Aza-*C*-disaccharides: Synthesis of 6-Deoxygalactonojirimycin *β*-C(1→3) Linked with D-Altrofuranosides and D-Galactose

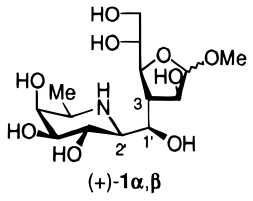
Alain Baudat and Pierre Vogel*

Section de Chimie de l'Université, BCH, 1015 Lausanne-Dorigny, Switzerland

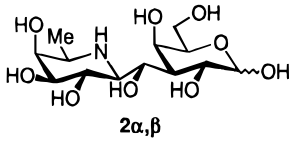
Received January 27, 1997[⊗]

Cross-aldolization of 3-*O*-benzyl-*N*-(benzyloxycarbonyl)-2,6,7-trideoxy-2,6-imino-4,5-*O*-isopropylidene-*β*-D-*glycero*-L-mannoheptose ((−)-**12**, derived from D-*glycero*-D-*gulo*-heptono-1,4-lactone in eight steps) with (+)-(1*R*,4*S*,5*S*,6*S*)- and (−)-(1*S*,4*R*,5*R*,6*R*)-6-chloro-5-(phenylseleno)-7-oxabicyclo-[2.2.1]heptan-2-one (obtained in one step from the "naked sugars" (−)- and (+)-7-oxabicyclo[2.2.1]hept-5-en-2-one) were highly stereoselective (lithium enolates, like modes), giving aldols (−)-**14** and (+)-**16**, respectively. Stereoselective methods were developed for the conversion of (−)-**14** into methyl 3-deoxy-3-*C*-[(1′*R*)-2′,6′,7′-trideoxy-2′,6′-imino-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-α- and -*β*-D-altrofuranoside ((+)-**1**α,*β*). The aza-*C*-disaccharide **1**α prefers a *anti* conformation (bonds C(2′)−C(3′) and C(1′)−C(3) are antiperiplanar) for the *β*-D-galactoside moiety ($^3J_{H,H}$ coupling constants, NOEs). Aldol (+)-**16** was converted stereoselectively into 3-deoxy-3-*C*-[(1′*S*)-2′,6′,7′-trideoxy-2′,6′-iminio-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-*β*-D-galactose trifluoroacetate.

Glycosidases are key enzymes in the biosynthesis and processing of glycoproteins, which are macromolecules involved in recognition (cell−cell, host−pathogen interactions) and control of biological mechanisms and structures.[1] Inhibition of glycosidases[2] may be useful for the treatment of diseases such as diabetes, cancer, viral and bacterial infections, and inflammation.[3] Polyhydroxypiperidines, pyrrolidines (azasugars), and azepanes are promising inhibitors;[4] unfortunately, they often inhibit more than one enzyme *in vivo*. It is believed that selectivity would be increased if the azasugar would include not only the steric and charge information of the glycosyl moiety which is liberated during the glycosidase-catalyzed hydrolysis but also that of the aglycon which it is attached to. Such inhibitors could be dideoxyiminoalditols linked to other sugars through nonhydrolyzable links such as in the aza-*C*-disaccharides. These disaccharides mimics could also be candidates as haptens for the generation of catalytic antibodies.[5] A first example (1,5-dideoxy-1,5-imino-D-mannitol linked at C(6) of D-galactose through a CH_2 unit) has been prepared by Johnson and co-workers[6] applying the Suzuki reaction. Other examples of "linear" aza-*C*-disaccharides were prepared recently by Martin et al.[7] In preliminary communications[8,9] we reported the synthesis of the first examples of "branched" aza-*C*-disaccharides in which trihydroxypiperidines are C-linked at position C(3) of hexoses.[10,11] We describe here the details of our syntheses of two aza-*C*-disaccharides in which 1,5,6-trideoxy-1,5-imino-*β*-D-galactose is linked at C(3) of methyl D-altrofuranosides (**1**α, **1***β*) for one case, and at C(3) of D-galactose for the second case, through a hydroxymethylene bridge. The aza-*C*-disaccharide **2** mimics the cancer marker or antigen T (Thomsen−Friedenreich) which has the structure *β*-D-Gal-*O*(1→3)-α-D-GalNAc-*O*-Ser(Thr).[5,12] A study by high-field NMR shows that an *anti* conformation (C(1′)-C(3) and C(2′)-C(3′) bonds are antiperiplanar) is preferred for **1**-α for pH 4.4 to 9.8. The pKa values of the conjugate acids of **1**α and **1***β* have also been determined.



(+)-**1**α,β



2α,β

Synthesis of Aza-*C*-*β*(1→3)-galactosides of Altrofuranosides. The commercially available D-*glycero*-D-

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) See, e.g.: Rademacher, T. W.; Parekh, R. B.; Dwek, R. A. *Annu. Rev. Biochem.* **1988**, *57*, 785. Hindsgaul, O.; Khare, D. P.; Bach, M.; Lemieux, R. U. *Can. J. Chem.* **1985**, *63*, 2653. Feizi, T. In *Carbohydrate Recognition in Cellular Function*; Ciba Geigy Symposium 145; Wiley: Chichester, 1989; pp 62−79. Kornfeld, R.; Kornfeld, S. *Annu. Rev. Biochem.* **1985**, *54*, 631. Moremen, K. W.; Trimble, R. B.; Herscovics, A. *Glycobiology* **1994**, *4*, 113. Rice, G. E.; Bevilacqua, M. P. *Science* **1989**, *246*, 1303. Smith, C. A.; Davis, T.; Anderson, D.; Solam, L.; Beckmann, M. P.; Jerzy, R.; Dower, S. K.; Cosman, D.; Goodwin, R. G. *Science* **1990**, *248*, 1019.

(2) See, e.g.: Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171. Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. Franck, R. W. *Bioorg. Chem.* **1992**, *20*, 77. Kirby, A. J. *Adv. Phys. Org. Chem.* **1994**, *5*, 605.

(3) See e.g.: Winchester, B.; Fleet, G. W. *J. Glycobiol.* **1992**, *2*, 199. Karlsson, G. B.; Butters, T. D.; Dwek, R. A.; Platt, R. M. *J. Biol. Chem.* **1993**, *268*, 570. Colman, P. M. *Pure Appl. Chem.* **1995**, *67*, 1683.

(4) See, e.g.: Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. Wong, C.-H.; Provencher, L.; Porco, J. A.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492. Wang, Y.-F.; Takaoka, Y., Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1242. Asano, N.; Oseki, K.; Kizu, H., Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701. McCarter, J. D.; Withers, S. G. *Curr. Opin. Struct. Biol.* **1994**, *4*, 885. Papandreou, G.; Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1993**, *115*, 11682. Moris-Varas, F.; Qian, X.-H.; Wong, C.-H. *Ibid.* **1996**, *118*, 7647. Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. Wong, C.-H.; Halcomb, R. L.; Ichikawa, Y., Kajimoto, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 521.

(5) See, e.g.: Rye, P. D.; Bovin, N. V.; Vlasova, E. V.; Walker, R. A. *Glycobiology* **1995**, *5*, 385.

(6) Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksebati, M. B. *Tetrahedron Lett.* **1994**, *35*, 8991.

(7) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991.

(8) Baudat, A.; Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 483.

(9) Frérot, E.; Marquis, C.; Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 2023.

(10) An azapyranosyl disaccharide with a thioglycosidic linkage has been described: Suzuki, K.; Hashimoto, H. *Tetrahedron Lett.* **1994**, *35*, 4119.

(11) *β*-L-Xylopyranosides (1→6) of 2,5-dideoxy-2,5-iminoaltitols have been prepared: Mikkelsen, G.; Christensen, T. V.; Bols, M.; Lundt, I.; Sierks, M. R. *Tetrahedron Lett.* **1995**, *36*, 6541. See also: Andrews, J. S.; Weimar, T.; Frandsen, T. P.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 10799.

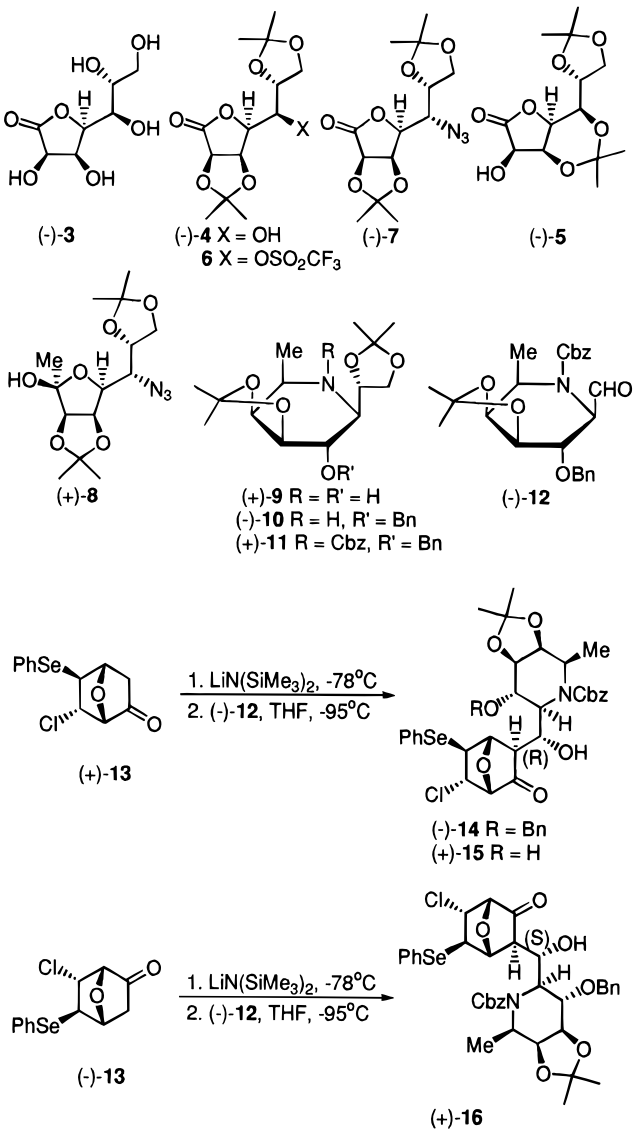
(12) See, e.g.: MacLean, G. D.; Longenecker, B. M. *Can. J. Oncol.* **1994**, *4*, 249.

S0022-3263(97)00151-5 CCC: $14.00

gulo-heptono-1,4-lactone ((−)-**3**) (two steps from D-glucose) is converted into a 1:13 (80%)[13] or 1:10 (73%)[14] mixture of the bis-acetonides (−)-**4** and (−)-**5** on treatment in acetone with H_2SO_4 (20 °C) and $ZnCl_2/H_3PO_4$ (20 °C), respectively. Although (−)-**4** and (−)-**5** can be readily separated and (−)-**5** reequilibrated into a mixture of (−)-**4** and (−)-**5**, we searched for conditions under which a larger proportion of (−)-**4**, our starting material, could be obtained. This was indeed the case when the acetalization was carried at 150 °C in acetone in the presence of *p*-toluenesulfonic acid and $CaSO_4$. After 1.5 h a 2:3 mixture of (−)-**4** and (−)-**5** was formed (63% yield, 76% conversion). Conversion of (−)-**4** into the corresponding azide (−)-**7** was achieved through S_N2 displacement of the intermediate triflate **6**. Addition of MeLi in Et_2O/THF gave (+)-**8**, the hydrogenation of which gave the corresponding primary amine which equilibrated with the corresponding imine resulting from intramolecular addition of the ulose moiety. Hydrogenation of the latter gave (+)-**9** selectively (58% based on (−)-**4**).[15] Benzylation of (+)-**9** afforded (−)-**10** (79%). Protection with benzyl chloroformate provided (+)-**11** (97%). Treatment of (+)-**11** with 8:1 AcOH/H_2O and $NaIO_4$ led to selective hydrolysis of the 7,8-*O*-isopropylidene group and oxidative cleavage into aldehyde (−)-**12** (94%).

Cross-aldolization of aldehyde (−)-**12** with the lithium enolate of the bicyclic ketone (+)-**13**[16] in THF at −95 °C led to a mixture of aldols (−)-**14** and (+)-**15** isolated in 45 and 26% yield, respectively (92% of conversion of (−)-**12**). Aldol (+)-**15** arises from the debenzylation of (−)-**14** as its proportion grew with the time of reaction. We have no good explanation to offer for this unexpected selective debenzylation. Perhaps the lithium aldolate generates mixed aggregates with the excess of $(Me_3Si)_2NLi$ which displaces the benzyl ether. Under the same conditions, the lithium enolate of (−)-**13**[16] reacted with aldehyde (−)-**12** to give a single aldol (+)-**16** (70%, 82% conversion).[17] Under similar conditions, the lithium enolate of racemic ketone (±)-**13** reacted with aldehyde (−)-**12** to give (−)-**14** (30%), (+)-**15** (6%), and (+)-**16** (35%) after separation and purification by flash column chromatography on silica gel. The structures of (−)-**14** and (+)-**16** were established in the following way. Reduction of ketone (−)-**14** with $NaBH_4$ in THF/MeOH provided the *endo* alcohol (+)-**17** (^3J(H-C(3′),H-C(4′)) = 5.8 Hz[18]) in 88% yield. Treatment of (+)-**17** with $(t\text{-}Bu)_2Si(OSO_2CF_3)_2$ and 2,6-lutidine gave the cyclic silyl acetal (+)-**18**, the ^{1}H NMR spectrum of which showed typical vicinal coupling constants ^3J(H-C(4),H-C(4a)) = 11.1 Hz, ^3J(H-C(8),H-C(8a)) = 4.6 Hz, ^3J(H-C(4a),H-C(5)) ≅ 0 Hz. Similarly, aldol (+)-**16** was converted into diol (−)-**19** (96%) and silyl acetal **20**, the ^{1}H NMR spectrum of which was difficult to analyze because of signal overlappings (mixtures of rotamers resulting from the benzyl carbamate). We thus treated **20** with *m*-chloroperbenzoic acid (mCPBA) in CH_2Cl_2; this furnished (+)-**21** (74%), the ^{1}H NMR spectrum of which displayed typical vicinal coupling constants ^3J(H-C(4),H-C(4a)) = 10.8 Hz, ^3J(H-C(8),H-C(8a)) = 4.4 Hz, ^3J(H-C(4a),H-C(5) ≅ 0 Hz, consistent only with an *exo-anti* aldol (+)-**16**, as for aldol (−)-**14**. NOEs measured between protons H*exo*-C(8a) and H-C(4) confirmed structures (+)-**18** and (+)-**21**.

For steric reasons only the *exo* face of the bicyclic lithium enolates of (+)-**13** and (−)-**13** can react with the aldehyde moiety of (−)-**12**. Both cross-aldolizations followed Zimmerman−Traxler models[19] (chair transition states) or Evans models[20] (boat transition states; steric repulsion minimization leads to the *like* mode[21] of addi-



(13) Brimacombe, J. S.; Tucker, L. C. N. *Carbohydr. Res.* **1966**, *2*, 341.

(14) Shing, T. K. M.; Zhou, Z.-H.; Tsui, H.-C.; Mak, T. C. W. *J. Chem. Soc., Perkin Trans. I* **1992**, 887.

(15) Baudat, A.; Picasso, S.; Vogel, P. *Carbohydr. Res.* **1996**, *281*, 277.

(16) (a) Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341. (b) Gasparini, F.; Vogel, P. *Ibid.* **1990**, *55*, 2451. (c) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173. (d) Reymond, J.-L.; Vogel, P. *Tetrahedron: Asymmetry* **1990**, *1*, 729.

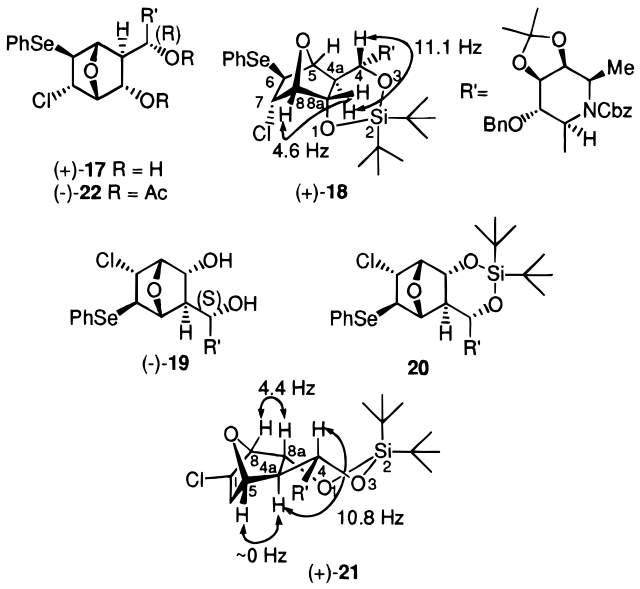
(17) For alternative methods of preparations of enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-ones precursors of (+)-**13** and (−)-**13**, see: Saf, R.; Faber, K.; Penn, G.; Griengl, H. *Tetrahedron* **1988**, *44*, 389. Ronan, B.; Kagan, H. B. *Tetrahedron: Asymmetry* **1991**, *2*, 75. Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979.

(18) Gagnaire, D.; Payo-Subiza, E. *Bull. Soc. Chim. Fr.* **1963**, 2627. Ramey, K. C.; Lini, D. C. *J. Magn. Reson.* **1970**, *3*, 94. Nelson, W. L.; Allen, D. R. *J. Heterocycl. Chem.* **1972**, *9*, 561. Kienzle, F. *Helv. Chim. Acta* **1975**, *58*, 1180. Mahaim, C.; Vogel, P. *Ibid.* **1982**, *65*, 866.

(19) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. See also: Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *Ibid.* **1977**, *99*, 247. Fellmann, P.; Dubois, J. E. *Tetrahedron* **1978**, *34*, 1349. Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. Anh, N. T.; Elkaïm, L.; Thanh, B. T.; Maurel, F.; Flament, J. P. *Bull. Soc. Chim. Fr.* **1992**, *129*, 468.

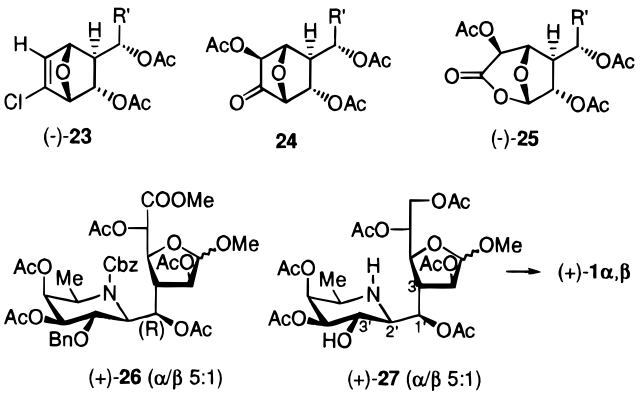
(20) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics Stereochem.* **1982**, *31*, 1.

(21) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.



tion, Figure 1) giving *anti* aldols. Contrary to α-methyl aldehydes[22] that lead to *anti* aldols with good double diastereoselectivity only with one of the two enantiomeric 7-oxanorbornanone lithium enolates (matched pair when the Felkin−Anh addition is compatible with the *like* mode of addition[23]), aldehyde (−)-**12** behaves as if the two α-substituents were of the same size.

Acylation of diol (+)-**17** with Ac_2O/pyridine/DMAP provided the diacetate (−)-**22**. Oxidative elimination of the phenylseleno group with mCPBA led to (−)-**23** (90%, based on (+)-**17**). Double hydroxylation of the chloroalkene (−)-**23** (Me_3NO, OsO_4, $NaHCO_3$) followed by acetylation (as above) gave the α-acetoxy ketone **24**, an unstable compound that was directly treated with mCPBA/$NaHCO_3$ to generate uronolactone (−)-**25** (67%). Methanolysis of (−)-**25** under acidic conditions (MeOH, $SOCl_2$) furnished a 5:1 mixture of the α- and *β*-furanoside (+)-**26**. No trace of the corresponding methyl pyranoside could be seen in the ^{1}H NMR spectrum of the crude reaction mixture. Reduction of (+)-**26** with $LiAlH_4$ or with DIBAH in THF, followed by acetylation (Ac_2O/pyridine/DMAP), led to untractable mixtures. Finally we found that the reduction of (+)-**26** with $LiBH_4$/THF, followed by acetylation and hydrogenolysis, provided a 5:1 α/*β*-mixture of the semiprotected aza-*C*-disaccharide (+)-**27** (72%). Transalcoholysis of (+)-**27** with MeOH/NH_3, followed by chromatography on an ion-exchange column, delivered a 5:1 mixture of **1**α and **1***β* ((+)-**1**α,*β*).



Qualitative conformational analysis of methyl 3-deoxy-3-[(1′*R*)-2′,6′,8′-trideoxy-2′,6′-imino-*β*-D-*glyc*-*ero*-L-*manno*-heptitol-1′-yl]-α-D-altrofuranoside. The 600 MHz ^{1}H NMR spectrum of the mixture of (+)-**1**α,*β* taken in 1:1 CD_3OD/D_2O at pH 5.7 suggested an *anti* conformation B (Figure 2A) for the aza-*C*-galactoside **1**α for the following reasons. A coupling constant of 1.3 Hz was measured between the anomeric proton H-C(2′) and H-C(1′) of the hydroxymethylene link. This excludes conformation C (Figure 2A) which features antiperiplanar protons H-C(2′) and H-C(1′). Since no NOE (2D NOESY spectrum) could be detected between protons Me-C(6′) of the 6-deoxygalactonojirimycin moiety and protons H-C(2), H-C(4) of the altrofuranoside unit, the *gauche* conformation A (Figure 2A) can be rejected. This conformation is expected to be destabilized due to steric repulsive effects between the two sugar moieties. A coupling constant of 10.1 Hz was measured between protons H-C(1′) of the link and H-C(3) of the aglycon. It is consistent only with an antiperiplanar arrangement for these two protons as shown in Figure 2B.

The other coupling constants (Figure 3) and the 2D NOESY spectrum of **1**α were consistent with the average conformation shown (Figures 2 and, 3). For numerous *C*-disaccharides with a CH_2 link, *anti* conformations of type B have been reported.[24] Data for *C*-lactose and derivatives with a CH(OH) link have shown that *gauche* conformations may be more populated than the corresponding *anti* conformations.[25]

Further discussion of our data for **1**α must await data for the corresponding *O*-disaccharide that are not avail-

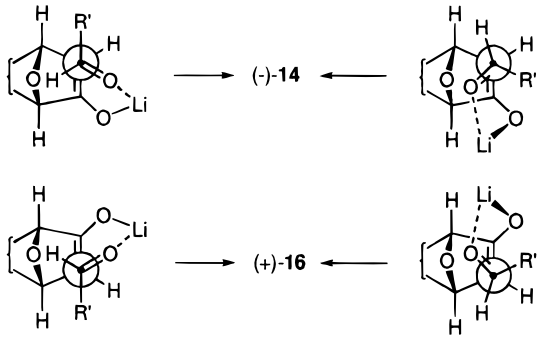


Figure 1. Representations of possible *like* mode of cross-aldolizations.

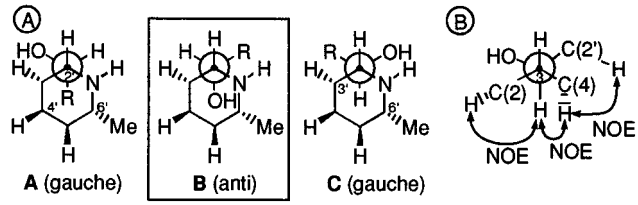


Figure 2. Representations of possible conformers for **1**α: (A) Newman projections along C(2′)−C(1′); (B) along C(3)−C(1′).

(22) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.
(23) Sevin, A. F.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 5920. Kernen, P.; Vogel, P. *Helv. Chim. Acta* **1995**, *78*, 301.
(24) Haneda, T.; Goekjian, P. G.; Kim, S. H.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 490. Ferritto, R.; Vogel, P. *Tetrahedron: Asymmetry* **1994**, *5*, 2077. Wei, A.; Boy, K. M.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9432. Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160. Berthault, P.; Birlirakis, N.; Rubinstenn, G.; Sinaÿ, P.; Desvaux, H. J. *J. Biomolecular NMR* **1996**, *8*, 23.
(25) Espinosa, J.-F.; Dietrich, H.; Martín-Lomas, M.; Schmidt, R. R., Jiménez-Barbero, J. *Tetrahedron Lett.* **1996**, *37*, 1467. Espinosa, J.-F.; Cañada, F. J.; Asensio, J. L.; Martín-Pastor, M.; Dietrich, H.; Martín-Lomas, M.; Schmidt, R. R.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1996**, *118*, 10862.

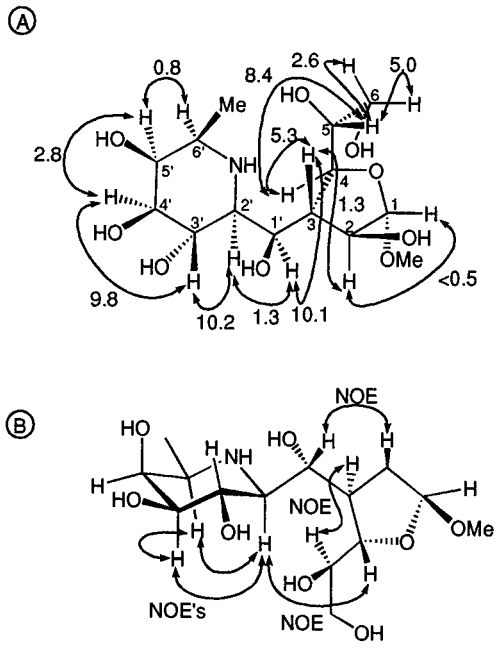
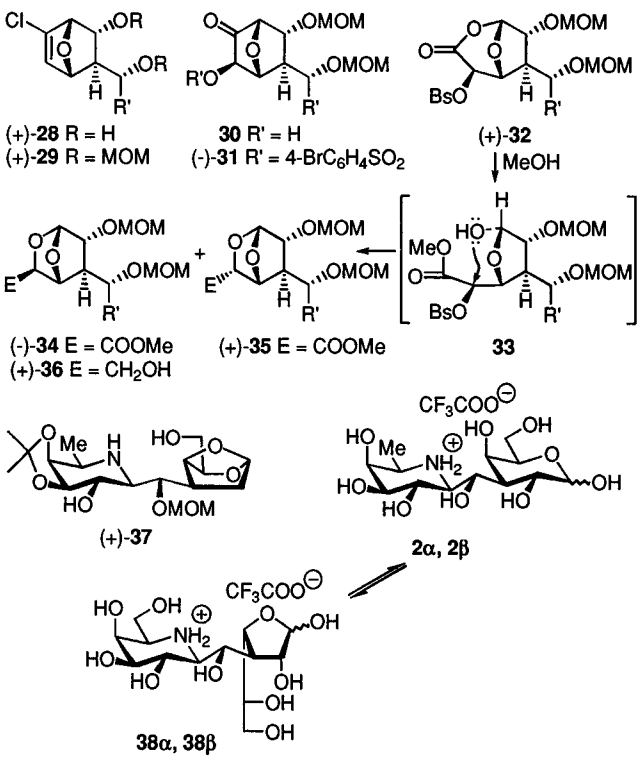


Figure 3. (A) Vicinal ^3J(H,H) coupling constants (Hz) measured for **1**α; (B) three-dimensional representation of the average conformation of **1**α with indication of the major NOE's (by 600 MHz NOESY).

able yet, as well as quantitative *J* and NOE analyses. As it has been shown for *C*-lactose and derivatives,[25] the conformational population of a *C*-disaccharide may depend on solvent and temperature. In order to test for an eventual temperature effect, we measured the ^{1}H NMR (600 MHz) spectrum of **1**α at 11, 25, 39, and 60 °C (pH 5.7, 1:1 CD_3OD/D_2O). No change could be detected for the vicinal coupling constants. We also tested for an eventual pH dependence of the conformation of **1**α and measured its ^{1}H NMR spectrum at pH = 4.4, 5.7, 8.0, 9.0, and 9.8 at 40 °C (1:1 CD_3OD/D_2O, addition of AcOH or NaOH diluted in 1:1 CD_3OD/D_2O). Expect for some changes in the chemical shifts, the largest effect being observed for proton H-C(2′), as expected (δ_H = 3.20 ppm at pH 4.4, 2.47 ppm at pH 9.8), no change of the vicinal coupling constants were observed, except for ^3J(H-C(2), H-C(3)) of the altrofuranoside unit which varied from 1.3 Hz at pH <5.7 to 3 Hz at pH >8.0. Apart from a possible change in the population of the conformations of the furanoside ring, the average conformation around the aza-*C*-glycosidic link and around the C-link and the aglycon was not affected by the pH.

By measuring the chemical shifts of the methyl groups of the 6-deoxygalactopyranoside moieties of **1**α and **1**β as a function of pH (titration curves) we evaluated the pK_a of the conjugate acid **1**αH^+ and **1**βH^+ to be 7.7 and 7.4, respectively, at 40 °C in 1:1 CD_3OD/D_2O.

Synthesis of an aza-*C*-β-galactoside (1→3) of Galactose. Oxidative elimination of the PhSe group of (−)-**19** (mCPBA, CH_2Cl_2) afforded (+)-**28** (95%). Its diol moiety was then protected as MOM ethers to obtain (+)-**29** (95%). Double hydroxylation of the chloroalkene (+)-**29** (Me_3NO, OsO_4, $NaHCO_3$, THF) led to an unstable α-hydroxy ketone **30** which was esterified without purification with 4-$BrC_6H_4SO_2Cl$ (Et_3N/CH_2Cl_2) into brosylate (−)-**31** (84%). Baeyer−Villiger oxidation of (−)-**31** furnished uronolactone (+)-**32**, the methanolysis of which (MeOH/DMF, anhydrous K_2CO_3) gave a 10:1 mixture of (−)-**34** (66%) and (+)-**35** (6%). The latter compound arises probably from the K_2CO_3-induced epimerization of (−)-**34**. The formation of (−)-**34** can be interpreted in terms of a S_Ni process that follows the MeOH addition onto the uronolactone and liberalization of the intermediate α-furanose **33**.[26]



Reduction of (−)-**34** with $LiBH_4$ in THF afforded (+)-**36** (82%). Debenzylation (H_2/Pd/C, THF, H_2O) of (+)-**36** gave (+)-**37** (97%). Treatment (+)-**37** with HCl in various media gave untractable mixtures of compounds, some of them resulting from aromatization through water elimination (formation of pyridine from the piperidine moiety). Finally smooth deprotection of (+)-**37** was achieved through acidic hydrolysis with CF_3COOH in 1:8 H_2O/THF at 37 °C (15 h). This led to a 68:32 mixtures of the galactopyranoses **2**α + **2**β (α:β, 2:3) and galactofuranoses **38**α + **38**β (α:β, 1:2), the structures of these aza-*C*-disaccharides being confirmed by NMR methods (^{1}H, ^{13}C, COSY-DQF, XHCOR, DEPT) for solutions in MeOH. All the structures given for the other compounds described above were consistent with their spectral data and elemental analyses (see Experimental Section) as well as with their modes of formation.[27]

Although the related (+)-3,7,8-trideoxy-3,7-imino-D-*threo*-L-*galacto*-octitol derived from (+)-**11** was found to be a competitive inhibitor of β-glucosidases from almonds and from *Caldocellum saccharolyticum*, the more complicated aza-*C*-galactosides (+)-**1**α,β and **2**α,β showed no significant (IC_{50} >10 mM) inhibition of these enzymes, nor did they inhibit the following commercially available glycosidases: α-glucosidases form yeast and rice, β-xylosidase from *Aspergillus niger*, α-L-fucosidase form bovine epididymis, β-mannosidase from *Helix pomatia* and α-mannosidases from beans and from almonds. As expected, the aza-*C*-disaccharides (+)-**1**α,β and **2**α,β

(26) Kraehenbuehl, K.; Vogel, P. *Tetrahedron Lett.* **1995**, *36*, 8595.
(27) Conformational analysis of **2**α,β and **31**α,β could not be carried out because of too many overlapping proton signals in the 600 MHz ^{1}H NMR spectrum of this mixture.
(28) Gasparini, F.; Vogel, P. *J. Org. Chem.* **1990**, *55*, 2451.

might be inhibitors of glycosidases that cleave specifically β-galactoside-*O*(1→3) links, what the above enzymes are not specialized for, apparently. Work will be initiated to search for such enzymes and for biological systems capable to interact with our aza-*C*-disaccharides.

Conclusion

The syntheses of branched, long-chain carbohydrates containing 13 carbon centers, a 1,5,6-trideoxy-1,5-imino-D-galactitol moiety β-C-linked to various hexoses has been possible through stereoselective (like mode) aldol condensations of a protected 3,4,5-trihydroxy-6-methylpiperidine-2-carbaldehyde with the lithium enolates of (+)-(1*R*,4*S*,5*S*,6*S*)- and (−)-(1*S*,4*R*,5*R*,6*R*)-6-chloro-5-(phenylseleno)-7-oxabicyclo[2.2.1]heptan-2-one. Stereoselective transformations of the aldols so-obtained led to two "branched" aza-*C*-disaccharides. In the first case, 6-deoxy-D-galactonojirimycin is β-linked at position C(3) of methyl α- and β-altrofuranoside (**1**) through a hydroxymethylene bridge. In the second case, 6-deoxy-D-galactonojirimycin is β-linked at position C(3) of D-galactose, through a hydroxymethylene group. The latter aza-*C*-disaccharide resembles somehow the tumor specific carbohydrate antigen D-Galβ(1→3) GalNAc (Thomsen−Friedenreich antigen (T)).[29] Conjugates with peptides will be tested as potential "anticancer vaccine".[30]

Experimental Section

General Remarks. See refs 23, 28. None of the procedures were optimized. Flash column chromatography (FC) was performed on Merck silica gel (230−400 mesh). Thin layer chromatography (TLC) was carried out on silica gel (Merck aluminum foils). ^{1}H NMR signal assignments were confirmed by double irradiation experiments and, when required, by 2-D-NOESY and COSY spectra. *J* values are given in hertz. 600 MHz ^{1}H NMR spectra were recorded on a Bruker AMX-600 FT spectrometer.

Methyl 3-Deoxy-3-[(1′*R*)-2′,6′,7′-trideoxy-2′,6′-imino-β-D-*glycero*-L-*manno*-heptitol-1′-yl]-α- and β-D-altrofuranoside ((+)-1α,β). Aqueous NH_3 (50%, 1 mL) was added to a stirred solution of (+)-**27** (12 mg, 0.02 mmol) in MeOH (2 mL). After 2 h of stirring, the solvent was evaporated. The residue was taken up in MeOH (0.2 mL) and 2 N HCl (0.5 mL) and deposited on a Dowex 50W X8 column (H^+ form, 3 g, 200−400 mesh) and washed first with H_2O, then with MeOH, and finally with 5% aqueous NH_3 to provide (+)-**1**α,β (7 mg, 95%) as a 5:1 mixture of α- and β-anomer which precipitated from MeOH/Et_2O: mp 208−210 °C dec; $[\alpha]^{25}_D = +1.3$, $[\alpha]^{25}_{577} = +1.8$, $[\alpha]^{25}_{546} = +2.2$, $[\alpha]^{25}_{435} = +3.4$, $[\alpha]^{25}_{405} = +4.0$ (*c* = 0.7, MeOH); IR (KBr) ν 3135, 2010, 1765, 1410 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD/D_2O, pH 5.7) δ 4.80 (br s, HC(1)), 4.36 (d, ^3J(2,3) = 1.3, HC(2)), 4.28 (dd, ^3J(1′,3) = 10.1, ^3J(1′,2′) = 1.5, HC(1′)), 4.04 (d, ^3J(2′,3′) = 10.2, ^3J(3′,4′) = 9.8, HC(3′)), 4.00 (ddd, ^3J(4′,5′) = 2.8, ^3J(5′,6′) = 0.8, HC(5′)), 3.92 (dd, ^3J(4,5) = 8.4, ^3J(3,4) = 5.3, HC(4)), 3.88 (dd, ^2J = 11.8, ^3J = 2.6) & 3.73 (dd, 11.8, 5.0, H_2C(6)), 3.77 (ddd, 8.4, 5.0, 2.6, HC(5)), 3.69 (dd, 9.5, 2.8, HC(4′)), 3.54 (qd, 6.7, 0.8, HC(6′)), 3.20 (dd, 10.2, 1.5, HC(2′)), 2.40 (ddd, 10.1, 5.3, 1.3, HC(3)), 1.43 (d, 6.7, Me-C(6′)); ^{13}C-NMR (100.61 MHz, $CDCl_3$, 50 °C) δ 110.9 (d, C(1)), 79.3, 79.0, 76.3, 75.3, 71.2, 67.0, 66.7 (7d), 64.4 (t, C(6)), 62.2, 56.1, 54.8, 54.5 (4d), 21.5 (q, $OCCH_3$); 15.3 (q, C(7′)); CI-MS (NH_3) *m*/*z* 355 (3), 354 (7), 322 (20), 292 (20), 278 (15), 250 (25), 160 (26), 146 (81), 123 (47), 109 (88), 97 (80), 81 (100); CI-MS (electrospray) 354.7 (100); for $C_{14}H_{27}O_9N$ (353.16).

3-Deoxy-3-[(1′*S*)-2′,6′,7′-trideoxy-2′,6′-iminio-β-D-*glycero*-L-*manno*-heptitol-1′-yl]-β-D-galactose Trifluoroacetate and Isomers ((−)-2α,β,38α,β). A solution of (+)-**37** (24 mg, 0.06 mmol) in trifluoroacetic acid/H_2O 8:2 (3 mL) was stirred at 37 °C for 15 h. Evaporation led to 23.4 mg (98%) of a mixture of **2**α,β and **38**α,β: a slightly yellow oil; $[\alpha]^{25}_D = -4.1$, $[\alpha]^{25}_{577} = -6.2$, $[\alpha]^{25}_{546} = -7.0$ (*c* = 1.2, MeOH); IR (film) ν 3425, 2925, 1685, 1435, 1210, 1135, 945, 840, 805, 725 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) of **2**α (signal attributions for **2**α in the mixture relies, when possible, upon 2D spectra (COSY, HMQC, DEPT)) δ 5.28 (d, 0.2 H, ^3J = 4.4, HC(1), β-Gal*f*), 5.26 (d, 0.1 H, ^3J = 4.5, HC(1), α-Gal*f*), 5.23 (d, 0.4 H, ^3J = 4.5, HC(1), β-Gal*p*), 5.21 (d, 0.3 H, ^3J = 4.5, HC(1), α-Gal*p*), 4.63−4.55 (m, 1.2 H), 4.52−4.43 (m, 1.5 H), 4.38−4.30 (m, 1.8 H, HC(2), Gal*f*), 4.26−4.16 (m, 1.5 H, HC(2), Gal*p*, HC(4′)), 4.10−3.85 (m, 6.8 H), 3.77−3.53 (m, 4.8 H), 3.51−3.38 (m, 1.9 H, H-C(6′)), 3.31−3.22 (m, 1.3 H), 2.80−2.62 (m, 1.5 H, H-C(2′), H-C(3)), 1.48−1.40 (m, 3 H, H_3-C(7′)); ^{13}C-NMR (150.92 MHz, CD_3OD) of **2**β and **2**α (β-Gal*p*), δ 161.0 (s, CF_3COO), 117.3 (q, CF_3COO), 96.6 (d, C(1)), 80.8 (d, C(4′)), 75.5, 72.8, 71.8, 70.5, 67.5, 65.3 (6d, C(2), C(4), C(5), C(1′), C(3′), C(5′)), 64.3 (t, C(6)), 64.2, 56.9, 48.8 (3d, C(6′), C(2′), C(3)), 15.1 (q, C(7′)), (α-Gal*p*), δ 161.2 (s, CF_3COO), 117.3 (q, CF_3COO), 96.6 (d, C(1)), 81.8 (d, C(4′)), 78.8, 75.5, 74.4, 71.7, 70.4, 67.4 (6d, C(2), C(4), C(5), C(1′), C(3′), C(5′)), 64.8 (d, C(6′)), 64.2 (t, C(6)), 56.6, 43.8 (2d, C(2′), C(3)), 15.1 (q, C(7′)); CI-MS (electrospray) 339 (100), 322 (33); CI-MS (NH_3) *m*/*z* 341 (1), 340 (1), 322 (5), 285 (8), 267 (7), 175 (8), 146 (26), 137 (39), 123 (100), 115 (25), 95 (60), 80 (44). Anal. Calc for $C_{13}H_{25}O_9N\cdot CF_3COOH$ (339.34 + 113.99): C, 39.72; H, 5.78. Found: C, 39.84; H, 5.84.

2,3:6,7-Di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone ((−)-4) and 3,5:6,7-Di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone ((−)-5). D-*glycero*-D-*gulo*-Heptono-1,4-lactone ((−)-**3**, Aldrich) (8 g, 38.4 mmol), *p*-toluenesulfonic acid (0.2 g, 1.05 mmol), and $CaSO_4$ (1 g, 7.64 mmol) were stirred in acetone (80 mL) in an autoclave at 150 °C. After 1.5 h the mixture was neutralized with Na_2CO_3 and then filtered. Silica gel (40 g) was added and the suspension carefully evaporated *in vacuo*. FC (silica gel (400 g), EtOAc/petroleum ether 3: 2, then EtOAc) yielded 2.78 g (25%) of (−)-**4**, 4.22 g (38%) of (−)-**5**, and 1.03 g (13%) of starting material ((−)-**3**). **Recycling of (−)-5 and (−)-3**. The same procedure as above was used starting with D-*glycero*-D-*gulo*-heptono-1,4-lactone ((−)-**3**) (1 g, 5.0 mmol) and (−)-**5** (4.2 g, 14.6 mmol), yielding 1.0 g (18%) of (−)-**4**, 2.1 g (37%) of (−)-**5** and 0.3 g (7%) of (−)-**3**. All spectral and physical data of (−)-**4** and (−)-**5** were identical to those published.[13,14]

4-*O*-Benzyl-3,7,8-trideoxy-3,7-imino-1,2:5,6-di-*O*-isopropylidene-D-*threo*-L-*galacto*-octitol ((−)-10). Heptono-1,4-lactone (−)-**4** was converted into 3,7,8-trideoxy-3,7-imino-1,2:5,6-di-*O*-isopropylidene-D-*threo*-L-*galacto*-octitol (+)-**9** as already described.[15] NaH, 55% in oil (302.4 mg, 6.93 mmol), benzyl bromide (0.85 mL, 6.93 mmol), and tetrabutylammonium iodide (60 mg, 0.17 mmol) were added successively to a stirred solution of (+)-**9** (995 mg, 3.46 mmol) in THF (10 mL). After 15 h of stirring, the mixture was poured into aqueous saturated $NaHCO_3$ solution (100 mL) and the aqueous layer was extracted with EtOAc (50 mL, 4 times). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by FC (silica gel (20 g), EtOAc/petroleum ether, 1:4): 1.03 g (79%) of (−)-**10**, colorless oil; $[\alpha]^{25}_D = -1.9$ (*c* = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (d, m), 4.93, 4.57 (2d, ^2J = 11.4), 4.24 (ddd, ^3J = 7.9, 6.2, 5.2), 4.12 (dd, ^3J = 6.9, 5.4), 4.05 (dd, ^3J = 5.4, 2.6), 3.97 (dd, ^2J = 8.1, ^3J = 6.2), 3.89 (dd, ^2J = 8.1, ^3J = 7.9), 3.41 (dd, ^3J = 10.0, 6.9), 3.03 (dd, ^3J = 6.7, 2.6), 2.44 (dd, ^3J = 10.0, 5.2), 1.55, 1.42, 1.40, 1.34 (4s), 1.28 (d, ^3J = 6.7).

4-*O*-Benzyl-N-(benzyloxycarbonyl)-3,7,8-trideoxy-3,7-imino-1,2:5,6-di-*O*-isopropylidene-D-*threo*-L-*galacto*-octitol ((+)-11). Method A (from (−)-10). $NaHCO_3$ (400 mg, 4.80 mmol) and benzyl chloroformate (0.48 mL, 3.28 mmol)

(29) Springer, G. F. *Science* **1984**, *224*, 1198. MacLean, G. D., Longenecker, B. L. *Semin. Cancer Biol.* **1991**, *2*, 443. Samuel, J.; Nouaim, A. A.; MacLean, G. D.; Suresh, M. R.; Longenecker, B. M. *Cancer Res.* **1990**, *250*, 4801. Zhuang, D.; Yousef, S.; Dennis, J. W. *Cancer Biochem. Biophys.* **1991**, *12*, 185. Rabinovich, N. R.; McInnes, P.; Klein, D. L.; Hall, P. F. *Science* **1994**, *265*, 1401.

(30) See, e.g.: MacLean, G. D.; Reddish, M.; Koganty, R. R.; Wong, T.; Gaudhi, S.; Smolenski, M.; Samuel, J.; Nabholtz, J. M.; Longenecker, B. M. *Cancer Immunol. Immunother.* **1993**, *36*, 215. See also: Hanessian, S.; Qiu, D.; Prabhanjan, H.; Reddy, G. V.; Lou, B. *Can. J. Chem.***1996**, *74*, 1738.

were added to a stirred solution of (−)-**10** (1.03 g, 2.73 mmol) in 50% aqueous EtOH (16.2 mL). After 2 h of stirring at 20 °C, the mixture was poured into aqueous saturated $NaHCO_3$ (100 mL) and the aqueous layer was extracted with EtOAc (50 mL, four times). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by FC (silica gel (20 g), EtOAc/petroleum ether, 1:6): 1.35 g (97%) of (+)-**11**, colorless oil.

Method B, from *N*-(Benzyloxycarbonyl)-3,7,8-trideoxy-3,7-imino-1,2:5,6-di-*O*-isopropylidene-D-*threo*-L-*galacto*-octitol (A). NaH, 55% in oil (47 mg, 0.95 mmol), benzyl bromide (0.12 mL, 0.93 mmol), and tetrabutylammonium iodide (6 mg, 0.02 mmol) were added successively to a stirred solution of **A** (124 mg, 0.94 mmol) in THF (2.5 mL). After 15 h of stirring at 20 °C, the mixture was poured into aqueous saturated $NaHCO_3$ solution (15 mL), and the aqueous layer was extracted with EtOAc (30 mL, four times). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by FC (silica gel (20 g), EtOAc/ petroleum ether 1:6): 145 mg (97%) of **(+)-11**, colorless oil; $[\alpha]^{25}_D = +50$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m), 5.12 (s), 4.87, 4.63 (2d, $^2J = 7.4$), 4.78 (qd, $^3J = 7.4, 7.4$), 4.40−4.33 (m), 4.20 (dd, $^3J = 8.2, 6.7$), 4.08 (dd, $^2J = 8.7$, $^3J = 4.5$), 4.03 (dd, $^2J = 8.7$, $^3J = 6.8$), 3.90 (dd, $^3J = 8.7, 8.2$), 3.47 (dd, $^3J = 8.7, 8.7$), 1.56, 1.53, 1.36, 1.33 (4s), 1.28 (d, $^3J = 7.4$).

***N*-(Benzyloxycarbonyl)-3,7,8-trideoxy-3,7-imino-1,2:5,6-di-*O*-isopropylidene-D-*threo*-L-*galacto*-octitol (A).** $NaHCO_3$ (58 mg, 0.69 mmol) and benzyl chloroformate (0.07 mL, 0.47 mmol) were added to a stirred solution of (−)-**9**[15] (113 mg, 0.394 mmol) in 50% aqueous EtOH (2 mL). After 2 h of stirring at 20 °C for 2 h, the mixture was poured into aqueous saturated $NaHCO_3$ (10 mL), and the aqueous layer was extracted with EtOAc (5 mL, five times). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by FC (silica gel (8 g), EtOAc/petroleum ether, 1:2): 124 mg (75%) of **A**, colorless oil; $[\alpha]^{25}_D = +78.3$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (m), 5.14 (s), 4.52−4.44 (m), 4.39 (dd, $^3J = 8.1, 7.8$), 4.23 (ddd, $^3J = 9.7, 8.3, 3.0$), 4.03 (dd, $^3J = 8.3, 8.1$), 3.98 (dd, $^3J = 9.7, 4.5$), 3.93 (dd, $^2J = 8.7, 6.0$), 3.62 (dd, $^2J = 8.7$, $^3J = 8.7$), 3.00 (d, $^3J = 3.0$), 1.50, 1.37, 1.35, 1.35 (4s), 1.24 (d, $^3J = 7.4$).

3-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2,6,7-trideoxy-2,6-imino-4,5-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptose ((−)-12). Method A. A mixture of (+)-**11** (203 mg, 0.397 mmol) and $NaIO_4$ (102 mg, 0.477 mmol) in acetic acid/water 8:1 (4.15 mL) was allowed to stand at 20 °C overnight. The mixture was poured into aqueous saturated $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL, four times). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by FC (silica gel (15 g), EtOAc/petroleum ether, 1:4): 167 mg (94%) of **(−)-12**, colorless oil; $[\alpha]^{25}_D = -2.7$ ($c = 1.4$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s), 7.36−7.30 (m), 5.14 (s), 4.78, 4.61 (2d, $^2J = 11.5$), 4.52 (qd, $^3J = 7.0, 6.9$), 4.49 (d, $^3J = 7.9$), 4.39 (dd, $^3J = 8.0, 6.9$), 4.30 (dd, $^3J = 7.9, 5.7$), 4.05 (dd, $^3J = 8.0, 5.7$), 1.55, 1.36 (2s), 1.27 (d, $^3J = 7.0$).

Method B. An aqueous solution of $NaIO_4$ (105 mg, 0.49 mmol in 1 mL of H_2O) was added to a stirred solution of **B** (see below) (115 mg, 0.244 mmol) in THF (2 mL). After 15 min at 20 °C, the mixture was diluted with CH_2Cl_2 (15 mL) and washed twice with brine. The aqueous layer was extracted with CH_2Cl_2 (5 mL, twice), and the combined organic extracts were dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by FC (silica gel (15 g), EtOAc/ petroleum ether, 1:4): 95 mg (89%) of (−)-**12**, a colorless oil.

(+)-4-*O*-Benzyl-*N*-(benzyloxycarbonyl)-3,7,8-trideoxy-3,7-imino-5,6-*O*-isopropylidene-D-*threo*-L-*galacto*-octitol (B). Dowex 50W-X8 (633 mg) was added to a solution of (+)-**11** (422 mg, 0.83 mmol) in 90% aqueous MeOH (6 mL). After being stirred at 20 °C overnight, the mixture was filtered, and the solvent was evaporated with toluene (15 mL, twice). FC (silica gel (15 g), EtOAc/petroleum ether, 1:4) of the residue permitted the recovery of 228 mg of starting material (conversion 46%), together with 154 mg (40%) of **B**, colorless oil: $[\alpha]^{25}_D = +34.4$ ($c = 1.2$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.37−7.30 (m), 5.16, 5.13 (2d, $^2J = 12.3$), 4.85, 4.60 (2d, $^2J = 11.5$), 4.67 (dq, $^3J = 7.1, 7.1$), 4.35 (dd, $^3J = 8.3, 7.1$), 4.24 (dd, $^3J = 8.3, 6.1$), 4.11 (dd, $^3J = 7.9, 6.4$), 3.93 (dd, $^3J = 7.9, 6.1$), 3.93−3.90 (m), 3.65−3.63, 3.59−3.57 (2m), 2.62 (br s), 2.55 (d, $^3J = 6.9$), 1.55, 1.36 (2s), 1.27 (d, $^3J = 7.1$).

(1*R*,3*R*,4*S*,5*S*,6*S*)-3-*exo*-[(1′*R*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-*endo*-chloro-5-*exo*-(phenylseleno)-7-oxabicyclo[2.2.1]heptan-2-one ((−)-14) and (1*R*,3*R*,4*S*,5*S*,6*S*)-3-*exo*-[(1′*R*)-N-(Benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-*endo*-chloro-5-*exo*-(phenylseleno)-7-oxabicyclo[2.2.1]heptan-2-one ((+)-15). A 1.6 M solution of BuLi in hexane (1.61 mL, 2.5 mmol) was added to a stirred solution of HMDS (0.37 mL, 1.76 mmol) at −10 °C in anhydrous THF (3.5 mL). After 20 min of stirring at −5 °C, the mixture was cooled to −78 °C, and a solution of ketone (+)-**13**[16a] (463 mg, 1.53 mmol) in anhydrous THF (3.5 mL) was added dropwise over a period of 30 min. At the end of the addition, the mixture was left at −78 °C for 20 min and then cooled to −95 °C. Aldehyde (−)-**12** (739 mg, 1.68 mmol) in anhydrous THF (1.2 mL) was added dropwise, and the mixture was maintained at −95 °C for 5.5 h and then poured into a 10% solution of AcOH in THF (40 mL) previously cooled to −95 °C. After being warmed to −10 °C, the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (50 mL, four times). The resulting organic phases were dried ($MgSO_4$), and the solvent was evaporated. FC (silica gel, 100 g, CH_2Cl_2/ petroleum ether/Et_2O, 1:5:1) afforded 90 mg of the starting ketone (19%), 60 mg of the starting aldehyde (−)-**12** (8%), 505 mg of (−)-**14** (45%), and 260 mg (26%) of (+)-**15** both as white crystals.

Data for (−)-14: mp 138.5−140 °C (Et_2O/petroleum ether); $[\alpha]^{25}_D = -7.5$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.72−7.48, 7.34−7.26 (2m), 5.24, 5.16 (2d, $^2J = 12.4$), 4.96 (br s), 4.88, 4.63 (2d, $^2J = 11.5$), 4.69 (dq, $^3J = 7.3, 7.3$), 4.42 (dd, $^3J = 5.7, 1.0$), 4.34 (ddd, $^3J = 5.7, 2.8$, $^4J = 1.0$), 4.27 (dd, $^3J = 7.2, 6.8$), 4.20 (dd, $^3J = 7.3, 6.8$), 4.16−4.05 (m), 3.40 (d, $^3J = 2.8$), 3.15 (br s), 2.29 (d, $^3J = 9.3$), 1.52, 1.34 (2s), 1.07 (d, $^3J = 7.3$).

Data for (+)-15: mp 195−196 °C (Et_2O); $[\alpha]^{25}_D = +35.0$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.58, 7.37−7.28 (2m), 4.80 (br s), 4.76, 4.55 (2d, $^2J = 11.6$), 4.41 (dd, $^3J = 7.4, 3.8$), 4.35 (d, $^3J = 5.7$), 4.33 (dd, $^3J = 5.7, 2.6$), 4.26 (dd, $^3J = 6.0, 6.0$), 4.12 (dd, $^3J = 6.0, 2.8$), 3.84 (dd, $^3J = 7.4, 7.4$), 3.63 (dq, $^3J = 7.1, 2.8$), 3.47 (d, $^3J = 2.6$), 2.64 (d, $^3J = 3.8$), 1.66 (d, $^3J = 7.1$), 1.51, 1.38 (2s).

(1*S*,3*S*,4*R*,5*R*,6*R*)-3-*exo*-[(1′*S*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-*endo*-chloro-5-*exo*-(phenylseleno)-7-oxabicyclo[2.2.1]heptan-2-one ((+)-16). A 1.6 M solution of BuLi in hexane (0.41 mL, 0.66 mmol) was added to a stirred solution of HMDS (0.22 mL, 0.72 mmol) at −10 °C in anhydrous THF (1.5 mL). After 20 min of stirring at −5 °C, the mixture was cooled to −78 °C and a solution of racemic ketone (±)-**13**[16a] (199 mg, 0.66 mmol) in anhydrous THF (1.5 mL) was added dropwise over a period of 30 min. At the end of the addition, the mixture was left at −78 °C for 20 min and then cooled to −95 °C. The aldehyde (−)-**12** (278 mg, 0.63 mmol) in anhydrous THF (0.4 mL) was added dropwise, and the mixture was maintained at −95 °C for 3.5 h and then poured into a 10% solution of AcOH in THF (35 mL) previously cooled to −78 °C. After being warmed to −10 °C, the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (30 mL, four times). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated. FC (silica gel, 40 g, CH_2Cl_2/ petroleum ether/Et_2O, 1:5:1) afforded 53 mg of the starting ketone (±)-**13** (27%), 120 mg of (+)-**16** (35%) as a colorless oil, 148 mg (30%) of (−)-**14** as white crystals, 50 mg (18%) of (−)-**12** and 25 mg (6%) of (+)-**15** as white crystals.

Data for (+)-16: $[\alpha]^{25}_D = +27.4$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.39−7.25 (m), 5.16, 5.12 (2s, $^2J = 14.5$), 4.88 (br s), 4.89, 4.69 (2d, $^2J = 10.8$), 4.68 (dq, $^3J = 7.3$,

7.3), 4.47 (dd, ^3J = 9.0, 7.2), 4.40 (br d, ^3J = 5.7), 4.38 (dd, ^3J = 8.2, 7.3), 4.24 (dd, ^3J = 8.2, 7.2), 4.21 (ddd, ^3J = 5.7, 2.7, ^4J = 1.0), 4.18 (br d, ^3J = 9.8), 3.85 (dd, ^3J = 9.0, 1.7), 3.35 (br s), 3.05 (d, ^3J = 2.7), 2.71 (d, ^3J = 9.8), 1.54, 1.38 (2s), 1.23 (d, ^3J = 7.3).

(1*R*,2*S*,3*S*,4*S*,5*S*,6*S*)-3-*exo*-[(1′*R*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-*endo*-chloro-5-*exo*-(phenylseleno)-7-oxabicyclo[2.2.1]heptan-2-*endo*-ol ((+)-17). $NaBH_4$ (30 mg, 0.78 mmol) was added to a stirred solution of (−)-**14** (197 mg, 0.27 mmol) in THF/MeOH, 1:1 (8 mL), cooled to 0 °C. After 0.5 h of stirring, the mixture was neutralized with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (20 mL, four times). The combined organic extracts were dried ($MgSO_4$) and the solvents evaporated. Purification of the residue by FC (silica gel, 15 g, EtOAc/petroleum ether, 1:1) afforded 174 mg (88%) of (+)-**17** as a colorless oil: $[\alpha]^{25}_D$ = +17.3 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.65−7.26 (m), 5.09, 5.05 (2d, ^2J = 11.3), 4.77, 4.62 (2d, ^2J = 11.6), 4.60 (dq, ^3J = 7.4, 7.2), 4.51 (br s), 4.37 (m), 4.31 (dd, ^3J = 8.3, 7.4), 4.22 (dd, ^3J = 8.3, 5.8), 4.12 (dd, ^3J = 7.7, 5.4), 3.97 (dd, ^3J = 7.7, 5.8), 3.86 (br dd, ^3J = 6.2, 5.4), 3.41 (br s), 2.65, 1.98 (2 br s), 1.89 (br dd, ^3J = 6.2, 4,4), 1.41, 1.34 (2s), 1.27 (d, ^3J = 7.2).

(4*R*,4a*R*,5*S*,6*S*,7*S*,8*R*,8a*S*)-[(1′*R*)-2′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-1′,5′,6′-trideoxy-1′,5′-imino-3′,4′-*O*-isopropylidene-*β*-D-*galacto*-hexitol-1′-yl]-2,2-di-*tert*-butyl-7-chloro-4a,5,6,7,8,8a-hexahydro-6-(phenylseleno)-5,8-epoxy-4*H*-1,3-dioxa-2-silanaphthalene ((+)-18). 2,6-Lutidine (0.009 mL, 0.07 mmol) and di-*tert*-butylsilyl ditriflate (0.001 mL, 0.028 mmol) were added to a stirred solution of (+)-**17** (17 mg, 0.023 mmol) in anhydrous $CHCl_3$ (1 mL). After 14 h of stirring at 50 °C, the mixture was neutralized with ice cold aqueous 1 M solution of HCl and extracted with CH_2Cl_2 (5 mL, four times). The combined organic extracts were dried ($MgSO_4$) and the solvents evaporated. Purification of the residue by FC (silica gel, 8 g, EtOAc/petroleum ether, 1:4) afforded 5 mg (25%) of (+)-**18** as a colorless oil: $[\alpha]^{25}_D$ = +6.2 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.20 (m), 5.02, 4.94 (2d, ^2J = 12.3), 4.74, 4.59 (2d, ^2J = 11.6), 4.58−4.50 (m), 4.51−4.45 (m), 4.35 (dd, ^3J = 4.6, 4.6), 4.27 (dd, ^3J = 8.0, 5.1), 4.22 (dd, ^3J = 4.6, 0.3), 4.21 (dd, ^3J = 8.0, 6.2), 3.97 (br d, ^3J = 6.9), 3.79 (m), 3.58 (dd, ^3J = 11.1, 3.1), 3.28 (br s), 1.91 (dd, ^3J = 11.1, 1.0), 1.52, 1.35 (2s), 1.20 (d, ^3J = 7.0), 1.01, 0.93 (2s).

(1*S*,2*R*,3*R*,4*R*,5*R*,6*R*)-3-*exo*-[(1′*S*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-*endo*-chloro-5-*exo*-(phenyseleno)-7-oxabicyclo[2.2.1]heptan-2-*endo*-ol ((−)-19). $NaBH_4$ (45 mg, 1.17 mmol) was added to a stirred solution of (+)-**16** (300 mg, 0.42 mmol) in THF/MeOH 1:1 (10 mL) cooled to 0 °C. After 0.5 h of stirring, the mixture was neutralized with an aqueous saturated solution of NH_4Cl and extracted with CH_2Cl_2 (30 mL, four times). The combined organic extracts were dried ($MgSO_4$), and the solvents were evaporated. Purification of the residue by FC (silica gel, 15 g, EtOAc/petroleum ether, 1:1) afforded 300 mg (96%) of (−)-**19**: colorless oil; mp 170−171 °C (Et_2O); $[\alpha]^{25}_D$ = −15.5 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.53−7.26 (m), 5.13 (s), 4.66, 4.58 (2d, ^2J = 11.3), 4.48−4.42 (m), 4.39−4.36 (m), 4.31−4.11 (m), 3.38 (d, ^3J = 3.7), 2.50 (br s), 2.07 (dd, ^3J = 6.1, 4.7), 1.50, 1.33 (2s), 1.30 (d, ^3J = 6.6).

(4*S*,4a*R*,5*R*,8*S*,8a*R*)-[(1′*S*)-2′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-1′,5′,6′-trideoxy-1′,5′-imino-3′,4′-*O*-isopropylidene-*β*-D-*galacto*-hexitol-1′-yl]-2,2-di-*tert*-butyl-7-chloro-4a,5,8,9-tetrahydro-5,8-epoxy-4*H*-1,3-dioxa-2-silanaphthalene ((+)-21). 2,6-Lutidine (0.024 mL, 0.21 mmol) and di-*tert*-butylsilyl ditriflate (0.029 mL, 0.084 mmol) were added to a stirred solution of (−)-**19** (52 mg, 0.07 mmol) in anhydrous CH_2Cl_2. After 20 h of stirring at 20 °C, the mixture was neutralized with ice cold aqueous 1 M solution of HCl and extracted with CH_2Cl_2 (10 mL, four times). The combined organic extracts were dried ($MgSO_4$), and the solvents were evaporated. Purification of the residue by FC (silica gel, 8 g, EtOAc/petroleum ether, 1:4) afforded 55 mg (89%) of a mixture of rotamers **20** as colorless oil. A solution of 85% *m*CPBA (12 mg, 0.06 mmol) in anhydrous CH_2Cl_2 (1.2 mL) was added dropwise to the stirred solution of **20** (50 mg, 0.056 mmol) in anhydrous CH_2Cl_2 (3 mL) cooled to −78 °C. After 3 h of stirring at −78 °C, the mixture was allowed to warm up to 20 °C over 10 h. CH_2Cl_2 (5 mL) was added, and the solution was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL, four times). The combined organic phases were washed with brine (15 mL) and dried ($MgSO_4$). After solvent evaporation *in vacuo*, the residue was purified by FC (silica gel, 15 g, EtOAc/petroleum ether, 1:4), yielding 28 mg (74%) of (+)-**21** as a foam (66% based on (−)-**19**): $[\alpha]^{25}_D$ = +12.8 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m), 5.58 (br s), 5.17, 5.10 (2d, ^2J = 12.2), 4.76, 4.45 (2d, ^2J = 10.4), 4.76 (br s), 4.57 (d, ^3J = 4.4), 4.55 (dd, ^3J = 4.4, 1.2), 4.49 (dq, ^3J = 7.3, 7.1), 4.36 (dd, ^3J = 8.3, 7.1), 4.31 (dd, ^3J = 8.3, 4.1), 4.33−4.24 (m), 4.15 (dd, ^3J = 10.8, 5.5), 1.82 (br d, ^3J = 10.8), 1.52, 1.35 (2s), 1.26 (d, ^3J = 7.1), 1.04, 0.99 (2s).

(1*R*,2*S*,3*S*,4*S*,5*S*,6*S*)-3-*exo*-[(1′*R*)-1′-*O*-Acetyl-3′-*O*-benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-*endo*-chloro-5-*exo*-(phenylseleno)-7-oxabicyclo[2.2.1]hept-2-*endo*-yl Acetate ((−)-22). A solution of (+)-**17** (167 mg, 0.225 mmol) in a 3:2 mixture of pyridine/Ac_2O (5 mL) was stirred overnight with DMAP (2 mg). After evaporation of the solvents, FC of the residue (silica gel, 15 g, EtOAc/petroleum ether, 1:6) afforded 184 mg (99%) of (−)-**22** as a colorless oil: $[\alpha]^{25}_D$ = −8.8 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.62−7.26 (m), 5.51 (dd, ^3J = 6.0, 5.8), 5.08 (s), 5.08 (m), 4.77 (dd, ^3J = 4.4, 4.4), 4.70, 4.53 (2d, ^2J = 11.5), 4.57 (s), 4.53 (m), 4.36 (m), 4.26 (dd, ^3J = 7.2, 7.0), 4.20 (dd, ^3J = 8.2, 5.4), 4.18 (m), 3.79 (dd, ^3J = 7.2, 5.4), 3.28 (br s), 2.51 (d, ^3J = 5.8, 4.7), 1.98, 1.92 (2s), 1.38, 1.32 (2s), 1.20 (d, ^3J = 7.1).

(1*R*,2*S*,3*S*,4*S*)-3-*exo*-[(1′*R*)-1′-O-Acetyl-3′-O-benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-4′,5′-*O*-isopropylidene-2′,6′-imino-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-chloro-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-yl Acetate ((−)-23). A solution of 85% *m*CPBA (42.3 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (1 mL) was added dropwise in 30 min to a stirred solution of (+)-**22** (164 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (2 mL) cooled to −78 °C. After 3 h of stirring at −78 °C, the mixture was allowed to warm up to 20 °C in 10 h. CH_2Cl_2 (10 mL) was added, and the solution was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (15 mL, four times), and the combined organic extracts were dried ($MgSO_4$). After solvent evaporation *in vacuo* the residue was purified by FC (silica gel, 15 g, EtOAc/petroleum ether, 1:4), yielding 119 mg (90%) of (−)-**23**, colorless oil; $[\alpha]^{25}_D$ = −61 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.38−7.27 (m), 5.93 (br s), 5.57 (dd, ^3J = 6.5, 5.2), 5.20 (br s), 5.18, 5.15 (2d, ^2J = 12.3), 4.95 (br s), 4.87 (d, ^3J = 4.3), 4.75, 4.56 (2d, ^2J = 10.9), 4.68 (dq, ^3J = 7.3, 7.3), 4.35−4.32 (m), 4.32 (dd, ^3J = 8.1, 7.3), 4.23 (dd, ^3J = 8.3, 6.2), 3.78 (dd, ^3J = 8.1, 6.2), 2.13−2.20 (m), 2.00 (2s), 1.54, 1.35 (2s), 1.22 (d, ^3J = 7.3).

(1*R*,2*S*,3*R*,4*S*,5*S*)-3-*exo*-[(1′*R*)-1′-*O*-Acetyl-3′-*O*-benzyl-N-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-oxo-7-oxabicyclo[2.2.1]heptane-2-*endo*,5-*exo*-diyl Diacetate (24). Me_3NO (23 mg, 0.2 mmol) in THF/H_2O, 5:1 (0.6 mL), was added dropwise to a stirred solution of (−)-**23** (45 mg, 0.07 mmol) in THF/H_2O, 5:1 (0.6 mL), $NaHCO_3$ (30 mg, 0.4 mmol), and 0.1 M solution of OsO_4 in CCl_4 (0.05 mL). After 2.5 h of stirring at 20 °C, EtOAc (10 mL) was added and the solution was washed with a saturated aqueous solution of $NaHSO_3$ (10 mL, three times) and then with brine (10 mL, twice). The combined aqueous phases were extracted with EtOAc (10 mL, three times), and the combined organic phases were dried ($MgSO_4$). After solvent evaporation *in vacuo* at 20 °C, the residue was dissolved in anhydrous pyridine (1 mL) and Ac_2O (0.8 mL), and DMAP (5 mg) was added. After 15 h of stirring at 20 °C for 15 h the solvents were removed *in vacuo*. Filtration through Florisil (5 g) eluting with EtOAc/petroleum ether, 1:4, afforded, after evaporation *in vacuo* at 20 °C, a very instable oil which was used without further purification. An analytical sample of **24** was purified by FC (Florisil, 5 g, EtOAc/petroleum ether, 1:4): ^{1}H NMR (400 MHz, $CDCl_3$, 50

°C) δ 7.40−7.26 (m), 5.58 (dd, ^3J = 6.3, 3.5), 5.24 (br s), 5.18, 5.13 (2d, ^2J = 12.2), 4.82−4.64 (m), 4.77, 4.56 (2d, ^2J = 11.1), 4.72 (br s), 4.62 (dq, ^3J = 7.3, 6.9), 4.50 (br d, ^3J = 5.6), 4.33 (dd, ^3J = 7.2, 6.9), 4.27 (dd, ^3J = 7.2, 6.0), 4.24 (dd, ^3J = 7.7, 6.0), 3.80 (dd, ^3J = 7.7, 6.3), 2.57 (dd, ^3J = 5.4, 3.5), 2.12, 1.94, 1.91 (3s), 1.55, 1.35 (2s), 1.18 (d, ^3J = 7.3).

(1*S*,4*S*,5*S*,6*R*,7*S*)-6-*exo*-[(1′*R*)-1′-*O*-Acetyl-3′-*O*-benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-3-oxo-2,8-dioxabicyclo[3.2.1]octane-4-*exo*,7-*endo*-diyl Diacetate ((−)-25). $NaHCO_3$ (10 mg, 0.16 mmol) and a solution of 85% *m*CPBA (17.5 mg, 0.07) in anhydrous CH_2Cl_2 (0.3 mL) were added successively to the crude product **24** obtained above dissolved in anhydrous CH_2Cl_2 (2 mL). After 14 h of stirring at 25 °C, CH_2Cl_2 (5 mL) was added and the mixture washed with a saturated aqueous solution of $NaHCO_3$ (5 mL, twice) and then brine (5 mL, twice). The combined aqueous phases were extracted with CH_2Cl_2 (15 mL, 3 times). The combined organic extracts were dried ($MgSO_4$), and the solvents were evaporated *in vacuo*, giving a residue which was purified by FC (silica gel, 8 g, EtOAc/petroleum ether, 1:2) yielding 34 mg (67%) of **(−)-25** as a colorless oil: $[\alpha]^{25}_D = -55$ (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.40−7.27 (m), 5.99 (br s), 5.55 (dd, ^3J = 6.0, 5.8), 5.18, 5.12 (2d, ^2J = 12.2), 5.17−5.12 (2m), 4.76, 4.55 (2d, ^2J = 11.1), 4.61−4.53 (2m), 4.33 (dd, ^3J = 7.2, 5.8), 4.24 (2dd, ^3J = 7.8, 5.8), 3.83 (dd, ^3J = 7.8, 5.8), 2.71 (ddd, ^3J = 5.4, 4.0, ^5J = 1.4), 2.12, 2.00, 1.91 (3s), 1.54, 1.35 (2s), 1.19 (d, ^3J = 7.2).

Methyl {Methyl 2,5-di-*O*-acetyl-3-deoxy-3-*C*-[(1′*R*)-1′,4′,5′-tri-*O*-acetyl-3′-*O*-benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-α- and -*β*-D-altrofuranosid}uronate ((+)-26). Freshly distilled $SOCl_2$ (0.01 mL, 0.153 mmol) was added dropwise to a stirred solution of (−)-**25** (8 mg, 0.01 mmol) in anhydrous MeOH (0.5 mL) cooled to 0 °C. After 28 h of stirring, the solvent was evaporated *in vacuo*. The residue was dissolved in pyridine (0.5 mL) and Ac_2O (0.3 mL), and DMAP (3 mg) was added. After 14 h of stirring at 20 °C, the solvents were removed, the residue was taken up with toluene, and the solvent was evaporated (three times). Purification of the residue by FC (silica gel, 8 g, EtOAc/petroleum ether, 1:4, then CH_2Cl_2/petroleum ether/MeOH, 4:4:1) afforded 6 mg (73%) of a 5:1 mixture of α- and *β*-anomer (+)-**26**: colorless oil; $[\alpha]^{25}_D = +32.6$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.53−7.28 (m), 5.52 (d, ^3J = 3.2), 5.46 (dd, ^3J = 6.8, 2.2), 5.36 (d, ^2J = 11.4), 5.27 (d, ^3J = 2.4), 5.20−5.00 (2m), 4.85 (br s), 4.75, 4.70, 4.68 (3d, ^2J = 10.7, 11.4, 10.7), 4.48 (dq, ^3J = 6.9, 6.8), 4.30 (br d, ^3J = 8.5), 3.86 (br d, ^3J = 5.3), 3.80 (s), 3.49 (s), 2.94 (dd, ^3J = 8.5, 3.2), 2.36, 2.12, 2.01 (3s), 1.79, 1.64 (2s), 1.01 (d, ^3J = 6.9).

Methyl 2,5,6-Tri-*O*-acetyl-3-deoxy-3-*C*-[(1′*R*)-1′,4′,5′-tri-*O*-acetyl-2′,6′,7′-trideoxy-2′,6′-imino-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-α- and -*β*-D-altrofuranoside ((+)-27). $LiBH_4$ (5 mg, 0.23 mmol) was added to a stirred solution of (+)-**26** (25 mg, 0.03 mmol) in anhydrous THF (4 mL) at 0 °C, and the temperature was allowed to reach 20 °C. After 4 h of stirring, AcOEt (0.5 mL) was added, and the reaction was left for an additional hour. Acetic acid (0.5 mL) followed 20 min later by pyridine (3 mL), Ac_2O (1 mL), and DMAP (5 mg) was added to the mixture. After 14 h of stirring at 20 °C, the solvent was removed and the residue filtered (silica gel, 8 g, EtOAc/petroleum ether, 3:2). The residue was taken up in 70% aqueous acetic acid (1 mL) and MeOH (1 mL) and was hydrogenolyzed in the presence of 10% Pd on charcoal (5 mg). After 24 h the mixture was filtered through Celite, and the solvents were evaporated. Purification of the residue by FC (silica gel, 8 g, CH_2Cl_2/MeOH 95:5) afforded 13 mg (72%) of a 5:1 mixture of α- and *β*-anomer (+)-**27**: colorless oil; $[\alpha]^{25}_D = +61$ (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 5.41 (ddd, ^3J = 8.9, 2.5, 2.0), 5.36 (dd, ^3J = 10.0, 2.5), 5.24 (dd, ^3J = 3.0, 1.2), 4.98 (s), 4.96 (dd, ^3J = 9.9, 3.0), 4.87 (s), 4.63 (dd, ^2J = 12.6, ^3J = 2.0), 4.17 (dd, ^2J = 12.6, ^3J = 8.9), 4.02 (dd, ^3J = 6.2, 2.5), 3.35 (dd, ^3J = 9.9, 8.0), 3.32 (s), 3.12 (br q, ^3J = 6.7), 2.79 (br dd, ^3J = 10.0, 6.2), 2.70 (br d, ^3J = 8.0), 2.23, 2.18, 2.15, 2.11, 2.10, 2.05, 2.03 (6s), 1.01 (d, ^3J = 6.7).

(1*S*,2*R*,3*R*,4*R*)-3-*exo*-[(1′*S*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-chloro-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-ol ((+)-28). A solution of 85% *m*CPBA (61 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (1.2 mL) was added dropwise to a stirred solution of (−)-**19** (190 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (5.4 mL) cooled to −78 °C over 30 min. After 3 h of stirring at −78 °C, the mixture was allowed to warm up to 20 °C over 10 h. CH_2Cl_2 (15 mL) was added, and the solution was washed with saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (15 mL, four times). The combined organic phases were washed with brine (15 mL) and dried ($MgSO_4$). After solvent evaporation *in vacuo* the residue was purified by FC (silica gel, 15 g, EtOAc/petroleum ether, 1:1) yielding 144 mg (95%) of (+)-**28** as a foam: mp 76−79 °C; $[\alpha]^{25}_D = +10$ (c = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.34−7.25 (m), 6.35 (br s), 5.25, 5.10 (2d, ^2J = 12.3), 4.77 (d, ^3J = 1.7), 4.75 (d, ^3J = 4.6), 4.67−4.63 (m), 4.61, 4.57 (2d, ^2J = 11.5), 4.58−4.54 (m), 4.47 (br d, ^3J = 10.1), 4.41 (dd, ^3J = 8.0, 6.2), 4.30 (dd, ^3J = 8.0, 2.0), 4.22 (dq, ^3J = 6.3, 6.2), 4.13 (dd, ^3J = 3.5, 2.0), 1.78 (dd, ^3J = 2.6, 2.5), 1.56, 1.36 (2s), 1.35 (d, ^3J = 6.3).

(1*S*,2*R*,3*R*,4*R*)-3-*exo*-[(1′*S*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-1′-*O*-(methoxymethyl)-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-6-chloro-2-*endo*-(methoxymethoxy)-7-oxabicyclo[2.2.1]hept-5-ene ((+)-29). Methoxymethyl chloride (2.5 mL, 33 mmol) was added to a stirred solution of (+)-**28** (374 mg, 0.64 mmol) in anhydrous CH_2Cl_2 (5 mL) and anhydrous diisopropylethylamine (5 mL) cooled to 0 °C. After addition of tetrabutylammonium iodide (30 mg, 0.08 mmol), the mixture was allowed to warm up to 20 °C in 18 h. MeOH (2 mL) was added and the mixture stirred for an additional hour. Then the mixture was diluted with CH_2Cl_2 (30 mL) and poured into ice cold 1 M HCl (30 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (30 mL, four times). The combined organic phases were dried ($MgSO_4$). After solvent evaporation *in vacuo*, the residue was purified by FC (silica gel, 15 g, EtOAc/petroleum ether, 1:1), yielding 144 mg (95%) of (+)-**29** as a colorless oil: $[\alpha]^{25}_D = +16$ (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.41−7.28 (m), 5.61 (br s), 5.17, 5.13 (2d, ^2J = 12.2) 4.89, 4.52 (2d, ^2J = 10.8), 4.85 (br s), 4.79, 4.62 (2d, ^2J = 6.3), 4.72, 4.59 (2d, ^2J = 5.6), 4.70 (dq, ^3J = 7.4, 7.3), 4.67 (br d, ^3J = 4.6), 4.40−4.35 (m), 4.31 (dd, ^3J = 8.1), 4.25 (dd, ^3J = 8.1, 6.6), 4.02−3.96 (m), 3.41, 3.34 (2s), 2.24 (dd, ^3J = 10.8, 2.3), 1.53, 1.36 (2s), 1.25 (d, ^3J = 7.3).

(1*R*,2*R*,4*S*,5*R*,6*R*)-6-*exo*-[(1′*S*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-1′-*O*-(methoxymethyl)-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-5-*endo*-(methoxymethoxy)-3-oxo-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl 4-Bromobenzenesulfonate ((−)-31). Me_3NO (160 mg, 1.44 mmol) in a 5:1 mixture of THF/H_2O (1 mL) was added dropwise to a stirred solution of (+)-**29** (330 mg, 0.49 mmol) in 5:1 THF/H_2O (9 mL) containing $NaHCO_3$ (216 mg, 2.57 mmol) and 0.1 M solution of OsO_4 in CCl_4 (0.37 mL). After 2.5 h of stirring at 20 °C, EtOAc (20 mL) was added, and the solution was washed with a saturated aqueous solution of $NaHSO_3$ (20 mL, twice) and then with brine (20 mL). The combined aqueous phases were extracted with EtOAc (20 mL, 3 times), and the combined organic extracts were dried ($MgSO_4$). After solvent evaporation *in vacuo*, the residue was dissolved in anhydrous CH_2Cl_2 (11.5 mL) at 0 °C, and then brosyl chloride (193 mg, 0.76 mmol) and Et_3N (0.215 mL, 1.55 mmol) were added. After 15 h of stirring at 20 °C, the mixture was diluted with CH_2Cl_2 (30 mL) and poured over ice cold 1 M HCl (30 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (30 mL, four times). The combined organic phases were dried ($MgSO_4$). After solvent evaporation *in vacuo* the residue was purified by FC (silica gel, 20 g, EtOAc/petroleum ether, 1:3), yielding 367 mg (84%) of (−)-**31** as a foam: mp 59−62 °C; $[\alpha]^{25}_D = -20.4$ (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.56−7.32 (m), 5.17 (s), 4.89, 4.57 (2d, ^2J = 10.8), 4.69−4.63 (m), 4.70, 4.58 (2d, ^2J = 5.9), 4.65, 4.44 (2d, ^2J = 6.6), 4.40 (dd, ^3J = 10.0, 6.1), 4.36−4.38 (m), 4.35−4.28

(m), 4.09 (s), 3.87 (dd, ^3J = 10.9, 0.5), 3.50 (br d, ^3J = 10.0), 3.37, 3.14 (2s), 2.69 (br d, ^3J = 10.9), 1.54, 1.40 (2s), 1.22 (d, ^3J = 7.3).

(1*R*,4*R*,5*R*,6*S*,7*R*)-6-*exo*-[(1′*S*)-3′-*O*-Benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-1′-*O*-(methoxymethyl)-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-7-*endo*-(methoxymethoxy)-3-oxo-2,8-dioxabicyclo[3.2.1]octan-4-*exo*-yl 4-Bromobenzenesulfonate ((+)-32). $NaHCO_3$ (30 mg, 0.96 mmol) and a solution of 95% *m*CPBA (76 mg, 0.44 mmol) in anhydrous CH_2Cl_2 (1.5 mL) were added successively to a solution of **(−)-31** (355 mg, 0.399 mmol) in anhydrous CH_2Cl_2 (7.5 mL) at 0 °C. After 15 h of stirring at 25 °C, further CH_2Cl_2 (15 mL) was added and the mixture washed with an aqueous saturated solution of $NaHCO_3$ (25 mL, twice) and brine (25 mL, twice). The combined aqueous phases were extracted with CH_2Cl_2 (25 mL, three times). The combined organic extracts were dried ($MgSO_4$), and the solvents were evaporated *in vacuo*, giving a residue which was purified by FC (silica gel, 20 g, EtOAc/petroleum ether, 1:2), yielding 345 mg (95%) of (+)-**32** as a foam: mp 62−65 °C; $[\alpha]^{25}_D$ = +34.7 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.63−7.27 (m), 5.75 (d, ^3J = 3.5), 5.24, 5.13 (2d, ^2J = 12.1), 4.85, 4.57 (2d, ^2J = 10.5), 4.88−4.83 (m), 4.74, 4.57 (2d, ^2J = 6.8), 4.73−4.68 (m), 4.70, 4.55 (2d, ^2J = 5.8), 4.42−4.37 (m), 4.36−4.28 (2m), 4.22 (dd, ^3J = 4.3, 3.5), 3.97 (br d, ^3J = 10.0), 3.65 (dd, ^3J = 9.8, 1.2), 3.43, 3.34 (2s), 2.77 (ddd, ^3J = 10.0, 4.3, 2.1), 1.55, 1.41 (2s), 1.22 (d, ^3J = 7.3).

Methyl 1,5-Anhydro-3-*C*-[(1′*S*)-3′-*O*-benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-O-isopropylidene-1′-*O*-(methoxymethyl)-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-3-deoxy-2-*O*-(methoxymethyl)-α-D-galactofuranuronate ((−)-34) and Methyl 1,5-Anhydro-3-*C*-[(1′*S*)-3′-*O*-benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-1′-*O*-(methoxymethyl)-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-3-deoxy-2-*O*-(methoxymethyl)-α-L-altrofuranuronate ((+)-35). K_2CO_3 (18.2 mg, 1.32 mmol) was flame-dried under an Ar atmosphere and then dissolved in anhydrous DMF (0.25 mL). Successively a solution of **(+)-32** (40 mg, 0.44 mmol) in anhydrous DMF (0.4 mL) and anhydrous MeOH (0.2 mL) were added. After 2.5 h, the mixture was evaporated *in vacuo*, taken up in with EtOAc (5 mL), and washed with aqueous saturated NH_4Cl solution (10 mL). The aqueous phases were extracted with EtOAc (8 mL, three times), and the combined organic extracts were dried ($MgSO_4$). The solvent was evaporated *in vacuo*, giving a residue which was purified by FC (silica gel, 8 g, EtOAc/petroleum ether, 1:2), yielding first 2 mg of (+)-**35** (6%) and then 20 mg (66%) of (−)-**34** as a foam.

Data for (−)-34: mp 52−54 °C; $[\alpha]^{25}_D$ = −5.7 (*c* = 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.38−7.26 (m), 5.66 (d, ^3J = 2.3), 5.19, 5.15 (2d, ^2J = 12.2), 4.97 (br s), 4.91, 4.58 (2d, ^2J = 11.1), 4.74, 4.60 (2d, ^2J = 6.6), 4.66 (dq, ^3J = 7.3, 7.0), 4.65, 4.54 (2d, ^2J = 5.9), 4.38 (dd, ^3J = 9.3, 6.4), 4.34 (dd, ^3J = 8.0, 6.4), 4.26 (dd, ^3J = 8.0, 7.0), 4.01 (dd, ^3J = 9.3, 2.1), 3.97 (br dd, ^3J = 2.9, 2.3), 3.91 (dd, ^3J = 10.7, 2.1), 3.29 (s), 3.41, 3.32 (2s), 2.34 (dd, ^3J = 10.7, 2.9), 1.53, 1.35 (2s), 1.24 (d, ^3J = 7.3).

Data for (+)-35: $[\alpha]^{25}_D$ = +33.4 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.50−7.28 (m), 5.54 (d, ^3J = 2.4), 5.30−4.90 (m), 5.06 (br s), 4.63, 4.48 (2d, ^2J = 7.0), 4.60, 4.52 (2d, ^2J = 11.5), 4.56, 4.54 (2d, ^2J = 6.6), 4.46 (dq, ^3J 7.6, 7.0), 4.24−4.16 (2m), 4.12−4.07 (2m), 3.92 (dd, ^3J = 2.8, 2.4), 3.69 (dd, ^3J = 8.7, 1.6), 3.60 (dd, ^3J = 10.0, 1.6), 3.29 (s), 3.15, 3.20 (2s), 2.33 (dd, ^3J = 8.7, 2.8), 1.23, 1.05 (2s), 0.94 (d, ^3J = 7.6).

1,5-Anhydro-3-*C*-[(1′*S*)-3′-*O*-benzyl-*N*-(benzyloxycarbonyl)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-1′-*O*-(methoxymethyl)-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-3-deoxy-2-*O*-(methoxymethyl)-α-D-galactofuranose ((+)-36). $LiBH_4$ (15 mg, 0.69 mmol) was added to a stirred solution of (−)-**34** (132 mg, 0.19 mmol) in anhydrous THF (5 mL). After 5 h of stirring, the mixture was cooled to −5 °C, neutralized with a 1 N solution of HCl and extracted with CH_2Cl_2 (15 mL, four times). The combined organic extracts were dried ($MgSO_4$), and the solvents were evaporated. Purification of the residue by FC (silica gel, 15 g, EtOAc/petroleum ether, 3:2) afforded 105 mg (82%) of (+)-**36** as a foam: mp 49−54 °C; $[\alpha]^{25}_D$= +1.1 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.42−7.26 (m), 5.50 (d, ^3J = 2.4), 5.19, 5.15 (2d, ^2J = 12.4), 4.94, 4.53 (2d, ^2J = 10.8), 4.75, 4.61 (2d, ^2J = 6.5), 4.70 (dq, ^3J = 7.3, 6.4), 4.68, 4.55 (2d, ^2J = 5.9), 4.53 (br s), 4.38 (dd, ^3J = 9.6, 6.5), 4.35 (dd, ^3J = 8.1, 6.5), 4.25 (dd, ^3J = 8.1, 6.4), 4.01, 3.96 (2m), 3.92 (dd, ^3J = 10.7, 1.2), 3.41, 3.35 (2s), 3.30−3.17 (m), 2.21 (dd, ^3J = 10.7, 2.6), 1.53, 1.36 (2s), 1.23 (d, ^3J = 7.3).

1,5-Anhydro-3-deoxy-3-*C*-[(1′*S*)-2′,6′,7′-trideoxy-2′,6′-imino-4′,5′-*O*-isopropylidene-1′-*O*-(methoxymethyl)-*β*-D-*glycero*-L-*manno*-heptitol-1′-yl]-2-*O*-(methoxymethyl)-α-D-galactofuranose ((+)-37). A solution of (+)-**36** (36 mg, 0.08 mmol) and 10% Pd on charcoal (5 mg) in THF/H_2O (10 mL) was stirred at 20 °C under a H_2 atmosphere for 24 h. Filtration through Celite, evaporation, and FC (silica gel (8 g), CH_2Cl_2/MeOH, 9:1) yielded (+)-**37** (36 mg, 97%) which precipitated from Et_2O/ petroleum ether, colorless crystals: mp 78−79 °C; $[\alpha]^{25}_D$ = +54.2 (*c* = 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 5.48 (d, ^3J = 2.4), 4.84, 4.69 (2d, ^2J = 7.0), 4.82, 4.63 (2d, ^2J = 6.6), 4.58 (br s), 4.11 (dd, ^3J = 5.1, 2.7), 3.97 (dd, ^3J = 3.1, 2.4), 3.94 (dd, ^3J = 7.4, 5.1), 3.81 (dd, ^3J = 7.4, 5.5), 3.78 (dd, ^3J = 8.6, 3.2), 3.65 (dd, ^3J = 10.6, 7.4), 3.47, 3.39 (2s), 3.42−3.39 (m), 3.13 (dq, ^3J = 6.7, 2.7), 2.79 (dd, ^3J = 10.6, 3.2), 2.33 (dd, ^3J = 8.6, 3.1), 1.54, 1.39 (2s), 1.28 (d, ^3J = 6.7).

Acknowledgment. We thank the Swiss National Science Foundation and the Fonds Herbette (Lausanne) for generous financial support.

Supporting Information Available: Spectral data and elemental analyses for all new compounds (18 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.

JO970151T