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Interhalogens (ICl/IBr) and AgOTf in Thioglycoside Activation; Synthesis of Bislactam Analogues of Ganglioside GD3

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The novel promoter system IX/AgOTf (X = Cl or Br) has been evaluated in the synthesis of two bislactam analogues of GD3. We have carried out two high-yielding galactosylations in 97% and 98% yield, respectively, using ICl/AgOTf, and four sialylations in 93%, 59%, 40%, and 44% yield, using IBr/AgOTf. The choice of interhalogen (IX) is determined by the donor type used in the glycosylation. We also report some mechanistic investigations leading to further optimization of the IX/AgOTf promoter system.

Introduction

O-Glycosides are biologically significant as, for example, tumor-associated antigens and receptors for various bacterial and viral pathogens. Consequently, numerous methods of *O*-glycosylation have been developed,[1] of which thioglycoside methodology is one of the most versatile and widespread. In short, such methodology employs a thioglycoside donor that is activated in the presence of a thiophilic agent, generated by a promoter system. We have recently introduced interhalogens (i.e., ICl and IBr) in combination with silver trifluoromethanesulfonate as promoter systems for thioglycoside activation.[2,3] We showed that ICl/AgOTf works well for glycosylations with donors carrying a participating group next to the anomeric center, whereas IBr/AgOTf is superior for donors not carrying any participating group (e.g., sialic acid donors).

We now report the synthesis of two ganglioside bislactam analogues assembled using a combination of the two promoter systems, vide supra, and present IX/AgOTf as a general promoter system in oligosaccharide synthesis. We also report some mechanistic investigations leading to further optimization of the IX/AgOTf promoter system.

Gangliosides are considered to be potent tumor immunogens, and several ganglioside derivatives have been evaluated in various studies.[4] Because gangliosides are hydroxy-carboxylic acids, they form lactones on treatment with acids. Lactonization changes the overall three-dimensional shape of the ganglioside in a dramatic way. However, immunizations using lactonized gangliosides as antigen will result in antibodies of low specificity as a result of the hydrolytical instability of the lactone. Despite its instability, the corresponding lactone of a ganglioside has been used to immunize patients, and it was concluded that the lactonized form is a stronger immunogen than the open form.[5] The need for hydrolytically stable analogues of ganglioside lactones has led to the synthesis of lactam analogues.

The lactam functionality is more hydrolytically stable and the structural similarities of lactones and lactams have been shown using both computational methods and NMR investigations.[6,7] The monolactam analogues of GM2, GM3, GM4, and GD3 have been synthesized earlier,[8,9] and we now present a synthesis of bislactam analogues of GD3.

The naturally occurring GD3 can form several different lactones. The carboxylic acid functionality of the terminal sialic acid residue readily forms a 1-9 lactone,[6] whereas the carboxylic acid functionality of the nonterminal sialic acid residue is capable of forming both a 1-2 as well as a 1-4 lactone.[10] The two possible bislactam analogues chosen as target compounds were the 1″-2′,1‴-9″ bislactam **1** and 1″-4′,1‴-9″ bislactam **2** (Figure 1). A retrosynthetic analysis of the target compounds led us to a convergent block synthesis approach, where three building blocks, **3**, **4**, and **5**, are formed from monosaccharide fragments **6**,[11] **7**, **8**,[12] **9**, and **10**[12] (Figure 1). The stereoselective construction of the α(2-8) bis-sialo bond is notoriously difficult, and several strategies have emerged.[9,13] The most recent application exchanges the acetamido functionality of the sialic acid donor and acceptor for a

(1) Davies, B. G. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *14*, 2137.
(2) Ercegovic, T.; Meijer, A.; Ellervik, U.; Magnusson, G. *Org. Lett.* **2001**, *3*, 913.
(3) Meijer, A.; Ellervik, U. *J. Org. Chem.* **2002**, *67*, 7407.
(4) Bitton, R. J.; Guthmann, M. D.; Gabri, M. R.; Carnero, A. J. L.; Alonso, D. F.; Fainboim, L.; Gomez, D. E. *Oncol. Rep.* **2002**, *9*, 267.
(5) Ragupathi, G.; Meyers, M.; Adluri, S.; Howard, L.; Musselli, C.; Livingston, P. O. *Int. J. Cancer* **2000**, *85*, 659.
(6) Ercegovic, T.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 179.
(7) Ray, A. K.; Nilsson, U.; Magnusson, G. *J. Am. Chem. Soc.* **1992**, *114*, 2256.
(8) Wilstermann, M.; Kononov, L. O.; Nilsson, U.; Ray, A. K.; Magnusson, G. *J. Am. Chem. Soc.* **1995**, *117*, 4742.
(9) Hossain, N.; Zapata, A.; Wilstermann, M.; Nilsson, U. J.; Magnusson, G. *Carbohydr. Res.* **2002**, *337*, 569.
(10) Ellervik, U.; Grundberg. H.; Magnusson, G. *J. Org. Chem.* **1998**, *63*, 9323.
(11) Komba, S.; Yamaguchi, M.; Ishida, H.; Kiso, M. *Biol. Chem.* **2001**, *382*, 233.
(12) Ellervik, U.; Magnusson, G. *J. Org. Chem.* **1998**, *63*, 9314.
(13) Castro-Palomino, J. C.; Simon, B.; Speer, O.; Leist, M.; Schmidt, R. R. *Chem. Eur. J.* **2001**, *7*, 2178.

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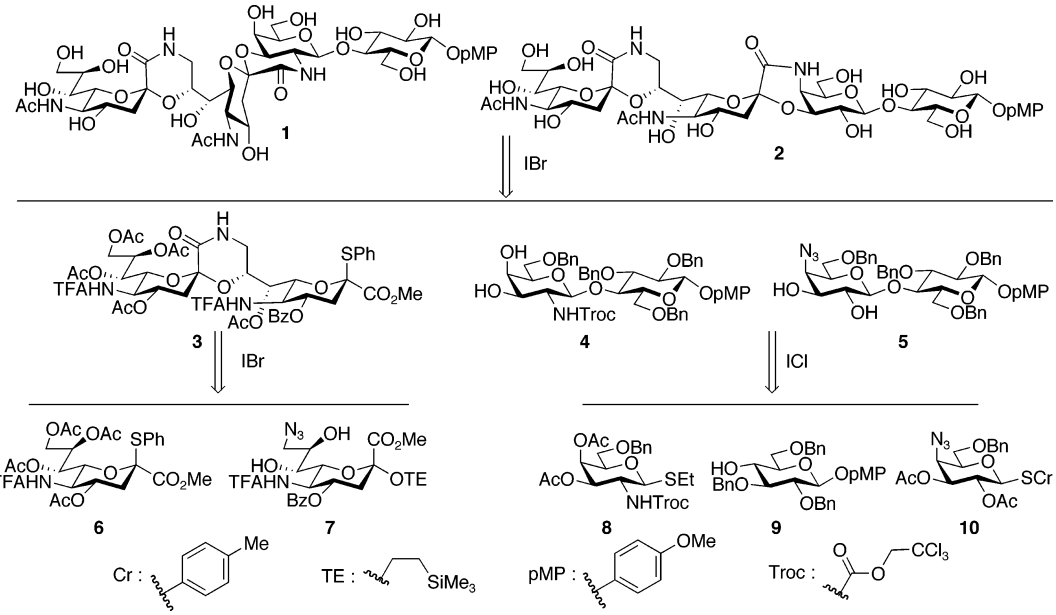
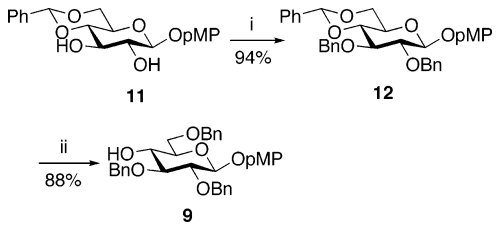


FIGURE 1. Retrosynthetic analysis of the synthesis of GD3 bislactam analogues using the IX/AgOTf promoter system.

SCHEME 1[a]



[a] Reaction conditions: (i) BnBr, NaH, DMF; (ii) $NaBH_3CN$, HCl, THF.

trifluoroacetamido group, which will ensure a stereoselective formation of the α(2-8) bond in high yields.[14] The TFA groups are removed at the end of the synthesis using mild conditions, and we therefore used this procedure.

Results and Discussion

Glucose acceptor **9** was synthesized by benzylation, using standard reaction conditions, followed by regioselective opening of the benzylidene acetal of the known compound **11**[15] (Scheme 1).

The first attempts to construct the 2′-deoxy-2′-aminolactose building block by glycosylation of acceptor **9** with Troc donor **8** under standard reaction conditions[1] gave only low yields (approximate 50%). After careful purification of the reaction products, a dehydroimidazole compound **15** was isolated in various yields, approximately 40% (Figure 2). Apparently the activated donor reacted with the solvent, thus trapping the intermediate *β*-nitrilium ion by an attack of the carbamate nitrogen, forming the dehydroimidazole **15**. When acetonitrile was left out, and the reaction was performed in neat dichloromethane, the yield rose to an excellent 97% (Scheme 2).[16]

Disaccharide **13** was then de-O-acetylated using a guanidinium nitrate buffer[17] to give acceptor **4** in 75% yield. The 4′-deoxy-4′-amino-lactose building block was constructed by glycosylation of acceptor **9** with the azide donor **10** in an excellent 98% yield, using ICl/AgOTf in neat dichloromethane. The disaccharide **14** was de-O-acetylated using NaOMe in MeOH to give acceptor **5** in 90% yield.

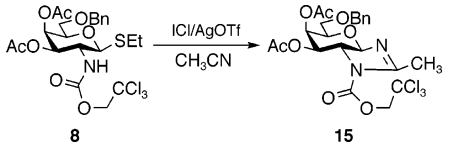
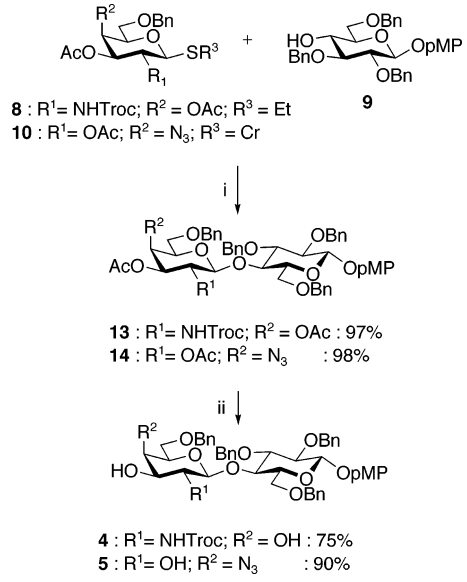


FIGURE 2. Formation of dehydroimidazole byproduct by reaction with acetonitrile.

SCHEME 2[a]



[a] Reaction conditions: (i) 1.5 equiv of donor, ICl/AgOTf, CH_2Cl_2, −45 °C; (ii) **13**: guanidinium nitrate/NaOMe/MeOH, **14**: NaOMe/MeOH.

(14) De Meo, C.; Demchenko, A.; Boons, G. J. *J. Org. Chem.* **2001**, *66*, 5490.
(15) Nitz, M.; Bundle, D. *J. Org. Chem.* **2000**, *65*, 3064.

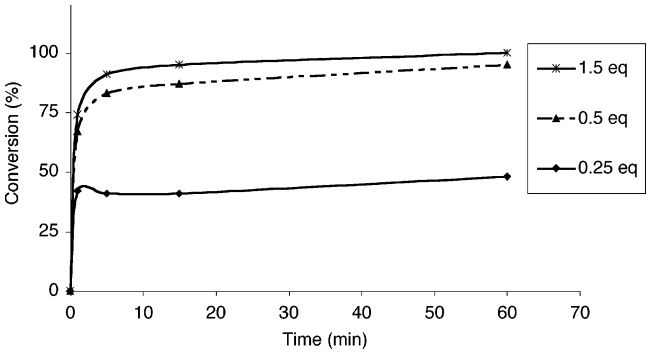


FIGURE 3. Graph illustrating the substoichiometric need of iodine monochloride in the glycosylation reaction between **8** and **9**.

During the investigations leading to the interhalogen promoter systems we have been able to isolate disulfides of the corresponding donor aglycons in the reaction mixtures.[3] This indicates that an electrophilic sulfur species is present in the reaction mixture.[18] We postulate that the species responsible are the sulfenyl iodides formed from the reaction between the iodonium ion (from IX/AgOTf) and the thio donor.[19] Thus, the role of the sulfur leaving group is not only to be reactive enough to be activated by the thiophilic species but also to form a "second" thiophilic species in the reaction mixture.

To investigate these thiophilic species, we performed the high yielding glycosylation of acceptor **9** and donor **8** (Scheme 2) using substoichiometric amounts of ICl, together with unimolecular amounts of acceptor, donor, and AgOTf. Several small-scale reactions were run and then quenched with diisopropylamine and cyclohexene at various time intervals, after which the conversion of donor into product was determined by NMR, using the *p*MP group as an internal standard.

A graph was constructed illustrating the substoichometric need of ICl for complete conversion of donor **8** into product **13** (Figure 3). Apparently only 0.5 equiv of ICl are necessary for complete activation, and 0.25 equiv of ICl result in almost 50% conversion. These results indicate that 1 equiv of ICl together with 2 equiv of AgOTf can activate 2 equiv of donor.

We suggest that interhalogens and silver triflate activate thioglycosides according to the mechanistic scheme found in Figure 4. The interhalogen forms an activated complex, depicted as an iodonium ion in Figure 4, with the silver ion, which then reacts with a thioglycoside **A** forming an activated complex **B**. This reactive complex then collapses into an oxocarbenium ion **C**, which can react with an acceptor to form product, and a sulfenyl iodide compound. The latter can be activated by a second silver ion, forming a reactive sulfonium ion species, which can activate a second thioglycoside **A**, forming the reactive intermediate **D**. This reactive complex collapses into an oxocarbenium ion **C** and a disulfide. Because of the lesser reactivity of the sulfonium species compared to that of the iodonium species, there will be an accumulation of sulfenyl iodide when equimolar amounts of interhalogen is used. The lower reactivity of the sulfonium ion has consequences for unreactive donors. When performing sialylations using donor **6** (Scheme 3) a substoichiometric amount of IBr failed to activate all donor.[20] The more reactive galactosyl donors **8** and **9** were both activated by 0.5 equiv of ICl.[21]

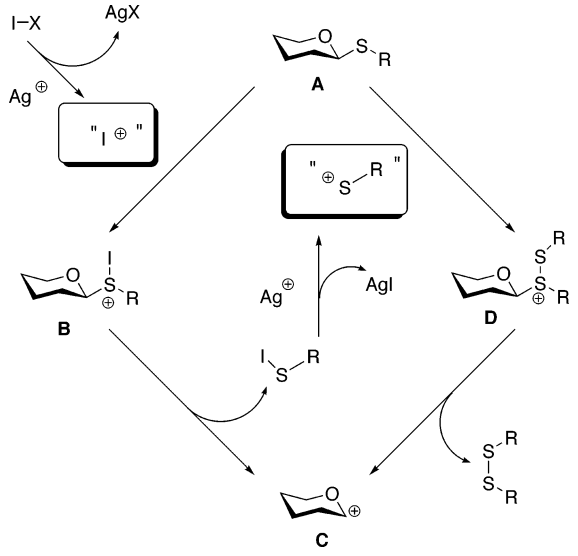
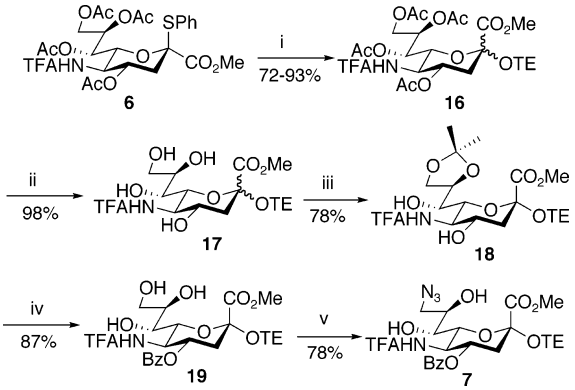


FIGURE 4. Proposed mechanistic scheme describing the reaction pathway of an IX/AgOTf-promoted thioglycoside activation.

SCHEME 3[a]



[a] Reaction conditions: (i) $Me_3Si(CH_2)_2OH$, IBr/AgOTf, CH_3CN, −40 °C, 1 h; (ii) NaOMe/MeOH; (iii) acetone, 2,2-dimethoxypropane, *p*TSA, 30 min; (iv) (a) pyridine, BzCl, 0 °C, 30 min, (b) HOAc, MeOH, reflux 2 h; (v) (a) TsCl, CH_2Cl_2, pyridine, 16 h, (b) NaN_3, DMF, 60 °C, 20 h.

The mechanistic scheme in Figure 4 explains the presence of disulfides in the reaction mixture, as well as the substoichiometric need of interhalogen for complete activation. A similar reaction pathway has recently been

(16) Because AgOTf is poorly soluble in dichloromethane it was anticipated that the reaction would form large amounts of galactosyl chloride, which is formed when the reaction is run in the absence of AgOTf; however, no chloride derivatives were found.

(17) Ellervik, U.; Magnusson, G. *Tetrahedron Lett.* **1997**, *38*, 1627.

(18) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702.

(19) Veeneman, G. H.; Van Leuwen, S. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.

(20) The low reactivity of donor **6** is due to the electron-withdrawing trifluoroacetyl group (TFA) on the C-5 nitrogen.

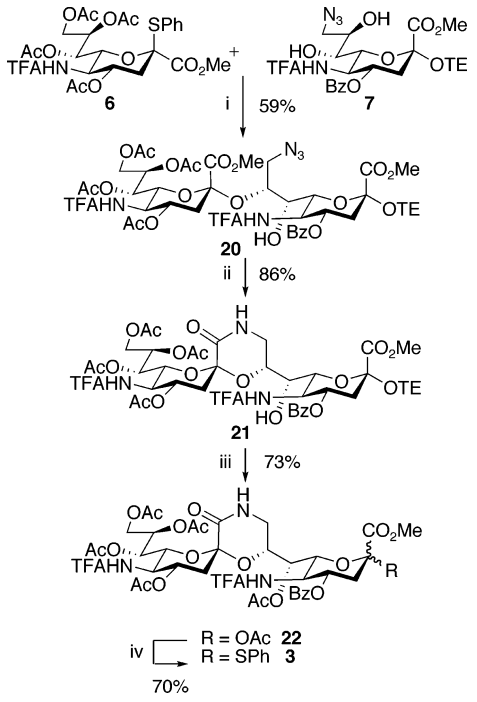
(21) For a compilation of the reactivity of thioglycosides, see: (a) Zhang, Z.; Ollmann, I. R.; Ye, X.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734. (b) Yu, C. S.; Niikura, K.; Lin, C. C.: Wong, C. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2900.

reported by Wong, where a substoichometric amount of promoter was used to activate thioglycosides using both a BSP/Tf_2O promoter protocol[22] and a modified NIS-TfOH-AgOTf[23] system, indicating the generality of the reaction pathway in Figure 4.

In the synthesis of the bis-sialic acid fragment we used the TFA methodology,[14] where a TFA-protected amide functionality will ensure high stereoselectivity and yield in the formation of the notoriously difficult α(2-8) bis-sialic acid bond. A temporary anomeric protecting group was introduced, using an improved procedure with IBr and AgOTf as promoter system, to give an inseparable mixture (α:*β* 88:12) of compound **16**[14] (Scheme 3).[24] Compound **16** was then de-O-acetylated using standard procedures to give compound **17**,[14] which was used without purification in the next step. The introduction of the azide functionality at the 9-position was more problematic than anticipated. Ercégovic[5] has previously been able to selectively tosylate the 9-hydroxyl of the acetamide analogue of compound **17** in an excellent yield of 91%. When the same reaction was performed on tetraol **17**, the reaction was too slow to be of practical value. The selectivity was also poor; the 4-hydroxyl and 9-hydroxyl seemed to be equally reactive, resulting in a reaction mixture consisting of unreacted **17** together with the products of mono- and bistosylation of the 4- and 9-hydroxyl groups. Increasing the reaction temperature and changing the solvent improved the reactivity and selectivity somewhat, but not enough to make the procedure a viable route to **7**.

Because the 4- and 9-hydroxyl groups are almost equally reactive, we decided to use an acetal to selectively protect the 9-hydroxyl.[14,25] Compound **17** was treated with 2,2-dimethoxypropane in acetone under acidic conditions to give the isopropylidene-protected sialoside. At this point the diastereomeric mixture obtained when introducing the anomeric protective group could be separated to give **18** as a pure α-anomer in excellent 78% yield. The 4-hydroxyl group was then selectively benzoylated using 1.2 equiv of benzoyl chloride in pyridine at 0 °C, and then the isopropylidene acetal was removed by refluxing in methanol and acetic acid to give compound **19** in 87% yield. The 7-hydroxyl group was deliberately left unprotected because it has been shown that acetate groups at the C-7 position are prone to migrate to the C-8 position under azide substitution conditions.[6] It was also shown that the 7-hydroxyl group is of such low reactivity that the 7,8-diol will selectively be sialylated at the 8-hydroxyl. With the reactive 4-hydroxyl group protected as a benzoate, the selective tosylation proceeded in high yield even with 5 equiv of tosyl chloride in dichloromethane and pyridine at room temperature for 16 h. The crude tosylation mixture was subjected to sodium azide in DMF to give acceptor **7** in 78% yield.

SCHEME 4[a]



[a] Reaction conditions: (i) 3 equiv of donor, IBr/AgOTf, CH_2Cl_2, CH_3CN, −72 °C; (ii) Ph_3P, THF, H_2O; (iii) (a) TFA, CH_2Cl_2, (b) pyridine, Ac_2O; (iv) PhSH, CH_2Cl_2, $BF_3{\cdot}OEt_2$.

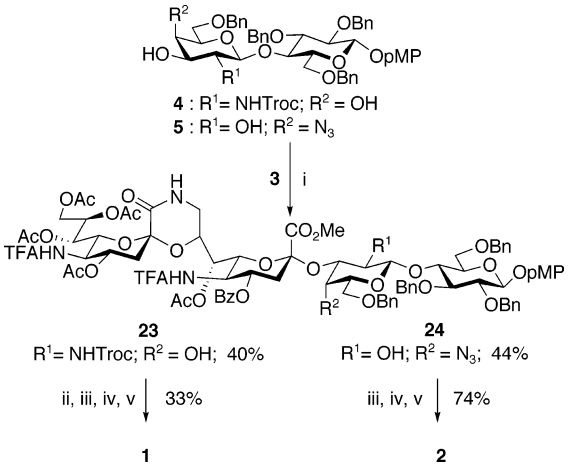
Acceptor **7** was then sialylated with 3 equiv of donor **6**, using IBr and AgOTf as promoter system, to form disialoside **20** in an excellent yield of 59%, as a single diastereomer (Scheme 4). The high yield and excellent stereoselectivity are attributed to the TFA groups of both the donor and the acceptor. Compound **20** was subjected to triphenylphosphine in THF and water at 60 °C to form lactam **21** in 86% yield.

The anomeric protective group of lactam **21** was then converted to thioglycoside **3**[26] (α:*β* 84:16) via the acetate **22**.

Sialylation of Troc acceptor **4** with donor **3** gave tetrasaccharide **23** in a yield of 40% as a single diastereomer (Scheme 5). Sialylation of azide acceptor **5** with donor **3** gave tetrasaccharide **24** in a slightly higher yield of 44% as a single diastereomer. The benzyl groups of tetrasaccharide **24** were removed by hydrogenolysis using Pd/C. The azide group was at the same time reduced to the free amine, which spontaneously formed the lactam according to MALDI-TOF mass analysis. The *N*-TFA groups were transformed into *N*-acetates, and the ester groups were deprotected by treatment with NaOMe at 50 °C[27] followed by acetylation to give bislactam **2** in 74% yield. The Troc-protected tetrasaccharide **23** was sonicated with activated zinc to give the free amine,[28] which lactamized upon addition of triethylamine according to NMR and MALDI-TOF analysis. The bislactam intermediate was then deprotected by hydrogenolysis, basic solvolysis, and acetylation using same procedures as

(22) Mong, T. K. K.; Lee, H. K.; Duron, S. G.; Wong, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 797.
(23) Zhang, Z.; Niikura, K.; Huang, X. F.; Wong, C. H. *Can. J. Chem.* **2002**, *80*, 1051.
(24) The yield of compound **16** is lowered when the reaction is performed at larger scale. The upscaling problems of this reaction are related to the acid lability of sialoside **16**. Apparently the molecular sieves are crucial for the neutralization of formed acid. However, due to the heterogeneous nature of the molecular sieves, the neutralization is sensitive to the stirring efficiency.
(25) von Itzstein, M.; Thomson, R. J. *Top. Curr. Chem.* **1997**, *186*, 119.
(26) The anomeric mixture could be separated using flash cromatography, but since the two diastereomers showed equal reactivity, the anomeric mixture was used in the following sialylation reactions.
(27) Otsubo, N.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **2001**, *330*, 1.
(28) Zhu, X.; Schmidt, R. R. *Synthesis* **2003**, 1262.

SCHEME 5[a]



[a] Reaction conditions: (i) 1 equiv of donor, IBr/AgOTf, CH_2Cl_2, CH_3CN, −72 °C; (ii) Zn, HOAc; (iii) H_2, Pd/C; (iv) NaOMe/MeOH, 50 °C; (v) Ac_2O/MeOH/H_2O.

above to give bislactam **1** in 33% yield. Surprisingly, the acetylation leading to compound **1** took 4 days compared to the acetylation leading to compound **2**, which took less than 2 h.[29] One reason for this large difference in reaction time might be that the tetrasaccharide is folding so that the free amine is hidden within the molecule.

Conclusions

We have for the first time been able to synthesize two GD3 bislactam analogues using a novel interhalogen promoter system strategy where the choice of either ICl or IBr is determined by the donor structure. We have carried out two high-yielding galactosylations in 97% and 98% yield, respectively, using ICl/AgOTf and four sialylations in 93%, 59%, 40%, and 44% yield using IBr/AgOTf.

Experimental Section

4-Methoxyphenyl (3,5-Dideoxy-5-acetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-[(9-amino-3,5,9-trideoxy-5-acetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)onate]-(2→3)-(2-amino-2-deoxy-*β*-D-galactopyranosyl)-(1→4)-*β*-D-glucopyranoside (1‴ -9″)-(1″-2′)-bislactam (1). Compound **23** (21 mg, 0.0106 mmol) was dissolved in HOAc (1.0 mL), and freshly activated Zn[10] (200 mg) was added. The mixture was sonicated for 1 h, filtered on Celite, and concentrated. The residue was dissolved in dichloromethane (2 mL) and triethylamine (0.5 mL) and concentrated. The residue was filtered on silica (heptane/EtOAc 1:1) to give the bislactam according to MALDI-TOF and NMR analysis. The bislactam was dissolved in MeOH (1.5 mL), and Pd/C (60 mg) was added. The reaction mixture was pressurized (1000 psi) with hydrogen gas for 1.5 h, filtered on Celite, and concentrated. The residue was dissolved in MeOH (2 mL), and NaOMe/MeOH (0.4 mL, 1 M) was added dropwise. The reaction mixture was heated in a sealed vessel at 50 °C for 64 h and then neutralized with Amberlite IR 120 H^+. After filtration and concentration the residue was dissolved in a mixture of MeOH/H_2O/Ac_2O (2.8:0.8:0.6 mL), stirred for 4 days, and then concentrated with toluene. The residue was purified first on a Sephadex (LH-20, MeOH/CH_2Cl_2 1:1) column and after concentration on a C-18 plug (H_2O/MeCN gradient) to give bislactam **1** (3.5 mg, 33%). $[\alpha]^{22}_D$ −19° (*c* 0.3, MeOH). ^{1}H NMR (MeOD) δ 6.98−6.90 (m, 2H), 6.76−6.70 (m, 2H), 4.73 (d, 1H, J = 7.8), 4.55 (d, 1H, J = 8.0), 4.37−4.24 (m, 2H), 4.01−3.88 (m, 3H), 3.83 (d, 1H, J = 1.0), 3.77−3.30 (m, 20H), 3.65 (s, 3H), 2.47 (dd, 1H, J = 5.4, 13.0), 2.37 (dd, 1H, J = 5.3, 13.0), 1.92, 1.91 (s, 3H each), 1.56−1.39 (m, 2H). ^{13}C NMR (MeOD) δ 174.4, 167.8, 151.8, 118.2, 114.2, 102.0, 98.1, 97.4, 80.9, 78.4, 76.6, 74.2, 73.7, 73.2, 72.3, 71.5, 71.0, 70.6, 68.8, 68.1, 66.0, 64.1, 62.2, 61.2, 54.8, 53.2, 52.4, 50.3, 42.1, 40.5, 21.5, 21.4. HRMS calcd for $C_{41}H_{60}N_4O_{24}Na$ (M + Na) 1015.3495, found 1015.3493.

4-Methoxyphenyl (3,5-Dideoxy-5-acetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-[(9-amino-3,5,9-trideoxy-5-acetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)onate]-(2→3)-(4-amino-4-deoxy-*β*-D-galactopyranosyl)-(1→4)-*β*-D-glucopyranoside (1‴ -9″)-(1″- 4′)-bislactam (2). Compound **24** (10 mg, 0.0055 mmol) was dissolved in MeOH (0.7 mL), and Pd/C (30 mg) was added. The mixture was pressurized (1000 psi) with hydrogen gas for 4 h. The residue was filtered on Celite and concentrated to give the bislactam intermediate according to MALDI-TOF. The mixture was dissolved in MeOH (2 mL), and NaOMe (1 M, 0.1 mL) was added dropwise. The mixture was heated at 50 °C in a sealed vessel for 48 h and then neutralized with Amberlite IR 120 H+. After filtration and concentration the residue was dissolved in a mixture of MeOH/H_2O/Ac_2O (2.8:0.8:0.6 mL), stirred for 2 h, and then concentrated with toluene. The residue was purified first on a Sephadex column (LH-20, MeOH/CH_2Cl_2 1:1) and after concentration on a C-18 column (H_2O/MeCN gradient) to give bislactam **2** (4 mg, 74%). $[\alpha]^{21}$ −28° (*c* 0.1, MeOH). ^{1}H NMR (MeOD) δ 7.05−7.00 (m, 2H), 6.85−6.80 (m, 2H), 4.80 (d, 1H, J = 7.8), 4.46 (d, 1H, J = 7.9), 4.24−4.13 (m, 2H), 4.31 (dd, 1H, J = 1.0, 4.8), 3.86−3.77 (m, 2H), 3.69 (d, 2H, J = 2.9), 3.65 (d, 2H, J = 3.5), 3.62−3.20 (m, 17H), 3.54 (s, 3H), 2.32 (dd, 1H, J = 5.5, 12.8), 2.26 (dd, 1H, J = 5.3, 12.8), 1.81 (s, 6H), 1,46 (t, 1H, J = 11.2), 1.29 (t, 1H, J = 11.4). ^{13}C NMR (MeOD) δ 173.8, 173.5, 154.8, 151.1, 117.3, 113.5, 101.3, 96.8, 96.7, 78.0, 74.6, 74.3, 72.8, 72.6, 71.5, 70.6, 70.5, 69.7, 69.4, 67.6, 66.9, 63.3, 61.6, 54.1, 52.3, 51.8, 50.2, 39.6, 39.5, 20.7, 20.6. HRMS calcd for $C_{41}H_{60}N_4O_{24}Na$ (M + Na) 1015.3495, found 1015.3495.

Methyl [(4,7,8,9-Tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-(phenyl 7-*O*-acetyl-9-amino-4-*O*-benzoyl-3,5,9-trideoxy-2-thio-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)]onate 1′-9 Lactam (3α) and Methyl [(4,7,8,9-Tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-(phenyl 7-*O*-acetyl-9-amino-4-*O*-benzoyl-3,5,9-trideoxy-2-thio-5-trifluoroacetamido-D-*glycero*-*β*-D-*galacto*-non-2-ulopyranoside)]onate 1′-9 Lactam (3*β*). Compound **22** (420 mg, 0.396 mmol) was dissolved in CH_2Cl_2 (7 mL), and then PhSH (0.12 mL, 1.2 mmol) and BF_3·OEt_2 (0.160 mL, 1.2 mmol) were added. After 18 h the reaction mixture was diluted with CH_2Cl_2 and extracted twice with saturated aqueous $NaHCO_3$ and once with water. The organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed (SiO_2, 4:1 → 1:1 toluene/acetone gradient) to give compound **3** (307 mg, 70%) as an anomeric mixture (84:16). The anomers could be separated (SiO_2, 1:1 → 1:3 toluene/EtOAc gradient). **Data for 3*β*:** $[\alpha]^{21}_D$ −34° (*c* 1.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.96−8.02 (m, 3H), 7.74−7.78 (m, 2H), 7.57−7.63 (m, 1H), 7.42−7.50 (m, 3H), 7.33−7.41 (m, 3H), 6.72−6.78 (bs, 1H), 5.67 (dt, 1H, J = 4.4, 11.2), 5.59−5.65 (m, 1H), 5.44 (dt, 1H, J = 4.8, 11.4), 5.35 (dd, 1H, J = 2.5, 9.0), 5.31 (dd, 1H, J = 2.1, 7.8), 5.19 (dd, 1H, J = 2.4, 10.6), 4.76 (dd, 1H, J = 2.1, 10.6), 4.37−4.47 (m, 2H), 4.33 (dd, 1H, J = 2.6, 12.5), 4.10−4.25 (m, 2H), 3.53 (s, 3H), 3.47−3.52 (m, 1H), 3.37−3.46 (m, 1H), 3.13 (dd, 1H, J = 4.6, 13.5), 2.49 (dd, 1H, J = 4.9, 13.1), 2.32 (dd, 1H, J = 11.7, 13.4), 2.21, 2.15, 2.08, 2.03, 1.69 (s, 3H each), 2.10−

(29) A MALDI-TOF analysis of the acetylation leading to **1** showed that one of the two amines was acetylated instantly while the second required 4 days of reaction time.

2.00 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 172.2, 171.3, 171.1, 171.0, 170.2, 169.4, 167.8 (C-1, $J_{C1-H-3ax} = 2.3$),[30] 166.3, 136.9, 133.9, 130.3, 130.2, 129.4, 129.1, 128.9, 96.5, 90.7, 73.6, 71.2, 70.4, 70.24, 70.20, 69.3, 68.6, 67.7, 63.0, 52.9, 50.7, 49.9, 41.2, 40.0, 39.5, 21.3, 21.2, 21.1, 21.0, 20.3. HRMS calcd for $C_{46}H_{49}F_6N_3O_{20}$-SNa (M + Na) 1132.2432, found 1132.2423. **Data for 3α:** $[\alpha]^{21}_D$ +3° (*c* 0.9, $CDCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.84−7.89 (m, 2H), 7.43−7.52 (m, 4H), 7.30−7.38 (m, 3H), 7.23−7.29 (m, 2H), 7.01−7.10 (m, 1H), 6.76−6.84 (bs, 1H), 5.30−5.40 (m, 2H), 5.13−5.25 (m, 2H), 5.01 (d, 1H, *J* = 8.7), 4.40 (dd, 1H, *J* = 3.0, 10.2), 4.35 (dd, 1H, *J* = 2.4, 12.5), 4.27 (dt, 1H, *J* = 3.7, 8.9), 4.06−4.20 (m, 4H), 3.67 (s, 3H), 3.43−3.50 (m, 1H), 3.25−3.35 (m, 1H), 3.03 (dd, 1H, *J* = 4.7, 12.8), 2.24 (dd, 1H, *J* = 5.2, 13.3), 2.15, 2.04, 2.02, 1.96, 1.90 (s, 3H each), 2.05−2.00 (m, 1H), 1.75 (t, 1H, *J* = 12.5). ^{13}C NMR ($CDCl_3$) δ 171.7, 171.5, 170.9, 170.6, 170.4, 168.3, 168.2, 166.4, 158.5, 158.1, 137.0, 134.0, 130.6, 130.2, 129.3, 129.2, 128.9, 97.5, 87.7, 73.7, 73.1, 71.2, 71.0, 70.5, 70.0, 69.6, 68.8, 62.9, 53.4, 50.4, 49.9, 41.8, 38.5, 38.2, 21.4, 21.2, 21.1, 21.03, 20.98. HRMS calcd for $C_{46}H_{49}F_6N_3O_{20}$SNa (M + Na) 1132.2432, found 1132.2437.

4-Methoxyphenyl (6-*O*-Benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (4). Compound **13** (300 mg) was dissolved in 16 mL of guanidine solution[31] at room temperature. After 20 min the reaction was neutralized with Amberlyst IR-120-H^+ and concentrated. Column purification (SiO_2, 3:1 → 1:1 heptane/EtOAc gradient) gave **4** (207 mg, 75%). $[\alpha]^{21}_D$ −2° (*c* 1.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.22−7.45 (m, 20H), 6.99−7.04 (m, 2H), 6.84−6.90 (m, 2H), 5.32−5.41 (bs, 1H), 5.00, 4.83 (ABq, 1H each, *J* = 11.2), 5.00, 4.82 (ABq, 1H each, *J* = 10.9), 4.86−4.90 (m, 1H), 4.77 (s, 2H), 4.74, 4.59 (ABq, 1H each, *J* = 12.0), 4.43, 4.36 (ABq, 1H each, *J* = 12.0), 4.38 (d, 1H, *J* = 8.0), 3.90−4.01 (m, 2H), 3.80−3.85 (m, 1H), 3.83 (s, 3H), 3.35−3.75 (m, 10H), 2.65 (d, 1H, *J* = 3.5). ^{13}C NMR ($CDCl_3$) δ 155.8, 151.8, 139.6, 138.7, 129.4, 129.2, 128.9, 128.8, 128.6, 128.2, 128.12, 128.07, 128.0, 127.7, 118.9, 115.0, 103.2, 101.0, 95.4, 83.0, 82.1, 75.7, 75.5, 75.2, 74.4, 74.3, 74.0, 73.5, 69.5, 69.1, 68.5, 56.6, 56.1. HRMS calcd for $C_{50}H_{54}Cl_3$-$NO_{13}Na$ (M + Na) 1004.2559, found 1004.2539.

4-Methoxyphenyl 2,3,6-Tri-*O*-benzyl-4-*O*-(6-*O*-benzyl-4-deoxy-4-azido-*β*-D-galactopyranosyl)-*β*-D-glucopyranoside (5). Compound **14** (100 mg, 0.109 mmol) was dissolved in methanol (8.5 mL), and NaOMe/MeOH (0.17 mL, 1 M) was added to the stirred mixture. After 15 min the reaction was neutralized with Amberlite IR-120-H^+. The mixture was filtered and concentrated, and the residue was chromatographed (SiO_2, 2:1 → 1:3 heptane/EtOAc gradient) to give compound **5** (82 mg, 90%). $[\alpha]^{21}$ −15° (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.42−7.29 (m, 20H), 7.08−7.03 (m, 2H), 6.90−6.85 (m, 2H), 5.04, 4.84 (ABq, 1H each, *J* = 10.9), 5.00−4.89 (m, 3H), 4.75, 4.63 (ABq, 1H each, *J* = 12.0), 4.59 (d, 1H, *J* = 7.42), 4.41 (s, 3H), 4.12−4.06 (m, 1H), 4.04−3.98 (m, 1H), 3.96 (d, 1H, *J* = 2.8), 3.86−3.81 (m, 1H), 3.83 (s, 3H), 3.78−3.71 (m, 2H), 3.70−3.63 (m, 1H), 3.62−3.44 (m, 3H), 3.32 (dd, 1H, *J* = 4.7, 8.3), 2.78−2.71 (m, 1H), 1.76−1.66 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 155.9, 151.8, 139.3, 138.5, 138.1, 137.7, 128.9, 128.9, 128.9, 128.69, 128.67, 128.5, 128.4, 128.29, 128.26, 127.8, 127.5, 119.1, 115.0, 103.9, 103.5, 84.0, 82.4, 75.6, 75.5, 74.8, 74.3, 73.9, 73.7, 73.3, 72.6, 68.9, 68.4, 61.6, 56.1. HRMS calcd for $C_{47}H_{51}N_3O_{11}Na$ (M + Na) 856.3421, found 856.3422.

Methyl [2-(Trimethylsilyl)ethyl 9-Azido-4-*O*-benzoyl-3,5,9-trideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (7). Compound **19** (580 mg, 0.992 mmol) was dissolved in CH_2Cl_2 (40 mL) and pyridine (2.5 mL). *p*TsCl (927 mg, 4.862 mmol) was added to the stirred solution at room temperature. After 16 h an excess of MeOH (2 mL) was added. The reaction mixture was concentrated with toluene and filtered on a short plug of silica (4:1 toluene/acetone) to give the crude tosylate intermediate, which was dissolved in DMF (6 mL). To the stirred solution were added NaN_3 (350 mg, 5.385 mmol) and 18-crown-6 (150 mg, 0.567 mmol). The solution was heated to 60 °C for 20 h, filtered on a short plug of silica (4:1 toluene/acetone), and concentrated. The residue was chromatographed (SiO_2, 6:1 → 4:1 toluene/acetone gradient) to give **7** (472 mg, 78%). Lyophilization from benzene gave **7** as a white powder. $[\alpha]^{25}_D$ −36° (*c* 1.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.03−7.98 (m, 2H), 7.59−7.65 (m, 1H), 7.44−7.50 (m, 2H), 7.36 (d, 1H, *J* = 7.9), 5.19−5.28 (m, 1H), 4.15−4.24 (m, 1H), 4.04−4.11 (m, 1H), 3.85−3.95 (m, 1H), 3.82 (d, 1H, *J* = 4.0), 3.79 (s, 3H), 3.73−3.79 (m, 1H), 3.67 (d, 1H, *J* = 5.8), 3.64 (dd, 1H, *J* = 2.2, 12.9), 3.36−3.55 (m, 3H), 2.87 (dd, 1H, *J* = 4.9, 13.0), 2.18 (t, 1H, *J* = 12.7), 0.88 (t, 2H, *J* = 7.8), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 169.8, 160.1, 159.8, 134.7, 130.4, 129.2, 98.9, 73.4, 71.0, 69.9, 69.8, 62.9, 54.0, 53.9, 52.6, 37.9, 18.3, −0.9. HRMS calcd for $C_{24}H_{33}F_3N_4O_9SiNa$ (M + Na) 629.1867, found 629.1876.

4-Methoxyphenyl 2,3,6-Tri-*O*-benzyl-*β*-D-glucopyranoside (9). To a slurry of compound **12** (2.95 g, 5.3 mmol) in THF (75 mL) at 0 °C were added molecular sieves (6 g, 3Å, activated) and $NaBH_3CN$ (4.65 g). An ice-cold saturated solution of HCl in Et_2O was slowly added until the pH reached 2. After 2 h the reaction mixture was filtered (Celite) and rinsed with CH_2Cl_2. The filtrate was washed with saturated aqueous $NaHCO_3$, water, and brine and then concentrated. The residue was chromatographed (SiO_2, 3:1 → 1:1 heptane/EtOAc gradient) to give compound **9** (2.60 g, 88%). $[\alpha]^{23}_D$ −15° (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.10−7.30 (m, 15H), 7.01−7.07 (m, 2H), 6.80−6.86 (m, 2H), 5.07, 4.84 (ABq, 1H each, *J* = 11.0), 4.98, 4.77 (ABq, 1H each, *J* = 11.4), 4.93 (d, 1H, *J* = 7.8), 4.62, 4.58 (ABq, 2H, *J* = 12.0, 14.9), 3.84 (dd, 1H, *J* = 3.7, 10.4), 3.80 (s, 3H), 3.65−3.77 (m, 3H), 3.51−3.61 (m, 2H), 2.54 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 155.8, 151.9, 139.0, 138.6, 138.4, 129.0, 128.9, 128.83, 128.77, 128.7, 128.4, 128.3, 128.2, 128.13, 128.09, 118.8, 115.0, 103.3, 84.5, 82.0, 75.8, 75.4, 74.8, 74.1, 71.8, 70.6, 56.1. HRMS calcd for $C_{34}H_{36}O_7Na$ (M + Na) 579.2359, found 579.2352.

4-Methoxyphenyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside (12). Compound **11** (1.96 g, 5.2 mmol) was dissolved in DMF (50 mL). NaH (1.8 g, 75 mmol) was added, followed by benzyl bromide (3.0 mL, 25 mmol). After 18 h the remaining NaH was quenched by addition of MeOH. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was chromatographed (SiO_2, 4:1 → 2:1 heptane/EtOAc gradient) to give compound **12** (2.72 g, 94%). $[\alpha]^{24}_D$ ±0° (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.45−7.54 (m, 2H), 7.28−7.41 (m, 13H), 6.99−7.03 (m, 2H), 6.83−6.86 (m, 2H), 5.60 (s, 1H), 5.01 (d, 1H, *J* = 7.5), 4.99, 4.86 (ABq, 1H each, *J* = 10.8), 4.95, 4.83 (ABq, 1H each, *J* = 11.4), 4.38 (dd, 1H, *J* = 5.0, 10.5), 3.69−3.86 (m, 4H), 3.79 (s, 3H), 3.45−3.55 (m, 1H).^{13}C NMR ($CDCl_3$) δ 156.0, 151.6, 138.9, 138.6, 137.7, 129.4, 128.81, 128.76, 128.7, 128.6, 128.5, 128.2, 128.1, 126.5, 119.0, 115.1, 103.7, 101.6, 82.3, 81.8, 81.3, 76.0, 75.6, 69.2, 66.6, 56.1. HRMS calcd for $C_{34}H_{34}O_7Na$ (M + Na) 577.2203, found 577.2200.

4-Methoxyphenyl (3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (13). To compound **8** (80 mg, 0.135 mmol), compound **9** (50 mg, 0.090 mmol), AgOTf (35 mg, 0.137 mmol), and molecular sieves (60 mg, 3Å, activated) was added CH_2Cl_2 (2.5 mL). The reaction mixture was cooled to −45 °C under Ar. ICl (0.068 mL, 1 M in CH_2Cl_2) was added dropwise. After 60 min the reaction was quenched by the addition of diisopropylamine (0.1 mL). The cold reaction mixture was filtered (SiO_2, 5:1 → 2:1 cyklohexane/EtOAc gradient) and concentrated to give compound **13** (95 mg, 97%). $[\alpha]^{21}_D$ −29° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.19−7.55 (m, 20H), 6.90−6.96 (m, 2H), 6.73−6.79 (m, 2H), 5.30, (d, 1H, *J* = 3.0), 4.90, 4.76 (ABq, 1H each, *J* = 10.9), 4.90, 4.68 (ABq, 1H each, *J* = 10.8), 4.78 (d, 1H, *J* = 7.4), 4.76, 4.30

(30) Hori, H.; Nakajima, T.; Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317.

(31) A clear stock solution of the guanidium solution was prepared by dissolving guanidinium nitrate (622 mg, 5 mmol) in MeOH/CH_2-$C1_2$ (50 mL, 9:1) and adding methanolic MeONa (1 mL, 1 M).

(ABq, 1H each, $J = 12.0$), 4.64, 4.59 (ABq, 2H, $J = 12.1, 16.0$), 4.55 (dd, 1H, $J = 3.0, 11.2$), 4.37, 4.11 (ABq, 1H each, $J = 12.0$), 4.24 (d, 1H, $J = 8.3$), 3.84−3.96 (m, 2H), 3.72 (s, 3H), 3.65−3.72 (m, 2H), 3.47−3.62 (m, 4H), 3.34 (d, 1H, $J = 9.7$), 3.09−3.23 (m, 2H), 1.92 (s, 3H), 1.90 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.70, 169.66, 154.9, 153.7, 151.1, 138.7, 138.0, 137.3, 137.0, 129.0, 128.7, 128.4, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.24, 127.20, 126.9, 118.1, 114.1, 102.5, 100.3, 82.2, 81.1, 75.0, 74.7, 74.1, 73.9, 73.4, 73.0, 71.2, 70.12 67.0, 66.3, 66.2, 55.3, 52.4, 20.2. HRMS calcd for $C_{54}H_{58}Cl_3NO_{15}Na$ (M + Na) 1088.2770, found 1088.2771.

4-Methoxyphenyl (3,4-Di-*O*-acetyl-4-azido-6-*O*-benzyl-4-deoxy-*β*-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (14). To compound **10** (65 mg, 0.135 mmol), compound **9** (50 mg, 0.090 mmol), AgOTf (35 mg, 0.137 mmol), and molecular sieves (60 mg, 3Å, activated) was added CH_2Cl_2 (2.5 mL). The reaction mixture was cooled to −45 °C under Ar. ICl (0.068 mL, 1 M in CH_2Cl_2) was added dropwise. After 60 min the reaction was quenched by the addition of diisopropylamine (0.10 mL). The cold reaction mixture was filtered on a short plug of silica (1:0 → 1:1 toluene/acetone gradient) followed by purification on sephadex LH-20. Some of the fractions of **14** were contaminated, but additional purification of these fractions on a short silica plug (1:1 toluene/EtOAc) gave pure compound **14**. Combination of all fractions gave pure **14** (80 mg, 98%). $[\alpha]^{21}_D$ −23° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.29−7.44 (m, 20H), 7.03−7.08 (m, 2H), 6.82−6.89 (m, 2H), 5.22 (dd, 1H, $J = 7.9, 10.2$), 5.03, 4.86 (ABq, 1H each, $J = 10.9$), 4.97 (dd, 1H, $J = 3.8, 10.2$), 4.95, 4.84 (ABq, 1H each, $J = 10.7$), 4.88 (d, 1H, $J = 7.6$), 4.76, 4.53 (ABq, 1H each, $J = 12.0$), 4.59 (d, 1H, $J = 7.9$), 4.45, 4.38 (ABq, 1H each, $J = 11.8$), 4.10 (d, 1H, $J = 3.0$), 3.99 (t, 1H, $J = 8.7$), 3.83 (s, 3H), 3.73−3.80 (m, 2H), 3.60−3.72 (m, 2H), 3.35−3.55 (m, 4H), 2.16 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.5, 169.6, 155.8, 151.9, 139.3, 138.8, 138.3, 138.1, 128.92, 128.91, 128.8, 128.6, 128.5, 128.34, 128.27, 128.26, 128.1, 127.8, 118.9, 115.0, 103.2, 100.8, 83.0, 82.0, 75.9, 75.6, 75.3, 74.0, 73.9, 73.3, 71.9, 70.5, 68.2, 67.8, 60.6, 56.1, 21.2, 21.0. HRMS calcd for $C_{51}H_{55}N_3O_{13}Na$ (M + Na) 940.3633, found 940.3636.

3,4-Di-*O*-acetyl-6-*O*-benzyl-1,2-dideoxy-1,2-*N*-[-3-(2,2,2-trichloroethoxycarbonyl)-acetamidine]-*β*-D-galactopyranose (15). Byproduct isolated in the glycosylation reaction of thioglycoside **8** and acceptor **9**. $[\alpha]^{24}_D$ −17° (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.27−7.37 (m, 5H), 5.70 (dd, 1H, $J = 1.7, 7.2$), 5.44 (d, 1H, $J = 3.3$), 5.12 (dd, 1H, $J = 3.3, 8.2$), 4.95, 4.68 (ABq, 1H each, $J = 12.0$), 4.57, 4.46 (ABq, 1H each, $J = 12.0$), 4.42 (dd, 1H, $J = 8.0, 7.4$), 4.12 (t, 1H, $J = 6.6$), 3.61 (dd, 1H, $J = 5.4, 9.5$), 3.39 (dd, 1H, $J = 7.3, 9.5$), 2.45 (d, 3H, $J = 1.9$), 2.10, 2.05 (s, 3H each). ^{13}C NMR ($CDCl_3$) δ 170.4, 170.1, 149.4, 137.5, 128.4, 127.9, 127.8, 94.4, 92.6, 75.5, 73.5, 71.4, 69.8, 67.6, 65.9, 58.2, 20.9, 20.7, 18.8. HRMS calcd for $C_{22}H_{26}Cl_3N_2O_8$ (M + H) 551.0754, found 551.0763.

Methyl [2-(Trimethylsilyl)ethyl 4,7,9-Tri-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-D-*galacto*-2-nonulopyranosid]onate (16). To compound **6** (500 mg, 0.784 mmol), powdered molecular sieves (650 mg, 3Å, activated) and AgOTf (300 mg, 1.176 mmol) was added MeCN (20 mL). The mixture was cooled to −40 °C under Ar and vigorous stirring. After 30 min trimethylsilylethanol (0.225 mL, 1.568 mmol) was added, followed by dropwise addition of IBr (0.865 mL, 1 M in CH_2Cl_2, 0.865 mmol). After 1 h the reaction was quenched by the addition of an excess of diisopropylamine (0.5 mL). The cold reaction mixture was filtered on a short plug of silica and concentrated. The residue was chromatographed (SiO_2, 4:1 → 1:1 heptane/EtOAc gradient) to give **16** (492 mg, 86%, α:*β* 88:12). The reaction is sensitive to upscaling, probably as a result of the acid sensitivity of the TMSEt group. When performed on a 5 g scale the yield dropped to 72% and when scaled down to 0.1 g the yield rose to 93%. Because no base is present the neutralization of the formed triflic acid is conducted by the molecular sieves, which action is dependent on the stirring efficiency. Compound identical to the one reported by Boons.[14]

Methyl [2-(Trimethylsilyl)ethyl 3,5-Dideoxy-5-trifluoroacetamido-D-*glycero*-D-*galacto*-2-nonulopyranosid]onate (17). To compound **16** (3.70 g, 5.73 mmol) was added MeOH (130 mL) and NaOMe/MeOH (29 mL, 1 M). After 1 h the reaction mixture was neutralized by addition of Amberlyst 1R-120-H^+, which was filtered off, and the reaction mixture was concentrated. Lyophilization from water gave **17** (2.63 g, 98%), which was used without further purification.

Methyl [2-(Trimethylsilyl)ethyl 3,5-Dideoxy-8,9-isopropylidene-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (18). Compound **17** (1.00 g, 2.09 mmol) was dissolved in acetone (30 mL) and stirred at room temperature. 2,2-Dimethoxypropane (2.95 mL, 24 mmol) together with a catalytic amount of *p*TSA (20 mg) were added. After 30 min the reaction was quenched by the addition of pyridine (1 mL) and concentrated with toluene. The residue was chromatographed (SiO_2, 6:1 → 1:4 toluene/EtOAc gradient) to give **18** (785 mg, 78%). $[\alpha]^{25}_D$ +7° (*c* 1.0, $CHCl_3$). ^{1}H NMR (CD_3OD) δ 4.20 (q, 1H, $J = 6.2, 12.3$), 3.84−4.07 (m, 4H), 3.78 (s, 3H), 3.74 (dd, 1H, $J = 1.1, 10.6$), 3.61−3.69 (m, 1H), 3.56 (d, 1H, $J = 5.8$), 3.46 (q, 1H, $J = 8.5, 16.9$), 2.62 (dd, 1H, $J = 4.7, 12.7$), 1.69 (t, 1H, $J = 12.6$), 1.33 (d, 6H, $J = 6.4$), 0.85 (t, 2H, $J = 8.2$), −0.01 (s, 9H). ^{13}C NMR (CD_3OD) δ 170.0, 108.6, 99.3, 76.7, 73.2, 68.9, 67.0, 65.9, 61.7, 52.8, 51.6, 40.6, 25.8, 24.6, 17.7, −2.5. HRMS calcd for $C_{20}H_{34}F_3NO_9SiNa$ (M + Na) 540.1853, found 540.1847

Methyl[2-(Trimethylsilyl)ethyl4-*O*-Benzoyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (19). Compound **18** (468 mg, 0.904 mmol) was dissolved in pyridine (7 mL) and cooled to 0 °C, after which benzoyl chloride (0.126 mL 1.085 mmol) was added dropwise. After 30 min an excess of MeOH was added, and the reaction mixture was concentrated with toluene. The residue was dissolved in AcOH/MeOH (14 mL, 4:1) and refluxed for 2 h, after which the mixture was concentrated with toluene. The residue was chromatographed (SiO_2, 6:1 → 1:2 heptane/acetone gradient) to give **19** (460 mg, 87%). $[\alpha]^{25}_D$ −14° (*c* 1.0, $CHCl_3$). ^{1}H NMR (CD_3OD) δ 7.75−7.79 (m, 2H), 7.38−7.43 (m, 1H), 7.23−7.29 (m, 2H), 4.98−5.06 (m, 1H), 4.25 (t, 1H, $J = 10.5$), 3.89 (dd, 1H, $J = 1.6, 10.6$), 3.73−3.81 (m, 1H), 3.70 (s, 3H), 3.61−3.69 (m, 2H), 3.46 (dd, 1H, $J = 5.9, 11.7$), 3.27−3.36 (m, 2H), 2.68, (dd, 1H, $J = 4.9, 12.5$), 1.76 (t, 1H, $J = 12.2$), 0.64−0.72 (m, 2H), −0.19 (s, 9H). ^{13}C NMR (CD_3OD) δ 169.4, 165.9, 133.4, 129.5, 128.4, 98.9, 72.4, 71.5, 70.5, 68.7, 63.4, 61.9, 52.2, 49.7, 37.6, 17.7, −2.5. HRMS calcd for $C_{24}H_{34}F_3NO_{10}SiNa$ (M + Na) 604.1802, found 604.1819.

Methyl [(Methyl 4,7,8,9-Tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-(2→8)-(2-(trimethylsilyl)ethyl 9-Azido-4-*O*-benzoyl-3,5,9-trideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)]onate (20). To a mixture of **6** (315 mg, 0.494 mmol), **7** (100 mg, 0.165 mmol), molecular sieves (415 mg, 3Å, activated), and AgOTf (170 mg, 0.664 mmol) was added CH_2Cl_2 (3.3 mL). The reaction mixture was stirred and cooled to −78 °C under Ar, and MeCN (3.3 mL) was added. After 45 min IBr (0.500 mL, 1 M in CH_2Cl_2, 0.5 mmol) was added dropwise. After an additional 120 min the reaction was quenched by addition of diisopropylamine (0.250 mL). The cold reaction mixture was filtered on silica (1:0 → 1:2 toluene/acetone gradient) and concentrated. The residue was purified on sephadex LH-20 to give compund **20** (110 mg, 59%) as a white powder. $[\alpha]^{25}_D$ +5° (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.95−8.01 (m, 2H), 7.57−7.63 (m, 2H), 7.43−7.54 (m, 3H), 6.44 (d, 1H, $J = 9.3$), 5.45−5.51 (m, 1H), 5.22−5.33 (m, 2H), 5.09−5.17 (m, 1H), 5.62−5.67 (m, 1H), 4.24−4.35 (m, 2H), 4.16 (dd, 1H, $J = 1.7, 10.8$), 4.06 (dd, 1H, $J = 1.1, 10.4$), 3.95 (q, 1H, $J = 10.2$), 3.88 (s, 3H), 3.82−3.88 (m, 1H), 3.78 (s, 3H), 3.74−3.79 (m, 1H), 3.65−3.70 (m, 1H), 3.58 (dd, 1H, $J = 7.8, 13.4$), 3.41−3.51 (m, 1H), 3.05 (d, 1H, $J = 7.0$), 2.77−2.88 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.03−2.14 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 0.89−0.95 (m, 2H), 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 171.68, 171.66, 171.5, 171.3, 170.6, 169.2(C-1,

$J_{C1-H-3ax}$ = 6.0),[30] 168.8(C-1, $J_{C1-H-3ax}$ = 6.0),[30] 167.0, 134.1, 130.2, 129.3, 129.0, 99.3, 97.9, 75.8, 73.9, 71.9, 69.7, 69.3, 69.0, 68.4, 67.2, 63.0, 62.7, 53.6, 51.9, 51.7, 50.9, 38.5, 38.1, 21.5, 21.1, 21.0, 20.9, 18.5, −1.0. HRMS calcd for $C_{44}H_{57}F_6N_5O_{21}$-SiNa (M + Na) 1156.3118, found 1156.3124.

Methyl [(4,7,8,9-Tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-(2-(trimethylsilyl)ethyl 9-Amino-4-*O*-benzoyl-3,5,9-trideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)]onate 1′-9 Lactam (21). Compound **20** (385 mg, 0.340 mmol) was dissolved in THF (26 mL) and water (6 mL), followed by addition of Ph_3P (280 mg, 1.07 mmol). The stirred reaction mixture was then heated to 60 °C in a sealed vessel for 48 h. The reaction mixture was then concentrated and chromatographed (SiO_2, 3:1 → 1:1 toluene/acetone gradient), followed by additional purification on sephadex LH-20 to give **21** (332 mg, 86%) as a white foam. $[\alpha]^{24}_D$ −21° (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.98−8.03 (m, 2H), 7.95 (d, 1H, *J* = 10.1), 7.57−7.63 (m, 1H), 7.50−7.61 (m, 1H), 7.42−7.48 (m, 2H), 7.16 (d, 1H, *J* = 7.1), 5.41−5.52 (m, 3H), 5.04−5.10 (m, 1H), 4.60 (dd, 1H, *J* = 1.6, 12.5), 4.42 (dd, 1H, *J* = 2.8, 10.4), 4.20−4.33 (m, 2H), 4.10−4.18 (m, 2H), 4.06 (dd, 1H, *J* = 8.5, 12.5), 3.40−3.86 (m, 1H), 3.84 (s, 3H), 3.62−3.71 (m, 1H), 3.50−3.59 (m, 3H), 3.47 (d, 1H, *J* = 7.2), 2.86 (dd, 1H, *J* = 4.9, 12.8), 2.58 (dd, 1H, *J* = 5.4, 12.9), 2.14 (s, 3H), 2.04−2.11 (m, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H), 1.72−1.80 (m, 1H), 0.86−0.92 (m, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 172.4, 171.4, 170.7, 170.4, 168.7, 168.1, 167.5, 134.3, 130.3, 129.2, 129.0, 99.4, 98.2, 73.9, 73.4, 72.1, 71.8, 71.1, 70.9, 69.4, 69.3, 63.4, 62.8, 53.2, 52.6, 49.2, 42.1, 38.2, 37.7, 21.6, 21.1, 21.0, 20.9, 18.5, −0.9. HRMS calcd for $C_{43}H_{55}F_6N_3O_{20}SiNa$ (M + Na) 1098.2950, found 1098.2961.

Methyl [(4,7,8,9-Tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-(2,7-di-*O*-acetyl-9-amino-4-*O*-benzoyl-3,5,9-trideoxy-5-trifluoroacetamido-D-*glycero*-α/*β*-D-*galacto*-non-2-ulopyranose)]onate 1′-9 Lactam (22). Compound **21** (332 mg, 0.309 mmol) was dissolved in CH_2Cl_2 (25 mL), and then TfOH (5 mL) was added to the stirred mixture. After 2 h pyridine (10 mL) was added slowly to the ice-cooled mixture, followed by addition of Ac_2O (10 mL). The reaction mixture was stirred at room temperature for 15 h and then quenched by addition of MeOH (10 mL). The reaction mixture was concentrated with toluene. The crude reaction mixture was dissolved in CH_2Cl_2, extracted twice with saturated aqueous $NaHCO_3$ and once with water, dried (Na_2SO_4), and concentrated. The residue was purified on sephadex LH-20, concentrated, and chromatographed (SiO_2, 5:1 → 3:1 toluene/acetone gradient). The residue was dissolved in ethyl acetate (50 mL) and stirred with activated charcoal (3 g). The mixture was filtered (Celite) and concentrated to give compound **22** (240 mg, 73%) as an inseparable anomeric mixture (82:18), which was used in the next step without separation.

4-Methoxyphenyl (4,7,8,9-Tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-[methyl(7-*O*-acetyl-9-amino-4-*O*-benzoyl-3,5,9-trideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)onate]-(2→3)-[6-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-*β*-D-galactopyranosyl]-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-gluco-pyranoside 1‴ -9″ Lactam (23). To a mixture of compound **3** (100 mg, 0.090 mmol), **4** (90 mg, 0.090 mmol), AgOTf (30 mg, 0.117 mmol), and molecular sieves (120 mg, 3Å, activated) were added CH_2Cl_2 (0.090 mL) and MeCN (0.090 mL) at −72 °C under Ar. The mixture was stirred for 30 min, and then IBr (0.090 mL, 1 M solution in CH_2Cl_2, 0.090 mmol) was added dropwise. After 2.5 h the reaction was quenched by addition of an excess of diisopropylamine (0.1 mL) and $Na_2S_2O_3$ (50 mg). The reaction mixture was concentrated and filtered on silica (4:1 → 1:2 heptane/acetone gradient). The residue was purified on sephadex LH-20 and then chromatographed (SiO_2, 1:1 → 1:3 heptane/EtOAc gradient) to give **23** (72 mg, 40%). $[\alpha]^{22}_D$ +17° (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.32 (d, 1H, *J* = 9.9), 8.03 (d, 2H, *J* = 7.5), 7.52−7.65 (m, 2H), 7.41−7.45 (m, 8H), 7.25−7.37 (m, 13H), 7.17 (d, 1H, *J* = 10.0), 7.00−7.06 (m, 2H), 6.82−6.88 (m, 2H), 6.50−6.58 (bs, 1H), 5.66 (dt, 1H, *J* = 5.3, 10.7), 5.50−5.57 (m, 1H), 5.30−5.39 (m, 1H), 5.33 (dd, 1H, *J* = 2.3, 9.1), 5.11 (dd, 1H, *J* = 1.5, 9.5), 5.03, 4.84 (ABq, 1H each, *J* = 11.0), 5.02, 4.84 (ABq, 1H each, *J* = 10.9), 4.97 (dd, 1H, *J* = 1.5, 10.9), 4.87−4.91 (m, 1H), 4.80, 4.49 (ABq, 1H each, *J* = 12.1), 4.61−4.72 (m, 2H), 4.39−4.54 (m, 3H), 4.45, 4.34 (ABq, 1H each, *J* = 11.8), 4.01−4.32 (m, 8H), 4.00 (s, 3H), 3.82 (s, 3H), 3.67−3.80 (m, 5H), 3.44−3.55 (m, 3H), 3.09−3.18 (m, 1H), 2.91−3.00 (m, 1H), 2.85−2.90 (bs, 1H), 2.82 (dd, 1H, *J* = 5.1, 13.0), 2.30 (dd, 1H, *J* = 4.6, 13.2), 2.15, 2.13, 2.10, 2.07, 2.05 (s, 3H each), 1.89−1.99 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 172.2, 171.4, 170.7, 169.8, 169.7, 167.8(C-1, $J_{C1-H-3ax}$ = 5.4),[30] 166.0, 155.8, 154.5, 151.9, 139.6, 138.9, 138.7, 138.5, 134.0, 130.1, 129.4, 129.3, 129.1, 128.8, 128.7, 128.7, 128.6, 128.2, 128.11, 128.05, 127.8, 127.7, 118.9, 117.4, 115.0, 103.2, 100.3, 95.8, 95.6, 83.3, 82.1, 75.8, 75.6, 75.0, 73.9, 73.8, 73.7, 72.9, 72.2, 70.3, 69.2, 69.0, 68.8, 68.6, 68.5, 67.5, 62.8, 56.1, 54.3, 53.6, 50.4, 50.1, 40.6, 21.2, 21.00, 20.96, 14.6. HRMS calcd for $C_{90}H_{97}$-$Cl_3F_6N_4O_{33}Na$ (M + Na) 2003.4903, found 2003.4877.

4-Methoxyphenyl (4,7,8,9-Tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)-(2→8)-[methyl(7-*O*-acetyl-9-amino-4-*O*-benzoyl-3,5,9-trideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)onate]-(2→3)-(4-azido-6-*O*-benzyl-4-deoxy-*β*-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside 1‴ -9″ Lactam (24). To a mixture of compound **3** (80 mg, 0.072 mmol), **5** (65 mg, 0.072 mmol), AgOTf (24 mg, 0.094 mmol), and molecular sieves (96 mg, 3Å, activated) were added CH_2Cl_2 (0.72 mL) and MeCN (0.72 mL) at −72 °C under Ar. The mixture was stirred for 30 min, and then IBr (0.090 mL, 1 M solution in CH_2Cl_2, 0.090 mmol) was added dropwise. After 2.5 h the reaction was quenched by addition of an excess of diisopropylamine (0.1 mL) and $Na_2S_2O_3$ (50 mg). The cold reaction mixture was filtered on silica (1:0 → 1:2 toluene/acetone gradient). The residue was purified on sephadex LH-20 and then chromatographed (SiO_2, 1:1 heptane/EtOAc) to give **24** (58 mg, 44%). $[\alpha]^{22}_D$ +20° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.02−7.97 (m, 2H), 7.89 (d, 1H, *J* = 9.9), 7.62−7.56 (m, 1H), 7.49−7.42 (m, 2H), 7.40−7.22 (m, 20H), 7.19−7.13 (m, 1H), 7.05−6.99 (m, 2H),6.85−6.80 (m, 2H), 6.64−6.57 (m, 1H), 5.53 (td, 1H, *J* = 5.0, 10.8), 5.44 (td, 1H, *J* = 2.5, 7.1), 5.40−5.32 (m, 2H), 5.04−4.99 (m, 1H), 5.01, 4.79 (ABq, 1H each, *J* = 10.8), 4.93 (s, 2H), 4.90−4.85 (m, 1H), 4.77 (dd, 1H, *J* = 2.8, 10.4), 4.68, 4.54 (ABq, 1H each, *J* = 11.6), 4.60 (d, 1H, *J* = 7.6), 4.47 (dd, 1H, *J* = 1.6, 10.7), 4.38−4.26 (m, 5H), 4.24−4.14 (m, 2H), 4.11−3.94 (m, 5H), 3.95 (s, 3H), 3.89−3.84 (m, 1H), 3.79 (s, 3H), 3.74−3.50 (m, 6H), 3.42−3.35 (m, 1H), 3.24 (dd, 1H, *J* = 4.8, 8.6), 3.11−2.95 (m, 1H), 2.88 (dd, 1H, *J* = 5.0, 13.5), 2.36 (dd, 1H, *J* = 4.8, 13.3), 2.27−2.19 (m, 1H), 2.11 (s, 3H), 2.06 (s, 3H), 2.04 (s, 6H), 1.97 (s, 3H), 1.96−1.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 172.0, 171.5, 171.2, 170.5, 170.1, 169.2, 168.1 (C-1, $J_{C1-H-3ax}$ = 6.1),[30] 166.3, 155.8, 151.8, 139.5, 138.5, 138.4, 138.0, 134.0, 130.2, 129.4, 129.0, 128.83, 128.75, 128.67, 128.61, 128.39, 128.35, 128.25, 128.1, 127.7, 127.6, 118.9, 115.0, 104.3, 103.4, 100.0, 96.3, 83.8, 82.3, 75.6, 75.5, 75.1, 74.2, 73.8, 73.6, 72.1, 71.8, 71.2, 70.3, 70.1, 70.0, 69.5, 68.4, 62.9, 62.6, 56.1, 53.5, 50.4, 50.0, 41.2, 39.6, 36.9, 30.1, 21.2, 21.01, 20.97. HRMS calcd for $C_{87}H_{94}F_6N_6O_{31}Na$ (M + Na) 1855.5765, found 1855.5756.

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Supporting Information Available: General experimental conditions and NMR spectra of compounds **1**−**5**, **7**, **9**, **12**−**15**, **18**−**21**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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