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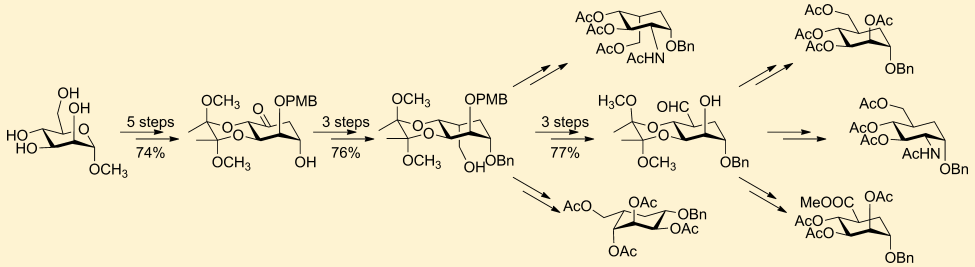
Syntheses of Carbocyclic Analogues of α-D-Glucosamine, α-D-Mannose, α-D-Mannuronic Acid, β-L-Idosamine, and β-L-Gulose

Yunshan Sun and Mark Nitz*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON, Canada M5S 3H6

Supporting Information



ABSTRACT: A versatile synthesis of orthogonally protected derivatives of carba-α-D-glucosamine, carba-α-D-mannose, carba-α-D-mannuronic acid, carba-β-L-idosamine, and carba-β-L-gulose from methyl α-D-mannoside is described. Our synthetic strategy utilizes the palladium-promoted Ferrier carbocyclization and persistent butane-2,3-diacetal protection to produce a key chiral cyclohexanone intermediate, from which all five carbasugar derivatives can readily be obtained.

INTRODUCTION

Carbasugars are useful probes in glycobiology, as they closely resemble their parent sugars but, because of the methylene replacement of the ring oxygen, do not participate the acetal chemistry of their sugar analogues. This increased stability makes carbasugar derivatives useful probes as competitive inhibitors of enzymes such as the glycosidases and glycosyltransferases.[1] Carbasugars have also been suggested as replacements for their sugar counterparts as non-nutritive sweeteners[2] and have been successfully used as enzyme substrates to generate stable oligosaccharides and sugar primers in cellular systems.[1b,3] Given the utility of carbasugars, it is perhaps not surprising that they have been the target of numerous synthetic routes since the first carbasugar synthesis reported by McCasland and co-workers in 1966.[1b,4]

Among many synthetic approaches for converting sugars into carbasugars, the well-known Ferrier carbocyclization reaction has been most widely used for the construction of these carbocycles.[5] The Ferrier carbocyclization, which converts 6-deoxyhex-5-enopyranosides into cyclohexanones, is typically catalyzed by mercury salts. Sinaÿ and co-workers discovered an alternative approach to the Ferrier carbocyclization that is mediated by a Lewis acid, such as triisobutylaluminum or titanium(IV) derivatives, and resulted in the retention of configuration at the anomeric center.[6] In 1988, Adam reported a modification of the Ferrier carbocyclization that uses catalytic amounts of palladium(II) salts, which promotes the same conversion in a more environmentally friendly manner.[7]

As part of our research on bacterial polysaccharides, we required a series of carbasugars as mechanistic probes of polymerizing glycosyltransferases; of particular interest to us is carba-*N*-acetylglucosamine. Several syntheses of derivatives of carba-*N*-acetylglucosamine have appeared.[8−10] The most commonly used route was reported by Quiclet-Sire in 1986 and uses a benzyl carbamate-protected glucosamine derivative as a precursor to a Ferrier carbocyclization followed by a homologation.[8] Alternatively, Ogawa and co-workers have reported a synthesis of the β-anomer of carba-*N*-acetylglucosamine from noncarbohydrate precursors, involving an initial resolution of Diels−Alder adduct, 7-*endo*-oxabicyclo[2.2.1]-hept-5-ene-2-carboxylic acid, derived from furan and acrylic acid.[9] Similarly, Chung et al. have relied upon an enzymatic resolution on route to (1*R*,2*S*,5*S*)-5-(*tert*-butyldiphenylsilanyloxymethy)cyclohex-3-ene-1,2-diol.[10b]

To support our ongoing interest in probes for biosynthesis of bacterial polysaccharides, we sought to develop a synthetic route which is capable of providing a series of carbasugars. Specifically, we were interested in carbasugar analogues of *N*-acetylglucosamine, mannose, and mannuronic acid because of their prevalence in bacterial exopolysaccharides. Herein we report this high yielding route to carba-α-D-glucosamine derivative **1**. Through this route, the carbasugar analogues of α-D-mannose (**2**), α-D-mannuronic acid (**3**), β-L-idosamine (**4**), and β-L-gulose (**5**), which might also be potential substrates for the preparation of biological probes or enzyme substrates, have also been synthesized.[11] This route provides an alternative to the challenges associated with manipulating glucosamine protecting groups in the Quiclet−Sire synthesis[8] and the deracemization protocols required in the Ogawa and Chung syntheses.[9,10b]

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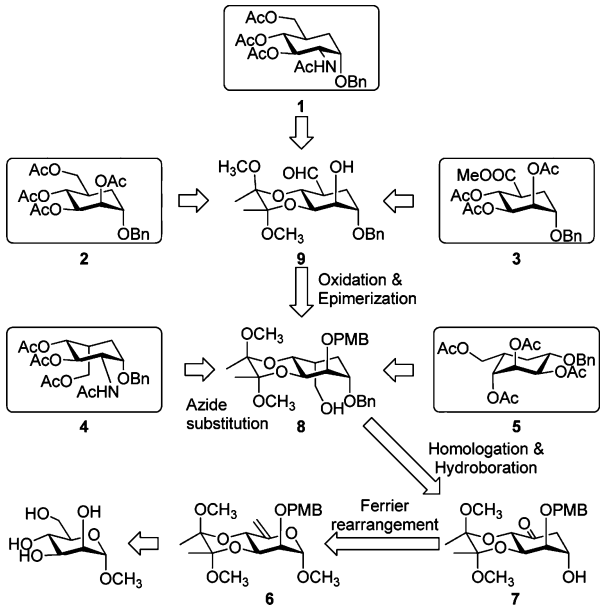
RESULTS AND DISCUSSION

Our syntheses of compounds **1**−**5**, outlined in Scheme 1, began with commercially available methyl α-D-mannoside. The use of

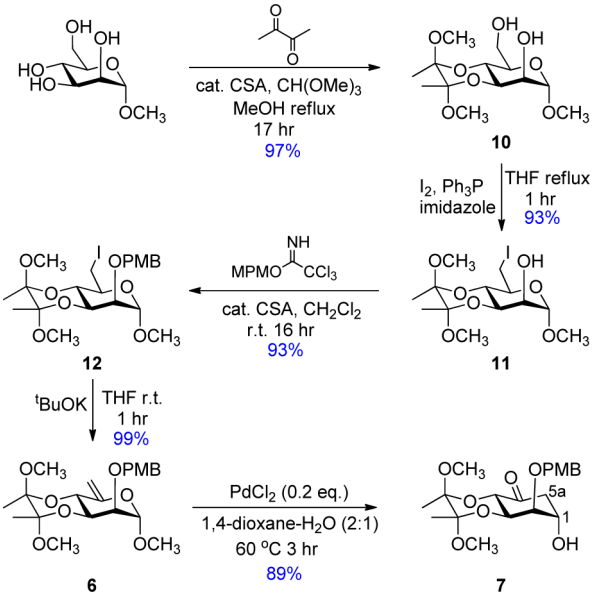
Scheme 1. Outline of Synthetic Approach toward Compounds 1−5



a butane-2,3-diacetal protecting group provides a rapid method to efficiently differentiate methyl α-D-mannoside on a large scale[12] and construct the Ferrier carbocyclization precursor **6**. Homologation and hydroboration followed the Ferrier carbocyclization to provide exclusively the axial hydroxymethyl-configured derivative **8**. The synthesis of carbasugar analogues of *N*-acetylglucosamine (**1**) α-D-mannose (**2**), and α-D-mannuronic acid (**3**) required epimerization of **8** to the equatorial aldehyde **9**. Carbocylic analogues of β-L-idosamine (**4**) and β-L-gulose (**5**) were constructed directly from compound **8**. The final products **1**−**5** bear an orthogonal pseudoanomeric benzyl group which can be removed to facilitate further manipulations such as phosphorylation required to generate glycosyl-1-phosphate analogues.

The key intermediate, cyclohexanone **7**, was synthesized in a high-yielding (74%) five-step sequence from methyl α-D-mannoside (Scheme 2). Treatment of methyl α-D-mannoside with butane-2,3-dione in the presence of catalytic camphorsulfonic acid and trimethyl orthoformate in boiling methanol produced almost exclusively the butane-2,3-diacetal intermediate **10**,[12] which upon treatment with triphenylphosphine, iodine, and imidazole in refluxing THF gave 6-iodo compound **11** in 93% yield. The 2-OH of **11** was then protected as a *p*-methoxybenzyl ether by an acid-catalyzed reaction[13] with MPM trichloroacetimidate.[14] Hydrogen iodide elimination from **12** was effected by potassium *tert*-butoxide in THF at room temperature to give the Ferrier reaction precursor **6** in a near-quantitative yield. Notably, treatment of **12** with DBU in DMF at 110 °C only produced **6** in a modest yield of 66%. In addition, if compound **11** was submitted to DBU-promoted elimination and the resulting eliminated product was then transformed into **6** with NaH and *p*-methoxybenzyl chloride, the overall yield of the two steps was low (47%). Compound **6** was subjected to palladium-catalyzed Ferrier reaction[7b] in 1,4-

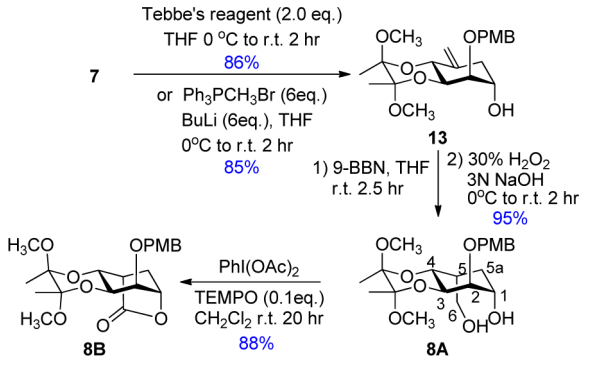
Scheme 2. Synthesis of Compound 7



dioxane and water to cleanly furnish the cyclohexanone **7** as a pure α isomer at pseudo C-1 in 89% yield. The absolute configuration of pseudo C-1 was confirmed by the ^{1}H NMR spectrum of **7** in $CDCl_3$ showing $^3J_{1H-5aH}$ 4.0 and 2.4 Hz. Notably, the Ferrier carbocyclization reaction in the Quiclet−Sire synthesis that was mediated by palladium chloride or mercuric sulfate only afforded a modest yield of cyclohexanone with a low ratio of α- to β-hydroxy isomer at pseudo C-1.[8c]

With the rapid synthesis of cyclohexanone **7** achieved, the stage was now set for the conversion of the ketone to the desired hydroxymethyl group (Scheme 3). The homologation

Scheme 3. Synthesis of Compounds 8A and 8B



of compound **7** was successfully effected by either Wittig olefination with methylenetriphenylphosphorane or Tebbe's methylenation[15] to give exocyclic alkene **13** in comparable yields. However, Wittig reaction of **7** with methoxymethylenetriphenylphosphorane yielded vinyl ether product in a low yield due to the formation of the corresponding butylidene product.[16] The exocyclic alkene **13** was subjected to hydroboration with 9-BBN followed by oxidative workup to give exclusively **8A** in 95% yield. The absolute configuration of **8A** was confirmed by a NOE correlation between the proton at pseudo C-3 and one of the two methylene protons at the hydroxymethyl group and a lack of correlation between the proton at pseudo C-5. Moreover,

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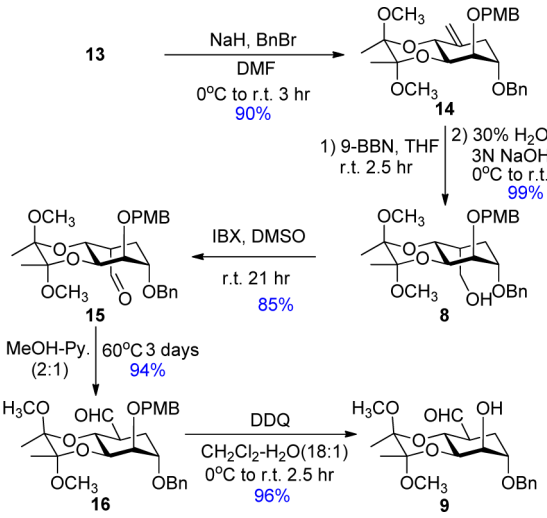
8A was also readily transformed into lactone **8B** by the protocol of Piancatelli and Margarita,[17] supporting the axial configuration of the hydroxymethyl group.

Disappointingly, all attempts to directly hydroborate the exocyclic alkene **13** to the equatorial hydroxymethyl group were unsuccessful. Rhodium(I)-catalyzed hydroboration of PMB-protected **13** with catecholborane,[18] or 9-BBN effected hydroboration of a more sterically hindered TBDPS derivative, gave exclusively the axial hydroxymethyl product. Epoxidation of **13** with m-CPBA followed by the regioselective reduction or transformation of **13** into its phosphinite followed by rhodium(I)-catalyzed hydroboration[15] only led to the formation of tertiary alcohol rather than primary alcohol.

We then employed an epimerization strategy[19] to invert the configuration of pseudo C-5 in compound **8A** via the exocyclic aldehyde (Scheme 4). The primary hydroxyl of **8A** could be

Scheme 4. Synthesis of Compounds 8 and 9

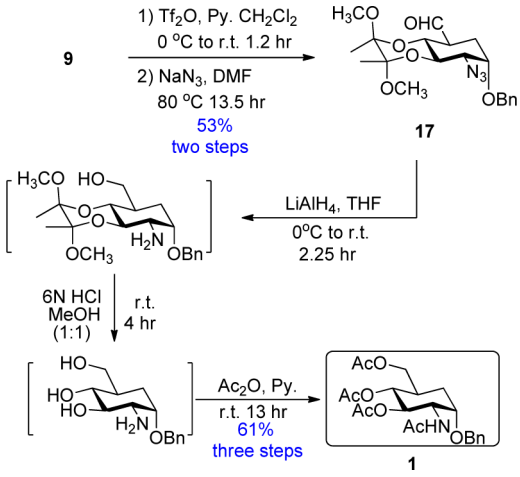


selectively oxidized to an aldehyde using stoichiometric $RuCl_2(PPh_3)_3$ to give hydroxyaldehyde in 63% yield. Other less expensive protocols such as using TEMPO-mediated oxidation led to mixtures of the desired hydroxyaldehyde and lactone **8B** before **8A** was completely consumed, while IBX oxidation always resulted in a mixture of ketone and hydroxyaldehyde.

On the basis of the undesired oxidation result, the secondary hydroxyl group was protected prior to oxidation. The protection of the β-hydroxyl of ketone **7** as a benzyl ether proved to be challenging under basic conditions, giving primarily elimination to the α,β-unsaturated ketone, and low yields were obtained under acidic conditions. Finally, compound **13** was efficiently transformed into its benzyl ether **14**, which upon treatment with 9-BBN and successive oxidation, afforded exclusively axial hydroxymethyl derivative **8**.[20] Interestingly, the hydroboration of **14** with BH_3·THF complex was less selective, giving a mixture of **8** and its regioisomeric tertiary alcohol with a mole ratio of 7.2 to 1. The subsequent IBX oxidation of alcohol **8** afforded the corresponding aldehyde **15** in good yield, which was efficiently epimerized under mildly basic conditions using a mixture of MeOH−pyridine (2:1) at 60 °C to give **16** in 94% yield. The reaction was monitored by ^{1}H NMR following the chemical shift of the aldehydic proton of compound **16** (9.83 ppm) versus that of compound **15** (10.08 ppm). The $^3J_{H-H}$ coupling between pseudo H-4 and pseudo H-5 was also indicative of the isomerization, as in compound **16** $^3J_{4H\text{-}5H}$ was 11.2 Hz, while in compound **15** it was 5.2 Hz. Upon treatment of **16** with DDQ, the hydroxyaldehyde **9** was produced in a near-quantitative yield.

With the equatorial aldehyde group installed, compound **9** was now converted into the carbocyclic analogue of α-D-glucosamine (Scheme 5). It was found that the aldehyde **9** was

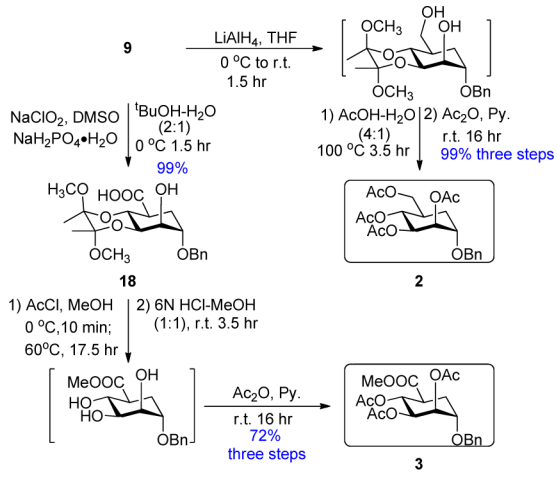
Scheme 5. Synthesis of Compound 1



sufficiently stable to allow introduction of the triflate leaving group at the pseudo 2-OH with triflic anhydride and pyridine in CH_2Cl_2 and to allow inversion at C-2 with sodium azide to furnish azidoaldehyde **17** in an overall yield of 53%. Reduction of the azido group and the aldehyde with $LiAlH_4$ in THF, followed by removal of the diacetal using a 6 N HCl aqueous MeOH solution (1:1) and subsequent acetylation, furnished the desired analogue of carba-α-D-glucosamine **1** in 61% yield over three steps.

The carbocyclic analogues of α-D-mannose and α-D-mannuronic acid were prepared smoothly from the hydroxyaldehyde **9** (Scheme 6). Reduction of the aldehyde group in **9** followed by removal of the diacetal group with acetic acid and water (4:1) and subsequent acetylation provided almost exclusively the protected 5a-carba-α-D-mannose derivative **2**. The synthesis of the derivative of carba-α-D-mannuronic acid

Scheme 6. Synthesis of Compounds 2 and 3



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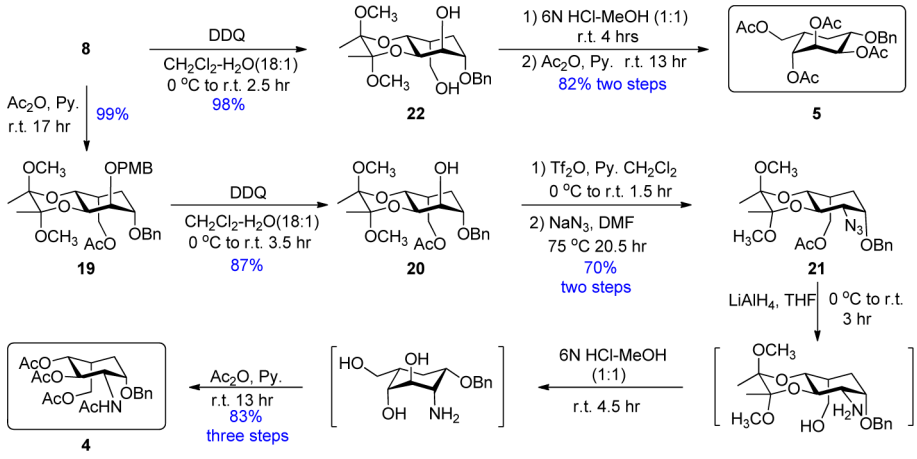
Scheme 7. Synthesis of Compounds 4 and 5

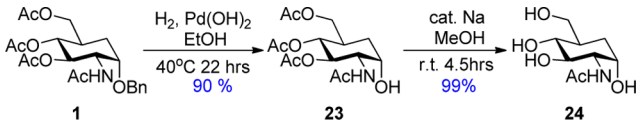


required the conversion of aldehyde into carboxylic acid, which was effected by sodium chlorite oxidation employing DMSO as a scavenger to yield acid **18** in a near-quantitative yield. Esterification of carboxylic acid **18** with acetyl chloride in methanol at 60 °C[21] followed by the complete removal of the diacetal group and subsequent acetylation gave the desired derivative of carba-α-D-mannuronic acid **3** in 72% yield over three steps.

To synthesize the analogue of carba-β-L-idosamine from the axial hydroxymethyl derivative **8**, we applied the same strategy used for the synthesis of carbasugar derivative **1** (Scheme 7). The hydroxyl of compound **8** was acetylated to give **19** in an almost quantitative yield, which was subjected to DDQ oxidation to afford **20** in 87% yield. **20** was then converted into the corresponding triflate ester, which was subjected to nucleophilic substitution with azide anion to afford the azido derivative **21** in 70% yield. This yield is higher than that for preparing the azidoaldehyde **17** (53%), indicating that the presence of an aldehyde group decreased the reaction yield in the transformation of **9** into **17**. Reduction of **21** followed by deprotection and acetylation furnished the analogue of carba-β-L-idosamine **4** in 83% yield over three steps. Analysis of the ^{1}H NMR of compound **4** was consistent with a $^4C_1$ chair, as large coupling constants were observed for H-3 and H-4 (H-3, dd, ^3J = 9.6, 9.6 Hz, H-4, dd, ^3J = 9.6, 5.6 Hz, see Supporting Information). The derivative of carba-β-L-gulose (**5**) was prepared from **8** following the sequence of DDQ oxidation, deprotection, and acetylation, with a total yield of 82% for the latter two steps. In contrast to the conformation of the ido-configured compound **4**, the ^{1}H NMR analysis showed the conformation of compound **5** to be consistent with a $^1C_4$ chair with small coupling constants (<4 Hz) observed for H-3 and H-4.

With the orthogonally protected carbasugar derivatives in hand, we then studied their deprotection reactions (Scheme 8). Compound **1** was readily converted into debenzylated compound **23** in good yield through catalytic hydrogenolysis employing palladium hydroxide on carbon, and compound **24** was also readily available from compound **23** by basic hydrolysis. Both **23** and **24** are valuable precursors for biological probes given that **23** is suitable for chemical manipulations while **24** for enzymatic functionalization.

Scheme 8. Synthesis of Compounds 23 and 24



CONCLUSION

In conclusion, a new versatile synthetic route to orthogonally protected carbocyclic analogue of α-D-glucosamine from methyl α-D-mannoside was developed. This route is also applicable to the syntheses of the carbocyclic analogues of α-D-mannose, α-D-mannuronic acid, β-L-idosamine, and β-L-gulose. The orthogonal pseudo OH-1 protecting group in the final products can be selectively removed to facilitate further chemical phosphorylation to give access to analogues of glycosyl-1-phosphates which occupy a central position in carbohydrate metabolism.

EXPERIMENTAL SECTION

General Methods. All reactions in anhydrous organic solvents were performed under an atmosphere of nitrogen with rigid exclusion of moisture from glassware. The other reactions were carried out in the presence of air unless otherwise noted. All chemicals and anhydrous solvents were purchased from commercial sources and used without further purification. Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a 400 spectrometer working at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Both ^{1}H and ^{13}C NMR chemical shifts are referenced relative to the solvent's residual signals ($CHCl_3$: δ 7.26 for ^{1}H NMR and δ 77.16 for ^{13}C NMR) and reported in parts per million (ppm) at 25 °C, unless otherwise stated. ^{1}H spectra were assigned with the assistance of 2D GCOSY experiment. Data are represented as follows: chemical shift, integration, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), coupling constant in hertz (Hz), and assignment. Infrared spectra were measured on a FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were determined with an automatic polarimeter. Melting points (mp) were recorded using an apparatus and not corrected. High resolution mass spectra were obtained from a quadrapole/TOF mass spectrometer with an ESI source. Silica column chromatography was performed using silica gel (230−400 mesh), unless otherwise stated. Compound **10** was prepared according to a previously reported procedure.[12]

3,4,6-Tri-O-acetyl-2-acetamido-1-O-benzyl-2-deoxy-5a-carba-α-D-glucopyranose (1). To a stirred solution of $LiAlH_4$ (0.78 mL, 1 M in THF, 0.78 mmol) in anhydrous THF (3 mL) was added dropwise a solution of compound **17** in dry THF (1 mL) (70 mg, 0.17 mmol) at 0 °C. The mixture was then stirred at room temperature for 2.25 h. The reaction was quenched by careful addition of $Na_2SO_4{\cdot}10H_2O$ solid,

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filtered, and evaporated in vacuo. The residue was dissolved in a mixture of MeOH (3 mL) and 6 N HCl (3 mL), and the mixture was stirred at room temperature for 4 h. The mixture was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was dissolved in pyridine (6 mL), and acetic anhydride (3 mL) was added slowly. The resulting solution was stirred at room temperature for 13 h. The solution was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:1 to 2:1 to 3:1) to yield compound **1** (46 mg, 61% over three steps) as a white foam. **1**: R_f = 0.32 (ethyl acetate/hexane 3:1); $[\alpha]_D^{27.9}$ = 85.0° (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.40 (5H, m), 5.83 (1H, d, *J* = 9.2 Hz, NH), 5.16 (1H, dd, *J* = 9.6, 10.8 Hz, H-3), 5.03 (1H, dd, *J* = 9.6, 10.8 Hz, H-4), 4.62 (1H, d, *J* = 12.0 Hz, $PhCH_2$), 4.36 (1H, d, *J* = 11.6 Hz, $PhCH_2$), 4.05−4.15 (2H, m, H-6 and H-2), 3.88 (1H, dd, *J* = 3.2, 11.6 Hz, H-6), 3.76−3.80 (1H, m, H-1), 2.22−2.33 (1H, m, H-5), 2.02−2.10 (1H, m, H-5a), 2.03 (3H, s), 2.00 (3H, s), 1.97 (3H, s), 1.81 (3H, s), 1.48 (1H, ddd, *J* = 1.6, 13.2 14.8 Hz, H-5a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.9, 169.9, 169.7, 137.8, 128.7, 128.2, 128.0, 75.1, 73.1, 71.7, 71.6, 63.5, 53.4, 34.8, 28.3, 23.2, 20.9, 20.8, 20.7; EI-HRMS (*m*/*z*) calcd for $C_{22}H_{30}NO_8$ [M + H^+] 436.1971, found 436.1984.

*1-O-Benzyl-2,3,4,6-tetra-O-acetyl-5a-carba-α-D-mannopyranose (**2**).* To a stirred solution of $LiAlH_4$ (0.85 mL, 1 M in THF, 0.85 mmol) in anhydrous THF (6 mL) was added dropwise a solution of compound **9** (0.13 g, 0.34 mmol) in dry THF (3.5 mL) at 0 °C. The mixture was then stirred at room temperature for 1.5 h. TLC (ethyl acetate/pentane 1:1) showed that the starting material was consumed completely. The reaction was quenched by careful addition of $Na_2SO_4{\cdot}10H_2O$ solid, filtered, evaporated in vacuo, and dried under high vacuum to give the crude product (0.13 g) as a white foam. The foam (78 mg) was dissolved in a mixture of acetic acid (6 mL) and distilled water (1.5 mL), and the mixture was stirred at 100 °C for 3.5 h. The mixture was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was dissolved in pyridine (4 mL), and acetic anhydride (2 mL) was added slowly. The resulting solution was stirred at room temperature for 16 h. The solution was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:3 to 1:2) to yield compound **2** (90 mg, 99% for three steps) as a colorless oil. **2**: R_f = 0.55 (ethyl acetate/hexane 1:1); $[\alpha]_D^{27.9}$ = 30.6° (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.37 (5H, m), 5.50 (1H, dd, *J* = 2.8, 2.8 Hz, H-2), 5.30 (1H, dd, *J* = 3.2, 10.4 Hz, H-3), 5.22 (1H, dd, *J* = 10.4, 10.8 Hz, H-4), 4.68 (1H, d, *J* = 12.0 Hz, $PhCH_2$), 4.54 (1H, d, *J* = 12.0 Hz, $PhCH_2$), 4.08 (1H, dd, *J* = 5.2, 11.2 Hz, H-6), 3.92 (1H, dd, *J* = 4.0, 11.6 Hz, H-6), 3.69 (1H, dd, *J* = 3.2, 6.4 Hz, H-1), 2.29−2.39 (1H, m, H-5), 2.11 (3H, s), 2.05 (3H, s), 2.02 (3H, s), 1.98 (3H, s), 1.90 (1H, ddd, *J* = 2.4, 2.8, 14.4 Hz, H-5a), 1.67−1.76 (1H, m, H-5a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.3, 170.2, 169.9, 137.6, 128.6, 128.0, 127.9, 73.3, 71.5, 71.2, 69.7, 69.5, 64.1, 35.4, 28.0, 21.1, 20.9, 20.8(2); EI-HRMS (*m*/*z*) calcd for $C_{22}H_{32}NO_9$ [M + NH_4^+] 454.2077, found 454.2091.

*Methyl 1-O-Benzyl-2,3,4-tri-O-acetyl-5a-carba-α-D-mannuronoate (**3**).* Acetyl chloride (37 μL, 0.52 mmol) was added dropwise to anhydrous MeOH (3 mL) at 0 °C. The solution was stirred at 0 °C for 10 min before a solution of compound **18** (68 mg, 0.17 mmol) in dry MeOH (2 mL) was added at 0 °C. The yellow solution was then stirred at 60 °C for an additional 17.5 h. The solution was evaporated in vacuo, and the residue was dissolved in a mixture of MeOH (3 mL) and 6 N HCl (3 mL), which was stirred at room temperature for 3.5 h. The mixture was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was dissolved in pyridine (5 mL), and acetic anhydride (2.5 mL) was added slowly. The resulting solution was stirred at room temperature for 16 h. The solution was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:3) to yield compound **3** (52 mg, 72% for three steps) as a colorless oil. **3**: R_f = 0.64 (ethyl acetate/hexane 1:1); $[\alpha]_D^{28.0}$ = 33.3° (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.37 (5H, m), 5.48 (1H, dd, *J* = 10.0, 10.4 Hz, H-4), 5.46−5.49 (1H, m, H-2), 5.28 (1H, dd, *J* = 3.2, 10.0 Hz, H-3), 4.67 (1H, d, *J* = 11.6 Hz, $PhCH_2$), 4.57 (1H, d, *J* = 11.6 Hz, $PhCH_2$), 3.72 (1H, dd, *J* = 3.2, 6.8 Hz, H-1), 3.67 (3H, s, $COOCH_3$), 3.02 (1H, ddd, *J* = 5.2, 10.8, 11.2 Hz, H-5), 2.11 (3H, s), 2.00−2.07 (2H, m, H-5a), 2.00 (3H, s), 1.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 170.1, 170.0, 169.8, 137.5, 128.6, 128.1, 127.9, 72.9, 71.5, 70.6, 69.5, 69.4, 52.3, 42.1, 27.8, 21.1, 20.9(2); EI-HRMS (*m*/*z*) calcd for $C_{21}H_{30}NO_9$ [M + NH_4^+] 440.1921, found 440.1919.

*3,4,6-Tri-O-acetyl-2-acetamido-1-O-benzyl-2-deoxy-5a-carba-β-L-idopyranose (**4**).* In the same manner as **1**, compound **4** was synthesized as a white foam (0.11 g, 83% for three steps) from compound **21** (0.13 g, 0.30 mmol), $LiAlH_4$ (1.34 mL, 1 M in THF, 1.34 mmol), a mixture of MeOH (6 mL) and 6 N HCl (6 mL), and a mixture of pyridine (4 mL) and acetic anhydride (2 mL). **4**: R_f = 0.20 (ethyl acetate/hexane 2:1); $[\alpha]_D^{27.9}$ = 35.2° (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.24−7.36 (5H, m), 5.84 (1H, d, *J* = 9.2 Hz, NH), 5.24 (1H, dd, *J* = 9.6, 9.6 Hz, H-3), 5.01 (1H, dd, *J* = 5.6, 9.2 Hz, H-4), 4.63 (1H, d, *J* = 11.6 Hz, $PhCH_2$), 4.31 (1H, d, *J* = 11.6 Hz, $PhCH_2$), 4.10−4.32 (3H, m, H-6 and H-2), 3.74 (1H, dd, *J* = 3.6, 6.4 Hz, H-1), 2.55−2.64 (1H, m, H-5), 2.13−2.24 (1H, m, H-5a), 2.02 (3H, s), 2.00 (3H, s), 1.99 (3H, s), 1.80 (3H, s), 1.55−1.65 (1H, m, H-5a); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 170.8, 170.5, 169.6(2), 137.5, 128.7, 128.2, 75.3, 72.4, 71.8, 69.6, 64.3, 52.7, 35.7, 26.3, 23.1, 20.8, 20.7(2); EI-HRMS (*m*/*z*) calcd for $C_{22}H_{30}NO_8$ [M + H^+] 436.1971, found 436.1979.

*1-O-Benzyl-2,3,4,6-tetra-O-acetyl-5a-carba-β-L-gulopyranose (**5**).* Compound **22** (66 mg, 0.17 mmol) was dissolved in a mixture of MeOH (2 mL) and 6 N HCl (2 mL). The mixture was stirred at room temperature for 4 h before it was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was dissolved in pyridine (3 mL), and acetic anhydride (1.5 mL) was added slowly. The resulting solution was stirred at room temperature for 13 h. The solution was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:3 to 1:1) to afford compound **5** (62 mg, 82% for two steps) as a white solid. **5**: mp 106−107 °C; R_f = 0.53 (ethyl acetate/hexane 1:1); $[\alpha]_D^{27.9}$ = 33.5° (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.36 (5H, m), 5.35 (1H, dd, *J* = 3.6, 4.0 Hz, H-4), 5.15 (1H, dd, *J* = 3.2, 9.6 Hz, H-2), 5.07 (1H, dd, *J* = 3.2, 3.2 Hz, H-3), 4.65 (1H, d, *J* = 12.0 Hz, $PhCH_2$), 4.59 (1H, d, *J* = 12.0 Hz, $PhCH_2$), 4.03 (1H, dd, *J* = 8.4, 11.2 Hz, H-6), 3.92 (1H, dd, *J* = 6.4, 11.2 Hz, H-6), 3.78 (1H, ddd, *J* = 5.2, 10.0, 10.4 Hz, H-1), 2.29−2.40 (1H, m, H-5), 2.10 (3H, s), 2.09 (3H, s), 2.03 (3H, s), 1.99 (3H, s), 1.97−2.05 (1H, m, H-5a), 1.53−1.65 (1H, m, H-5a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.1, 169.5, 169.2, 138.4, 128.5, 127.7, 127.4, 74.5, 72.6, 72.2, 68.8, 68.4, 63.6, 34.0, 28.1, 21.0, 20.9(2), 20.8; EI-HRMS (*m*/*z*) calcd for $C_{22}H_{32}NO_9$ [M + NH_4^+] 454.2077, found 454.2087.

*Methyl 6-Deoxy-2-O-(p-methoxy)benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-α-D-lyxo-hex-5-enopyranoside (**6**).* To a stirred solution of compound **12** (9.00 g, 16.70 mmol) in anhydrous THF (140 mL) was added potassium *tert*-butoxide (5.63 g, 50.20 mmol) in one portion at room temperature. Significant formation of a white precipitate was noted. The suspension was stirred at room temperature for 1 h, and ^{1}H NMR of a reaction aliquot showed that the starting material was consumed completely. The mixture was filtered, and the filtrate was diluted with ethyl acetate (100 mL). The organic solution was washed with saturated NH_4Cl aqueous solution (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:10) to give compound **6** (6.80 g, 99%) as a white solid. **6**: mp 81−83 °C; R_f = 0.65 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.6}$ = 133.3° (*c* 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 8.8 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 4.91 (1H, d, *J* = 11.6 Hz, *p*-MeOPhCH_2), 4.66−4.73 (3H, m, H-6 and H-1), 4.61 (1H, d, *J* = 11.2 Hz, *p*-MeOPhCH_2), 4.59−4.61 (1H, m, H-4), 4.02 (1H, dd, *J* = 2.4, 10.4 Hz, H-3), 3.81 (3H, s, *p*-CH_3OPh), 3.75 (1H, dd, *J* = 2.0, 2.4 Hz, H-2), 3.35 (3H, s, OCH_3-1), 3.28 (3H, s), 3.26 (3H, s), 1.36 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.9, 130.8, 129.8, 113.8, 101.6, 100.0, 99.9, 93.1, 75.4, 73.2, 69.0, 64.8, 55.4, 55.0,

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48.1(2), 18.0(2); EI-HRMS (m/z) calcd for $C_{21}H_{34}NO_8$ [M + NH_4^+] 428.2284, found 428.2286.

*(2S,3S,4aS,7S,8R,8aR)-7-Hydroxy-2,3-dimethoxy-8-((p-methoxybenzyl)oxy)-2,3-dimethylhexahydrobenzo[b][1,4]dioxin-5-(4aH)-one (**7**).* To a stirred solution of compound **6** (2.77 g, 6.75 mmol) in a mixture of 1,4-dioxane (32 mL) and distilled water (16 mL) under N_2 was added $PdCl_2$ (0.24 g, 1.35 mmol) in one portion at room temperature. The suspension was stirred at 60 °C for 3 h, and TLC (ethyl acetate/pentane 1:10) showed that the starting material was consumed completely. The mixture was filtered, and the filtrate was diluted with ethyl acetate (80 mL). The organic solution was washed with water (30 mL), and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:1 to 2.5:1) to give compound **7** (2.39 g, 89%) as a white solid. **7**: mp 190−192 °C; R_f = 0.31 (ethyl acetate/hexane 1:1); $[\alpha]_D^{27.5}$ = 97.2° (*c* 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.8 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 5.03 (1H, d, *J* = 11.2 Hz, *p*-MeOPhCH_2), 4.88 (1H, d, *J* = 11.2 Hz, H-4), 4.64 (1H, d, *J* = 11.2 Hz, *p*-MeOPhCH_2), 4.21−4.26 (2H, m, H-1 and H-3), 3.90−3.93 (1H, m, H-2), 3.82 (3H, s, *p*-CH_3OPh), 3.28 (3H, s), 3.24 (3H, s), 2.92 (1H, ddd, *J* = 1.2, 4.0, 14.8 Hz, H-5a), 2.38 (1H, ddd, *J* = 1.2, 2.4, 14.8 Hz, H-5a), 1.78 (1H, d, *J* = 3.2 Hz, OH), 1.40 (3H, s), 1.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 159.4, 130.9, 129.9, 113.9, 100.2, 99.6, 77.0, 73.7, 73.1, 70.7, 69.4, 55.4, 48.4, 48.1, 44.4, 17.9, 17.7; EI-HRMS (m/z) calcd for $C_{20}H_{32}NO_8$ [M + NH_4^+] 414.2128, found 414.2132.

*3,4-O-(2,3-Dimethoxybutane-2,3-diyl)-2-O-(p-methoxybenzyl)-5a-carba-β-L-gulopyranose (**8A**).* To a stirred solution of compound **13** (0.57 g, 1.50 mmol) in anhydrous THF (10 mL) was added a solution of 9-BBN (8.7 mL, 0.5 M in THF, 4.35 mmol) dropwise at room temperature. The resulting solution was stirred at room temperature for 2.5 h. TLC (ethyl acetate/pentane 1:1) showed that the starting material was consumed completely. To the above solution were slowly added 3 N NaOH aqueous solution (3 mL, 9.00 mmol) and 30% H_2O_2 solution (3 mL) in turn at 0 °C, and then the mixture was stirred for 2 h at room temperature before adding a 0.5 N $Na_2S_2O_3$ aqueous solution (10 mL) and diluting with CH_2Cl_2 (50 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (acetone:hexane 1:3 to 1:2) to give compound **8A** (0.57 g, 95%) as a colorless oil. **8A**: R_f = 0.11 (acetone/hexane 1:3); $[\alpha]_D^{27.8}$ = 102.4° (*c* 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.8 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 4.87 (1H, d, *J* = 11.2 Hz, *p*-MeOPhCH_2), 4.51 (1H, d, *J* = 11.2 Hz, *p*-MeOPhCH_2), 4.35 (1H, dd, *J* = 6.0, 10.8 Hz, H-4), 4.16 (1H, dd, *J* = 2.4, 10.8 Hz, H-3), 3.83−3.92 (2H, m, H-6 and H-1), 3.80 (3H, s, *p*-CH_3OPh), 3.74−3.81 (1H, m, H-6), 3.66−3.70 (1H, m, H-2), 3.26 (3H, s), 3.23 (3H, s), 2.10−2.21 (2H, m, H-5 and H-5a), 1.60−1.67 (1H, m, H-5a), 1.32 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 131.6, 129.6, 113.7, 99.8, 99.5, 79.2, 73.2, 68.6, 67.5, 67.4, 63.1, 55.4, 47.93, 47.91, 38.5, 30.6, 18.0(2); EI-HRMS (m/z) calcd for $C_{21}H_{36}NO_8$ [M + NH_4^+] 430.2441, found 430.2450.

*1-O-Benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-2-O-(p-methoxybenzyl)-5a-carba-β-L-gulopyranose (**8**).* In the same manner as **8A**, compound **8** was synthesized as a colorless oil (2.24 g, 99%) from compound **14** (2.18 g, 4.49 mmol), 9-BBN (26.60 mL, 0.5 M in THF, 13.30 mmol), 3 N NaOH aqueous solution (8.9 mL, 26.70 mmol), and 30% H_2O_2 solution (8.9 mL) in dry THF (33 mL). **8**: R_f = 0.19 (ethyl acetate/hexane 1:3); $[\alpha]_D^{28.0}$ = 124.3° (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.8 Hz), 7.21−7.35 (5H, m), 6.86 (2H, d, *J* = 8.4 Hz), 4.86 (1H, d, *J* = 11.2 Hz), 4.49 (1H, d, *J* = 12.0 Hz), 4.47 (1H, d, *J* = 11.2 Hz), 4.40 (1H, d, *J* = 11.6 Hz), 4.38 (1H, dd, *J* = 5.6, 10.8 Hz, H-4), 4.28 (1H, dd, *J* = 9.6, 11.2 Hz, H-6), 4.19 (1H, dd, *J* = 2.4, 10.8 Hz, H-3), 3.80 (3H, s, *p*-CH_3OPh), 3.77−3.80 (1H, m, H-2), 3.56 (1H, dd, *J* = 2.8, 6.0 Hz, H-1), 3.47 (1H, dd, *J* = 3.6, 11.6 Hz, H-6), 3.27 (3H, s), 3.22 (3H, s), 2.70−2.95 (1H, br, OH), 2.25−2.34 (1H, m, H-5), 1.94 (1H, ddd, *J* = 3.2, 6.4, 15.2 Hz, H-5a), 1.72 (1H, d, *J* = 14.8 Hz, H-5a), 1.31 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.4, 131.4, 129.7, 128.5, 127.7, 127.3, 113.7, 99.5 (2), 76.7, 76.5, 73.2, 71.3, 68.9, 67.0, 65.0, 55.4, 48.0, 47.8, 39.4, 27.5, 18.0(2); EI-HRMS (m/z) calcd for $C_{28}H_{42}NO_8$ [M + NH_4^+] 520.2910, found 520.2917.

*1,6-Anhydro-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-2-O-(p-methoxybenzyl)-5a-carba-β-L-guluronic Acid (**8B**).* To a stirred solution of compound **8A** (32 mg, 0.078 mmol) in anhydrous CH_2Cl_2 (1 mL) were added TEMPO (1.3 mg, 0.0083 mmol) and $PhI(OAc)_2$ (52 mg, 0.16 mmol) in turn at room temperature. The resulting solution was stirred at room temperature for 2 h at which time a second addition of $PhI(OAc)_2$ (26 mg, 0.080 mmol) was made. The solution was stirred at room temperature for another 18 h. TLC (ethyl acetate/pentane 1:1) showed that the starting material was consumed completely. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 0.5 N $Na_2S_2O_3$ aqueous solution (5 mL × 1) and brine (5 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:3) to give compound **8B** (21 mg, 88%) as a colorless oil. **8B**: R_f = 0.25 (ethyl acetate/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.8 Hz), 6.88 (2H, d, *J* = 8.8 Hz), 4.89 (1H, d, *J* = 11.6 Hz, *p*-MeOPhCH_2), 4.53 (1H, d, *J* = 11.6 Hz, *p*-MeOPhCH_2), 4.52 (1H, dd, *J* = 5.2, 4.8 Hz, H-1), 4.05 (1H, dd, *J* = 2.4, 10.0 Hz, H-4), 3.99 (1H, dd, *J* = 4.0, 4.8 Hz, H-2), 3.89 (1H, dd, *J* = 4.0, 10.0 Hz, H-3), 3.82 (3H, s, *p*-CH_3OPh), 3.26 (3H, s), 3.20 (3H, s), 2.63 (1H, dd, *J* = 2.4, 5.6 Hz, H-5), 2.38 (1H, d, *J* = 12.4 Hz, H-5a), 2.24 (1H, ddd, *J* = 5.6, 5.6, 12.0 Hz, H-5a), 1.33 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 159.5, 130.5, 129.8, 113.9, 100.9, 100.8, 78.0, 73.4, 72.6, 70.6, 67.0, 55.4, 48.1, 47.9, 41.1, 31.6, 18.0, 17.9; EI-HRMS (m/z) calcd for $C_{21}H_{32}NO_8$ [M + NH_4^+] 426.2128, found 426.2136.

*1-O-Benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-2-O-(p-methoxybenzyl)-5a-carba-α-D-mannopyranose (**8C**).* To a stirred solution of $LiAlH_4$ (0.50 mL, 1 M in THF, 0.50 mmol) in anhydrous THF (1 mL) at 0 °C was added a solution of compound **16** (0.20 g, 0.40 mmol) in dry THF (1.5 mL) dropwise. The mixture was then stirred at room temperature for 1.5 h. TLC (ethyl acetate/pentane 1:3) showed that the starting material was almost consumed. The reaction was quenched by careful addition of wet Na_2SO_4 solid, filtered and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:2) to give compound **8C** (0.18 g, 92%) as a colorless oil. **8C**: R_f = 0.20 (ethyl acetate/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.4 Hz), 7.23−7.35 (5H, m), 6.86 (2H, d, *J* = 8.4 Hz), 4.86 (1H, d, *J* = 11.2 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.49 (1H, d, *J* = 11.6 Hz), 4.41 (1H, d, *J* = 12.0 Hz), 4.04 (1H, dd, *J* = 10.0, 10.4 Hz, H-4), 3.98 (1H, dd, *J* = 2.4, 10.0 Hz, H-3), 3.81 (3H, s, *p*-CH_3OPh), 3.78 (1H, dd, *J* = 2.4, 2.8 Hz, H-2), 3.70 (1H, dd, *J* = 7.6, 10.8 Hz, H-6), 3.62 (1H, dd, *J* = 2.8, 5.6 Hz, H-1), 3.58 (1H, dd, *J* = 4.0, 10.8 Hz, H-6), 3.30 (3H, s), 3.25 (3H, s), 2.50−2.70 (1H, br, OH), 2.08−2.20 (1H, m, H-5), 1.70 (1H, ddd, *J* = 2.8, 2.8, 14.0 Hz, H-5a), 1.48 (1H, ddd, *J* = 2.8, 13.2, 14.0 Hz, H-5a), 1.32 (3H, s), 1.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.5, 131.4, 129.6, 128.5, 127.7, 127.5, 113.7, 99.6, 99.4, 76.1, 75.8, 73.2, 71.5, 71.0, 70.7, 67.0, 55.4, 48.0(2), 37.0, 27.0, 18.1, 18.0; EI-HRMS (m/z) calcd for $C_{28}H_{42}NO_8$ [M + NH_4^+] 520.2910, found 520.2917.

*(2S,3S,4aR,5S,7S,8R,8aR)-7-(Benzyloxy)-8-hydroxy-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[b][1,4]dioxine-5-carbaldehyde (**9**).* To a stirred mixture of compound **16** (0.65 g, 1.30 mmol) in a mixture of CH_2Cl_2 (28 mL) and distilled water (1.6 mL) was added DDQ (0.45 g, 1.90 mmol) in one portion at 0 °C. The resulting green mixture was stirred at 0 °C for 10 min and then at room temperature for 2.5 h. TLC (ethyl acetate/pentane 1:10) showed that the starting material was consumed completely. The mixture was filtered and the filter cake was washed with CH_2Cl_2 (10 mL × 3). The combined filtrates were washed with saturated $NaHCO_3$ aqueous solution (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:2.5 to 1:1) to give compound **9** (0.48 g, 96%) as a white solid. **9**: mp 56−58

°C; R_f = 0.13 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.8}$ = 112.3°(*c* 0.13, $CHCl_3$); IR (KBr) ν 3453, 2949, 1727, 1379, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (1H, d, *J* = 2.0 Hz, CHO), 7.25−7.36 (5H, m), 4.60 (1H, d, *J* = 12.0 Hz), 4.49 (1H, d, *J* = 12.0 Hz), 4.22 (1H, dd, *J* = 10.0, 11.2 Hz, H-4), 4.03 (1H, dd, *J* = 2.8, 2.8 Hz, H-2), 3.97 (1H, dd, *J* = 2.8, 10.0 Hz, H-3), 3.79 (1H, dd, *J* = 2.8, 5.6 Hz, H-1), 3.25 (3H, s), 3.24 (3H, s), 2.85−2.95 (1H, m, H-5), 2.59−2.70 (1H, br, OH), 1.98 (1H, ddd, *J* = 2.8, 2.8, 14.4 Hz, H-5a), 1.82 (1H, ddd, *J* = 2.8, 12.8, 14.4 Hz, H-5a), 1.31 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 138.1, 128.5, 127.8, 127.6, 100.4, 99.9, 75.6, 71.4, 69.8, 69.7, 66.2, 48.2, 48.1, 47.4, 24.4, 17.9, 17.8; EI-HRMS (*m*/*z*) calcd for $C_{20}H_{32}NO_7$ [M + NH_4^+] 398.2179, found 398.2180.

*Methyl 6-Deoxy-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-6-iodo-α-D-mannoside (**11**).* To a stirred solution of compound **10** (19.00 g, 0.062 mol), triphenylphosphine (19.40 g, 0.074 mol), and imidazole (6.68 g, 0.098 mol) in THF (300 mL) was added a solution of iodine in THF (75 mL) dropwise (18.80 g, 0.074 mol) under reflux over 15 min. During the last stages of the addition, precipitates formed. After the addition was complete, the brown suspension was refluxed for an additional 40 min. TLC (neat Et_2O) showed the reaction to be complete. The mixture was filtered, and the filtrate was diluted with ethyl acetate (150 mL). The organic solution was washed with a 0.5 N $Na_2S_2O_3$ aqueous solution (30 mL) followed by brine (50 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/pentane 1:5 to 1:3 to 1:2) to give compound **11** (24.00 g, 93%) as a white foam. **11**:[12b] R_f = 0.26 (ethyl acetate/hexane 1:3); ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, s, H-1), 3.98 (1H, dd, *J* = 3.2, 10.0 Hz, H-3), 3.91 (1H, dd, *J* = 1.6, 3.2 Hz, H-2), 3.86 (1H, dd, *J* = 10.0, 9.6 Hz, H-4), 3.62−3.68 (1H, m, H-5), 3.55 (1H, dd, *J* = 2.4, 10.8 Hz, H-6), 3.44 (3H, s, OCH_3-1), 3.27 (3H, s), 3.26 (3H, s), 3.23−3.28 (1H, m, H-6), 2.20−2.50 (1H, br, OH), 1.31 (3H, s), 1.28 (3H, s).

*Methyl 6-Deoxy-2-O-(p-methoxy)benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-6-iodo-α-D-mannoside (**12**).* To a stirred solution of compound **11** (29.76 g, 0.071 mol) in CH_2Cl_2 (280 mL) were added MPM trichloroacetimidate[14] (40.84 g, 0.15 mol) and camphorsulfonic acid monohydrate (1.76 g, 7.03 mmol) in turn at room temperature. The solution was stirred at room temperature for 16 h, and TLC (ethyl acetate/pentane 1:3) showed that the reaction was complete. The mixture was filtered to remove the white precipitate of trichloroacetamide, and the filtrate was concentrated under vacuum. During the evaporation, more white precipitates formed, which were removed by filtration and washed with pentane (30 mL × 3). The combined filtrates were evaporated in vacuo, and the residue was purified by column chromatography (ethyl acetate/pentane 1:16 to 1:10) to afford compound **12** (35.54 g, 93%) as a white solid. Spectroscopic and analytical data agree with the previous report.[22]

*6-Deoxy-2-O-(p-methoxybenzyl)-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-5a-carba−α-D-lyxo-hex-5-enopyranoside (**13**).* (a) Via Wittig olefination: To a stirred suspension of methyltriphenylphosphonium bromide (5.41 g, 15.14 mmol) in anhydrous THF (40 mL) was added dropwise a solution of *n*-BuLi (9.46 mL, 1.6 M in hexane, 15.10 mmol) at 0 °C. After the addition, the yellow suspension was stirred at room temperature for 1 h. To the above yellow suspension was added a solution of compound **7** (1.00 g, 2.52 mmol) in dry THF (10 mL) dropwise at 0 °C. The resulting suspension was stirred at room temperature for 2 h, and TLC (ethyl acetate/pentane 1:1) showed that the starting material was consumed completely. The reaction was quenched by the addition of saturated NH_4Cl (aq) solution (50 mL), and the mixture was then diluted with ethyl acetate (80 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:3) to give compound **13** (0.85 g, 85%) as a colorless oil. (b) Via Tebbe's methylenation: To a stirred solution of compound **7** (0.10 g, 0.25 mmol) in anhydrous THF (4 mL) was added dropwise a solution of the Tebbe reagent (0.56 mL, 1.0 M in toluene, 0.56 mmol) at 0 °C. After the addition, the brown solution was allowed to warm to room temperature slowly and was stirred at room temperature for 2 h. TLC (ethyl acetate/pentane 1:1) showed that the starting material was consumed completely. The reaction was quenched carefully by the addition of saturated $NaHCO_3$ aqueous solution (1 mL) at 0 °C, and the mixture was stirred at room temperature for 15 min. The mixture was filtered through Celite, and the filter cake was washed with CH_2Cl_2 (10 mL × 2). The combined filtrates were concentrated in vacuo, and the residue was purified by column chromatography (ethyl acetate/pentane 1:4 to 1:2) to give compound **13** (86 mg, 86%) as a colorless oil. **13**: R_f = 0.2 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.7}$ = 96.2° (*c* 0.42, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.8 Hz), 6.88 (2H, d, *J* = 8.4 Hz), 5.27−5.30 (1H, m, H-6), 4.91−4.96 (2H, m, H-6 and *p*-$MeOPhCH_2$), 4.56 (1H, d, *J* = 11.2 Hz, *p*-$MeOPhCH_2$), 4.54 (1H, d, *J* = 9.2 Hz, H-4), 3.89−3.95 (1H, m, H-1), 3.80 (3H, s, *p*-CH_3OPh), 3.74−3.79 (2H, m, H-3 and H-2), 3.27 (3H, s), 3.24 (3H, s), 2.73 (1H, dd, *J* = 1.6, 14.4 Hz, H-5a), 2.20 (1H, dd, *J* = 2.0, 14.4 Hz, H-5a), 1.59 (1H, d, *J* = 6.8 Hz, OH), 1.36 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 140.4, 131.4, 129.6, 113.7, 110.2, 99.70, 99.66, 78.0, 73.3, 72.1, 69.2, 68.2, 55.4, 48.0(2), 37.1, 17.9(2); EI-HRMS (*m*/*z*) calcd for $C_{21}H_{34}NO_7$ [M + NH_4^+] 412.2335, found 412.2338.

*Benzyl 6-Deoxy-2-O-(p-methoxybenzyl)-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-α-D-lyxo-hex-5-enopyranoside (**14**).* To a stirred suspension of NaH (0.43 g, 11.00 mmol) in anhydrous DMF (10 mL) at 0 °C was added a solution of compound **13** (2.09 g, 5.30 mmol) in dry DMF (10 mL) dropwise. The suspension was stirred at 0 °C for 10 min, and benzyl bromide (0.82 mL, 6.90 mmol) was added at 0 °C. The suspension was then stirred at room temperature for 3 h. TLC (ethyl acetate/pentane 1:3) showed that the starting material was almost consumed. The reaction was quenched carefully by the addition of saturated NH_4Cl aqueous solution (5 mL) at 0 °C, and the mixture was diluted with ethyl acetate (50 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (15 mL × 3). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:16 to 1:10) to yield compound **14** (2.32 g, 90%) as a yellow oil. **14**: R_f = 0.22 (ethyl acetate/hexane 1:16); $[\alpha]_D^{27.7}$ = 112.4° (*c* 0.39, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.8 Hz), 7.21−7.30 (5H, m), 6.86 (2H, d, *J* = 8.4 Hz), 5.19−5.21 (1H, m, H-6), 4.91 (1H, d, *J* = 11.2 Hz), 4.83−4.85 (1H, m, H-6), 4.56 (1H, d, *J* = 10.4 Hz, H-4), 4.53 (1H, d, *J* = 12.0 Hz), 4.52 (1H, d, *J* = 11.2 Hz), 4.37 (1H, d, *J* = 12.0 Hz), 3.88 (1H, dd, *J* = 2.8, 10.4 Hz, H-3), 3.82 (1H, dd, *J* = 2.4, 2.8 Hz, H-2), 3.79 (3H, s, *p*-CH_3OPh), 3.62−3.65 (1H, m, H-1), 3.26 (3H, s), 3.21 (3H, s), 2.49 (1H, dd, *J* = 2.0, 14.8 Hz, H-5a), 2.41 (1H, dd, *J* = 1.2, 14.4 Hz, H-5a), 1.36 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 141.1, 138.5, 131.4, 129.6, 128.4, 127.53, 127.5, 113.7, 108.1, 99.54, 99.52, 76.6, 76.0, 73.2, 72.0, 70.4, 68.1, 55.3, 47.9, 47.8, 33.7, 18.0(2); EI-HRMS (*m*/*z*) calcd for $C_{28}H_{40}NO_7$ [M + NH_4^+] 502.2805, found 502.2822.

*(2S,3S,4aR,5R,7S,8R,8aS)-7-(Benzyloxy)-2,3-dimethoxy-8-((4-methoxybenzyl)oxy)-2,3-dimethyloctahydrobenzo[b][1,4]dioxine-5-carbaldehyde (**15**).* IBX (4.30 g, 15.40 mmol) was dissolved in DMSO (30 mL) by stirring at room temperature for 15 min. A solution of compound **8** (2.24 g, 4.38 mmol) in DMSO (15 mL) was added to the IBX solution at room temperature. White precipitates formed, and the mixture was stirred at room temperature. TLC (ethyl acetate/pentane 1:3) showed that only a small amount of starting material remained after stirring for 21 h. The mixture was filtered, and the filter cake was washed with CH_2Cl_2 (100 mL). Water (20 mL) was added, and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:6) to give compound **15** (1.89 g, 85%) as a colorless oil. **15**: R_f = 0.45 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.9}$ = 130.9° (*c* 0.16, $CHCl_3$); IR (neat) ν 2937, 1756, 1718, 1612, 1455, 1377, 1250, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.08 (1H, d, *J* = 2.0 Hz, CHO), 7.31 (2H, d, *J* = 8.4 Hz), 7.19−7.31 (5H, m), 6.85 (2H, d, *J* = 8.8 Hz), 4.88 (1H, d, *J* = 11.2 Hz), 4.48 (1H,

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d, J = 11.2 Hz), 4.45 (1H, d, J = 12.0 Hz), 4.35 (1H, dd, J = 5.2, 11.2 Hz, H-4), 4.31 (1H, dd, J = 2.4, 11.2 Hz, H-3), 4.22 (1H, d, J = 12.0 Hz), 3.80 (4H, m, *p*-CH_3OPh- and H-2), 3.59 (1H, dd, J = 2.4, 6.0 Hz, H-1), 3.27 (3H, s), 3.24 (3H, s), 2.46−2.51 (1H, m, H-5), 2.27 (1H, d, J = 14.4 Hz, H-5a), 1.95 (1H, ddd, J = 2.0, 6.0, 14.8 Hz, H-5a), 1.34 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 159.2, 138.1, 131.2, 129.7, 128.5, 127.7, 127.6, 113.7, 100.0, 99.9, 76.3, 75.5, 73.2, 70.4, 68.0, 65.8, 55.4, 48.0(2), 47.2, 27.0, 18.0, 17.8; EI-HRMS (m/z) calcd for $C_{28}H_{40}NO_8$ [M + NH_4^+] 518.2754, found 518.2769.

*(2S,3S,4aR,5S,7S,8R,8aS)-7-(Benzyloxy)-2,3-dimethoxy-8-((4-methoxybenzyl)oxy)-2,3-dimethyloctahydrobenzo[b][1,4]dioxine-5-carbaldehyde (**16**).* A solution of compound **15** (1.89 g, 3.77 mmol) in a mixture of MeOH (60 mL) and pyridine (30 mL) was stirred at 60 °C for 3 days, and ^{1}H NMR showed that the starting material was consumed completely. The solution was concentrated and coevaporated with toluene (10 mL × 2) in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:6 to 1:5) to give compound **16** (1.78 g, 94%) as a colorless oil. **16**: R_f = 0.45 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.9}$ = 173.8° (c 0.13, $CHCl_3$); IR (neat) ν 2949, 1728, 1613, 1455, 1377, 1250, 1143 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, d, J = 2.0 Hz, CHO), 7.31 (2H, d, J = 8.0 Hz), 7.22−7.34 (5H, m), 6.86 (2H, d, J = 8.8 Hz), 4.86 (1H, d, J = 11.2 Hz), 4.51 (1H, d, J = 12.0 Hz), 4.49 (1H, d, J = 11.6 Hz), 4.40 (1H, d, J = 12.0 Hz), 4.33 (1H, dd, J = 10.4, 11.2 Hz, H-4), 4.02 (1H, dd, J = 2.4, 10.4 Hz, H-3), 3.81 (3H, s, *p*-CH_3OPh), 3.79 (1H, dd, J = 2.8, 2.8 Hz, H-2), 3.66 (1H, dd, J = 2.8, 6.0 Hz, H-1), 3.28 (3H, s), 3.26 (3H, s), 2.80−2.89 (1H, m, H-5), 1.89 (1H, ddd, J = 2.8, 3.2, 14.4 Hz, H-5a), 1.77 (1H, ddd, J = 2.4, 12.8, 14.4 Hz, H-5a), 1.33 (3H, s), 1.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 159.3, 138.2, 131.2, 129.6, 128.5, 127.8, 127.6, 113.8, 99.9, 99.6, 75.8, 75.2, 73.3, 71.2, 70.4, 66.6, 55.4, 48.2, 48.0, 47.8, 24.6, 18.0, 17.9; EI-HRMS (m/z) calcd for $C_{28}H_{40}NO_8$ [M + NH_4^+] 518.2754, found 518.2732.

*(2S,3S,4aR,5S,7S,8S,8aR)-8-Azido-7-(benzyloxy)-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[b][1,4]dioxine-5-carbaldehyde (**17**).* To a stirred solution of compound **9** (0.43 g, 1.10 mmol) and dry pyridine (0.46 mL, 5.60 mmol) in anhydrous CH_2Cl_2 (18 mL) at 0 °C was added triflic anhydride (0.38 mL, 2.26 mmol) dropwise. The solution was stirred at 0 °C for 30 min and then at room temperature for 30 min. TLC (ethyl acetate/pentane 1:1) showed that the starting material was consumed completely. The reaction was diluted with CH_2Cl_2 (30 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered through Celite, and evaporated in vacuo. The residue was dried under high vacuum and used for next step directly without further purification. The above residue was dissolved in dry DMF (20 mL), and sodium azide (0.74 g, 11.38 mmol) was added. The resulting mixture was stirred at 80 °C in dark for 13.5 h. TLC (ethyl acetate/pentane 1:3) showed that the triflate ester was consumed completely. The mixture was filtered, and the filter cake was washed with ethyl acetate (20 mL × 2). The combined filtrates were washed brine (10 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:3) to give compound **17** (0.24 g, 53%) as a pale yellow oil. **17**: R_f = 0.42 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.9}$ = 204.0° (c 0.12, $CHCl_3$); IR (neat) ν 2916, 2105, 1726, 1456, 1261 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (1H, d, J = 1.2 Hz, CHO), 7.27−7.37 (5H, m), 4.64 (1H, d, J = 11.6 Hz), 4.59 (1H, d, J = 12.0 Hz), 4.30 (1H, dd, J = 9.6, 10.4 Hz, H-3), 3.90 (1H, dd, J = 2.8, 5.2 Hz, H-1), 3.86 (1H, dd, J = 9.6, 11.2 Hz, H-4), 3.38 (3H, s), 3.25 (3H, s), 3.22−3.27 (1H, m, H-2), 2.97−3.06 (1H, m, H-5), 2.11 (1H, ddd, J = 3.6, 3.6 14.8 Hz, H-5a), 1.32−1.38 (1H, m, H-5a), 1.36 (3H, s), 1.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 137.7, 128.6, 128.0, 127.9, 100.3, 100.1, 75.1, 72.4, 70.3, 69.3, 62.4, 48.6, 48.4, 46.4, 26.6, 17.9, 17.7; EI-HRMS (m/z) calcd for $C_{20}H_{31}N_4O_6$ [M + NH_4^+] 423.2244, found 423.2254.

*1-O-Benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-α-D-manuronic Acid (**18**).* Compound **9** (0.10 g, 0.26 mmol) was dissolved in a mixture of ^{t}BuOH (6 mL) and distilled water (3 mL). $NaH_2PO_4{\cdot}H_2O$ (0.14 g, 1.01 mmol), DMSO (0.28 mL, 3.95 mol), and $NaClO_2$ (60 mg, 0.53 mmol, 80% purity) were added in turn at 0 °C. The mixture was stirred at 0 °C for 1.5 h, and TLC (ethyl acetate/pentane 1:3) showed that the reaction was complete. The reaction was quenched by the addition of 0.5 N $Na_2S_2O_3$ aqueous solution (5 mL), and then ethyl acetate (50 mL) and water (10 mL) were added. The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (15 mL × 2). The combined organic phases were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:2, with 0.1% of HCOOH) to yield compound **18** (0.11 g, 99%) as a white foam. **18**: R_f = 0.25 (ethyl acetate/hexane 1:1, trace HCOOH); $[\alpha]_D^{28.0}$ = 171.4° (c 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.36 (5H, m), 4.62 (1H, d, J = 12.0 Hz), 4.49 (1H, d, J = 11.6 Hz), 4.24 (1H, dd, J = 10.4, 10.8 Hz, H-4), 4.02 (1H, dd, J = 2.8, 2.8 Hz, H-2), 3.91 (1H, dd, J = 2.8, 10.8 Hz, H-3), 3.77 (1H, dd, J = 2.8, 5.6 Hz, H-1), 3.27 (3H, s), 3.23 (3H, s), 2.83−2.92 (1H, m, H-5), 2.14 (1H, ddd, J = 2.8, 3.2, 14.4 Hz, H-5a), 1.96−2.05 (1H, m, H-5a), 1.30 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 138.1, 128.5, 127.8, 127.6, 100.4, 100.0, 75.6, 71.4, 69.8, 69.5, 66.6, 48.2, 48.1, 41.3, 27.9, 17.9, 17.8; EI-HRMS (m/z) calcd for $C_{20}H_{32}NO_8$ [M + NH_4^+] 414.2128, found 414.2131.

*6-O-Acetyl-1-O-benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-2-O-(p-methoxybenzyl)-5a-carba-β-L-gulopyranoside (**19**).* Compound **8** (0.20 g, 0.40 mmol) was dissolved in pyridine (2 mL), and acetic anhydride (1 mL) was added slowly. The resulting solution was stirred at room temperature for 17 h. The solution was concentrated and coevaporated with toluene (5 mL × 3) in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:6) to afford compound **19** (0.22 g, 99%) as a colorless oil. **19**: R_f = 0.68 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.8}$ = 126.5° (c 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.36 (7H, m), 6.86 (2H, d, J = 8.4 Hz), 4.88 (1H, d, J = 11.2 Hz), 4.55 (1H, d, J = 12.0 Hz), 4.51 (1H, dd, J = 6.4, 10.8 Hz, H-6), 4.47 (1H, d, J = 11.2 Hz), 4.40 (1H, dd, J = 10.8, 10.8 Hz, H-6), 4.39 (1H, d, J = 12.4 Hz), 4.28 (1H, dd, J = 6.0, 11.2 Hz, H-4), 3.97 (1H, dd, J = 2.8, 11.2 Hz, H-3), 3.81 (3H, s, *p*-CH_3OPh), 3.77−3.80 (1H, m, H-2), 3.62 (1H, dd, J = 2.8, 6.4 Hz, H-1), 3.26 (3H, s), 3.20 (3H, s), 2.24−2.32 (1H, m, H-5), 2.04−2.12 (1H, m, H-5a), 2.03 (3H, s, CH_3CO), 1.69−1.79 (1H, m, H-5a), 1.30 (3H, s), 1.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.2, 138.6, 131.5, 129.7, 128.5, 127.6, 127.3, 113.7, 99.4(2), 77.4, 76.7, 73.3, 71.2, 67.2, 66.3, 64.6, 55.4, 47.9, 47.8, 36.3, 24.4, 21.2, 18.0, 17.9; EI-HRMS (m/z) calcd for $C_{30}H_{44}NO_9$ [M + NH_4^+] 562.3016, found 562.3036.

*6-O-Acetyl-1-O-benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-β-L-gulopyranoside (**20**).* In the same manner as **9**, compound **20** was synthesized as a colorless oil (88 mg, 87%) from compound **19** (0.13 g, 0.24 mmol) and DDQ (0.11 g, 0.46 mmol) in a mixture of CH_2Cl_2 (9 mL) and distilled water (0.5 mL). **20**: R_f = 0.25 (ethyl acetate/hexane 1:3); $[\alpha]_D^{27.9}$ = 92.9° (c 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.36 (5H, m), 4.62 (1H, d, J = 12.4 Hz), 4.50 (1H, dd, J = 4.8, 10.4 Hz, H-6), 4.46 (1H, d, J = 12.4 Hz), 4.40 (1H, dd, J = 10.8, 10.8 Hz, H-6), 4.14 (1H, dd, J = 6.0, 11.2 Hz, H-4), 3.99−4.03 (1H, m, H-2), 3.90 (1H, dd, J = 3.2, 10.8 Hz, H-3), 3.70−3.75 (1H, m, H-1), 3.21 (3H, s), 3.19 (3H, s), 2.48−2.57 (1H, br, OH), 2.26−2.35 (1H, m, H-5), 2.13−2.21 (1H, m, H-5a), 2.04 (3H, s, CH_3CO), 1.79 (1H, ddd, J = 4.0, 4.4, 11.2 Hz, H-5a), 1.27 (3H, s), 1.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 138.5, 128.5, 127.7, 127.4, 100.0, 99.8, 77.4, 71.5, 70.6, 66.4, 65.8, 64.3, 48.0, 47.9, 36.2, 24.2, 21.2, 17.8(2); EI-HRMS (m/z) calcd for $C_{22}H_{36}NO_8$ [M + NH_4^+] 442.2441, found 442.2453.

*6-O-Acetyl-2-azido-1-O-Benzyl-2-deoxy-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-β-L-gulopyranoside (**21**).* To a stirred solution of compound **20** (0.28 g, 0.66 mmol) and pyridine (0.34 mL, 4.20 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0 °C was added triflic anhydride (0.28 mL, 1.70 mmol) dropwise. The solution was allowed to warm to room temperature slowly and stir for 1.5 h. TLC (ethyl acetate/pentane 1:3) showed that the starting material was consumed completely. The reaction was diluted with CH_2Cl_2 (30 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered through Celite, and evaporated in vacuo. The residue was dried under high vacuum and used for the next step directly without further purification. The above residue was dissolved in dry DMF (6 mL), and sodium

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azide (0.72 g, 11.10 mmol) was added. The resulting mixture was stirred at 75 °C in dark for 20.5 h. TLC (ethyl acetate/pentane 1:3) showed that the triflate ester was consumed completely. The mixture was filtered, and the filter cake was washed with ethyl acetate (30 mL × 1). The combined filtrates were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/pentane 1:6) to give compound **21** (0.21 g, 70%) as a colorless oil. **21**: R_f = 0.44 (ethyl acetate/hexane 1:3); $[\alpha]_D^{28.0}$ = 102.3° (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.35 (5H, m), 4.64 (1H, d, *J* = 12.0 Hz), 4.57 (1H, d, *J* = 12.0 Hz), 4.52 (1H, dd, *J* = 4.8, 11.2 Hz, H-6), 4.36 (1H, dd, *J* = 10.8, 11.2 Hz, H-6), 4.21 (1H, dd, *J* = 10.4, 10.8 Hz, H-3), 3.84 (1H, dd, *J* = 2.8, 6.0 Hz, H-1), 3.78 (1H, dd, *J* = 6.0, 10.4 Hz, H-4), 3.33 (3H, s), 3.23 (3H, s), 3.19 (1H, dd, *J* = 3.2, 10.8 Hz, H-2), 2.26−2.37 (2H, m, H-5 and H-5a), 2.04 (3H, s, CH_3CO), 1.28−1.36 (1H, m, H-5a), 1.32 (3H, s), 1.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 137.8, 128.5, 127.9, 127.8, 99.9, 99.8, 76.6, 72.3 70.2, 66.3, 64.1, 63.0, 48.4, 48.1, 35.8, 26.2, 21.1, 17.9, 17.7; EI-HRMS (*m*/*z*) calcd for $C_{22}H_{35}N_4O_7$ [M + NH_4^+] 467.2506, found 467.2519.

*1-O-Benzyl-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-β-L-gulopyranose (**22**).* In the same manner as **9**, compound **22** was synthesized as a white foam (0.15 g, 98%) from compound **8** (0.20 g, 0.40 mmol) and DDQ (0.11 g, 0.48 mmol) in CH_2Cl_2 (6.6 mL) and distilled water (0.4 mL). **22**: R_f = 0.29 (ethyl acetate/hexane 1:1); $[\alpha]_D^{28.0}$ = 132.5° (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.36 (5H, m), 4.59 (1H, d, *J* = 12.0 Hz), 4.48 (1H, d, *J* = 12.0 Hz), 4.20−4.29 (2H, m, H-6 and H-4), 4.12 (1H, dd, *J* = 2.8, 10.8 Hz, H-3), 4.02 (1H, dd, *J* = 2.4, 2.8 Hz, H-2), 3.67 (1H, dd, *J* = 3.2, 5.6 Hz, H-1), 3.54 (1H, ddd, *J* = 3.6, 10.8, 11.2 Hz, H-6), 3.23 (3H, s), 3.21 (3H, s), 3.07 (1H, d, *J* = 10.0 Hz, OH), 2.60 (1H, br, OH), 2.26−2.34 (1H, m, H-5), 1.99 (1H, ddd, *J* = 3.2, 6.0, 15.2 Hz, H-5a), 1.80−1.87 (1H, m, H-5a), 1.28 (3H, s), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.6, 127.8, 127.4, 100.0, 99.8, 76.9, 71.7, 70.3, 68.3, 66.4, 64.5, 48.0(2), 39.3, 27.0, 17.9, 17.8; EI-HRMS (*m*/*z*) calcd for $C_{20}H_{34}NO_7$ [M + NH_4^+] 400.2335, found 400.2333.

*3,4,6-Tri-O-acetyl-2-acetamido-2-deoxy-5a-carba-α-D-glucopyranose (**23**).* A suspension of compound **1** (46 mg, 0.11 mmol) and $Pd(OH)_2$ (10 mg, 20 wt % on carbon, wet) in EtOH (5 mL) was stirred under 2.1 bar of H_2 at 40 °C for 22 h. TLC (MeOH/CH_2Cl_2 1:10) showed that the starting material was consumed completely. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (neat ethyl acetate to MeOH/CH_2Cl_2 1: 15) to yield compound **23** (33 mg, 90%) as a colorless oil. **23**: R_f = 0.23 (MeOH/CH_2Cl_2 1:15); $[\alpha]_D^{27.8}$ = 34.62° (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (1H, d, *J* = 8.8 Hz, NH), 5.20 (1H, dd, *J* = 9.6, 10.8 Hz, H-3), 5.03 (1H, dd, *J* = 9.6, 11.2 Hz, H-4), 4.02−4.16 (3H, m, H-6 and H-2 and H-1), 3.90 (1H, dd, *J* = 3.2, 11.2 Hz, H-6), 3.10−3.30 (1H, br, OH), 2.34−2.45 (1H, m, H-5), 2.03 (3H, s), 2.00 (3H, s), 1.99 (3H, s), 1.95 (3H, s), 1.88−1.96 (1H, m, H-5a), 1.66 (1H, ddd, *J* = 2.0, 12.8, 14.8 Hz, H-5a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.1, 170.5, 170.0, 72.7, 72.0, 67.7, 63.7, 54.4, 34.5, 32.4, 23.3, 20.90, 20.88, 20.8; EI-HRMS (*m*/*z*) calcd for $C_{15}H_{24}NO_8$ [M + H^+] 346.1502, found 346.1503.

*2-Acetamido-2-deoxy-5a-carba-α-D-glucopyranose (**24**).* To a stirred solution of compound **23** (38 mg, 0.11 mmol) in anhydrous MeOH (3 mL) was added catalytic sodium at room temperature. The solution was stirred at room temperature for 4.5 h. The solution was concentrated in vacuo, and the residue was purified by C18 column (neat water to 5% CH_3CN in water) to yield compound **24** (24 mg, 99%) as a gray powder. **24**: $[\alpha]_D^{27.8}$ = 36.28° (*c* 0.10, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 3.99 (1H, m, H-1), 3.56−3.70 (4H, m), 3.28 (1H, dd, *J* = 8.4, 10.4 Hz), 2.00 (3H, s), 1.90−2.00 (1H, m, H-5), 1.84 (1H, ddd, *J* = 3.6, 3.6, 14.0 Hz, H-5a), 1.44 (1H, ddd, *J* = 2.4, 12.8, 14.4 Hz, H-5a); ^{13}C NMR (100 MHz, MeOD) δ 173.6, 76.4, 74.2, 68.8, 64.5, 57.6, 39.6, 33.3, 22.8; EI-HRMS (*m*/*z*) calcd for $C_9H_{18}NO_5$ [M + H^+] 220.1185, found 220.1180.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mnitz@chem.utoronto.ca.

Notes

The authors declare no competing financial interest.

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