Synthesis of galactosaminyl D-chiro-inositol

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Abstract—All six isomeric D-galactosaminopyranosyl-D-chiro-inositol have been prepared by glycosylation of appropriate penta-O-benzyl-D-chiro-inositol. The three requisite protected D-chiro-inositol were prepared by SmI 2-promoted pinacol coupling of dialdehydes derived ultimately from L-arabinose.

Keywords: Inositol phosphate glycans; chiro-inositol; Insulin signal transduction

1. Introduction

Several glycosylated chiro-inositol have been isolated from natural sources, including plants, fungi, insects, and mammals. In plants, chiro-inositol-containing di- and trisaccharides are believed to confer desiccation tolerance to seeds, while in mammals, the inositol phosphoglycan (IPG) class of oligosaccharides are believed to be involved in insulin signal transduction. Because of their putative role in glucose homeostasis, the IPGs and their analogues are of considerable interest as possible treatments for Type II diabetes.

Two distinct classes of IPGs have been identified, one containing a glucosamine glycosidically linked to a myo-inositol, and the other containing a galactosamine glycosidically linked to a D-chiro-inositol. In the latter case, no information about the position or configuration of this terminal anomic linkage has been published.

The chemical synthesis of glycosylated D-chiro-inositol is complicated by the relative difficulty in obtaining suitably protected D-chiro-inositol to serve as glycosyl acceptors.

While several differentially protected chiro-inositol have been synthesized, we sought a general strategy for the syntheses of a complete set of penta-O-benzyl-D-chiro-inositol, each with a different unprotected hydroxyl group for glycosylation. Since chiro-inositol has a C2 axis of symmetry, the set consists of only three different penta-O-benzyl-chiro-inositol: 8, 9, and 10. With these three precursors in hand, all monoglycosylated D-chiro-inositol positional isomers may be prepared. Herein, we report a convenient synthesis of compounds 8, 9, and 10, from 2,3,4-tri-O-benzyl-L-arabinopyranose (1), and demonstrate the utility of this set of precursors by preparing the peracetylated derivatives of all six possible isomers of 2-acetamido-2-deoxy-D-galactopyranosyl-D-chiro-inositol, 18α,β, 19α,β, and 20α,β. The complete set of pseudodisaccharides may be valuable as structurally defined standards for use in the elucidation of the position and configuration of the galactosaminyl-D-chiro-inositol linkage in natural IPGs. The α anomers of the unacetylated disaccharides have been previously prepared by other methods.

2. Results and discussion

The six-membered ring of the D-chiro-inositol 8, 9, and 10 was constructed using an intramolecular samarium diiodide coupling of an appropriately protected 1,6-dialdehyde. SmI 2 is known to produce predominantly cis-diols that are trans-aligned with respect to neighboring alkoxy substituents and has previously been used for the synthesis of chiro-inositol.

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The aldehydes needed for pinacol coupling were prepared as follows. 2,3,4-Tri-O-benzylarabinopyranose (1, Scheme 1), available in three steps from L-arabinose by a literature procedure, was treated with 10 equiv of vinylmagnesium bromide in THF to give alcohols 2 (1.7:1 syn:anti). The resulting mixture was exhaustively silylated with tert-butylchlorodimethylsилane to produce 3, which was treated with ozone, followed by NaBH₄ to give alcohols 4a, 4b, and 4c (1.7:1.0:0.2). Presumably, alcohols 4a and 4b result from migration of the TBS group under the basic conditions of the borohydride reduction as has been previously observed. At this stage the three isomers are easily separated, and either 4a or 4c can be carried on in the synthesis with the same outcome (vide infra).

Alklylation of either alcohol 4a or 4c gave compound 5 in good yield. It appears that the basic (NaH) alkylation conditions generate the same equilibrating mixture of alkoxy silanes from either precursor (4a or 4c) and that the subsequent alkylation occurs faster with the intermediate in which both silyl groups are on primary hydroxyl groups. Thus, alkylation of either 4a or 4c with benzyl bromide produces 5a, while alkylation of 4a or 4c with p-methoxybenzyl bromide produces 5b. The PMB-substituted compound 5b is unstable on silica gel and, therefore, was carried on to the next step without purification.

Treatment of either 5a or 5b with tetrabutylammonium fluoride resulted in removal of the TBS-groups furnishing diols 6a and 6b, respectively. Each diol was subjected to a one-pot sequence of Swern oxidation, followed by SmI₂ pinacol coupling affording chiro-inositols 7a and 7b.

The structure of 7a was confirmed by an independent synthesis of the same compound starting from L-xylose. The structure of 7b was confirmed by its transformation into 12 and comparison with penta-O-benzyl-(−)-quebrachitol (12), obtained by exhaustive benzylation of (−)-quebrachitol as shown in Scheme 3.

Selective benzylation of the equatorial hydroxyl group of 7a via the dibutylstannyl ester (Scheme 2) afforded 8 without any detectable amount of the axially alkylated isomer (82% yield). The structure of 8 was established by ¹H NMR analysis of its acetyl derivative. Compound 9 was synthesized as previously described. Exhaustive benzylation of 7b, followed by oxidative (DDQ) removal of the p-methoxybenzyl group, provided compound 10.

With the three suitably protected chiro-inositols in hand, we proceeded to prepare the galactosaminyl-chiro-inositol isomers. We found that the glycosylation reaction of each of the three different acceptors 8, 9, and 10 was optimally performed with a different glycosyl donor. In the case of acceptor 10, glycosylation was most effectively accomplished with trichloroacetimidate (Scheme 5), readily available from triacetylgalactal as previously reported. Thus, treatment of chiro-inositol isomer 10 with 17 in the presence of trimethylsilyl triflate produced a 72% yield of a separable mixture of disaccharides 11a and 11b.
charides 22\(\alpha\) and 22\(\beta\) in a ratio of 1:1.8. Each anomer was individually subjected to dissolving metal reduction followed by acetic anhydride to produce the acetylated galactosaminyl-(1\(\rightarrow\)3)-chiro-inositol anomers 18\(\alpha\) and 18\(\beta\), respectively.

By contrast, with chiro-inositol acceptor 9, the highest coupling yield was obtained by glycosylation with glycosyl fluoride 14, readily available from known \(^{32}\) azide 13, by treatment with DAST \(^{33}\) (Scheme 4). Treatment of 14 with 9 in the presence of silver triflate and Cp\(_2\)ZrCl\(_2\) \(^{34}\) produced an 89% yield of anomeric disaccharides 23\(\alpha\) and 23\(\beta\) (2.8:1), each of which underwent clean reduction and acetylation as above to produce the acetylated galactosaminyl-(1\(\rightarrow\)2)-chiro-inositol anomers 19\(\alpha\) and 19\(\beta\). The anomeric configuration was confirmed by examining the magnitude of the \(J_{\text{H,C}}\) coupling constant for the anomeric carbon in the \(^{13}\text{C}\) NMR spectrum according to the established method. \(^{35,36}\)

As expected, glycosylation of chiro-inositol 8 at its free axial hydroxyl group proved more difficult than
the others. In every case we attempted in which the glycosyl donor did not have a participating group at position 2, exclusive formation of the α-disaccharide was observed. This is consistent with earlier observations of complete α-selectivity in glycosylations of certain axial hydroxyl groups with 2-azido-2-deoxypyranosyl donors, possibly representing a steric mismatch in the transition state for the β-glycoside. The best yield of α-disaccharide was obtained by glycosylation with methyl thioglycoside 15α, prepared as shown in Scheme 4.

Thus, treatment of 8 with 15α in the presence of silver triflate and phenylselenyl chloride (Scheme 6) produced the α disaccharide in 67% yield as the only anomer. Reduction and acetylation, as before, produced the acetylated α-D-galactosaminyl-(1→1)-chiro-inositol 20α.

To prepare the β anomer, we utilized glycosyl donor 16, possessing the participating benzyloxy carbonyl (Cbz) protective group at position 2. Compound 16 was prepared as shown in Scheme 4. Treatment of 16 with 8, silver triflate, and phenylselenyl chloride, as above, produced a 1:1 mixture of anomic disaccha-

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\text{Scheme 5. Reagents and conditions: (a) 10, TMSOTf, 4 Å MS, Et}_2\text{O, }-78 ^\circ \text{C (72% yield); (b) Na, NH}_3\text{(l), }-78 ^\circ \text{C; (c) Ac}_2\text{O, Et}_3\text{N, DMAP, THF, DMF; (d) 9, AgOTf, Cp}_2\text{ZrCl}_2, \text{toluene, 4 Å MS, }-42 ^\circ \text{C to rt (89% yield).}
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\text{Scheme 6. Reagents and conditions: (a) 8, AgOTf, PhSeCl, 4 Å MS, toluene, }-42 ^\circ \text{C; (b) Na, NH}_3\text{(l), }-78 ^\circ \text{C; (c) Ac}_2\text{O, Et}_3\text{N, DMAP, THF, DMF; (d) 8, AgOTf, PhSeCl, 4 Å MS, 3:1 toluene–CH}_2\text{Cl}_2, \text{ }-42 ^\circ \text{C.}
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rides (Scheme 6) in 76% yield. These were separated chromatographically, and the β anomer was reduced and acetylated as before to supply the acetylated β-D-galactosaminyl-(1→1)-chiro-inositol 20β. The lack of β selectivity despite the participating Cbz group probably reflects a strong steric mismatch in the β transition state.

3. Conclusions

We have developed an enantiospecific synthesis for the three penta-O-benzyl-D-chiro-inositol isomers 8, 9, and 10 from L-arabinose. These partially protected cyclitols will be useful in the preparation of D-chiro-inositol-containing oligosaccharides. We have demonstrated this utility by preparing all of the six isomers in the 2-acetamido-2-deoxy-D-galactopyranosyl-D-chiro-inositol series. Since D-arabinose is also readily available, our synthesis may, in principle, also be used to prepare L-chiro-inositols and their derivatives.

4. Experimental

4.1. General methods

All reactions, with the exception of ozonolysis, were performed under an atmosphere of argon. Solvents and reagents obtained from commercial sources were used without further purification with the following exceptions. Tetrahydrofuran (THF) was distilled prior to use from sodium–benzophenone ketyl; pyridine and benzene were distilled from CaH2; Ac2O was fractionally distilled. Anhydrous reactions were performed with material dried by repeated coevaporation with toluene. TLC and preparative TLC were performed using J. T. Baker glass-backed silica gel plates (0.25 mm thickness) with 254-nm fluorescent indicator. The chromatograms were visualized by (a) ultraviolet illumination and (b) dipping in the Hanes–Isherwood solution (1 g of (NH4)6Mo7O24Æ4H2O, 10 mL of 1 N HCl, 3 mL of HClO4 in 90 mL of H2O), followed by heating. Flash chromatography was performed on J. T. Baker silica gel (40 mesh). Ozone was generated using an ozone generator purchased from Ozone Pure Water, Inc. (model 2HD). NMR spectra were recorded on a Bruker AM 300 spectrometer using Me4Si as an internal standard for 1H in CDCl3. Solutions of SmI2 were titrated with I2 prior to use.

4.2. (2R,3S,4S,5R/S)-2,3,4-Tri-O-benzyl-1,6-bis-O-(tert-butyldimethylsilyl)hexane-1,2,3,4,5,6-hexaol (4a/4b)

A solution of 1 (1.8 g, 4.3 mmol) in THF (27 mL) was slowly added over a period of 1 h to a stirred solution of vinylmagnesium bromide in THF (25.2 mL of 1.7 M solution, 42.8 mmol) at 0 °C. After the solution was stirred at 0 °C for 8 h and then overnight at room temperature, satd aq NH4Cl and 2 M HCl were added. The layers were separated, and the aqueous layer was extracted with Et2O. The combined organic layers were washed, dried with MgSO4 and evaporated. After chromatography of the residue on silica gel (2:1 hexanes–EtOAc), 2 (1.75 g, 91%) was obtained. The ratio was about 1:7:1 favoring the syn-diol as determined by 1H NMR spectroscopy. Data for 2a: 1H NMR δ 7.35–7.22 (m, 15H, aromatic), 5.93 (ddd, 1H, J 17.1, 10.6, 5.6 Hz), 5.33 (dd, 1H, J 17.2, 3.0 Hz), 5.20 (dd, 1H, J 10.6, 3.0 Hz), 4.75–4.33 (m, 7H), 3.91–3.61 (m, 5H), 2.8 (br s, 1H, OH), 2.2 (br s, 1H, OH). Data for 2b: 1H NMR δ 7.25–7.22 (m, 15H, aromatic), 5.94 (ddd, 1H, J 17.2, 10.6, 5.4 Hz), 5.41 (ddd, 1H, J 17.2, 2.9, 1.4 Hz), 5.25 (ddd, 1H, J 10.6, 2.9, 1.5 Hz), 4.76–4.39 (m, 7H), 3.96–3.91 (m, 2H), 3.82–3.69 (m, 2H), 3.60 (dd, 1H, J 5.3, 3.3 Hz), 2.82 (d, 1H, OH), 2.20 (τt, 1H, OH).

To a solution of 2 (1.75 g, 3.9 mmol) in DMF (4.2 mL) were added imidazole (2.12 g, 31.2 mmol) and TBSiCl (2.35 g, 15.6 mmol) at 0 °C and stirred for 12 h. Satd aq NaHCO3 was added, the layers were separated, and the aqueous layer was extracted with CH2Cl2. The combined organic layers were dried with MgSO4 and evaporated. After chromatography of the residue on silica gel (29:1 hexanes–Et2O), 3 (2.3 g, 86%) was obtained. Data for 3a: 1H NMR δ 7.35–7.22 (m, 15H, aromatic), 6.05 (ddd, 1H, J 17.2, 10.6, 5.1 Hz), 5.19 (ddd, 1H, J 17.2, 3.5, 1.7 Hz), 5.08 (ddd, 1H, J 10.6, 3.5, 1.6 Hz), 4.72–4.35 (m, 6H, CH2Ph), 4.32 (τt, 1H, J 5.5 Hz), 3.98 (dd, 1H, J 11.1, 2.3 Hz), 3.87 (dd, 1H, J 5.6, 2.2 Hz), 3.78 (dd, 1H, J 5.5, 2.2 Hz), 0.88 (2s, 18H), 0.05 (2s, 12H). Data for 3b: 1H NMR δ 7.35–7.22 (m, 15H, aromatic), 5.99 (ddd, 1H, J 17.2, 10.3, 6.8 Hz), 5.25 (dd, 1H, J 17.2, 1.4 Hz), 5.16 (dd, 1H, J 10.3, 1.4 Hz), 4.77–4.43 (m, 6H, CH2Ph), 4.32 (m, 2H, J 3.96 (dd, 1H, J 11.2, 2.9 Hz), 3.89–3.83 (m, 2H), 3.72–3.66 (m, 2H), 0.88 (2s, 18H), 0.05 (2s, 12H).

A solution containing 3 (150 mg, 0.22 mmol) and pyridine (50 μL) in CH2Cl2 (0.5 mL)–MeOH (1.5 mL) was treated with ozone at −78 °C until TLC (3:1 hexanes–Et2O) showed complete disappearance of the starting material, at which point NaBH4 (99.0 mg, 2.64 mmol) was added. The resulting mixture was allowed to reach room temperature. After stirring overnight at this temperature, the solvent was removed under reduced pressure. The residue was dissolved in Et2O and washed with water. The aqueous layer was then extracted with Et2O, and the combined organic extracts were dried over MgSO4 and evaporated. Flash-column chromatography (14:1 hexanes–Et2O) gave 4a (66.9 mg), 4b (43.6 mg), and 4c (7.4 mg) (combined yield 78%). Data for 4a: 1H NMR δ 7.35–7.15 (m, 15H, aromatic), 4.76–4.54 (m,
overnight at room temperature. Satd aq NH4Cl was slowly added at 0 °C (0.008 mmol) were added. The white slurry was stirred for 3 days at room temperature. After cooling of the mixture to 0 °C, the mixture was quenched with satd aq NaHCO3 (25 mL), and the resulting white slurry was extracted with EtOAc (2 x 25 mL). The organic layer was washed with 10% Na2S2O3 (25 mL) and dried with MgSO4. Evaporation of the solvent and column chromatography (2:1 hexanes–EtOAc) afforded pure 7a (61 mg, 55% over two steps). Data for 7a: 1H NMR δ 7.4–7.2 (m, 20H, aromatic), 5.02, 4.81 (2d, 2H, Jgen 11.3 Hz, CH2Ph), 4.99, 4.65 (2d, 2H, Jgen 10.5 Hz, CH2Ph), 4.81, 4.65 (2d, 2H, Jgen 10.7 Hz, CH2Ph), 4.72, 4.61 (2d, 2H, Jgen 11.7 Hz, CH2Ph), 4.07–3.86 (m, 5H, CH-OR), 3.64 (4s, 1H, J3,4 9.1 Hz, H-3 or H-4), 2.31, 2.32 (2br d, 2OH).

4.3. 1,2,3,4,5-Penta-O-benzyl-D-Chiro-inositol (8)

To a solution of 4a (56 mg, 0.082 mmol) in THF (450 μL) at 0 °C was added NaH (60%, 9.9 mg, 0.25 mmol), and the mixture was stirred at room temperature for 1 h. After cooling of the mixture to 0 °C, benzyl bromide (20 μL, 0.16 mmol) and TBAI (3 mg, 0.008 mmol) were added. The white slurry was stirred overnight at room temperature. Satd aq NH4Cl was slowly added at 0 °C, the mixture was diluted with CH2Cl2, the layers were separated, and the aqueous layer was extracted with CH2Cl2. The combined organic layers were dried with MgSO4 and evaporated. Flash-column chromatography (24:1 hexanes–Et2O) gave 5a (55.8 mg, 88%). Data for 5a: 1H NMR δ 7.35–7.15 (m, 20H, aromatic), 4.84–4.39 (m, 4H), 4.06–3.82 (m, 4H), 3.74–3.66 (m, 4H), 0.85 (2s, 18H), 0.05 (4s, 12H).

To a solution of 5a (570 mg, 0.74 mmol) in THF (2.8 mL) was added TBAF (3 mL of 1 M solution in THF, 3 mmol) at 0 °C, and the resulting solution was warmed to room temperature and stirred for 2 h. The mixture was then treated with satd aq NH4Cl, diluted with water and extracted with EtOAc. The combined organic extracts were dried with MgSO4 and concentrated. The residue was chromatographed on silica gel (2:1 hexanes–Et2O) to afford diol 6a (357 mg, 89%). Data for 6a: 1H NMR δ 7.4–7.2 (m, 20H, aromatic), 4.81–4.36 (m, 8H, CH2Ph), 3.93 (4s, 1H, J 4.8 Hz, 4.6 Hz), 3.87 (dd, 1H, J 12.2, 3.9 Hz), 3.82–3.76 (m, 2H), 3.74–3.66 (m, 3H), 3.54 (dd, 1H, J 13.2, 6 Hz), 2.35 (br s, 1H, OH), 2.15 (br s, 1H, OH).

To a solution of (COCl)2 (54 μL, 0.62 mmol, 3 equiv) in THF (890 μL) at −78 °C was added dropwise DMSO (88 μL, 1.24 mmol, 6 equiv). After 10 min, a solution of 6a (112 mg, 0.21 mmol) in THF (1.6 mL) was added dropwise via a cannula. After 30 min, i-Pr2EtN (360 μL, 2.1 mmol, 10 equiv) was added, and the mixture was stirred for 30 min at −78 °C and for 2.5 h at room temperature. After this time, it was diluted with 6.9 mL THF and t-BuOH (59 μL, 0.62 mmol, 3 equiv). A freshly prepared solution of SmI2 (1.26 mmol, 6 equiv) in THF (12.6 mL) was slowly added via a cannula to the above mixture at −78 °C over a period of 30 min. The mixture was stirred for 3 h at −78 °C, after which time it was quenched with satd aq NaHCO3 (25 mL), and the resulting white slurry was extracted with EtOAc (2 x 25 mL). The organic layer was washed with 10% Na2S2O3 (25 mL) and dried with MgSO4. Evaporation of the solvent and column chromatography (2:1 hexanes–EtOAc) afforded pure 7a (61 mg, 55% over two steps). Data for 7a: 1H NMR δ 7.4–7.2 (m, 20H, aromatic), 5.02, 4.81 (2d, 2H, Jgen 11.3 Hz, CH2Ph), 4.99, 4.65 (2d, 2H, Jgen 10.5 Hz, CH2Ph), 4.81, 4.65 (2d, 2H, Jgen 10.7 Hz, CH2Ph), 4.72, 4.61 (2d, 2H, Jgen 11.7 Hz, CH2Ph), 4.07–3.86 (m, 5H, CH-OR), 3.64 (4s, 1H, J3,4 9.1 Hz, H-3 or H-4), 2.31, 2.32 (2br d, 2OH).

A suspension of 7a (22.3 mg, 0.041 mmol) and dibutyltin oxide (0.045 mmol, 11.3 mg) in benzene (20 mL) was fitted with a distillation head and placed in an oil bath at 110 °C until most of the benzene had distilled. An additional portion of benzene (10 mL) was added to the residue, and the mixture was refuxed until again most of the benzene had distilled. The reaction mixture was cooled and treated with BnBr (0.082 mmol, 10 μL) and TBABr (0.045 mmol, 14.6 mg). The mixture was then refuxed for an additional 15 min. At the end of the reaction time, NaHCO3 was added, and the mixture was extracted with CH2Cl2. The combined organic extracts were dried with MgSO4 and concentrated to dryness. Preparative chromatography (1:1 hexanes–EtOAc) of the residue gave 21.3 mg of product 8 (62% yield). Data for 8: 1H NMR δ 7.35–7.25 (m, 25H, aromatic), 4.95–4.51 (m, 10H, CH2Ph), 4.0–3.74 (m, 6H), 2.4 (s, 1H, OH).

A solution of 8 (3.3 mg, 0.005 mmol) in pyridine (192 μL) was treated with Ac2O (0.035 mmol, 3.3 μL). After aqueous workup, 2.7 mg of the acetylated product was obtained. 1H NMR (inositol numbering is the same as in 8) δ 7.35–7.25 (m, 25H, aromatic), 5.33 (4s, 1H, J 3.4 Hz, H-6), 4.94–4.47 (m, 10H, CH2Ph), 3.95 (4s, 1H, J 9.4 Hz), 3.89 (dd, 1H, J 9.7, 3.2 Hz), 3.76 (4s, 1H, J 9.3 Hz), 3.72–3.69 (m, 2H), 2.0 (s, 3H, OAc).

4.4. 1,2,3,5,6-Penta-O-benzyl-D-Chiro-inositol (10)

To a solution of 4b (298 mg, 0.44 mmol) in THF (2.1 mL) at 0 °C was added NaH (60%, 69.9 mg, 1.76 mmol), and the mixture was stirred at room temperature for 1 h. After cooling of the mixture to 0 °C, p-methoxybenzyl chloride (237 μL, 1.76 mmol) and TBAI (81 mg, 0.22 mmol) were added. The resulting white slurry was stirred for 3 days at room temperature. Satd aq NH4Cl was slowly added at 0 °C, the mixture was diluted with CH2Cl2, the layers were separated,
and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with MgSO₄ and evaporated. The residue was diluted with THF (1.7 mL) and treated with TBAF (1.75 mL of 1 M solution in THF, 1.75 mmol) at 0 °C. The resulting solution was warmed to room temperature and stirred for 2 h. The mixture was then treated with satd aq NaHCO₃, diluted with water, and extracted with EtOAc. The combined organic extracts were dried with MgSO₄ and concentrated. The residue was chromatographed on silica gel (2:1 hexanes–EtOAc) to afford diol 6b (183 mg, 73% over two steps). Data for 6b: ¹H NMR δ 7.35–7.2 (m, 17H, aromatic), 6.85 (d, 2H, aromatic), 4.81–4.36 (m, 8H, CH₂Ph), 3.92 (ψt, 1H, J 4.7 Hz), 3.88–3.65 (m, 6H), 3.78 (s, 3H, OCH₃), 3.54 (m, 1H), 2.28 (ψt, 1H, OH), 1.99 (ψt, 1H, OH).

To a solution of (COCl)₂ (56 µL, 0.64 mmol, 3 equiv) in THF (1 mL) at −78 °C was added dropwise DMSO (91 µL, 1.28 mmol, 6 equiv). After 10 min, a solution of 6b (122 mg, 0.21 mmol) in THF (1.6 mL) was added dropwise via a cannula. After 30 min, d-Pr₂EtN (370 µL, 2.1 mmol, 10 equiv) was added, and the mixture was stirred for 30 min at −78 °C and for 2.5 h at room temperature. After this time, it was diluted with THF (6.9 mL) and t-BuOH (61 µL, 0.63 mmol, 3 equiv). A freshly prepared ⁴⁰ solution of SmI₂ (1.28 mmol, 6 equiv) in THF (12.8 mL) was slowly added via a cannula to the above mixture at −78 °C over a period of 30 min. The mixture was stirred for 3 h at −78 °C, after which time it was quenched with satd aq NaHCO₃ (2 mL). The organic layer was washed with 10% Na₂S₂O₃ (25 mL), and dried with MgSO₄. Evaporation of the solvent and column chromatography (2:1 hexanes–EtOAc) afforded pure 7b (53 mg, 43% over two steps). Data for 7b: ¹H NMR δ 7.35–7.2 (m, 17H, aromatic), 6.85 (d, 2H, aromatic), 5–5.57 (m, 8H, CH₂Ph), 4.05 (ψt, 1H, J 3.2 Hz), 3.97 (ψt, 1H, J 9.1 Hz), 3.92–3.91 (m, 2H), 3.86 (dd, 1H, J 9.4, 3.0 Hz), 3.78 (s, 3H, OCH₃), 3.62 (ψt, 1H, J 9.1 Hz), 2.5 (s, 1H, OH), 2.35 (s, 1H, OH).

A solution of 7b (68.5 mg, 0.12 mmol) in DMF (1.1 mL) at 0 °C was treated with NaH (0.72 mmol, 29 mg of a 60% oil dispersion). After 0.5 h, the mixture was treated with benzyl bromide (0.6 mmol, 72 µL) and allowed to warm to room temperature. After overnight stirring, the mixture was cooled to 0 °C, and water was added. The aqueous layer was washed three times with CH₂Cl₂, and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. A solution of the above residue in CH₂Cl₂ (3 mL) at 0 °C was treated with 330 µL of water and DDQ (0.12 mmol, 28.4 mg), and stirred at room temperature for 2 h. Satd aq NaHCO₃ was added, and the aqueous layer was separated from the organic layer and washed three times with CH₂Cl₂. The combined organic extracts were dried with MgSO₄ and concentrated to dryness. Column chromatography (2:1 hexanes–Et₂O) gave 54.5 mg of 10 (72% yield for two steps). Data for 10: ¹H NMR δ 7.4–7.10 (m, 25H, aromatic), 4.94–4.30 (m, 10H, CH₂Ph), 3.98 (m, 1H), 3.82–3.75 (m, 2H), 3.70–3.62 (m, 3H), 2.5 (s, 1H, OH). Racemic 10 has been previously reported. ⁴¹

4.5. Methyl 3,4,6-tri-O-benzyl-2-benzyloxy-carboxamido-2-deoxy-1-thio-b-D-galactopyranoside (16)

Compound 13 (191 mg, 0.40 mmol) was dissolved in THF (2.3 mL), and the resulting solution was cooled to −42 °C. DAST (59 µL, 0.60 mmol) was added, and the bath was removed immediately. The mixture was stirred at room temperature for 20 min, and the excess DAST was quenched with MeOH at −42 °C. CH₂Cl₂ (5 mL) was added, and the organic layer was washed with NaHCO₃ (2 × 3 mL) and dried with MgSO₄. Purification via flash silica gel chromatography (9:1 hexanes–EtOAc) afforded 80.6 mg of 14b and 62 mg of 14z (89% combined yield). ¹H NMR (CDCl₃) of 14b: δ 7.40–7.20 (m, 15H, aromatic), 4.95 (dd, 1H, J 52.6, 7.6 Hz, H-1 β anomer), 4.89 (d, 1H, J 11.6 Hz, CH₂Ph), 4.72 (d, 1H, J 11.7 Hz, CH₂Ph), 4.66 (d, 1H, J 11.7 Hz, CH₂Ph), 4.56 (d, 1H, J 11.4 Hz, CH₂Ph), 4.48 (d, 1H, J 11.7 Hz, CH₂Ph), 4.41 (d, 1H, J 11.7 Hz, CH₂Ph), 3.99–3.89 (m, 2H), 3.64–3.60 (m, 3H), 3.52 (dd, 1H, J 10.4, 2 Hz), ¹H NMR (CDCl₃) of 14z: δ 7.40–7.20 (m, 15H, aromatic), 5.67 (dd, 1H, J 54.6, 2.6 Hz, H-1 α anomer), 4.89 (d, 1H, J 11.2 Hz, CH₂Ph), 4.76 (d, 1H, J 11.4 Hz, CH₂Ph), 4.70 (d, 1H, J 11.4 Hz, CH₂Ph), 4.54 (d, 1H, J 11.2 Hz, CH₂Ph), 4.52 (d, 1H, J 11.7 Hz, CH₂Ph), 4.43 (d, 1H, J 11.7 Hz, CH₂Ph), 4.11 (ψt, 1H, J 6.6 Hz), 4.09 (ψs, 1H), 4.04–3.90 (m, 2H), 3.58 (ψd, 2H, J 6.6 Hz).

A mixture of fluorides 14 (142 mg, 0.29 mmol) was dried by coevaporation with toluene and then cooled to 0 °C. Bu₄SnMe in CH₂Cl₂CH₂Cl (0.44 mmol, 2 mL, of a 74 mg/mL stock solution) was added, and the resulting solution was stirred for 5 min. SnCl₄ in CH₂Cl₂CH₂Cl (0.44 mmol, 3.2 mL of a 37.1 mg/mL stock solution) was added, and stirring was continued for 30 min at 0 °C. The reaction was quenched by addition of 1 M NaHCO₃ (2 mL). The organic layer was separated from the aqueous layer and the latter was extracted with CH₂Cl₂ (2 × 3 mL). The combined organic extracts were dried with MgSO₄ and concentrated. Purification via flash silica gel chromatography (6:1 hexanes–Et₂O) afforded 26.8 mg of 15b (48% yield over two steps). ¹H NMR (CDCl₃) of 15b: δ 7.40–7.25 (m, 15H, aromatic), 4.89 (d, 1H, J 11.6 Hz, CH₂Ph), 4.73 (d, 1H, J 11.6 Hz, CH₂Ph), 4.68 (d, 1H, J 11.6 Hz, CH₂Ph), 4.56 (d, 1H, J 11.6 Hz, CH₂Ph), 4.46 (d, 1H, J 11.7 Hz, CH₂Ph), 4.40 (d, 1H, J 11.7 Hz, CH₂Ph), 4.14 (d, 1H, J 10 Hz, H-1 β anomer),
3.96 (ψd, 1H, J 2.6 Hz), 3.87 (ψt, 1H, J 9.9 Hz), 3.61–3.52 (m, 3H), 3.42 (dd, 1H, J 9.7, 2.7 Hz), 2.20 (s, 3H, SCHA). 3H NMR (CDCl3) of 15z: d 7.40–7.25 (m, 15H, aromatic), 5.31 (d, 1H, J 5.5 Hz, H-1 α anomer), 4.88 (d, 1H, J 11.3 Hz, CH2Ph), 4.71 (s, 2H, CH2Ph), 4.52 (d, 1H, J 11.3 Hz, CH2Ph), 4.50 (d, 1H, J 11.8 Hz, CH2Ph), 4.41 (d, 1H, J 11.8 Hz, CH2Ph), 3.46 (dd, 1H, J 10.5, 5.5 Hz), 4.24 (q, 1H, J 6.4 Hz), 3.97 (ψd, 1H, J 1.9 Hz), 3.76 (dd, 1H, J 10.5, 2.7 Hz), 3.59 (dd, 1H, J 9.3, 6.6 Hz), 3.54 (dd, 1H, J 9.3, 6.3 Hz), 2.21 (s, 3H, SCHA). A mixture of 15β (70.7 mg, 0.14 mmol) and Lindlar’s catalyst (141 mg) in THF (16.5 mL) was stirred at room temperature under an H2 atmosphere for 7 h. The reaction mixture was filtered through Celite, rinsed with EtOAc, and concentrated. The residue (34.3 mg) was dissolved in CH2Cl2 (390 μL), and Cbz-Cl (12.2 μL, 0.086 mmol) was added, followed by slow addition of pyridine (7 μL). The mixture was stirred for 2 h at room temperature, after which it was diluted with CH2Cl2 (4 mL), and the organic phase was washed with 1 M NaHCO3 (1 mL), dried with MgSO4, and concentrated. Purification via flash silica gel chromatography (3:1 hexanes–EtOAc) afforded 40.1 mg of 16 (91% yield over two steps). 3H NMR (CDCl3) of 16: δ 7.40–7.20 (m, 20H, aromatic), 5.14 (s, 2H, CH2Ph), 4.95 (d, 1H, J 11.6 Hz, CH2Ph), 4.84 (m, 1H), 4.68 (d, 1H, J 11.8 Hz, CH2Ph), 4.65 (br s, 1H), 4.62 (d, 1H, J 11.6 Hz, CH2Ph), 4.50 (d, 1H, J 11.8 Hz, CH2Ph), 4.48 (d, 1H, J 11.8 Hz, CH2Ph), 4.45 (d, 1H, J 11.7 Hz, CH2Ph), 4.04 (m, 1H), 3.87–3.86 (m, 2H), 3.64–3.62 (m, 3H), 2.21 (s, 3H, SCHA). HRESIMS: calculated for [C30H41O19N]+, m/z 636.2390; found, m/z 636.2405.

4.6. 3-O-(2-Azido-3,4,6-tri-O-acetyl-2-deoxy-α-d-galactopyranosyl)-1,2,4,5,6-penta-O-acetyl-d-chiroinositol (22α,β)

To a pre-dried mixture of 10 (5.2 mg, 0.0082 mmol) and 17 (11.3 mg, 0.0182 mmol) were added 4 Å MS and 290 μL anhyd Et2O. The reaction mixture was cooled to −78 °C, and TMSOTf (15 μL of 10 μL TMSOTf/mL of Et2O solution) was added. The resulting mixture was stirred at −78 °C for 10 min and was quenched by the addition of 1 M NaHCO3 (2 mL). It was filtered through Celite, the organic layer was separated from the aqueous layer, and the latter was extracted with Et2O (3 × 3 mL). The combined organic extracts were dried with MgSO4 and concentrated. Purification via preparative TLC (4:1 hexanes–EtOAc) yielded 2.3 mg of the α anomer, 22α, and 4.1 mg of the β anomer, 22β (72% combined yield). Data for 22α: 3H NMR (CDCl3) δ 7.4–7.05 (m, 40H, aromatic), 5.63 (d, 1H, J 3.3 Hz, H-1 α anomer), 5.01 (d, 1H, J 10.4 Hz, CH2Ph), 4.84 (d, 1H, J 10.4 Hz, CH2Ph), 4.79 (d, 1H, J 11.4 Hz, CH2Ph), 4.66–4.24 (m, 14H), 4.16 (dd, 1H, J 9.4, 9.2 Hz), 3.96 (dd, 1H, J 9.7, 9.2 Hz), 3.88–3.73 (m, 5H), 3.56–3.43 (m, 4H). HRESIMS: calculated for [C68H69N3O10+Na]+, m/z 1110.4875; found, m/z 1110.4893. Data for 22β: 3H NMR (CDCl3) δ 7.4–7.05 (m, 40H, aromatic), 4.99 (d, 1H, J 10 Hz, CH2Ph), 4.96 (d, 1H, J 11.2 Hz, CH2Ph), 4.83 (d, 1H, J 8 Hz, H-1 β anomer), 4.74–4.14 (m, 15H), 3.95–3.55 (m, 10H), 3.29 (dd, 1H, J 10.4, 2.8 Hz). HRESIMS: calculated for [C68H69N3O10+Na]+, m/z 1110.4875; found, m/z 1110.4888.

4.7. 3-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl)-1,2,4,5,6-penta-O-acetyl-d-chiroinositol (18β)

Sodium (43 mg, 1.87 mmol) was added to NH3 [(l), ~5 mL] at −78 °C, and the mixture was stirred for 2 min under N2 to form a blue solution, into which was added compound 22a (8.8 mg, 0.0081 mmol) in dry THF (2 mL). The resulting mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with abs MeOH (1.5 mL) at −78 °C. The NH3 was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (407 mg), the mixture was filtered, rinsed with satd NH3 in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dissolved in DMF–THF (470 μL, 1:1), and DMAP (small amount), Et3N (235 μL), and finally Ac2O (80 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 3 mL), dried with MgSO4, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 3.1 mg of 18β (53% over two steps). The 3H NMR spectrum was identical to that published. HRESIMS: calculated for [C36H41O19N+H]+, m/z 720.2351; found, m/z 720.2369.

4.8. 3-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl)-1,2,4,5,6-penta-O-acetyl-d-chiroinositol (18β)

Sodium (28.5 mg, 1.24 mmol) was added to NH3 [(l), ~5 mL] at −78 °C, and the mixture was stirred for 2 min under N2 to form a blue solution, into which was added compound 22β (4.1 mg, 0.0038 mmol) in dry THF (2 mL). The resulting mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with abs MeOH (2 mL) at −78 °C. The NH3 was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (270 mg), the mixture was filtered, rinsed with satd NH3 in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dis-
To a pre-dried mixture of donor 14 (6.8 mg, 0.014 mmol; see Experimental for 16 for preparation of 14) and acceptor 9 (13.6 mg, 0.022 mmol) were added 4 Å MS, toluene (1.3 mL), and Cp₂ZrCl₂ (20.7 mg, 0.071 mmol). The mixture was cooled to −42 °C, and AgOTf (36.5 mg, 0.14 mmol) was added. It was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). The resulting mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with abs MeOH (3.5 mL) at −78 °C. The NH₃ was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (391 mg), the mixture was filtered, rinsed with satd NH₃ in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dissolved in 1:1 DMF–THF (560 μL), and DMAP (small amount), Et₃N (280 μL), and finally Ac₂O (90 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 3 mL), dried with MgSO₄, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 3.5 mg of 19α (53% over two steps). ¹H NMR (CDCl₃): δ 6.12 (d, 1H, J 9.3 Hz), 5.64–5.26 (m, 6H), 5.03 (d, 1H, J 3.5 Hz, H-1 β anomer), 4.91 (dd, 1H, J 11.6, 3.2 Hz), 4.57 (ddd, 1H), 4.23–4.04 (m, 3H), 3.93 (dd, 1H, J 10.4, 5.4 Hz), 2.25 (s, 3H, Ac), 2.20 (s, 3H, Ac), 2.15 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.82 (s, 3H, Ac). HRE-SIMS: calc'd for [C₁₀H₁₄O₁₀Na⁺]⁺, m/z 720.2351; found, m/z 720.2377.

4.10. 2-O-(2-Azetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl)-1,3,4,5,6-penta-O-acetyl-D-chiro-inositol (19β)

Sodium (41.4 mg, 1.8 mmol) was added to NH₃ [(l), ~5 mL] at −78 °C, and the mixture was stirred for 2 min under N₂ to form a blue solution, into which was added compound 23β (10 mg, 0.0092 mmol) in dry THF (2 mL). The resulting mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with abs MeOH (3.5 mL) at −78 °C. The NH₃ was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (391 mg), the mixture was filtered, rinsed with satd NH₃ in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dissolved in 1:1 DMF–THF (260 μL), and DMAP (small amount), Et₃N (110 μL), and finally Ac₂O (35 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 2 mL), dried with magnesium sulfate, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 1.5 mg of 18β (56% over two steps). ¹H NMR (CDCl₃): δ 10.1 mg of 1110.4865. Data for 23β: ¹H-Coupled ¹³C NMR (CDCl₃) of 23β: δ 102.78 (d, J 163 Hz), which confirmed the presence of the β-glycosidic bond. 35,36

Sodium (20.1 mg, 0.87 mmol) was added to NH₃ [(l), ~5 mL] at −78 °C, and the mixture was stirred for 2 min under N₂ to form a blue solution, into which was added compound 23β (4.7 mg, 0.0043 mmol) in dry THF (2 mL). The resulting mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with abs MeOH (2 mL) at −78 °C. The NH₃ was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (270 mg), the mixture was filtered, rinsed with satd NH₃ in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dissolved in 1:1 DMF–THF (260 μL), and DMAP (small amount), Et₃N (280 μL), and finally Ac₂O (90 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 3 mL), dried with MgSO₄, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 3.5 mg of 19α (53% over two steps). ¹H NMR (CDCl₃): δ 6.24 (d, 1H, J 11.8 Hz), 5.54–4.72 (m, 6H), 4.93 (d, 1H, J 3.5 Hz, H-1 β anomer), 4.89 (dd, 1H, J 11.6, 3.2 Hz), 4.60 (dd, 1H), 4.25–4.04 (m, 3H), 3.90 (dd, 1H, J 10.4, 5.4 Hz), 2.25 (s, 3H, Ac), 2.18 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.82 (s, 3H, Ac). HRE-SIMS: calc'd for [C₁₀H₁₄O₁₀Na⁺]⁺, m/z 720.2351; found, m/z 720.2377.

4.11. 2-O-(2-Azetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl)-1,3,4,5,6-penta-O-acetyl-D-chiro-inositol (19β)

Sodium (20.1 mg, 0.87 mmol) was added to NH₃ [(l), ~5 mL] at −78 °C, and the mixture was stirred for 2 min under N₂ to form a blue solution, into which was added compound 23β (4.7 mg, 0.0043 mmol) in dry THF (2 mL). The resulting mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with abs MeOH (2 mL) at −78 °C. The NH₃ was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (270 mg), the mixture was filtered, rinsed with satd NH₃ in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dissolved in 1:1 DMF–THF (260 μL), and DMAP (small amount), Et₃N (280 μL), and finally Ac₂O (90 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 3 mL), dried with MgSO₄, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 3.5 mg of 19α (53% over two steps). ¹H NMR (CDCl₃): δ 6.12 (d, 1H, J 9.3 Hz), 5.64–5.26 (m, 6H), 5.03 (d, 1H, J 3.5 Hz, H-1 β anomer), 4.91 (dd, 1H, J 11.6, 3.2 Hz), 4.57 (ddd, 1H), 4.23–4.04 (m, 3H), 3.93 (dd, 1H, J 10.4, 5.4 Hz), 2.25 (s, 3H, Ac), 2.20 (s, 3H, Ac), 2.15 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.82 (s, 3H, Ac). HRE-SIMS: calc'd for [C₁₀H₁₄O₁₀Na⁺]⁺, m/z 720.2351; found, m/z 720.2377.
amount), Et₃N (130 μL), and finally Ac₂O (40 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 2 mL), dried with MgSO₄, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 1.3 mg of 19β (42% over two steps). ¹H NMR (CDCl₃): δ 5.54 (dd, 1H, J 11.2, 3.4 Hz), 5.48–5.32 (m, 5H), 5.23 (dd, 1H, J 10.1, 3.2 Hz), 5.10 (d, 1H, J 8.1 Hz, H-1 β anomer), 4.25 (dd, 1H, J 9.5, 3.4 Hz), 4.19–4.13 (m, 2H), 4.08 (dd, 1H, J 11.2, 5.8 Hz), 3.94 (m, 1H), 3.53 (m, 1H, NHAc), 2.22 (s, 3H, Ac), 2.21 (s, 3H, Ac), 2.18 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.95 (s, 3H, Ac). HRESIMS: calcd for [C₃₀H₄₁O₁₉N⁺H]+, m/z 720.2351; found, m/z 720.2320.


To a flame-dried flask were added 4 Å MS, phenylsele-
nium chloride (5.6 mg, 0.029 mmol), and toluene (220 μL). The mixture was cooled to −42 °C and AgOTf (9.1 mg, 0.035 mmol) was added. A solution of 15α (18.4 mg, 0.029 mmol) and 8 (7.4 mg, 0.012 mmol) in toluene (850 μL) was added to the vigorously stirred mixture. After 1.5 h, 1 M NaHCO₃ (1 mL) was added slowly to the reaction mixture. It was filtered through Celite, the organic layer was separated from the aqueous layer, and the latter was extracted with CH₂Cl₂ (3 × 3 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated. Purification via preparative TLC (4:1 hexanes–EtOAc) gave 8.6 mg of 24 (67% yield). ¹H NMR (CDCl₃): δ 7.45–7.15 (m, 40H, aromatic), 4.92 (d, 1H, J 10.5 Hz, CH₂Ph), 4.89 (d, 1H, J 10.6 Hz, CH₂Ph), 4.86–4.59 (m, 10H), 4.51 (d, 1H, J 12.1 Hz, CH₂Ph), 4.50 (d, 1H, J 11.1 Hz, CH₂Ph), 4.43 (d, 1H, J 12.1 Hz, CH₂Ph), 4.28 (dd, 1H, J 8.3, 5.8 Hz), 4.25 (d, 1H, J 11.7 Hz, CH₂Ph), 4.19 (d, 1H, J 11.6 Hz, CH₂Ph), 4.03 (m, 1H), 3.97 (dd, 1H, J 10, 2.7 Hz), 3.92–3.84 (m, 3H), 3.85 (dd, 1H, J 7.7, 3.1 Hz), 3.81–3.70 (m, 3H), 3.50 (ψ, 1H, J 8.5 Hz), 3.28 (dd, 1H, J 8.5, 5.4 Hz). HRESIMS: calcd for [C₃₈H₄₇N₄O₁₉Na⁺]⁺, m/z 1110.4875; found, m/z 1110.4846. ¹H-Coupled ¹³C NMR (CDCl₃): δ 97.02 (d, J 16.5 Hz) confirmed the presence of the α-glycosidic bond.³⁵,³⁶

4.13. 1-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl)-2,3,4,5,6-penta-O-acetyl-D-chiro-inositol (20β)

Sodium (36.3 mg, 1.58 mmol) was added to NH₃ [(l), ~5 mL] at −78 °C, and the mixture was stirred for 2 min under N₂ to form a blue solution, into which was added compound 24 (8.6 mg, 0.0079 mmol) in dry THF (2 mL). The resulting mixture was stirred for 20 min at −78 °C, and then the reaction was quenched with abs MeOH (3 mL) at −78 °C. The NH₃ was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (280 mg), the mixture was filtered, rinsed with satd NH₃ in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dissolved in 1:1 DMF–THF (470 μL), and DMAP (small amount), Et₃N (235 μL), and finally Ac₂O (75 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 3 mL), dried with MgSO₄, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 3.8 mg of 20β (68% over two steps). ¹H NMR (CDCl₃): δ 6.11 (d, 1H, J 9.2 Hz), 5.48 (dd, 1H, J 2.2, 1.1 Hz), 5.41 (dd, 1H, J 9.6, 8.6 Hz), 5.41–5.35 (m, 2H), 5.30–5.26 (m, 2H), 5.22 (dd, 1H, J 11.7, 11.2 Hz), 4.98 (d, 1H, J 3.5 Hz, H-1 α anomer), 4.69 (dd, 1H, J 12.3, 9.2, 3.5 Hz), 4.40 (t, 1H, J 6.8 Hz), 4.15–4.09 (m, 2H), 4.02 (dd, 1H, J 11.2, 6.2 Hz), 2.17 (s, 3H, Ac), 2.16 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.01 (s, 3H, Ac). HRESIMS: calcd for [C₃₀H₄₁O₁₉N⁺H⁺], m/z 720.2351; found, m/z 720.2346.


To a flame-dried flask were added 4 Å MS, phenylsele-
with abs MeOH (5 mL) at 1218.5322. 1H-Coupled 13C NMR (CDCl 3): δ 97.87 (d, J 172 Hz), which confirmed the presence of the α-glycosidic bond. 35,36 Data for 21β: 1H NMR (CDCl 3) δ 7.40–7.15 (m, 45H, aromatic), 5.10 (d, 1H, J 12.2 Hz, CH2Ph), 5.0 (d, 1H, J 11.8 Hz, CH2Ph), 4.93 (d, 1H, J 10.7 Hz, CH2Ph), 4.85–4.47 (m, 17H), 4.45 (m, 1H), 3.99 (m, 1H), 3.96–3.80 (m, 6H), 3.61–3.50 (m, 2H), 3.45 (m, 1H). HRESIMS: calcd for [C76H77NO12+Na]+, m/z 1218.5338; found, m/z 1218.5307. 1H-Coupled 13C NMR (CDCl 3): δ 102.69 (d, J 163 Hz), which confirmed the presence of the β-glycosidic bond. 35,36

4.15. 1-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl)-2,3,4,5,6-penta-O-acetyl-β-D-chiro-inositol (20β)

Sodium (43.8 mg, 1.9 mmol) was added to NH3 [l], ~5 mL at –78 °C, and the mixture was stirred for 2 min under N2 to form a blue solution, into which was added compound 21β (11.4 mg, 0.0095 mmol) in dry THF (2 mL). The resulting mixture was stirred for 20 min at –78 °C, and then the reaction was quenched with abs MeOH (5 mL) at –78 °C. The NH3 was removed with a stream of air, and additional MeOH was added to bring the total volume of solution in the reaction flask to ~10 mL. After neutralization with Dowex-50 X8 (670 mg), the mixture was filtered, rinsed with satd NH3 in MeOH (3 mL), dried with MgSO4, and then the reaction was quenched with NH3 in MeOH (20 mL), and concentrated under reduced pressure. The crude product was further dissolved in 1:1 DMF–THF (580 μL), and DMAP (small amount), Et3N (290 μL), and finally Ac2O (100 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted with EtOAc (10 mL). It was washed with water (2 × 3 mL), dried with MgSO4, and concentrated under reduced pressure. Purification via preparative TLC (EtOAc) gave 3.4 mg of 20β (50% over two steps). 1H NMR (CDCl 3): δ 5.75 (dd, 1H, J 11.3, 3.4 Hz), 5.69 (t, 1H, J 7.6 Hz), 5.55–5.37 (m, 5H), 5.26 (dd, 1H, J 10.1, 2.7 Hz), 5.16 (d, 1H, J 8.2 Hz), 4.19 (t, 1H, J 3.3 Hz), 4.18–4.09 (m, 2H), 3.96 (t, 1H, J 6.5 Hz), 3.52 (m, 1H, NHaC), 2.22 (s, 3H, Ac), 2.19 (s, 3H, Ac), 2.13 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.05 (s, 6H, Ac), 2.04 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.02 (s, 3H, Ac). HRESIMS: calcd for [C30H41O19N+H]+, m/z 720.2351; found, m/z 720.2365.

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Supplementary data

Images of NMR spectra for compounds within this paper are available in Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.03.031.

References


