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A novel glycosyl donor for synthesis of 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranosides

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ABSTRACT

2-Azido-4-benzylamino-4-*N*-,3-*O*-carbonyl-2,4,6-trideoxy-D-galactopyranosyl trichloroacetimidate (**14**) was conveniently prepared in six steps by regioselective introduction of an *N*-benzyl carbamate at O-3 of 6-deoxy-D-glucal **6**, followed by mesylation at O-4. Intramolecular displacement of the leaving group afforded oxazolidinone **11**. Azidonitration of the bicyclic glycal **11** gave the glycosyl nitrate anomers **12** in good yield and stereoselectivity. Hydrolysis of the anomeric nitrates under aqueous conditions gave the pyranose **13**, which was easily converted into the imidate **14**. Glycosylation of cyclohexanol by **14** gave glycosides **16α** and **16β** in a ratio of 4:1.

1. Introduction

2-Acetamido-4-amino-2,4,6-trideoxy-D-galactopyranose is a constituent of a number of Gram-positive and Gram-negative bacterial polysaccharides either as an α- or β-pyranose.[1,2] Its occurrence as an α-pyranose residue in the repeating unit of the capsular polysaccharides of *Streptococcus pneumoniae* type 1,[3,4] *Streptococcus mitis*,[5] and *Bacteroides fragilis*[6,7] is notable since the 4-amino functionality is an essential element in the zwitterionic motif that endows these polysaccharides with unique T-cells-activating properties, via MHC-II presentation.[8,9]

A variety of approaches have been used to synthesize methyl 2-acetamido-4-amino-2,4,6-trideoxy-D-galactopyranoside.[10–14] However, methyl glycosides especially possessing the 2-acetamido-2-deoxy function are not well suited for further manipulation to create glycosyl donors. Approaches that address this requirement have been described by the groups of van Boom[15] and van der Marel.[16] Our group has also reported the synthesis of this residue by manipulation at the disaccharide stage.[17]

As part of our efforts to synthesize repeating unit sequences of the *S. pneumoniae* type 1 zwitterionic polysaccharide, we have developed a concise synthesis of a novel 4-amino-2-azido-2,4,6-trideoxy-D-galactopyranosyl donor **14** that is well suited to a stereoselective α-glycosylation.

2. Results and discussion

Retrosynthetic analysis identified tri-*O*-acetyl-D-glucal as starting point for the synthesis of the diamino-trideoxyhexose. This would require the introduction and regioselective differentiation of amino groups at C-2 and C-4 and the relatively straight forward task of C-6 deoxygenation (Scheme 1). With an appropriately protected D-glucal derivative, reduction introduces the C-6 deoxy functionality, while an intramolecular nucleophilic cyclization can be employed to install a 4-amino group. Finally, azidonitration of the glycal provides a non-participating azido group at C-2 to facilitate α-glycosylation reactions. This approach was realized via the following synthetic transformations.

Deoxygenation at C-6 was conveniently achieved on a large scale by a two-step displacement reduction sequence (Scheme 2). Deacetylation of **1**, followed by selective tosylation of **2**, provides the known derivative **3**.[18] Reaction of **3** with LiI in THF afforded the 6-deoxy-6-iodo derivative **4**[19] followed by reductive removal of the iodide using Bu_3SnH and AIBN to give **5**[19] in 85% yield over the displacement and reduction steps.[18,20,21] This sequence was preferred to reduction of 3,4-di-*O*-acetyl-6-*O*-*p*-toluenesulfonyl-D-glucal (**3**)[18] with $LiAlH_4$, $NaBH_4$ or DIBAL, all of which afforded 6-deoxy-D-glucal (**6**) in only modest yields. Diacetate **5** was transesterified to obtain 6-deoxy-D-glucal (**6**).[19]

Attempts to introduce the amino functionality at C-4 of **6** by S_N2 substitution of a sulfonate ester were unsuccessful. Selective protection of the C-3 hydroxyl group by TBDMSCl gave the hindered 3-*O*-TBDMS derivative **7**[22] (Scheme 2). Mesylate **8**[22] could be obtained in good yield, but inversion of configuration at C-4 by azide

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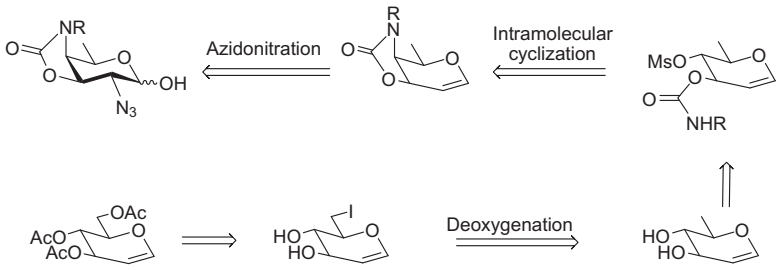
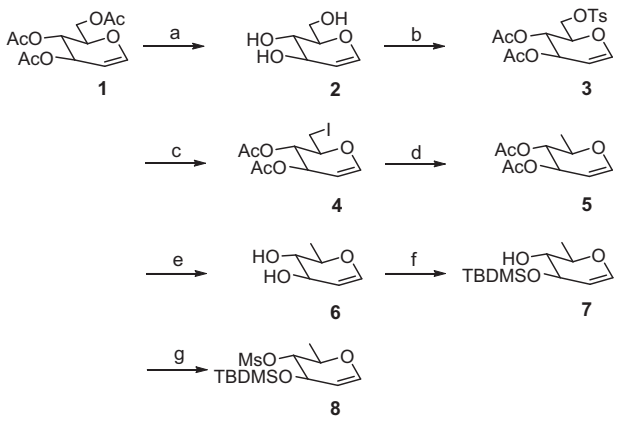


Scheme 1. Retrosynthesis of a suitably protected 4-amino-2-azido-2,4,6-trideoxyhexose.



Scheme 2. Reagents: (a) NaOMe, MeOH, 92%; (b) TsCl, Py, then Ac_2O, Py, 77% (over two-steps); (c) LiI, THF; (d) AIBN, Bu_3SnH, 85% (over two-steps); (e) NaOMe, MeOH, 90%; (f) TBDMSCl, DMF, Imidazole, 90%; (g) MsCl, Py, 86%.

was unsuccessful. Leaving groups such as triflate and tosylate also failed to provide the desired product. Even when the bulky TBDMS group was removed by treating **8** with TBAF, azide displacement of the mesylate failed.

We chose to introduce the 4-amino group by exploiting displacement by a neighboring carbamate group. Cyclic carbamates (oxazolidinones) bridging a vicinal amino alcohol such as C-2 and C-3 of 2-amino-2-deoxy-D-hexopyranoses have been used as protecting groups in glucosamine and galactosamine chemistry.[23–25] For the synthesis of a 4-amino-4-deoxy-hexose, intramolecular delivery of a temporarily tethered nitrogen nucleophile in S_N2 fashion to an electrophilic site is a convenient way to simultaneously introduce and protect the 4-amino function with excellent control over the regiochemistry and stereochemistry of the amino group, while minimizing the extent of side reactions.[26] In addition, because the resulting cyclic intermediate simultaneously protects both the amino and the alcohol groups, it can be converted into the target amino alcohol late in the synthesis (Fig. 1).[27,28] Carbamate derivatives are readily formed under neutral conditions, the carbamate anion easily generated, and treatment with a stronger base hydrolyzes the oxazolidinone ring.[26,28,29]

The C-3 hydroxyl group of compound **9** was converted into a substituted carbamate by condensation of compound **9** with benzyl isocyanate to give benzylcarbamate **10** in excellent yield (Scheme 3). Treatment of compound **10** with *t*-BuOK generated the potassium salt of the *N*-benzylcarbamate anion which cyclized in situ to afford the *N*-benzyloxazolidinone **11**.[27] It was subsequently realized that the synthesis of **11** was accomplished most efficiently by avoiding the protection and deprotection of the C-3 hydroxyl by a TBDMS group, since the C-3 hydroxyl group of **6** could be regioselectively protected with benzylisocyanate in good yield (Scheme 4). The free hydroxyl group at C-4 of **15** was then activated for an intramolecular cyclization reaction by conversion to mesylate **10** under carefully monitored conditions.

The stereoselective azidonitration of glycals to the corresponding 2-azido-2-deoxyglycosyl nitrates is significantly influenced by the configuration at C-4 such that galactals yield predominately the 2-azido-2-deoxy-galactopyranose product with very little of the corresponding *talo* derivative.[30] As expected the reaction of oxazolidinone protected 6-deoxy-D-galactose **11** with ceric ammonium nitrate (CAN) and sodium azide resulted in the formation of the glycosyl nitrate anomers **12** with excellent stereoselectivity. Conventional conditions for the removal of the anomeric nitrates by halide ions,[30] thiophenoxide ion,[31] sulfide ions, and acetolysis[30] gave very poor yields and, in some cases, decomposition occurred. It was found that the treatment of the anomeric azidonitrates **12** in acetonitrile and water gave the desired pyranose **13** in good yield (Scheme 3).

Reaction of hemiacetal **13** with trichloroacetonitrile and K_2CO_3 in dichloromethane gave trichloroacetimidate **14**, which could be obtained in excellent yield as an anomeric mixture (α/β 3:2) without the need for chromatographic purification (Scheme 3). The effectiveness of this glycosyl donor was accessed by reaction with cyclohexanol. In the presence of the trimethylsilyl triflate, as

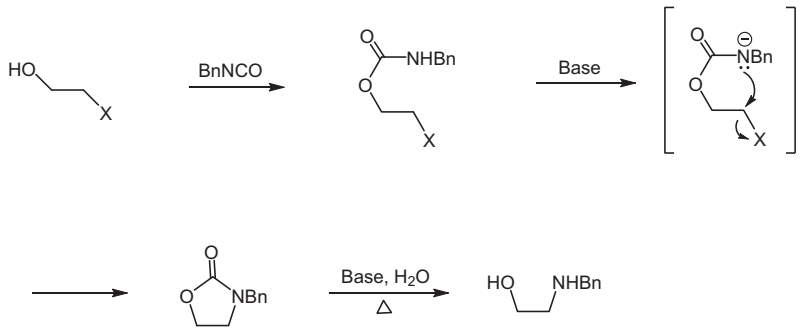
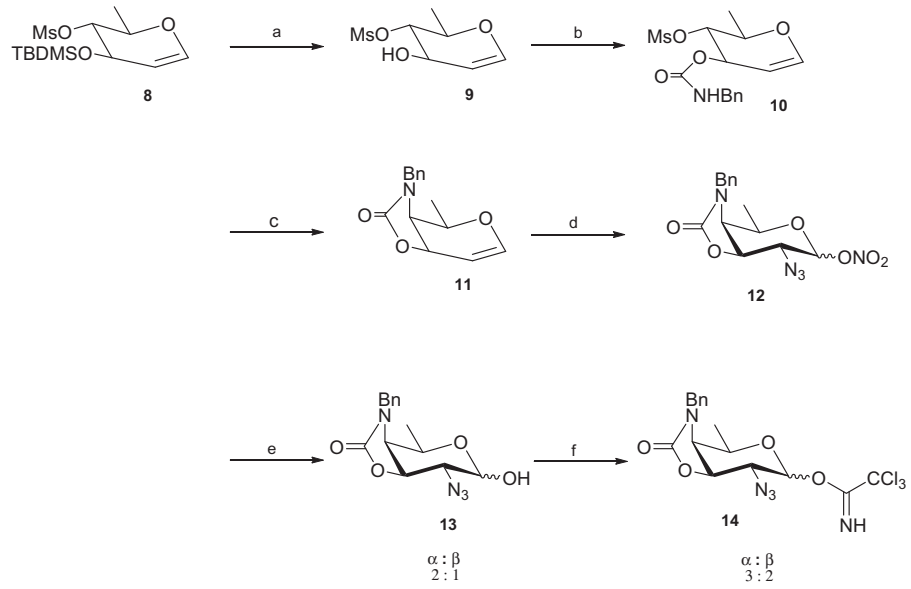
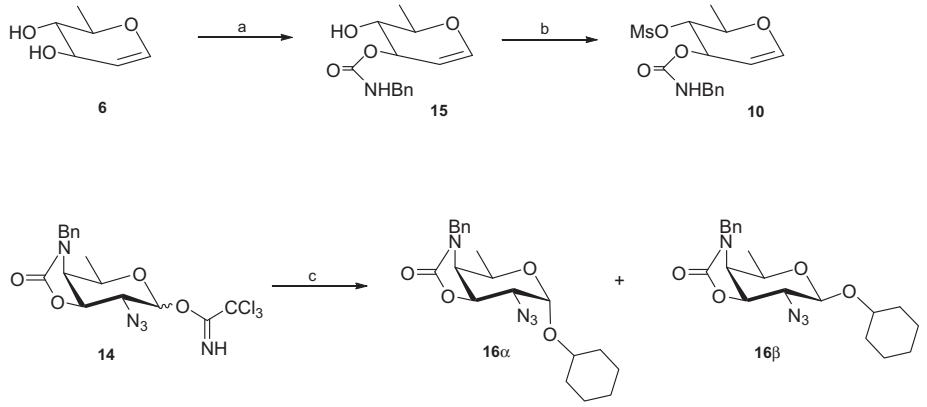


Figure 1. Synthesis of an oxazolidinone ring by an attack of a tethered, internal nucleophile on an electrophilic intermediate, and subsequent aqueous hydrolysis to expose the latent amino group.



Scheme 3. Reagents: (a) TBAF, THF, 87%; (b) BnNCO, DCM, 90%; (c) *t*-BuOK, THF, 95%; (d) NaN_3, CAN; (e) H_2O, MeCN, 78% (over two-steps); (f) Cl_3CCN, DCM, K_2CO_3, 100%.



Scheme 4. Reagents and conditions: (a) BnNCO, DCM, 85%; (b) MsCl, Py, 0 °C, 87%; (c) cyclohexanol, TMSOTf, −10 °C to 0 °C, 70%, (α/β = 4:1).

promoter **14** reacted with cyclohexanol to give the 2,4,6-trideoxy-galactopyranoside **16** as an α/β mixture (4:1) in 70% yield (Scheme 4). The potential of imidate **14** as a valuable and readily prepared building block for assembly of larger oligosaccharide structures has been confirmed by its use in the synthesis of the trisaccharide repeating unit α-D-Fuc*p*N2AcN4-(1→4)-α-D-Gal*p*A-(1→3)-D-Gal*p*A-(1→OMe of the *S. pneumoniae* type 1 polysaccharide (manuscript in preparation).

3. Experimental

3.1. General methods

All chemical reagents were of analytical grade and used as obtained from commercial sources unless otherwise indicated. Solvents used in water-sensitive reactions were purified by successive passage through columns of alumina and copper under nitrogen. Unless otherwise noted, reactions were carried out at room temperature, and water-sensitive reactions were performed under an atmosphere of argon. Molecular sieves were flame dried and then allowed to cool to room temperature under argon before use. Reactions were monitored by analytical thin-layer chromatography (TLC) performed on Silica Gel 60-F_{254} (E. Merck). Plates were visualized under UV light, and/or by treatment with 5% H_2SO_4 in EtOH followed by heating. Organic solvents were removed under vacuum at <40 °C. Medium-pressure chromatography was conducted using silica gel (230–400 mesh, Silicycle, Montreal) at flow rates of 5–10 mL min^{-1}. ^1H NMR spectra were recorded at 500 or 600 MHz, and chemical shifts, reported in δ (ppm), were referenced to internal residual protonated solvent signals or to external acetone (0.1% ext. acetone at δ 2.225 ppm) in the case of D_2O. ^{13}C NMR was recorded at 125 MHz, and chemical shifts are referenced to internal $CDCl_3$ (δ 77.23) or external acetone (δ 31.07).

3.2. 3-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-D-glucal (7)

To a solution of 6-deoxy-D-glucal[19] (**6**, 2.10 g, 16.2 mmol) and imidazole (1.65 g, 24.2 mmol, 1.5 equiv) in dry DMF (12 mL) was added TBDMSCl (4.88 mL, 17.76 mmol, 1.1 equiv) dropwise at 0 °C. The resulting mixture was stirred for 6 h at room temperature. The reaction mixture was cooled to 0 °C and quenched with MeOH, and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM (25 mL) and washed with an equal volume of water and brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated. Column chromatography on silica gel using 10:1 hexanes–EtOAc afforded the monosilyl

derivative **7** (3.55 g, 90%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.26 (dd, 1H, $J_{1,2}$ = 6.0 Hz, $J_{1,3}$ = 1.1 Hz, H-1), 4.63 (ddd, 1H, $J_{1,2}$ = 6.1 Hz, $J_{2,3}$ = 2.2 Hz, $J_{2,4}$ = 1.1 Hz, H-2), 4.25–4.19 (m, 1H, H-3), 3.91 (dq, $J_{4,5}$ = 8.9 Hz, $J_{5,6}$ = 6.5 Hz, H-5), 3.47 (app t, 1H, $J_{3,4}$ = 7.8 Hz, $J_{4,5}$ = 7.9 Hz, H-4), 1.39 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6 CH_3), 0.92 (s, 9H, C(CH_3)$_3$), 0.13 (s, 6H, SiCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.6, 103.4, 74.9, 74.3, 70.5, 25.8, 18.1, 17.2, −4.3, −4.5. HRESIMS: calcd for $C_{12}H_{24}O_3SiNa$ (M+Na): 267.1387, found 267.1385. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 55.83; H, 9.72.

3.3. 3-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-4-*O*-mesyl-D-glucal (8)

MsCl (2.25 mL, 19.7 mmol, 1.5 equiv) was added to a solution of silyl derivative **7**[22] (3.20 g, 13.1 mmol) in a mixture of dry DCM and dry pyridine (4:1, v/v, 20 mL) at 0 °C. The reaction mixture was warmed to room temperature while being stirred for 2.5 h. The solution was diluted with DCM (20 mL) and washed with an equal volume of water and brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated. Chromatography on silica gel with 9:1 hexanes–EtOAc as eluent gave **8**[22] (3.63 g, 86%). $[\alpha]_D$ −33.1 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.33 (dd, 1H, $J_{1,2}$ = 6.2 Hz, $J_{1,3}$ = 1.2 Hz, H-1), 4.72 (dd, 1H, $J_{1,2}$ = 6.2 Hz, $J_{2,3}$ = 3.1 Hz, H-2), 4.58 (dd, 1H, $J_{3,4}$ = 5.5 Hz, $J_{4,5}$ = 7.1 Hz, H-4), 4.41–4.36 (m, 1H, H-3), 4.20–4.15 (m, 1H, H-5), 3.09 (s, 3H, CH_3SO_2), 1.45 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6 CH_3), 0.93–0.89 (s, 9H, C(CH_3)$_3$), 0.13 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.7, 102.1, 82.1, 72.6, 66.5, 39.0, 25.8, 18.0, 16.9, −4.3, −4.4. HRESIMS: calcd for $C_{13}H_{26}O_5SSiNa$ (M+Na): 345.1162, found 345.1162. Anal. Calcd for $C_{13}H_{26}O_5SiS$: C, 48.42; H, 8.13; S, 9.94. Found: C, 48.63; H, 8.18; S, 9.51.

3.4. 6-Deoxy-4-*O*-mesyl-D-glucal (9)

A solution of silyl ether **8**[22] (2.70 g, 8.38 mmol) in dry THF (20 mL) was treated with TBAF (1.0 M in THF, 2.63 mL, 10.1 mmol, 1.2 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred at this temperature for 3 h. The solution was then diluted with EtOAc (20 mL), washed with equal volume of water and brine, then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (6:4 hexanes–EtOAc) to afford the title compound **9** (1.52 g, 87%) as a white solid. $[\alpha]_D$ 18.5 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.36 (d, 1H, $J_{1,2}$ = 6.9 Hz, H-1), 4.77 (dd, 1H, $J_{1,2}$ = 6.0 Hz, $J_{2,3}$ = 2.3 Hz, H-2), 4.48 (m, 2H, H-4, H-3), 3.99 (dq, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6}$ = 6.4 Hz, H-5), 3.20 (s, 3H, CH_3SO_2), 2.43 (s, 1H, 2-OH), 1.43 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6 CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 102.4, 84.0, 72.5, 68.2, 38.8, 17.1. HRESIMS: calcd for $C_7H_{12}O_5SNa$ (M+Na): 231.0298, found 231.0289. Anal. Calcd for $C_7H_{12}O_5S$: C, 40.38; H, 5.81; S, 15.40. Found: C, 40.54; H, 5.85; S, 15.54.

3.5. 3-*O*-(*N*-Benzyl)-carbamoyl-6-deoxy-4-*O*-mesyl-D-glucal (10)

A solution of mesylate **9** (1.05 g, 5.05 mmol) in DCM (12 mL) was treated with benzylisocyanate (1.00 mL, 7.57 mmol, 1.5 equiv) in the presence of TEA (1.3 mL, 12.6 mmol, 2.5 equiv) at room temperature for 16 h. The solvent was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using 3:1 hexanes–EtOAc as eluent to obtain the carbamate **10** as a white crystalline solid (1.48 g, 90%). $[\alpha]_D$ 66.9 (*c* 0.33, CH_2Cl_2); ^{1}H NMR (498 MHz, $CDCl_3$): δ 7.39–7.24 (m, 5H, ArH), 6.41 (dd, 1H, $J_{1,2}$ = 6.0 Hz, $J_{2,3}$ = 1.3 Hz, H-1), 5.43 (ddd, 1H, J = 6.5 Hz, J = 2.9 Hz, J = 1.6 Hz, H-3), 5.23 (s, 1H, OCONH*Bn*), 4.81 (dd, 1H, $J_{1,2}$ = 6.1 Hz, $J_{2,3}$ = 2.9 Hz, H-2), 4.68 (dd, 1H, $J_{3,4}$ = 6.7 Hz, $J_{4,5}$ = 8.4 Hz, H-4), 4.36 (d, 2H, J = 6.0 Hz, PhCH_2), 4.12 (q, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6}$ = 6.4 Hz, H-5), 3.01 (s, 3H, CH_3SO_2), 1.41 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6 CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 146.0, 138.0, 128.7, 127.7, 127.5, 99.0, 79.3, 72.7, 69.2, 45.2, 38.8, 16.8. HRESIMS: calcd for $C_{15}H_{19}NO_6SNa$ (M+Na): 364.0825, found 364.0824.

3.6. 4-Benzylamino-4-*N*-,3-*O*-carbonyl-4,6-dideoxy-D-galactal (11)

The carbamate derivative **10** (0.34 g, 1.0 mmol) was dissolved in dry THF (15 mL) and treated with *t*-BuOK (0.13 g, 0.12 mmol, 1.2 equiv) in portions. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with satd aq NH_4Cl; then it was diluted with EtOAc (10 mL). The organic phase was washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (4:1 hexanes–EtOAc) yielded oxazolidinone derivative **11** (0.23 g, 95%) as a white solid. $[\alpha]_D$ 69.0 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (498 MHz, $CDCl_3$): δ 7.56–7.24 (m, 5H, ArH), 6.56 (d, 1H, $J_{1,2}$ = 6.2 Hz, H-1), 5.03 (dd, 1H, $J_{1,2}$ = 6.2 Hz, $J_{2,3}$ = 3.7 Hz, H-2), 4.93–4.88 (d, 1H, J_{gem} = 15.8 Hz, PhCH_2), 4.87 (dd, 1H, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 7.8 Hz, H-3), 4.22 (d, 1H, J_{gem} = 15.8 Hz, PhCH_2), 4.15 (dq, 1H, $J_{4,5}$ = 3.5 Hz, $J_{5,6}$ = 6.9 Hz, H-5), 3.82 (dd, 1H, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 1.35 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6 CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 147.6, 135.6, 128.9, 128.0, 127.9, 99.0, 70.5, 67.2, 55.3, 47.8, 15.2. HRESIMS: calcd for $C_{14}H_{16}NO_3Na$ (M+Na): 246.1125, found 246.1125. Anal. Calcd for $C_{14}H_{16}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.22; H, 6.58; N, 5.61.

3.7. 2-Azido-4-benzylamino-4-*N*-,3-*O*-carbonyl-2,4,6-trideoxy-α/β-D-galactopyranose (13)

A mixture of cerium(IV) ammonium nitrate (2.35 g, 4.29 mmol, 3 equiv) and NaN_3 (0.14 g, 2.14 mmol, 1.5 equiv) was added to a solution of the oxazolidinone derivative of 6-deoxy-D-galactal (0.35 g, 1.43 mmol) **11** in dry MeCN (7 mL) at −15 °C under argon. The resulting suspension was vigorously stirred at this temperature until TLC analysis (3:2 hexanes–EtOAc) indicated a complete consumption of starting material. After the reaction was complete, the mixture was diluted with EtOAc and concentrated. The residue was redissolved in Et_2O, filtered through Celite, and concentrated under reduced pressure. The resulting residue was dissolved in MeCN (5 mL), and H_2O (2 mL) was added to this solution. The reaction mixture was stirred at room temperature for 16 h and then MeCN was evaporated. The residue dissolved in EtOAc (7 mL) was washed with an equal volume of water and brine, and then the solution was dried over Na_2SO_4, filtered, and concentrated. Column chromatography on silica gel using 3:2 hexanes–EtOAc afforded the azido derivative **13** (α/β 2:1, 0.33 g, 78% over two-steps) as a mixture of anomers. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (m, 5H, ArH), 7.27–7.21 (m, 5H, ArH), α anomer: 5.41 (app t, $J_{1,2}$ = 4.6 Hz, $J_{1,OH}$ = 4.6 Hz, H-1), 5.04 (d, 1H, J_{gem} = 15.6 Hz, PhCH_2), 4.63 (dd, 1H, $J_{2,3}$ = 4.7 Hz, $J_{3,4}$ = 8.4 Hz, H-3), 4.32 (dq, 1H, $J_{4,5}$ = 2.4 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 4.18 (d, 1H, J_{gem} = 15.6 Hz, PhCH_2), 4.11 (app t, 1H, $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 4.5 Hz, H-2) 3.55 (dd, 1H, $J_{3,4}$ = 8.3 Hz, $J_{4,5}$ = 2.5 Hz, H-4), 3.20 (d, 1H, J = 4.9 Hz, 1-OH), 1.30 (d, 3H, $J_{5,6}$ = 6.7 Hz, H-6 CH_3). β Anomer: 4.97 (d, 1H, J_{gem} = 15.9 Hz, PhCH_2), 4.73 (app t, $J_{1,2}$ = 6.5 Hz, $J_{1,OH}$ = 6.5 Hz, H-1), 4.36 (app t, 1H, $J_{2,3}$ = 7.5 Hz, $J_{3,4}$ = 7.5 Hz, H-3), 4.32 (d, 1H, J_{gem} = 16.0 Hz, PhCH_2), 4.11 (dq, 1H, $J_{4,5}$ = 2.5 Hz, $J_{5,6}$ = 7.2 Hz, H-5), 3.77 – 3.63 (m, 2H, H-2, H-4), 3.44 (d, 1H, J = 6.4 Hz, 1-OH), 1.39 (d, 3H, $J_{5,6}$ = 7.4 Hz, H-6 CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, from HMQC): δ 129.0, 129.0, 128.2, 128.0, 127.8, 127.7, 127.6, α anomer: δ 158.6, 135.4, 90.3, 72.3, 65.0, 57.9, 55.1, 49.3, 17.6. β Anomer: δ 159.5,

135.1, 95.7, 74.8, 69.1, 64.5, 56.8, 49.1, 17.7. HRESIMS: calcd for $C_{14}H_{16}N_4O_4Na$ (M+Na): 327.1064, found 327.1062.

3.8. 2-Azido-4-benzylamino-4-*N*-,3-*O*-carbonyl-2,4,6-trideoxy-α,β-D-galactopyranosyl trichloroacetimidate (14)

A mixture of α and β 6-deoxy-galactopyranoses **13** α,β (2.0 g, 6.6 mmol) was dissolved in freshly distilled DCM (15 mL). CCl_3CN (4.75 mL, 32.9 mmol, 5 equiv) and K_2CO_3 (2.73 g, 19.7 mmol, 3 equiv) were added to the resulting solution, and the mixture was vigorously stirred at room temperature under argon. After 14 h, the mixture was concentrated. The residue was dissolved in freshly distilled DCM (10 mL) and filtered through a microfilter to remove inorganic salts. The filtrate was concentrated under reduced pressure to afford imidate **14** as an α,β anomeric mixture (α/β 3:2, 2.94 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$): α anomer: δ 8.76 (s, 1H, N*H*COCl$_3$), 7.48–7.31 (m, 5H, ArH), 6.42 (d, $J_{1,2}$ = 4.6 Hz, H-1), 5.06 (d, 1H, J_{gem} = 15.4 Hz, PhC*H*$_2$), 4.69 (dd, 1H, $J_{2,3}$ = 4.8 Hz, $J_{3,4}$ = 8.4 Hz, H-3), 4.40 (app t, 1H, $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 4.38 (qd, 1H, $J_{4,5}$ = 2.5 Hz, $J_{5,6}$ = 7.0 Hz, H-5), 4.15 (d, 1H, J_{gem} = 15.4 Hz, PhC*H*$_2$), 3.62 (dd, 1H, $J_{3,4}$ = 8.4 Hz, $J_{4,5}$ = 2.4 Hz, H-4), 1.34 (d, 3H, $J_{5,6}$ = 6.8 Hz, H-6 C*H*$_3$). β Anomer: δ 8.72 (s, 1H, N*H*COCl$_3$), 7.28–7.22 (m, 5H, ArH), 5.87 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 4.95 (d, 1H, J_{gem} = 15.3 Hz, PhC*H*$_2$), 4.45 (dd, 1H, $J_{2,3}$ = 7.5 Hz, $J_{3,4}$ = 8.7 Hz, H-3), 4.21 (d, 1H, J_{gem} = 15.3 Hz, PhC*H*$_2$), 4.09 (app t, 1H, $J_{1,2}$ = 7.3 Hz, $J_{2,3}$ = 7.3 Hz, H-2), 4.05 (qd, 1H, $J_{4,5}$ = 3.8 Hz, $J_{5,6}$ = 7.2 Hz, H-5), 3.81 (dd, 1H, $J_{3,4}$ = 8.7 Hz, $J_{4,5}$ = 3.8 Hz, H-4), 1.43 (d, 3H, $J_{5,6}$ = 7.2 Hz, H-6 CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, from HMQC): δ 129.1, 129.0, 128.3, 128.3, 128.0, 127.9, α anomer: 160.5, 157.9, 135.3, 93.9, 72.0, 67.4, 56.7, 54.5, 49.3, 17.3. β Anomer: δ 161.0, 158.4, 134.7, 96.4, 73.5, 69.8, 62.1, 55.3, 48.8, 17.7. HRESIMS: calcd for $C_{16}H_{16}Cl_3N_5O_4Na$ (M+Na): 470.0160, found 470.0161.

3.9. 3-*O*-(*N*-Benzyl)-carbamoyl-6-deoxy-D-glucal (15)

A solution of 6-deoxy-D-glucal (**6**)[19] (0.06 g, 0.46 mmol) in DCM (2 mL) was treated with benzylisocyanate (0.07 mL, 0.55 mmol, 1.2 equiv) in the presence of TEA (0.07 mL, 0.69 mmol, 1.5 equiv) at 0 °C for 6 h. The solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography using 3:1 hexanes–EtOAc as eluent to obtain the monocarbamate **15** as a white crystalline solid (0.10 g, 85%). $[\alpha]_D$ −14.2 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42–7.27 (m, 5H, ArH), 6.43 (dd, 1H, $J_{1,2}$ = 6.2 Hz, $J_{1,3}$ = 1.4 Hz, H-1), 5.15 (ddd, 1H, $J_{1,3}$ = 1.8 Hz, $J_{2,3}$ = 2.5 Hz, $J_{3,4}$ = 6.7 Hz, H-3), 4.65 (dd, 1H, $J_{1,2}$ = 6.1 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.37 (d, 2H, *J* = 6.0 Hz, PhC*H*$_2$), 4.34 (s, 1H, OCON*H*Bn) 3.88 (dq, 1H, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.4 Hz, H-5), 3.59 (ddd, 1H, $J_{3,4}$ = 6.8 Hz, $J_{4,5}$ = 8.6 Hz, $J_{4,4OH}$ = 1.2 Hz, H-4), 1.41 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6 C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.0, 146.7, 137.8, 128.8, 128.7, 127.5, 99.0, 75.2, 74.9, 73.3, 45.3, 17.2. HRESIMS: calcd for $C_{14}H_{17}NO_4Na$ (M+Na): 286.1050, found 286.1053. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.88; H, 6.48; N, 5.41.

3.10. Cyclohexyl 2-azido-4-benzylamino-4-*N*-,3-*O*-carbonyl-2,4,6-trideoxy-α-D-galactopyranoside (16)

Cyclohexanol (0.07 mL, 0.7 mmol, 10 equiv) and imidate **14** (0.03 g, 0.07 mmol) were dissolved in freshly distilled DCM (2 mL), and the mixture was stirred under argon at room temperature in the presence of powdered 4 Å molecular sieves for 30 min before being cooled to −10 °C. TMSOTf (7.6 μL, 0.01 mmol, 0.5 equiv) was then added, and the reaction mixture was stirred for a further 1 h at −10 °C; then it was allowed to warm to 0 °C, at which point the reaction was completed. The reaction was quenched by addition of TEA and stirred for an additional 20 min, after which the mixture was diluted, filtered through Celite, and concentrated. Chromatography of the residue on silica gel with a stepped gradient of 15–20% EtOAc in hexanes afforded compound **16** as colorless syrup (α/β 4:1, 0.02 g, 70%). α Anomer: $[\alpha]_D$ 16.2 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.21 (m, 5H, ArH), 5.15 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.98 (d, 1H, J_{gem} = 15.6 Hz, PhC*H*$_2$), 4.58 (dd, 1H, $J_{2,3}$ = 8.0 Hz, $J_{3,4}$ = 5.8 Hz, H-3), 4.28–4.24 (qd, 1H, $J_{4,5}$ = 2.2 Hz, $J_{5,6}$ = 6.9 Hz, H-5), 4.25–4.19 (d, 1H, J_{gem} = 15.7 Hz, PhC*H*$_2$), 3.88 (dd, 1H, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 5.7 Hz, H-2), 3.65 (m, 1H, OC*H*(CH$_2$)$_5$), 3.58 (d, 1H, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 2.3 Hz, H-4), 2.03–1.79 (m, 4H, OCH(C*H*$_2$)$_2$(CH$_2$)$_3$), 1.77–1.64 (m, 6H, OCH(CH$_2$)$_2$(C*H*$_2$)$_3$), 1.55 (d, 3H, $J_{5,6}$ = 6.9 Hz, H-6 C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 135.6, 128.9, 128.0, 127.7, 94.7, 76.5, 72.3, 70.3, 64.3, 57.9, 55.9, 49.2, 35.6, 33.4, 31.5, 25.5, 24.1, 23.7, 17.5. HRESIMS: calcd for $C_{20}H_{26}N_4O_4Na$ (M+Na): 409.1846, found 409.1845.

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