Synthesis of a New Class of N-Linked Lewis and LacNAc Analogues as Potential Inhibitors of Human Fucosyltransferases: A General Method for the Incorporation of an Iminocyclitol as a Transition-State Mimetic of the Donor Sugar to the Acceptor

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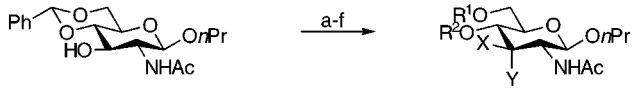
A short and effective synthesis of N-linked di- and trisaccharides is described. In a high-yielding reaction sequence, the glucosamine derivative **1** was transformed to the 3-azido-2,3-dideoxy sugar **2e** under excellent stereocontrol. The LacNAc analogue **4d** was synthesized as a single isomer in three steps starting from **2e**. In a one-pot procedure, iminocyclitol **5** was transformed into aldehyde **6** and successfully used for reductive amination with **4c** and **2f** to give trisaccharide **8a** and disaccharide **7a**, respectively. This procedure represents a general strategy for the incorporation of an iminocyclitol as a transition-state mimic of the donor sugar moiety to the acceptor.

Many complex oligosaccharides on the cell surface are fucosylated.[1] These fucose containing structures are involved in cell−cell interactions, which mediate inflammation, tumor development, and blood clotting.[2] The biosynthesis of these structures requires the action of several glycosyltransferases, of which fucosylation by a class of fucosyltransferases (FucT) is the last and critical step.[3] Inhibitors of FucT are therefore potentially useful as antiinflammatory and antitumor agents. To date, only limited success has been achieved in the development of potent inhibitors of this important class of enzymes. In addition to unreactive analogues of GDP-fucose,[4] a bisubstrate inhibitor of α-1,2-fucosyltransferase has been reported.[5] Very recently, we and others have synthesized trisubstrate analogues of α-1,3-fucosyltransferase (FucT V).[6,7a] Although FucT V has been shown to have a catalytic residue with pK_a = 4.1, presumably an active site carboxylate, it has never been considered in the design of inhibitors until recently.[8] Product inhibition studies with human α-1,3-fucosyltransferase have been used to establish that FucT V has an ordered, sequential, bi−bi mechanism with guanosine 5′-diphospho-*β*-1-fucose (GDP-Fuc) binding first and the product releasing last.[7] Our approach to the construction of fucosyltransferase inhibitors is to mimic the proposed transition state of the sugar moiety by covalently linking an iminocyclitol to the 3-position of the acceptor substrate. It is expected that the trisaccharide analogue would form a charged complex with GDP and provide synergistic inhibition and that a basic two-carbon spacer could block the catalytic base residue and improve the inhibition by additional hydrogen bonding[9] (Figure 1). Here, we report the chemoenzymatic synthesis of this type of inhibitor, as illustrated in the synthesis of a new class of Lewis and LacNAc analogues as potential inhibitors of fucosyltransferases.

Scheme 1[a]



1 **2**

2a	X= OMs	Y= H	$R^1 = R^2$ = benzylidene
2b	X= H	Y= OH	$R^1 = R^2$ = benzylidene
2c	X= H	Y= OMs	$R^1 = R^2$ = benzylidene
2d	X= H	Y= OMs	R^1 = Bn, R^2 = H
2e	X= N_3	Y= H	R^1 = Bn, R^2 = H
2f	X= NH_2	Y= H	R^1 = H, R^2 = H

[a] Key: (a) MsCl/pyridine, 0 °C, 24 h, 68%; (b) NaOAc, 2-methoxyethanol/H_2O (95:5), reflux, 48 h, 80%; (c) MsCl/pyridine, 0 °C to room temperature, 24 h, 90%; (d) $NaCNBH_3$, HCl/Et_2O, rt, 6 h, 70%; (e) NaN_3/DMF, 80 °C, 2 h, 93%; (f) HOAc/H_2O, (1:1), $Pd(OH)_2$/C-20%, Degussa-type, 24 h, rt, 1 atm, H_2, quant.

Results and Discussion

Initially, it appeared that oxidation of alcohol **1** (Scheme 1) to the corresponding ketone followed by reductive

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(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97−130. (b) Hakomori, S. *Adv. Cancer Res.* **1989**, *52*, 257. (c) Hakomori, S.; Nudelman, E.; Levery, S. B. *J. Biol. Chem.* **1984**, *259*, 4672. (d) Feizi, T. *Nature* **1985**, *314*, 53.

(2) (a) Ichikawa, Y.; Halcomb, R.; Wong, C.-H. *Chem. Br.* **1994**, 117. (b) Parekh, R. B.; Edge, C. J. *TIBTECH* **1994**, *12*, 339.

(3) Natsuka, S.; Lowe, J. B. *Curr. Opin. Struct. Biol.* **1994**, *4*, 683. (b) Holme, E. H.; Ostrander, G. K.; Hakomori, S. *J. Biol. Chem.* **1986**, *261*, 3737. (c) Kornfeld, R.; Kornfeld, S. *Annu. Rev. Biochem.* **1985**, *54*, 631−664.

(4) (a) Cai, S.; Stroud, M. R.; Hakomori, S.; Toyokuni, T. *J. Org. Chem.* **1992**, *57*, 6693. (b) Luengo, J. T.; Gleason, J. G. *Tetrahedron Lett.* **1992**, *33*, 6911.

(5) Palcic, M. M.; Heerze, L. D.; Srivastrara, O. P.; Hindsgaul, O. *J. Biol. Chem.* **1989**, *264*, 17174.

(6) (a) Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **1995**, *51*, 8397. (b) Heskamp, B. M.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1995**, *14*, 1265.

(7) (a) Qiao, L.; Murray, B. W.; Shimazaki, M.; Schultz, J.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7653. (b) Murray, B. W.; Wittmann, V.; Burkart, M. D.; Hung, S. H.; Wong, C.-H. *Biochemistry* **1997**, *36*, 823.

(8) Murray, B. W.; Takayama, S.; Schultz, J.; Wong, C.-H. *Biochemistry* **1996**, *34*, 11183.

(9) For synergistic inhibition, see: (a) Wong, C.-H.; Dumas, D. P.; Ichikawa, Y.; Koseki, K.; Danishefski, D. J.; Weston, B. W.; Lown, J. B. *J. Am. Chem. Soc.* **1992**, *114*, 7321. (b) Ichikawa, Y.; Lin, Y.-C.; Dumas, D. P.; Shen, G.-J.; Garcia-Junceda, E.; Williams, M. A.; Bayer, R.; Ketcham, C.; Walker, L. E.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 9283.

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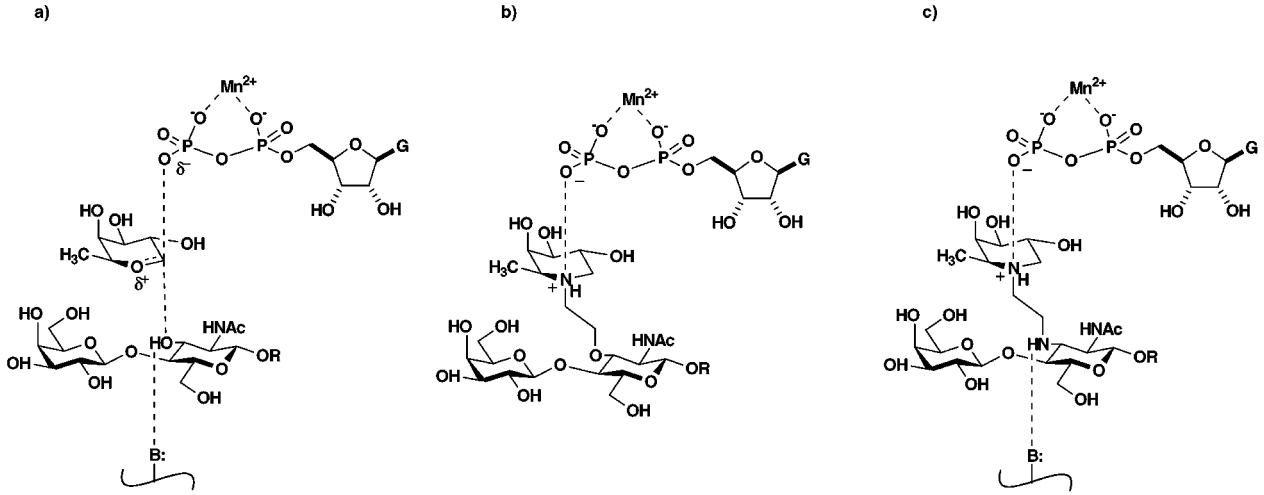
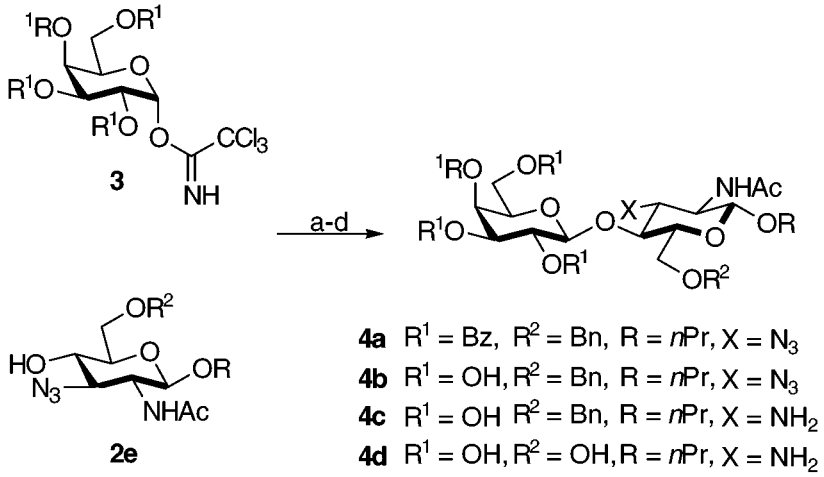


Figure 1. (a) Proposed transition-state structure of the human α-1,3-fucosyltransferase reaction, (b) a synergistic inhibitor complex with GDP,[7a] (c) designed new inhibitor with an H-bonding interaction with the proposed base (a carboxylate group).

Scheme 2[a]



[a] Key: (a) BF_3/CH_2Cl_2, 0 °C to room temperature, 36 h, 70%; (b) $NaOCH_3$/MeOH, rt, 2 h, quant; (c) $P(OMe)_3$, THF/H_2O, (10:1), NaOH, rt, 1 h, 81%; (d) HOAc/H_2O (1:1), $Pd(OH)_2$/C-20%, Degussa-type, 1 atm, H_2, 24 h, rt, quant.

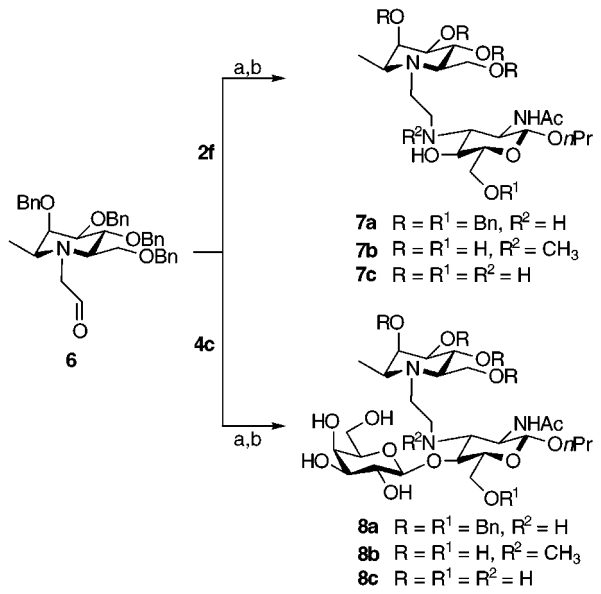
amination using allylamine should give an intermediate containing an appropriate spacer. This approach proved to be problematic under a variety of reaction conditions. Both oxidation and reductive amination of **1** proceed in low yield (15% overall); in addition, this methodology was unacceptable because it led almost exclusively to the undesired allo-configured pyranose derivative. However, a successful route to the desired gluco isomer via an S_N2-type chemistry with excellent stereocontrol and yield was then found. Mesylation of **1** under standard conditions (Scheme 1) gave **2a** (68%), which was reacted with NaOAc in 2-methoxyethanol to yield exclusively the allo-configured alcohol **2b**.[10] Mesylation of **2b** was accomplished in high yield (90%) leading to **2c**. Reductive cleavage of the benzylidene using[11] $NaCNBH_3$ and HCl/Et_2O afforded mesylate **2d** (70%), which was transformed using NaN_3 in DMF to the equatorial azide **2e** as a single isomer (93%). The azido group not only activates the 4-OH for glycosylation but it can also be used to attach the iminocyclitol moiety.

Preparation of the LacNAc mimetic **4c** (Scheme 2) involved a glycosylation step of alcohol **2e**. The $BF_3 \cdot Et_2O$ promoted coupling of **2e** using the known imidate **3** produced the desired disaccharide **4a** as a single isomer (70%).[12] Benzoate cleavage using $NaOCH_3$/MeOH and Staudinger[13] reduction of the crude product in THF/H_2O using $P(OMe)_3$ afforded amine **4c** in good yield over two steps (81%). Hydrogenolysis of **4c** in HOAc/H_2O using $Pd(OH)_2$/C, 20%-Degussa-type, and size exclusion chromatography provided the LacNAc mimetic **4d** in quantitative yield.

The convergent strategy for the synthesis of the Lewis analogue **8c** (Scheme 3) involved a coupling of a C-2 functionalized iminocyclitol **5** with the LacNAc mimetic **4c**. Because iminocyclitol **5** is known to have an unusually low pK_a and nucleophilicity, we assumed that only strong electrophiles could lead to N-alkylation.[14] In a one-pot procedure (Scheme 4) treatment of the readily

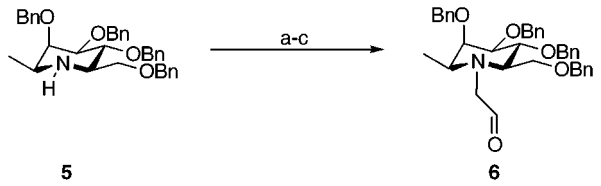
(10) Meyer zu Reckendorf, W. *Chem. Ber.* **1969**, *102*, 4207.
(11) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10.
(12) Rio, S.; Beau, J. M.; Jacquinet, J. C. *Carbohydr. Res.* **1991**, *219*, 71.
(13) For a review on this subject, see: Sriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297 and references therein.
(14) Hanozet, G.; Pircher, H. P.; Vanni, P.; Oesch, B.; Semenza, G. J. *Biol. Chem.* **1981**, *256*, 3703.

Scheme 3[a]



[a] Key: (a) $NaCNBH_3$, MeOH, rt, 6 h; (b) $HOAc/H_2O$ (1:1), $Pd(OH)_2/C$, 20%, Degussa-type, 1 atm, H_2, then Bio-Gel P-2, 52% (**8c**), 57% (**7c**), overall.

Scheme 4[a]



[a] Key: (a) Methanesulfonicacid/trifluro-(2,2-dimethyl-1,3-dioxolan-4-yl)/methylester, 0 °C to room temperature, 24 h, $EtN(^iPr)_2$; (b) THF/3 M HCl, 60 °C, 1 h; (c) $NaIO_4$, THF/H_2O, 0 °C, 45 min, 52%, overall.

available iminocyclitol **5** recently described[7a] by us, with the triflate of isopropylideneglycerol prepared in situ,[15] gave, after acid-induced cleavage of the acetal and $NaIO_4$ mediated oxidation of the diol intermediate, aldehyde **6** (52% overall) with only one purification step. Treatment of aldehyde **6** with amine **4c** in a reductive amination sequence using $NaCNBH_3$ in MeOH afforded the desired trisaccharide **8c** after hydrogenolysis (52% overall). The reductive amination of **6** with amine **2f** leads to disaccharide **7c**, respectively (57% overall). It should be noted that hydrogenolysis of the benzyl groups using Pd/C afforded mixtures of partially hydrogenated products under a variety of reaction conditions even at 60 psi. Interestingly, when $Pd(OH)_2/C$, 20% Degussa-type, was used in MeOH, debenzylation was quantitative; however, byproducts could be detected. On the basis of ^1H NMR and HRMS, **7b** and **8b** were formed as a result of reductive amination with formaldehyde, which was probably generated in situ by Pd^{II} oxidation of MeOH.[16] However, when $HOAc/H_2O$ was used in the hydrogenolysis of **7a** and **8a**, the reactions proceeded cleanly and quantitatively. Suprisingly, compound **8c** showed no improvement in the inhibition of human fucosyltransferase V as compared to the corresponding O-linked analogue **7a**. Work is in progress to investigate the inhibition of other fucosyltransferases.

In summary, we have developed a short and effective synthesis of a new class of Lewis and LacNAc analogues as potential inhibitors of fucosyltransferases. The method described in this paper represents a general procedure for the incorporation of an iminocyclitol as a transition-state mimic of the sugar moiety of the donor to the acceptor substrate and may find use in the development of other glycosyltransferase inhibitors.

Experimental Section

General. Anhydrous solvents were purchased from Aldrich and used without further purification. Cation-exchange resin AG 50W-X2 (H^+ form, strongly acidic) was purchased from Bio-Rad Laboratories and converted to the appropriate salt form prior to its use. All reactions were run under dry Ar in oven-dried glassware, unless otherwise indicated. Analytical thin-layer chromatography was performed using silica gel 60 F_{254} precoated glass plates (Merck) and visualized by quenching of fluorescence and by charring after treatment with cerium molybdophosphate. Size exclusion chromatography was performed on Bio-Gel P-2 gel, fine (Bio-Rad Laboratories). ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 500 or Bruker AMX-400 and referenced to internal standard TMS ($\delta_H = 0.00$), $CDCl_3$ ($\delta_H = 7.26$, $\delta_C = 77.0$), CD_3OD ($\delta_H = 4.87$, $\delta_C = 49.2$), or D_2O ($\delta_H = 4.80$).

***n*-Propyl 2-Acetamido-3-*O*-mesyl-4,6-benzylidene-2-deoxy-β-D-glucopyranoside (2a).** Compound **1** (2.5 g, 7.12 mmol) was dissolved in pyridine (40 mL) and cooled to 0 °C. At this temperature (1.65 mL, 21.36 mmol), MsCl was added and stirring was continued for 24 h. All volatiles were removed in vacuo, and the residue was chromatographed with $CHCl_3$/MeOH (100:1) to give **2a**, 2.1 g (68%). ^1H NMR: δ_H 0.88 (t, $J = 7.4$ Hz, 3H), 1.51−1.60 (m, 2H), 2.00 (s, 3H), 3.38−3.49 (m, 2H), 3.54−3.60 (m, 1H), 3.68−3.82 (m, 3H), 4.36 (dd, $J = 10.6$ Hz, 5.0 Hz, 1H), 5.10 (d, $J = 8.1$ Hz, 1H), 5.21 (t, $J = 9.7$ Hz, 1H), 5.90 (d, $J = 7.7$ Hz, 1H), 7.33−7.35 (m, 3H), 7.39−7.41 (m, 2H). ^{13}C NMR: δ_C 10.0, 22.5, 22.8, 38.4, 56.1, 65.4, 65.5, 71.9, 78.8, 79.0, 100.5, 101.5, 125.8, 128.3, 129.2, 136.4, 172.0. HRMS for $C_{19}H_{27}NO_8SNa$, $(M + Na)^+$: calcd, 452.1355; found, 452.1366.

***n*-Propyl 2-Acetamido-3-hydroxy-4,6-benzylidene-2-deoxy-β-D-allopyranoside (2b).** Mesylate **2a** (2.0 g, 4.66 mmol) was suspended in a mixture of methoxyethanol/H_2O (30 mL, 95:5), NaOAc (3.8 g, 46.30 mmol) was added, and the resulting mixture was heated to reflux for 48 h, cooled to room temperature, and evaporated to dryness. The residue was dissolved in 30 mL of H_2O, and the water layer was extracted with $CHCl_3$ (3 × 100 mL), dried over $MgSO_4$, and concentrated. Flash chromatography ($CHCl_3$/MeOH, 20:1) gave the title compound, 1.32 g (80%), as a white solid. ^1H NMR: δ_H 0.90 (t, $J = 7.4$ Hz, 3H), 1.52−1.61 (m, 2H), 1.97 (s, 3H), 3.40−3.47 (m, 1H), 3.65 (dd, $J = 9.6$ Hz, 2.7 Hz, 1H), 3.73−3.80 (m, 2H), 3.94 (dd, $J = 8.6$ Hz, 2.9 Hz, 1H), 3.98 (dt, $J = 9.9$ Hz, 5.0 Hz, 1H), 4.13 (t, $J = 2.6$ Hz, 1H), 4.29 (dd, $J = 10.2$ Hz, 5.1 Hz, 1H), 4.74 (d, $J = 8.6$ Hz, 1H), 5.62 (s, 1H), 7.31−7.34 (m, 3H), 7.48−7.50 (m, 2H). ^{13}C NMR: δ_C 10.9, 22.6, 24.0, 54.8, 64.6, 69.3, 70.1, 72.5, 80.5, 101.2, 103.0, 127.6, 129.0, 129.9, 139.2, 175.0. HRMS for $C_{18}H_{25}NO_6$ $(M + H)^+$: calcd, 352.1760; found, 352.1752.

***n*-Propyl 2-Acetamido-3-*O*-mesyl-4,6-benzylidene-2-deoxy-β-D-allopyranoside (2c).** Starting from **2b** (1.32 g, 3.76 mmol) following the procedure described for the synthesis of **2a**, with the exception that the mixture was allowed to warm to room temperature, afforded the title compound, 1.45 g (90%), as a white solid. ^1H NMR: δ_H 0.89 (t, $J = 7.4$ Hz, 3H), 1.23−1.64 (m, 2H), 2.01 (s, 3H), 2.95 (s, 3H), 3.41 (dt, $J = 9.4$ Hz, 6.8 Hz, 1H), 3.47−3.93 (m, 4H), 4.26 (dt, $J = 8.5$ Hz, 2.8 Hz, 1H), 4.39 (dd, $J = 10.4$ Hz, 4.9 Hz, 1H), 4.65 (m, 3H), 5.25 (t, $J = 2.6$ Hz, 1H), 5.72 (d, $J = 8.5$ Hz, 1H), 7.31−7.36 (m, 3H),

(15) Berkowitz, D. B.; Shen, Q.; Maeng, J. H. *Tetrahedron Lett.* **1994**, *35*, 6445.

(16) Choudary, B. M.; Prabhakar Reddy, N.; Lakshmi Kantam, M.; Jamil, Z. *Tetrahedron Lett.* **1985**, *26*, 6257.

7.37−7.41 (m, 2H). ^{13}C NMR: δ_C 10.4, 22.7, 23.1, 38.9, 51.6, 64.0, 69.0, 71.6, 76.4, 79.0, 99.5, 101.9, 125.9, 128.4, 129.3, 132.7, 171.0. HRMS for $C_{19}H_{27}NO_8Cs$ (M + Cs)$^+$: calcd, 562.0512; found, 562.0492.

***n*-Propyl 2-Acetamido-3-*O*-mesyl-4-hydroxy-6-*O*-benzyl-2-deoxy-β-D-allopyranoside (2d).** At room temperature, acetal **2c** (1.04 g, 2.42 mmol) was dissolved in THF (50 mL), and 12 g of molecular seives (3 Å) was added followed by $NaCNBH_3$ (46.6 mL of a 1 M solution in THF) and HCl in Et_2O (20 mL of a 1 M solution). The resulting mixture was stirred at room temperature for an additional 6 h and diluted with $CHCl_3$ (300 mL) and H_2O (100 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography using $CHCl_3$/MeOH (20:1) to give the title compound, 730 mg (70%), as a white solid. ^{1}H NMR: δ_H 0.91 (t, J = 7.5 Hz, 3H), 1.56−1.65 (m, 2H), 1.95 (s, 3H), 3.14 (s, 3H), 3.47 (dt, J = 9.3 Hz, 6.8 Hz, 1H), 3.64−3.70 (m, 1H), 3.73−3.88 (m, 5H), 4.65−4.60 (m, 1H), 4.66 (d, J = 8.7 Hz, 1H), 5.06 (s, br, 1H), 7.24−7.37 (m, 5H), 8.34 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ_C 10.8, 22.5, 23.9, 39.0, 53.9, 66.9, 70.7, 72.3, 72.9, 74.5, 74.9, 83.7, 99.7, 128.7, 128.8, 129.7, 139.5, 139.8, 173.0. HRMS for $C_{19}H_{29}NO_8S$ (M + H)$^+$: calcd, 432.1692; found, 432.1669.

***n*-Propyl 2-Acetamido-3-azido-4-hydroxy-6-*O*-benzyl-2,3-dideoxy-β-D-allopyranoside (2e).** Mesylate **2d** (380 mg, 0.88 mmol) was dissolved in dry DMF (15 mL), and NaN_3 (860 mg, 13.2 mmol) was added. The resulting mixture was heated to 80 °C for 2 h, cooled to room temperature, and evaporated to dryness. The residue was purified by flash chromatography using $CHCl_3$/MeOH (20:1) to give the title compound, 310 mg (93%). ^{1}H NMR: δ_H 0.89 (t, J = 7.5 Hz, 3H), 1.55−1.58 (m, 2H), 2.01 (s, 3H), 3.06−3.15 (m, 1H), 3.40−3.81 (m, 9H), 4.18 (dd, J = 10.5 Hz, 9.0 Hz, 1H), 4.59 (AB_q, J = 12.0 Hz, 2H), 4.91 (d, J = 8.5 Hz, 1H), 5.89 (d, J = 7.5 Hz, 1H), 7.30−7.35 (m, 5H). ^{13}C NMR: δ_C 10.3, 22.7, 23.5, 56.6, 64.5, 70.5, 71.4, 72.6, 73.7, 74.1, 99.4, 127.8, 127.9, 128.5, 137.8, 171.0. HRMS for $C_{18}H_{26}N_4O_5$ (M + H)$^+$: calcd, 379.1981; found, 379.1984.

***n*-Propyl 2-Acetamido-3-amino-2,3-dideoxy-β-D-glucopyranoside (2f).** Compound **2e** (100 mg, 0.26 mmol) was dissolved at room temperature in HOAc/H_2O (3 mL, 1:1), 10 mg of $Pd(OH)_2$/C, 20% Degussa-type, was added, and H_2 was introduced by two evaporations in a vacuum. The resulting mixture was stirred at room temperature for 24 h, filtered over a thin pad of Celite, and concentrated in a vacuum. Size exclusion chromatography using Bio-Gel P-2 (200 mM NH_4HCO_3 as eluant) gave, after lyophylization, **2f** as a white solid, 69.3 mg (100%). ^{1}H NMR: δ_H 1.31−1.43 (m, 2H), 1.84 (s, 3H), 2.71−2.76 (m, 1H), 3.28 (dd, J = 7.3 Hz, 7.1 Hz, 1H), 3.30−3.40 (m, 1H), 3.45−3.57 (m, 3H), 3.62−3.67 (m, 1H), 3.69 (d, J = 5.0 Hz, 1H), 3.73 (d, J = 2.6 Hz, 1H), 4.35 (d, J = 10.0 Hz, 1H). ^{13}C NMR: δ_C 10.4, 22.8, 22.9, 54.7, 57.0, 61.3, 69.3, 73.1, 77.6, 102.0, 175.5. HRMS for $C_{11}H_{22}N_2O_5$ (M + H)$^+$: calcd, 263.1607; found, 263.1613.

***n*-Propyl 2-*N*-Acetamido-3-azido-6-*O*-benzyl-2,3-dideoxy-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-β-D-glucopyranoside (4a).** At 0 °C, BF_3 (25 μL, 0.2 mmol) was added dropwise to a solution of alcohol **2e** (250 mg, 0.66 mmol) and imidate **3** (1.22 g, 1.64 mmol) in dry CH_2Cl_2 (8 mL). The mixture was allowed to warm to room temperature and stirred for an additional 6 h. Then, another portion of BF_3 (25 μL, 0.2 mmol) and imidate **3** (540 mg, 0.73 mmol) was added, and stirring continued for an additional 30 h. Then, NEt_3 (100 μL, 0.70 mmol) and 15 mL of toluene were added, the mixture was evaporated to dryness in a vacuum, and the residue was purified by flash chromatography using hexane/EtOAc (1:1) to give the title compound, 442 mg (70%). ^{1}H NMR: δ_H 0.86 (t, J = 7.5 Hz, 3H), 1.51−1.57 (m, 2H), 2.01 (s, 3H), 2.93−2.99 (m, 1H), 3.32−3.40 (m, 2H), 3.51 (dd, J = 9.4 Hz, 1.5 Hz, 1H), 3.65 (dd, J = 11.0 Hz, 3.0 Hz, 1H), 3.71−3.76 (m, 1H), 3.98 (t, J = 9.4 Hz, 1H), 4.10 (t, J = 6.6 Hz, 1H), 4.29 (dd, J = 10.8 Hz, 9.1 Hz, 1H), 4.34 (d, J = 12.1 Hz, 1H), 4.41 (dd, J = 11.2 Hz, 7.0 Hz), 4.69 (t, J = 8.6 Hz, 1H), 4.72 (d, J = 12.1 Hz, 1H), 4.87 (dd, J = 8.1 Hz, 4.1 Hz, 1H), 5.42 (dd, J = 10.4 Hz, 3.3 Hz, 1H), 5.73 (dd, J = 10.4, 8.0 Hz, 1H), 5.89 (d, J = 7.5 Hz, 1H), 5.93 (d, J = 3.1 Hz, 1H), 7.21−7.25 (m, 2H), 7.35−7.59 (m, 15H), 7.76−7.88 (m, 4H), 8.03−8.07 (m, 4H). ^{13}C NMR: δ_C 10.3, 22.6, 23.5, 56.4, 61.7, 62.8, 67.5, 67.7, 69.8, 70.9, 71.3, 71.5, 73.5, 74.7, 75.9, 99.4, 99.9, 128.1, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.3, 129.5, 129.6, 129.7, 130.0, 133.2, 133.3, 133.4, 137.8, 164.7, 165.4, 165.5, 165.9, 170.5. HRMS for $C_{52}H_{52}N_4O_{14}Cs$ (M + Cs)$^+$: calcd, 1089.2534; found, 1089.2565.

***n*-Propyl 2-*N*-Acetamido-3-amino-6-*O*-benzyl-2,3-dideoxy-β-D-galactopyranosyl-β-D-glucopyranoside (4c).** Disaccharide **4a** (270 mg, 0.28 mmol) was dissolved in dry MeOH (5 mL), and $NaOCH_3$ (30 μL of a 0.5 M solution in MeOH) was added. The resulting mixture was stirred for 2 h, neutralized with cation exchange resin AG 50W-X2 (H^+ form), and concentrated. The residue was dissolved in THF/H_2O (14 mL, 10:1), and NaOH (15 μL of a 1 M aq solution) was added followed by $P(OMe)_3$ (283 μL of a 1 M solution in THF). The mixture was stirred at room temperature for 1 h, concentrated, and purified by flash chromatography using (CH_2Cl_2/MeOH, 5:1 containing 3% NEt_3) to give the title compound as a white solid, 117 mg (81%), over two steps. ^{1}H NMR: δ_H 0.92 (t, J = 7.5 Hz, 3H), 1.56−1.59 (m, 2H), 2.00 (s, 3H), 3.57−3.59 (m, 2H), 3.65 (dd, J = 11.5 Hz, 3.5 Hz, 1H), 3.73−3.84 (m, 6H), 3.90 (t, J = 10.0 Hz, 1H), 3.96 (dd, J = 11.0 Hz, 3.5 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 8.5 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 5.23 (s, 2H), 7.27−7.38 (m, 5H). ^{13}C NMR: δ_C 10.9, 23.0, 23.9, 53.6, 54.9, 57.1, 63.1, 63.4, 69.1, 70.5, 72.4, 72.5, 74.3, 74.5, 74.6, 76.8, 102.6, 104.2, 128.7, 128.9, 129.4, 139.6, 174.1. HRMS for $C_{24}H_{38}N_2O_{10}$-Cs (M + Cs)$^+$: calcd, 647.1581; found, 647.1603.

***n*-Propyl 2-*N*-Acetamido-3-amino-2,3-dideoxy-β-D-galactopyranosyl-β-D-glucopyranoside (4d).** Disaccharide **4c** (19 mg, 40 μmol) was dissolved in HOAc/H_2O (1:1, 2 mL), Pd-$(OH)_2$/C-20%, Degussa-type, was added, and H_2 was introduced by two evaporations in vacuo. The mixture was stirred at room temperature for 24 h, filtered over a thin pad of Celite, and concentrated in a vacuum. Size exclusion chromatography using Bio-Gel P-2 gave **4d**, after lyophylization, as a white solid, 10.8 mg (100%). ^{1}H NMR: δ_H 0.66 (t, J = 7.5 Hz, 3H), 1.30−1.39 (m, 2H), 1.85 (s, 3H), 2.85 (t, J = 9.8 Hz, 1H), 3.29−3.86 (m, 13H), 4.24 (d, J = 7.8 Hz, 1H), 4.38 (d, J = 8.4 Hz, 1H). ^{13}C NMR: δ_C 10.3, 22.8, 22.9, 54.8, 55.5, 60.6, 61.2, 61.9, 69.3, 71.7, 73.1, 73.2, 76.1, 76.5, 102.0, 103.5, 175.4. HRMS for $C_{17}H_{32}N_2O_{10}$ (M + H)$^+$: calcd, 425.2135; found, 425.2147.

***n*-Propyl 2-*N*-Acetamido-2,3-dideoxy-(β-D-galactopyranosyl)-6-*O*-benzyl-3-amino-(2-(*N*-(1,3,4,5-tetra-*O*-benzyl-β-L-homofuconojirimycinyl))aminoethyl-β-D-glucopyranoside (8a).** Aldehyde **6** (10.8 mg, 18.6 μmol) and disaccharide **4c** (7.8 mg, 15.1 μmol) were dissolved in dry MeOH (1.5 mL), and $NaCNBH_3$ (7.82 mg, 124 μmol) was added. The mixture was stirred at room temperature until TLC (CH_2Cl_2/MeOH, 10:1) showed the disappearance of the disaccharide and the formation of a new product (R_f = 0.1). The mixture was evaporated to dryness and purified by flash chromatography using (CH_2Cl_2/MeOH, 10:1) to give the title compound as a glassy solid, 8.5 mg (52%). ^{1}H NMR: δ_H 0.88 (t, J = 7.0 Hz, 3H), 1.21 (d, J = 6.5 Hz, 3H), 1.56 (m, 2H), 1.96 (s, 3H), 2.90−3.05 (m, 6H), 3.32−3.96 (m, 30H), 4.30 (d, J = 7.5 Hz, 1H), 4.41 (d, J = 11.0 Hz, 1H), 4.47−4.60 (m, 7H), 4.69 (AB_q, J = 14.0 Hz, 2H), 4.80 (d, J = 11.0 Hz, 1H), 4.87 (d, J = 11.5 Hz, 1H), 6.78 (s, 1H), 7.10−7.40 (m, 25H). ^{13}C NMR: δ_C 10.4, 16.6, 22.7, 23.1, 51.3, 62.3, 62.4, 63.4, 64.8, 64.9, 67.5, 67.6, 68.3, 71.3, 71.6, 72.7, 73.2, 73.5, 73.6, 74.1, 74.4, 74.7, 74.8, 74.9, 75.1, 78.2, 100.5, 101.7, 127.5, 127.7, 128.0, 128.1, 128.2, 128.4, 128.8, 128.9, 129.8, 137.8, 137.9, 138.2, 138.4, 172.6. HRMS for $C_{61}H_{79}N_3O_{14}$ (M + H)$^+$: calcd, 1078.5640; found, 1078.5723.

***n*-Propyl 2-*N*-Acetamido-2,3-dideoxy-6-*O*-benzyl-3-amino-(2-(*N*-(1,3,4,5-tetra-*O*-benzyl-β-L-homofuconojirimycinyl))aminoethyl-β-D-glucopyranoside (7a).** Following the procedure described for the synthesis of **8a**, aldehyde **6** (25 mg, 43 μmol) and monosaccharide **2f** (10.5 mg, 30 μmol) gave the title compound as a white solid, 14.2 mg (57%). ^{1}H NMR: δ_H 0.87 (t, J = 7.0 Hz, 3H), 1.06 (d, J = 7.5 Hz, 3H), 1.51−1.60 (m, 2H), 1.95 (s, 3H), 2.51−2.77 (m, 6H), 3.32−3.89 (m, 13H), 4.23 (d, J = 7.5 Hz, 1H), 4.28−4.36 (m, 1H), 4.43 (t, J = 14.2 Hz, 1H) 4.55−4.73 (m, 6H), 4.82 (d, J = 14.5 Hz,

1H), 7.19 (d, $J = 7.4$ Hz, 1H), 7.25−7.39 (m, 25H). HRMS for $C_{55}H_{69}N_3O_9Cs$ $(M + Cs)^+$: calcd, 1048.4088; found, 1048.4072.

***n*-Propyl 2-*N*-Acetamido-2,3-dideoxy-4-*O*-(*β*-D-galactopyranosyl)-3-amino-(2-(*N*-(*β*-L-homofuconojirimycinyl))-aminoethyl-*β*-D-glucopyranoside (8c).** Hydrogenolysis of **8a** (8.3 mg, 7.7 μmol) following the procedure described for the synthesis of **4d** gave the title compound as a glassy solid, 4.8 mg (100%). ^{1}H NMR: δ_H 0.66 (t, $J = 7.0$ Hz, 3H), 1.21 (d, $J = 6.5$ Hz, 3H), 1.45 (m, 2H), 1.96 (s, 3H), 2.47 (s, br, 3H), 3.13 (m, 5H), 3.29−3.95 (m, 24H), 4.30 (d, $J = 8.0$ Hz, 1H), 4.34 (d, $J = 8.5$ Hz, 1H). ^{13}C NMR: δ_C 10.4, 16.6, 22.9, 23.0, 45.5, 52.1, 58.4, 58.5, 61.0, 61.6, 65.4, 67.5, 67.6, 69.3, 72.6, 72.7, 72.8, 73.0, 73.1, 73.3, 75.1, 75.9, 76.9, 102.4, 102.7, 174.7. HRMS for $C_{26}H_{49}N_3O_{14}Cs$ $(M + Cs)^+$: calcd, 760.2269; found, 760.2244.

***n*-Propyl 2-*N*-Acetamido-2,3-dideoxy-3-amino-(2-(*N*-(*β*-L-homofuconojirimycinyl))aminoethyl-*β*-D-glucopyranoside (7c).** Hydrogenolysis of **7a** (14.1 mg, 15.3 μmol) following the procedure described for the synthesis of **4d** gave the title compound as a glassy solid, 7.0 mg (100%). ^{1}H NMR: δ_H 0.67 (t, $J = 7.0$ Hz, 3H), 1.17 (d, $J = 6.5$ Hz, 3H), 1.36 (m, 2H), 1.85 (s, 3H), 2.65 (m, 1H), 2.81−3.16 (m, 6H), 3.28−3.39 (m, 4H), 3.46 (t, $J = 10.0$ Hz, 1H), 3.55 (dd, $J = 7.5$ Hz, 1.0 Hz, 1H), 3.60 (t, $J = 9.5$ Hz, 1H), 3.62−3.88 (m, 7H), 4.36 (d, $J = 8.5$ Hz, 1H). ^{13}C NMR: δ_C 10.4, 15.9, 22.8, 22.9, 39.5, 46.0, 52.1, 56.7, 59.9, 61.3, 62.5, 66.1, 66.3, 66.8, 72.5, 73.1, 74.4, 77.5, 102.2, 175.4. HRMS for $C_{20}H_{39}N_3O_9$ $(M + H)^+$: calcd, 466.2766; found, 466.2776.

1,3,4,5-Tetra-*O*-benzyl-2,6-(*N*-2-oxoethylimino)-2,6,7-trideoxy-L-*glycero*-D-*manno*-heptitol (6). At 0 °C, amine **5** (240 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and $EtN(iPr)_2$ (100 μL, 0.57 mmol) was added followed by the triflate of isopropylideneglycerol[15] (1.18 g, 4.5 mmol). The resulting mixture was stirred at 0 °C for 10 min and an additional 24 h at room temperature, diluted with CH_2Cl_2 (30 mL), and washed with saturated $NaHCO_3$ (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated in a vacuum. The oil observed above was dissolved in THF/3 M HCl (8 mL, 1:1), heated to 60 °C for 1 h, and cooled to room temperature, and the pH was adjusted to 8.5 using $NaHCO_3$. The mixture was extracted with EtOAc (3 × 20 mL) and the organic layer was dried over $MgSO_4$ and concentrated to give a white solid. The solid was dissolved in THF (6 mL) and cooled to 0 °C, $NaIO_4$ (96 mg, 0.45 mmol) dissolved in water (6 mL) was added in one portion, and the resulting mixture was stirred at 0 °C for 45 min. Then, EtOAc (50 mL) was added and the organic layer was washed with saturated $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated in a vacuum. Flash chromatography using hexane/EtOAc (2:1) gave **6** ($R_f = 0.3$) as a colorless oil, 135 mg (52%, overall). ^{1}H NMR: δ_H 1.07 (d, $J = 7.0$ Hz, 3H), 3.55 (dd, $J = 9.5$ Hz, 3.0 Hz, 1H), 3.60−3.65 (m, 3H), 3.96 (m, 1H), 3.71 (d, $J = 2.5$ Hz, 1H), 3.72 (d, $J = 2.5$ Hz, 1H), 3.80 (t, $J = 10.0$ Hz, 1H), 4.35 (AB_q, $J = 13.5$ Hz, 2H), 4.52 (d, $J = 10.5$ Hz, 1H), 4.62 (d, $J = 12.0$ Hz, 1H), 4.75 (AB_q, $J = 12.5$ Hz, 2H), 4.90 (d, $J = 11.0$ Hz, 1H), 5.01 (d, $J = 11.5$ Hz, 1H), 7.10−7.38 (m, 20H), 9.54 (s, 1H). ^{13}C NMR: δ_C 16.9, 56.8, 57.7, 64.1, 68.4, 72.6, 73.0, 74.5, 74.8, 75.2, 78.7, 86.3, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 137.5, 138.4, 138.5, 138.8, 139.5, 204.0. HRMS for $C_{37}H_{41}NO_5$, $(M + Cs)^+$: calcd, 712.2039; found, 712.2009.

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Supporting Information Available: ^{1}H NMR and/or ^{13}C NMR spectra off all new compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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