Practical Synthesis of Building Blocks for Oligosaccharides Containing the β-D-Gal*p*-(1→3)-β-D-Glc*p*NAc Motif

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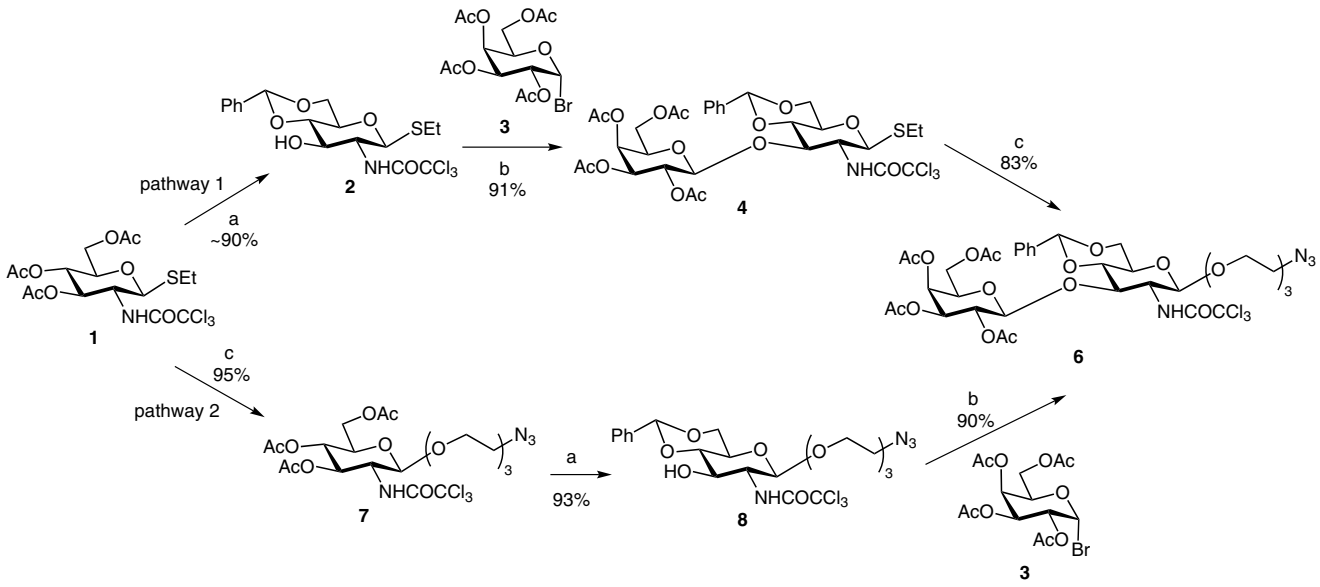
Abstract: An efficient, new pathway for the synthesis of the title sequence has been developed. The sequence has been obtained as a glycosyl donor, β-D-Gal*p*-(1→3)-β-D-Glc*p*NAc-1-SEt, or equipped with a linker (spacer) suitable for conjugation to other molecules, β-D-Gal*p*-(1→3)-β-D-Glc*p*NAc-1-$(OCH_2CH_2)_3N_3$. Both disaccharides have been obtained in crystalline condition for the first time and fully characterized. The existing synthesis of the intermediate disaccharide glycosyl donor was improved by conducting the silver triflate mediated glycosylation under base-deficient conditions in the presence of 1,1,3,3-tetramethylurea and in the absence of molecular sieves.

Key words: carbohydrates, oligosaccharides, synthetic methods, thioglycosides, protecting groups



Scheme 1 *Reagents and conditions*: (a) (1) NaOMe, MeOH, r.t., (2) $PhCH(OMe)_2$, CSA, MeCN; (b) AgOTf, 1,1,3,3-tetramethylurea, CH_2Cl_2; (c) 8-azido-3,6-dioxaoctan-1-ol (**5**), NIS, AgOTf, 4 Å MS, CH_2Cl_2.

Derivatives of common sugars that are 'standard building blocks' in chemical oligosaccharide synthesis are of continuing interest in this laboratory. The thioglycoside β-D-Gal*p*-(1→3)-β-D-Glc*p*NAc-1-SEt represents a motif present in human milk oligosaccharides (e.g., Lacto-N-biose, Lacto-N-tetraose and its sialylated/fucosylated derivatives), and in carbohydrate moieties of glycoproteins and glycolipids[1–4] (e.g., Type I glycans, Lewis a, Sialyl Lewis a, and Lewis b antigens).

Introducing a linker (spacer) to this building block allows conjugation to other molecules (e.g., proteins). Also, both the thioglycoside and its linker-equipped counterpart can act as intermediates for the preparation of several upstream di-, tri-, and tetrasaccharide fragments of the O-antigen of *Vibrio cholerae* O139.[5,6]

We describe herein two efficient synthetic pathways (Scheme 1) for the total synthesis of 8-azido-3,6-dioxaoctyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-trichloroacetamido-β-D-glucopyranoside (**6**) starting from the known ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (**1**).[7] The 2-deoxy-2-trichloroacetamido

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group is a powerful stereocontrolling auxiliary in the synthesis of 1,2-*trans*-linked 2-aminosugar-containing oligosaccharides.[8]

Pathway 1

Thioglycoside **1**[7] was O-deacetylated (Zemplén) and the formed triol was treated with benzaldehyde dimethyl acetal in acetonitrile in the presence of 10-camphorsulfonic acid (CSA) to give the crystalline 4,6-*O*-benzylidene acetal **2** in ~90% yield.[7]

Disaccharide **4** has been originally prepared by Sherman and co-workers[7] within their study of glycosylation with *N*-trichloroacetyl-protected D-glucosamine derivatives. According to the original protocol,[7] 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**3**)[9] was condensed in dichloromethane with ethyl 4,6-*O*-benzylidene-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (**2**), in the presence of 4 Å molecular sieves using silver triflate as promoter and *sym*-collidine (0.5 equiv relative to **3**) as acid scavenger. Formation of byproducts was observed, including cleavage of the acid-labile benzylidene group. The highest yield of the desired disaccharide obtained under these conditions was 60%. As an alternative, the same authors used the corresponding imidate as the glycosyl donor, which resulted in improved yield (70%). A higher yield of compound **4** (~90%)[10] from the same synthons was obtained in this laboratory by using a larger relative amount of base during the glycosylation step; however, when we repeated the same protocol at a few later occasions using different batches of molecular sieves, we observed that the yields were inconsistent. We hypothesized that the basicity of molecular sieves from different batches/suppliers was not identical, which made it virtually impossible to rationalize the optimum amount of base to be used.

To ensure isomerization of the plausible orthoester intermediate,[11,12] the reaction had to be conducted under base-deficient conditions, while the acidity during the reaction had to be low, to keep the acid-labile benzylidene group intact. Our revised protocol, which we have followed successfully on a multigram scale, has consistently afforded disaccharide **4** in ~90% yield. It employs 1,1,3,3-tetramethylurea as base[11] and does not require the use of molecular sieves.

The β-configuration of the interglycosidic linkage follows from the ^{1}H NMR spectrum (δ 4.76, d, $J_{1,2}$ = 7.9 Hz, H-1^{II}). Formation of the α-isomer was not observed. In addition, the ^{13}C NMR spectrum showed the two anomeric carbons at δ 83.1 (C-1^{I}) and 99.3 (C-1^{II}), and an additional signal at δ 101.3 corresponding to the benzylidene carbon (Ph*C*H).

Treatment of the thioglycoside disaccharide **4** in dichloromethane at low temperature with 8-azido-3,6-dioxaoctan-1-ol (**5**),[5] in the presence of *N*-iodosuccinimide and a catalytic amount of silver triflate gave the spacer-equipped disaccharide **6** in 83% yield, after chromatography. The compound was now obtained crystalline for the first time. The ^{1}H NMR spectrum of **6** showed two doublets for anomeric protons at δ 4.74 ($J_{1,2}$ = 8.0 Hz) and 5.12 ($J_{1,2}$ = 8.3 Hz) assigned by a COSY experiment to H-1 of the β-D-galactose and β-D-glucose moieties, respectively. Both the ^{1}H and ^{13}C NMR spectra confirmed the presence of the linker signals, and 2D spectroscopy permitted the complete nuclei–signal assignments.

Pathway 2

Experimental evidence from a large number of complex oligosaccharide syntheses dictates that, whenever possible, it is advantageous to run glycosylations with small-size glycosyl donors, compared to running this type of reaction with larger size glycosyl donors. Therefore, an alternative strategy for the construction of the target disaccharide **6** was explored.

Glycosidation of *N*-trichloroacetyl-D-glucosaminyl thioglycoside donor **1**[7] with the linker molecule 8-azido-3,6-dioxaoctan-1-ol (**5**)[5] gave exclusively the corresponding β-glycoside **7** in virtually theoretical yield. The anomeric configuration followed from the ^{1}H NMR data (δ 4.91, d, $J_{1,2}$ = 8.5 Hz for H-1).

Deacetylation of **7**, followed by 4,6-benzylidination, furnished the new spacer-equipped monosaccharide acceptor **8** in excellent yield (93%). The ^{1}H NMR spectrum of **8** showed a doublet at δ 3.09 (J = 3.4 Hz), which showed correlation with the signal for H-3 (δ 4.24) and disappeared after exchange with deuterium oxide, and was therefore assigned to 3-OH.

Using our revised protocol for the preparation of **4**, coupling of the glycosyl bromide **3** with the *N*-trichloroacetyl-D-glucosamine derivative **8** at low temperature, with silver triflate as promoter in the presence of 1,1,3,3-tetramethylurea and, again, in the absence of molecular sieves, afforded the crystalline β-linked disaccharide **6** in 90% yield.

The two routes gave the target disaccharide **6**, which is a versatile intermediate in complex oligosaccharide synthesis, in 68% and 80% overall yield, respectively, showing the advantage of pathway 2 over pathway 1.

Optical rotations were measured at ambient temperature for solutions in $CHCl_3$ with a Perkin-Elmer model 341 automatic polarimeter. Melting points were measured on a Kofler hot-stage apparatus. Thin-layer chromatography (TLC) was performed on silica gel 60 coated glass slides. Column chromatography was performed by elution from prepacked (Varian, Inc.) columns of silica gel with an Isolera flash chromatograph (Biotage) connected to an external evaporative light scattering detector (Varian, Inc., model 380-LC). NMR spectra were measured at 600 MHz (^{1}H) and 150 MHz (^{13}C) with a Bruker Avance spectrometer. Assignments of NMR signals were made using homonuclear and heteronuclear two-dimensional correlation spectroscopy, run with the software supplied with the spectrometers. For the reporting of assignments of NMR signals, nuclei associated with the spacer are denoted with a prime; sugar residues are serially numbered, beginning with the one bearing the aglycone, and are identified by a Roman numeral superscript in listings of signal assignments. Liquid chromatography–electrospray ionization mass spectrometry (ESIMS) was performed with a Hewlett-Packard 1100 MSD spectrometer. Crystalline acetobromo-

α-D-galactose (**3**) was purchased from Sigma-Aldrich.[13] Solutions in organic solvents were dried with anhydrous Na_2SO_4, and concentrated at 40 °C/2 kPa.

Ethyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-thio-2-trichloroacetamido-β-D-glucopyranoside (4)

A solution of acetobromo-α-D-galactose[13] (**3**; 307.5 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added, at –30 °C in one portion, to a mixture of glycosyl acceptor **2**[7] (228.4 mg, 0.5 mmol), 1,1,3,3-tetramethylurea (119.6 μL, 0.95 mmol), and powdered AgOTf (218.4 mg, 0.85 mmol) in anhydrous CH_2Cl_2 (5 mL). The cooling was removed and, with continued stirring, the mixture was allowed to warm to r.t. (~1 h), when TLC (toluene–acetone, 8:1) indicated that all acceptor had been consumed. Et_3N (0.5 mL) was added, and the mixture was diluted with CH_2Cl_2 (5 mL) and filtered through a Celite® pad. The filtrate was washed successively with 0.5 M aq HCl (20 mL), aq $NaHCO_3$ (20 mL), and brine (20 mL), then dried. After concentration, chromatography (toluene–acetone, 15:1) gave the desired disaccharide **4**; yield: 358 mg (91%).

Mp 203.5–204.0 °C (*i*-PrOH).

$[\alpha]_D$ –20 (*c* 1.0, $CHCl_3$) [Lit.[7] $[\alpha]_D$ –28 (*c* 2.0, CH_2Cl_2)].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.49–7.37 (m, 5 H, Ph), 7.01 (d, J = 7.9 Hz, 1 H, NH), 5.56 (s, 1 H, PhC*H*), 5.32 (dd, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 0.8 Hz, 1 H, H-4^{II}), 5.19 (dd, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 10.4 Hz, 1 H, H-2^{II}), 5.10 (d, $J_{1,2}$ = 10.4 Hz, 1 H, H-1^{I}), 4.92 (dd, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.4 Hz, 1 H, H-3^{II}), 4.76 (d, $J_{1,2}$ = 7.9 Hz, 1 H, H-1^{II}), 4.48 (t, J = 9.5 Hz, 1 H, H-3^{I}), 4.36 (dd, J = 4.9, 10.6 Hz, 1 H, H-6$^{I}_a$), 4.11 (dd, J = 6.9, 11.3 Hz, 1 H, H-6$^{II}_a$), 4.01 (dd, J = 6.5, 11.3 Hz, 1 H, H-6$^{II}_b$), 3.82–3.73 (m, 3 H, H-6$^{I}_b$, H-4^{I}, H-5^{II}), 3.67 (m, 1 H, H-2^{I}), 3.57 (m, 1 H, H-5^{I}), 2.74 (m, 2 H, SCH_2), 2.12, 2.03, 1.95, 1.89 (4 s, 12 H, 4 $COCH_3$), 1.28 (t, J = 7.4 Hz, 3 H, SCH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3–169.6 (4 O*C*OCH$_3$), 161.5 (N*C*OCCl$_3$), 136.9 (ipso Ph), 129.3, 128.3, 126.1 (Ph), 101.3 (Ph*C*H), 99.3 (C-1^{II}), 92.3 (CCl_3), 83.1 (C-1^{I}), 78.7 (C-4^{I}), 77.1 (C-3^{I}), 70.9 (C-3^{II}), 70.7 (C-5^{I}), 70.6 (C-5^{II}), 68.8 (C-2^{II}), 68.5 (C-6^{I}), 66.8 (C-4^{II}), 61.3 (C-6^{II}), 57.5 (C-2^{I}), 24.9 (SCH_2), 20.7–20.5 (4 OCO*C*H$_3$), 15.1 (SCH_2CH_3).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{31}H_{38}Cl_3NO_{14}NaS$: 808.0971; found: 808.0971.

Anal. Calcd for $C_{31}H_{38}Cl_3NO_{14}S$: C, 47.31; H, 4.87; Cl, 13.51; N, 1.78; S, 4.07. Found: C, 47.23; H, 4.82; Cl, 13.66; N, 1.84; S, 3.88.

8-Azido-3,6-dioxaoctyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (7)

A mixture of thioglycoside **1**[7] (5 g, 10.1 mmol), 8-azido-3,6-dioxaoctan-1-ol[5] (**5**; 2.5 g, 14.1 mmol), and 4-Å MS (2.5 g) in anhydrous CH_2Cl_2 (40 mL) was stirred for 30 min under nitrogen. The mixture was cooled to –20 °C and NIS (3.4 g, 15.2 mmol) followed by powdered AgOTf (1.3 g, 5.1 mmol) were added with stirring. After 1 h, the mixture was treated with Et_3N (3.0 mL), filtered through Celite®, and the filtrate was concentrated. Chromatography (toluene–acetone, 19:1 → 6:1) gave the spacer-equipped monosaccharide **7**; yield: 5.9 g (95%).

$[\alpha]_D$ –11.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.01 (d, J = 8.9 Hz, 1 H, NH), 5.29 (dd, J = 9.3, 10.6 Hz, 1 H, H-3), 5.12 (t, J = 9.6 Hz, 1 H, H-4), 4.91 (d, $J_{1,2}$ = 8.5 Hz, 1 H, H-1), 4.29 (dd, J = 4.7, 12.3 Hz, 1 H, H-6$_b$), 4.16 (dd, J = 2.4, 12.3 Hz, 1 H, H-6$_a$), 4.03 (dt, $J_{1,2}$ = $J_{2,NH}$ ~8.5 Hz, $J_{2,3}$ = 10.6 Hz, 1 H, H-2), 3.91–3.84 (m, 2 H, H-1′), 3.78–3.62 (m, 9 H, H-2′, H-3′, H-4′, H-5′, H-5), 3.48 (t, J = 5.0 Hz, 2 H, H-6′), 2.10, 2.03, 2.02 (3 s, 9 H, 3 $COCH_3$).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.7–169.4 (3 O*C*OCH$_3$), 162.0 (N*C*OCCl$_3$), 100.9 (C-1), 92.4 (CCl_3), 72.2 (C-3), 72.0 (C-5), 71.2 (CH_2), 70.6, 70.3, 69.9 (3 CH_2), 68.4 (C-4), 68.3 (C-1′), 62.1 (C-6), 56.0 (C-2), 50.6 (C-6′), 20.8, 20.6, 20.5 (3 OCO*C*H$_3$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{20}H_{29}Cl_3N_4O_{11}Na$: 629.0791; found: 629.0791.

Anal. Calcd for $C_{20}H_{29}Cl_3N_4O_{11}$: C, 39.52; H, 4.81; N, 9.22. Found: C, 39.67; H, 4.88; N, 9.34.

8-Azido-3,6-dioxaoctyl 4,6-*O*-Benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (8)

Acetate **7** (11.37 g, 18.7 mmol) was treated with 1 M methanolic NaOMe (3.0 mL) in MeOH (300 mL) overnight. The mixture was neutralized with Amberlite IR-120, filtered, concentrated, and dried in vacuo to give the expected intermediate triol, which was used without further purification.

^{1}H NMR (600 MHz, acetone-d_6 + D_2O): δ = 4.72 (d, $J_{1,2}$ = 8.2 Hz, 1 H, H-1), 3.91–3.88 (m, 1 H, H-1′$_a$), 3.84 (dd, J = 2.5, 11.8 Hz, 1 H, H-6$_b$), 3.76–3.72 (m, 1 H, H-3), 3.70–3.57 (m, 11 H, H-1′$_b$, H-2′, H-3′, H-4′, H-5′, H-2, H-6$_a$), 3.41–3.38 (m, 3 H, H-4, H-6′), 3.33–3.30 (m, 1 H, H-5).

^{13}C NMR (150 MHz, acetone-d_6 + D_2O): δ = 162.7 (N*C*OCCl$_3$), 101.6 (C-1), 93.9 (CCl_3), 77.4 (C-5), 74.6 (C-3), 72.1 (C-4), 71.1, 71.0, 70.9, 70.5 (4 CH_2), 69.2 (C-1′), 62.4 (C-6), 58.6 (C-2), 51.2 (C-6′).

HRMS (ESI): m/z $[M + NH_4]^+$ calcd for $C_{14}H_{27}Cl_3N_5O_8$: 498.0925; found: 498.0932.

A solution of the foregoing triol in MeCN (150 mL) was treated with benzaldehyde dimethyl acetal (5.1 mL, 33.7 mmol) and CSA (82 mg) for 2 h at r.t. The reaction was quenched with Et_3N (5.0 mL) and concentrated. Chromatography ($CHCl_3$–acetone, 9:1 → 5:1) afforded **8**; yield: 9.9 g (93% over two steps).

$[\alpha]_D$ –35.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50–7.36 (m, 5 H, Ph), 7.24 (d, J = 7.2 Hz, 1 H, NH), 5.55 (s, 1 H, PhC*H*), 4.98 (d, $J_{1,2}$ = 8.4 Hz, 1 H, H-1), 4.35 (dd, J = 4.9, 10.5 Hz, 1 H, H-6$_b$), 4.24 (br ddd, J = 3.4, 9.1, 9.9 Hz, 1 H, H-3), 3.95–3.92 (m, 1 H, H-1′$_a$), 3.84–3.78 (m, 2 H, H-6$_a$, H-1′$_b$), 3.72–3.61 (m, 9 H, H-2′, H-3′, H-4′, H-5′, H-2), 3.57 (t, J = 9.2 Hz, 1 H, H-4), 3.53–3.49 (m, 1 H, H-5), 3.41 (t, J = 5.0 Hz, 2 H, H-6′), 3.09 (d, J = 3.4 Hz, 1 H, D_2O exchange, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.7 (N*C*OCCl$_3$), 136.9 (ipso Ph), 129.3, 128.3, 126.1 (Ph), 101.9 (Ph*C*H), 100.4 (C-1), 92.4 (CCl_3), 81.5 (C-4), 70.8, 70.6 (2 CH_2), 70.5 (C-3), 70.4, 70.0 (2 CH_2), 68.7 (C-1′), 68.5 (C-6), 66.2 (C-5), 59.3 (C-2), 50.6 (C-6′).

HRMS (ESI): m/z $[M + NH_4]^+$ calcd for $C_{21}H_{31}Cl_3N_5O_8$: 586.1238; found: 586.1241.

Anal. Calcd for $C_{21}H_{27}Cl_3N_4O_8$: C, 44.26; H, 4.78; N, 9.83. Found: C, 44.26; H, 4.68; N, 9.75.

8-Azido-3,6-dioxaoctyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-trichloroacetamido-β-D-glucopyranoside (6)

Pathway 1

A mixture of thioglycoside disaccharide **4** (787 mg, 1.0 mmol), 8-azido-3,6-dioxaoctan-1-ol[5] (**5**; 262 mg, 1.5 mmol), and 4-Å MS (0.5 g) in anhydrous CH_2Cl_2 (10 mL) was stirred for 30 min under nitrogen. The mixture was cooled to –15 °C and NIS (337 mg, 1.5 mmol) followed by powdered AgOTf (128 mg, 0.5 mmol) were added with stirring. After 1 h, the mixture was treated with Et_3N (1.0 mL), filtered through Celite®, and the filtrate was concentrated. Chromatography (hexane–acetone, 2:1) gave the spacer-equipped disaccharide **6**; yield: 751 mg (83%).

Mp 124.0–124.5 °C (*i*-PrOH).

$[\alpha]_D$ –15.1 (*c* 1.8, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50–7.37 (m, 5 H, Ph), 7.10 (d, J = 7.5 Hz, 1 H, NH), 5.55 (s, 1 H, PhC*H*), 5.31 (dd, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 0.6 Hz, 1 H, H-4^{II}), 5.19 (dd, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 10.4 Hz, 1 H, H-2^{II}), 5.12 (d, $J_{1,2}$ = 8.3 Hz, 1 H, H-1^{I}), 4.91 (dd, $J_{2,3}$ = 10.4 Hz,

$J_{3,4}$ = 3.5 Hz, 1 H, H-3^{II}), 4.74 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1^{II}), 4.55 (t, J = 9.6 Hz, 1 H, H-3^{I}), 4.35 (dd, J = 4.9, 10.5 Hz, 1 H, H-6$^{I}_{a}$), 4.11 (dd, J = 7.1, 11.2 Hz, 1 H, H-6$^{II}_{a}$), 3.98 (dd, J = 6.5, 11.2 Hz, 1 H, H-6$^{II}_{b}$), 3.95–3.92 (m, 1 H, H-1′$_{a}$), 3.83–3.77 (m, 2 H, H-6$^{I}_{b}$, H-1′$_{b}$), 3.74–3.70 (m, 2 H, H-4^{I}, H-5^{II}), 3.68–3.61 (m, 8 H, H-2′, H-3′, H-4′, H-5′), 3.55–3.50 (m, 2 H, H-2^{I}, H-5^{I}), 3.41 (t, J = 5.0 Hz, 2 H, H-6′), 2.11, 2.01, 1.95, 1.90 (4 s, 12 H, 4 $COCH_3$).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3–169.5 (4 O*C*OCH$_3$), 161.9 (N*C*OCCl$_3$), 136.9 (ipso Ph), 129.3, 128.3, 126.1 (Ph), 101.4 (Ph*C*H), 99.6 (C-1^{I}), 99.5 (C-1^{II}), 92.5 (CCl_3), 79.0 (C-4^{I}), 76.0 (C-3^{I}), 71.0 (C-3^{II}), 70.7 (2 C, 2 CH_2), 70.6 (C-5^{II}), 70.5 (CH_2), 70.0 (CH_2), 68.9 (C-2^{II}), 68.8 (C-1′), 68.6 (C-6^{I}), 66.8 (C-4^{II}), 66.2 (C-5^{I}), 61.2 (C-6^{II}), 58.7 (C-2^{I}), 50.6 (C-6′), 20.7–20.5 (4 OCO*C*H$_3$).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{45}Cl_3N_4O_{17}Na$: 921.1737; found: 921.1739.

Anal. Calcd for $C_{35}H_{45}Cl_3N_4O_{17}$: C, 46.70; H, 5.04; N, 6.22. Found: C, 46.88; H, 5.06; N, 6.21.

Pathway 2

A solution of acetobromo-α-D-galactose[13] (**3**; 1.4 g, 3.4 mmol) in anhydrous CH_2Cl_2 (8 mL) was added, at –30 °C in one portion, to a mixture of glycosyl acceptor **8** (1.1 g, 1.89 mmol), 1,1,3,3-tetramethylurea (520 μL, 4.37 mmol), and powdered AgOTf (971 mg, 3.78 mmol) in anhydrous CH_2Cl_2 (20 mL). The cooling was removed and, with continued stirring, the mixture was allowed to warm to r.t. (~1 h), when TLC (hexane–acetone, 3:2) indicated that all acceptor had been consumed. Et_3N (0.5 mL) was added, and the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a Celite® pad. The filtrate was washed successively with 0.5 M aq HCl (50 mL), aq $NaHCO_3$ (50 mL), and brine (50 mL), then dried. After concentration, chromatography (hexane–acetone, 2:1) gave the desired disaccharide **6**; yield: 1.53 g (90%).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(13) Freshly crystallized and thoroughly dried. Amorphous material or crystalline material that had been stored for a longer time may be partially hydrolyzed and contain a small amount of HBr. Introducing such material into the reaction mixture may, eventually, change the acidity of the reaction mixture, resulting in (partial) cleavage of the benzylidene group.

