I), 1.99 (s, 3H, $COCH_3$), 1.81–1.72 (m, 1H, CH_2), 1.68–1.56 (m, 1H, CH_2). ^{13}C NMR (62.5 MHz, CD_3OD): 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 $C_{22}H_{31}NO_{12}$ 501.1846; found: 501.1840 [M]; 500.1773 [M−H] (calcd 500.1768).

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Supplementary data

Crystallographic data, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with CCDC No. 646876. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.05.031.

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