Synthesis of 2-Azido-6-amino and 2-Fluoro-6-amino Analogues of 1-Deoxynojirimycin

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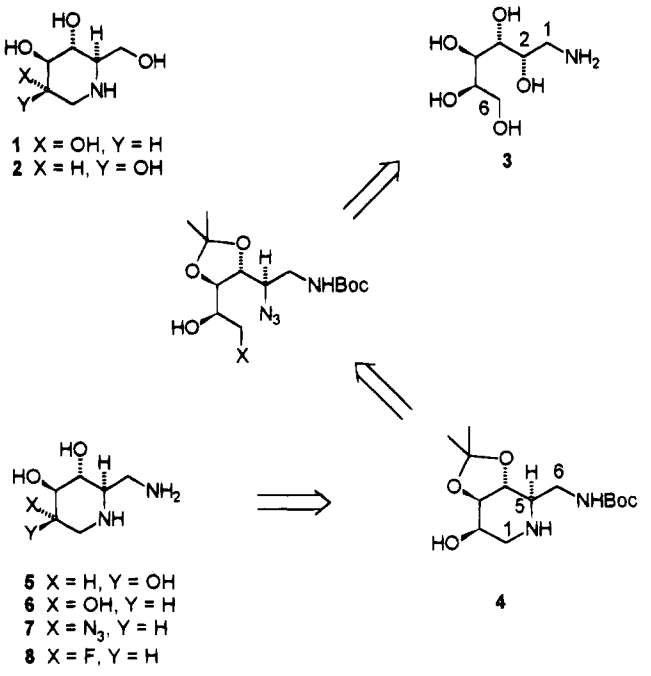
Received May 2, 1995[⊗]

1-Aminoglucitol (**3**) was transformed into iminosugars **5**–**8**, piperidine analogues of manno- and glucopyranose, by using a reversed-chain strategy in which the 1-amino group of **3** is retained as the 6-substituent of the iminosugars and the ring nitrogen is derived from an azido group introduced at C-2 of the *N*-Boc-3,4:5,6-*O*-diisopropylidene protected derivative **9**. Successive deprotection of the 5,6-diol moiety, reduction of the azido group, and displacement of 6-OH with a bromo substituent result in generation of the iminosugar synthon **4**. This can be deprotected directly or following inversion at the C-2 position to afford 6-amino-1,6-dideoxymannojirimycin (**5**) or 2-azido- and 2-fluoro-6-amino-1,6-dideoxynojirimycin **7** and **8**.

Biologically active natural products are valuable templates for new drugs. In recent years, polyhydroxylated piperidine, pyrrolidine, indolizidine, and pyrrolidizine alkaloids have attracted much attention, due to their ability to act as selective glycosidase inhibitors. Such inhibition may be useful for treatment of diabetes,[1] cancer,[2] obesity,[3] malaria,[4] and some viral infections including AIDS. The high therapeutic potential of these alkaloids has prompted considerable efforts toward their structural modification, most notably for the natural azasugars 1-deoxynojirimycin[5] (**1**) and 1-deoxymannojirimycin[6] (**2**). As piperidine analogues of gluco- and mannopyranose, the latter compounds function as inhibitors of glucosidases[7] and mannosidases,[8] respectively. Synthetic analogues of **1** and **2** have been evaluated for anticancer,[9] antidiabetic,[10] antiviral (anti-HIV),[11] and glycosidase inhibitory[12] activities.

Recently, we reported two approaches for conversion of 1-amino-1-deoxy-D-glucitol (**3**) into 1-deoxynojirimycin analogues. In each case cyclization was effected by the 1-amino nitrogen, which was attached to C-5 *via* either two-fold inversion at C-5,[13] or diastereoselective addition to an α,β-unsaturated carbonyl system.[14] We now present (Scheme 1) a reversed-chain strategy in which the 1-amino group is retained as the 6-substituent of the iminosugars and the ring nitrogen is derived from an azido group introduced at the C-2 position. Ring closure then affords the 6-amino synthon **4**, which can be deprotected to give the 6-amino analogue of 1-deoxymannojirimycin (**5**). Alternative substitution at the C-2

Scheme 1



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[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1995.

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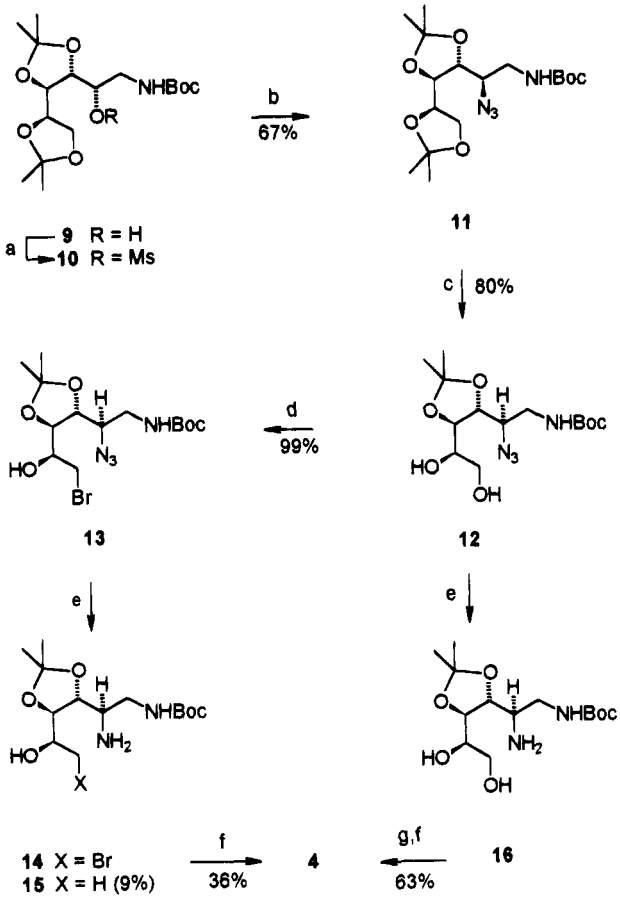
Scheme 2[a]



[a](a) MsCl, DMAP, Et_3N, CH_2Cl_2, rt, 10 min; (b) NaN_3, DMF, 110 °C, 8 h; (c) PPTS, $MeOH/H_2O$ (9:1), 60 °C, 2 h; (d) PPh_3 (2.5 equiv), CBr_4 (1.2 equiv), THF, rt, 30 min; (e) H_2, 10% Pd/C, EtOH, 30 psi, 2–4 h; (f) $NaHCO_3$, CH_3CN, reflux, 1 h; (g) THF, MsOH (1 equiv); solution added to a mixture of Ph_3P (1.5 equiv) and CBr_4 (1.1 equiv) in THF.

position of **4** provides access to the epimeric compound **6** described before,[13] and to the 2-azido and 2-fluoro target compounds **7** and **8**. Binding of sugars to the active site of the enzymes may result from both hydrogen-bond donor and acceptor interactions.[15] Hydrogen donation could be inforced by the readily protonated 1,6-diamino moiety of compounds **5–8,** since the existence of an anionic site was postulated to explain the binding characteristics of **1** to sweet almond β-glucosidase.[16] Substitution of an OH-group with the isosteric fluorine may reveal its properties as a hydrogen-bond acceptor; this was demonstrated for the 2-OH group of glucose by the observation that glucose and 2-fluoro-2-deoxy-D-glucose act equally well as inhibitors of glycogen phosphorylase.[15] The syntheses of the 2- and 3-fluoro,[17] and the 6-fluoro[18] analogues of **1** and inhibition data of the former compounds with yeast α-glucosidase[17,19] have already been reported.

Our synthetic sequence (Scheme 2) started from the 3,4:5,6-diacetonide compound **9**, readily available from aminoglucitol **3**.[14] The free OH group was activated as the 2-*O*-methanesulfonyl derivative **10**. This was converted to the crystalline azide **11** (67%) by heating with sodium azide in dimethylformamide. Selective hydrolysis of the 5,6-*O*-isopropylidene group (**11** → **12**) was achieved in high yield (80%) by heating compound **11** with pyridinium *p*-toluenesulfonate in aqueous methanol.

Two procedures were utilized for conversion of azido diol **12** to the piperidine compound **4**, which differed by the order of introduction of a leaving group at C-6 and reduction of the azido function. In the first sequence, the 6-bromo alcohol **13** was prepared in 99% yield by treating the 5,6-diol with triphenylphosphine and CBr_4 in tetrahydrofuran.[20] Subsequent reduction of the azido group (**13** → **14**) was attempted first with the reagent system PPh_3-H_2O in THF.[21] However, the stable iminophosphorane product failed to hydrolyze even at reflux temperature. Hydrogenation of compound **13** in ethanol using 10% palladium on charcoal led to partial loss of the bromo substituent. The resulting mixture of primary amines **14** and **15** was not separated but was subjected directly to conditions designed for cyclization (reflux with $NaHCO_3$ in acetonitrile). Chromatographic separation afforded the desired piperidine compound **4** (36%) along with the hydrogenolyzed product **15** (9%).

To avoid the latter side reaction, we then reversed the operational sequence: following hydrogenation of azido diol **12**, amino diol **16** was protected *in situ* as the methanesulfonate salt, and the THF solution of the salt was added to the brominating agent. Final cyclization under the above conditions afforded the piperidine compound **4** in 63% overall yield from azido diol **12** (34% from diacetonide **9**). Analysis of the ^1H NMR spectrum of compound **4** confirmed the equatorial position of proton H-2 which appeared as a quartet (^3J = 2 Hz), corresponding to coupling with protons H-1 and H-3ax.

Synthon **4** was converted into various target compounds (Scheme 3). This involved protection of the secondary amine as the *N,N'*-bis-*tert*-butoxycarbonyl derivative **17** (see below for the conformational characteristics of the bis-*N*-Boc derivatives), substitution at C-2 using different modes for activation of the 2-OH group, and final deprotection under acidic conditions. Mesylation (**17** → **18**) and displacement with sodium azide afforded the azido compound **19** in 68% overall yield. The analogous fluoride compound **20** was prepared (55%) *via* direct substitution of the 2-OH group using (diethylamido)sulfur trifluoride (DAST). Finally, inversion of the alcohol to give the 2-*O*-acetylated compound **21** was accomplished (80%) *via* Mitsunobu reaction[22] using PPh_3, diethyl azodicarboxylate, and acetic acid. On treatment of compound **4** with methanolic HCl the mannojirimycin analogue **5** was isolated as the hydrochloride (96%). Similar deprotection also provided the hydrochlorides of the 2-azido and 2-fluoro target compounds **7** (95%) and **8** (96%).

From the coupling constant values in the ^1H NMR spectra it appears clearly that the bis-*N*-Boc compounds **17, 21,** and **17ac** (the C-2 epimer of **21,** prepared *via* *O*-acetylation of **17**) do not conform to the expected chair

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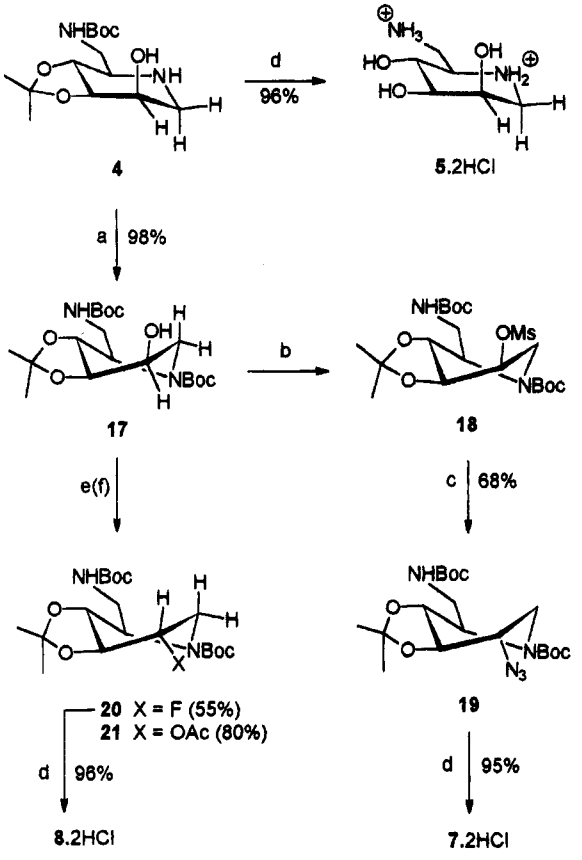
Scheme 3[a]



[a](a) Boc_2O, MeOH, rt; (b) MsCl, DMAP, Et_3N, CH_2Cl_2, rt, 10 min; (c) NaN_3, DMF, 110 °C, 3 h; (d) HCl–MeOH, rt, 1 h; (e) DAST, 0 °C, 10 min, and then Et_3N; (f) DEAD, PPh_3, HOAc, THF, rt.

conformation. In this chair form, an upward orientation is imposed on the *N*-Boc substituent by the trigonal nature of the sp^2 ring nitrogen, resulting in a strong repulsive interaction with the nearly coplanar methylene group of the side chain. This repulsion can be removed by a downward movement of the ring nitrogen to generate the twist-boat conformers depicted in Scheme 3. The divergent torsional angles associated with the twist-boat and chair forms are demonstrated most clearly by comparing the coupling values for H-1,H-2 to those for the corresponding free amino compounds **4, 5** and **7, 8,** i.e.: (a) $^3J_{1,2}$ = 8 and 6 Hz for **17, 17ac** (1–3 Hz for **4, 5**); and (b) $^3J_{1,2}$ = 0 and 5 Hz for **21** (10–12 and 5 Hz for **7, 8**). The zero value for compound **21** indicates a dihedral angle of *ca.* 90° for the *trans*-disposed protons H-2 and H-1eq, in clear opposition to the value 10–12 Hz expected for a diaxial orientation. From a molecular mechanics calculation, the torsional angles for protons H-2,H-3 could be estimated as *ca.* 40° (^3J = 5 Hz) for **17** and **17ac**, and *ca.* 150° (^3J = 7 Hz) for **21.** The coupling values for the diaxial protons H-3 and H-4 were similar to those determined for the the free amino compounds ($^3J_{3,4}$ = 9–10.5 Hz). The twist-boat conformational forms may be significant with regard to the reactivity in the displacement reactions at C-2, as depicted in Scheme 3.

The relative location of the amino nitrogen atoms in compounds **5–8** is similar to that in numerous alkaloids and piperazine or piperidine drugs. Further modification at either amino function therefore may provide access to a large number of monocyclic and bicyclic analogues. In particular alkylation of the ring nitrogen may provide interesting biological activities;[5b] these results will be reported in due course.

Experimental Section

General Methods. Melting points are uncorrected. ^1H NMR spectra were recorded at 400 and 250 MHz and ^{13}C spectra at 100 and 62.9 MHz, respectively. The assignments were based on homo- and heteronuclear decoupling. Torsional angles, inferred from the coupling constant values in the spectra of compounds **17, 17ac,** and **21,** were verified by molecular modeling and minimization of the energy of various conformers using a molecular mechanics calculation. Mass spectra were run at an ion source temperature of 150–250 °C as required. Exact mass measurements were performed at a resolution of 10 000. Analytical and preparative thin layer chromatography was performed using Merck silica gel 60 PF-224. Column chromatography was carried out using 70–230 mesh silica gel 60 (E. M. Merck). The purity of compounds was checked by TLC using the solvent systems mentioned for column chromatography. Solutions were dried over $MgSO_4$. All nonaqueous reactions were performed under a nitrogen atmosphere. Dry solvents were freshly distilled before use. 1-Amino-1-deoxy-D-glucitol was supplied by Cerestar, Vilvoorde, Belgium.

2-Azido-1-[(*tert*-butoxycarbonyl)amino]-3,4:5,6-di-*O*-isopropylidene-1,2-dideoxy-D-mannitol (11). To a solution of diacetonide **9** (9.05 g, 25 mmol) in dry CH_2Cl_2, (50 mL) were added MsCl (3.15 mL, 40 mmol), DMAP (1.46 g, 12 mmol), and Et_3N (15 mL). The mixture was stirred at rt for 10 min after which time it was washed with aqueous K_2CO_3. The organic phase was dried and evaporated. The residue was dissolved in DMF (50 mL), NaN_3 (4.88 g, 75 mmol) was added, and the mixture was heated at 110 °C for 8 h. Water (100 mL) was added to the cooled solution, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). After evaporation of the organic phase, the residue was purified by column chromatography (hexanes–EtOAc, 7:3). Compound **11** was obtained as an oily residue which solidified on standing (6.50 g, 67%); mp 70.2–70.8°C; $[\alpha]^{18}_D$ = +60.7° (*c* = 0.08 in $CHCl_3$); ^1H-NMR (400 MHz, $CDCl_3$, TMS) δ = 5.03 (br, 1 H, NHCO), 4.18 (m, 2 H, H-3,4), 4.05 (dt, ^3J = 8, 6 Hz, 1 H, H-5), 3.90–3.98 (m, 2 H, H-6), 3.86 (br m, 1 H, H-2), 3.35 (br m, 1 H, H-1a) and 3.21 (br m, 1 H, H-1b), 1.44, 1.40, 1.35, 1.33 (4 s, 21 H, 7 CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 155.7 (OCONH), 110.2, 109.1 (Me_2CO_2), 80.9 (C-3), 79.7 (Me_3CO), 78.2 (C-4), 77.2 (C-5), 68.0 (C-6), 62.4 (C-2), 41.0 (C-1), 28.3 (Me_3CO), 27.2, 26.9, 26.4, 25.2 (Me_2CO_2); MS (70 eV) *m/z* (%) 371 (2) [$M^+ - CH_3$], 315 (2) [$M^+ - CH_3 - CH_2CMe_2$], 257 (2) [$M^+ - CH_3 - CH_2CMe_2$ – acetone], 57 (100) [Me_3C^+]; HRMS calcd for $C_{16}H_{27}N_4O_6$ [$M^+ - CH_3$] 371.1931, found 371.1930 (10%). Anal. Calcd for $C_{17}H_{30}N_4O_6$: C, 52.8, H, 7.8, N, 14.5. Found: C, 52.7, H, 7.9, N, 14.3.

2-Azido-1-[(*tert*-butoxycarbonyl)amino]-3,4-*O*-isopropylidene-1,2-dideoxy-D-mannitol (12). To a solution of azide **11** (6.05 g, 15.7 mmol) in 90% aqueous MeOH (160 mL) was added PPTS (3.94 g, 15.7 mmol), and the mixture was heated at 60 °C for 2 h. The solvent was removed and the residue was purified by column chromatography (hexanes–EtOAc, 2:3). Compound **12** was obtained as an oily residue which solidified on standing (4.34 g, 80%); mp 81.4–83.5 °C; $[\alpha]^{18}_D$ = +75.8° (*c* = 0.13 in MeOH); ^1H-NMR (400 MHz, $CDCl_3$, TMS) δ = 5.13 (br, 1 H, NHCO), 4.23 (dd, ^3J = 6, 4 Hz, 1 H, H-3), 4.01 (t, ^3J =7 Hz, 1 H, H-4), 3.89 (br m, 2 H, H-2, H-6a), 3.77 (br m, 3 H, H-5, H-6b, OH), 3.50 (br m, 1 H, H-1a) and 3.23 (br m, 1 H, H-1b), 3.0 (1 H, OH), 1.48 (s, 12 H, 4 CH_3), 1.40 (s, 3 H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 156.2 (OCONH), 110.1 (Me_2CO_2), 80.4 (C-3), 80.2 (Me_3CO), 77.4 (C-4), 73.4 (C-5), 64.0 (C-6), 62.9 (C-2), 41.1 (C-1), 28.4 (Me_3CO), 27.1, 26.9 (Me_2CO_2); MS (CI, methane) *m/z* (%) 347 (8) [MH^+], 291 (31) [$MH^+ - CH_2CMe_2$], 247 (100) [$MH^+ - CH_2CMe_2 - CO_2$], 189 (31) [$MH^+ - CH_2CMe_2 - CO_2$ – acetone]; HRMS calcd for $C_{13}H_{23}N_4O_6$ [$M^+ - CH_3$] 331.1618, found 331.1617 (0.6%). Anal. Calcd for $C_{14}H_{26}N_4O_6$: C, 48.6, H, 7.6, N, 16.2. Found: C, 48.5, H, 7.6, N, 16.3.

2-Azido-6-bromo-1-[(*tert*-butoxycarbonyl)amino]-3,4-*O*-isopropylidene-1,2,6-trideoxy-D-mannitol (13). Diol **12**

(0.27 g, 0.78 mmol) was treated with CBr_4 (0.34 g, 0.94 mmol) and PPh_3 (0.475 g, 1.79 mmol) in THF (10 mL) for 30 min at rt. After evaporation of the solvent, the residue was purified by column chromatography (hexanes–EtOAc, 7:3) to give compound **13** (0.32 g, 99%) as an oil; $[\alpha]^{18}_D = +45.6°$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$, TMS) $\delta = 5.13$ (br, 1 H, NHCO), 4.20 (dd, $^3J = 6$, 5 Hz, 1 H, H-3), 3.93 (dd, $^3J = 8$, 6 Hz, 1 H, H-4), 3.87 (br m, 1 H, H-2), 3.80 (br m, 2 H, H-5, H-6a), 3.55 (dd, $^2J = 11$, $^3J = 8$ Hz, 1 H, H-6b), 3.42 (br m, 1 H, H-1a), 3.23 (br m, 1 H, H-1b), 3.15 (br m, 1 H, OH), 1.48 (d, 12 H, 4 CH_3), 1.40 (s, 3 H, CH_3); ^{13}C-NMR (63 MHz, $CDCl_3$) δ = 156.0 (OCONH), 110.3 (Me_2CO_2), 80.5 (C-3), 80.0 (Me_3CO), 78.0 (C-4), 73.0 (C-5), 62.9 (C-2), 41.2 (C-1), 37.9 (C-6), 28.3 (Me_3CO), 27.1, 27.0 (Me_2CO_2); MS (CI, methane) *m/z* (%) 353, 355 (20) [$MH^+ - CH_2CMe_2$], 309, 311 (50) [$MH^+ - CH_2CMe_2 - CO_2$], 251, 253 (80) [[$MH^+ - CH_2CMe_2 - CO_2$ – acetone]; HRMS calcd for $C_{13}H_{22}O_5N_4Br$ [$M^+ - CH_3$] 393.0773, found 393.0780 (0.3%).

6-[(*tert*-Butoxycarbonyl)amino]-1,5-imino-3,4-*O*-isopropylidene-1,5,6-trideoxy-D-mannitol (4). Diol **12** (0.50 g, 1.44 mmol) was dissolved in EtOH (30 mL), and 10% Pd (C) (0.125g) was added. The mixture was hydrogenated in a Parr apparatus at 30 psi for 2–4 h and then was filtered on Celite. The catalyst was washed thoroughly with EtOH, the solvent was evaporated, and the residue was dried by coevaporating it twice with toluene. After dissolving the product in dry THF (10 mL), it was converted to the ammonium salt by addition of MsOH (0.141 g, 1.44 mmol). The salt solution was added to a mixture of CBr_4 (0.793 g, 2.17 mmol) and PPh_3 (0.710 g, 2.267 mmol) in THF (20 mL). Samples of the reaction mixture were neutralized with methanolic ammonia and analyzed by TLC (EtOAc). After completion of the reaction (30 min), CH_3CN (30 mL), and $NaHCO_3$ (0.40 g) were added, and the mixture was evaporated to dryness. CH_3CN (40 mL) was added to the residue, and the mixture was heated under reflux for 1 h. The solvent was removed, and the residue was distributed between water and CH_2Cl_2. After further extraction with CH_2Cl_2 and evaporation of the organic phase, the residue was purified by column chromatography ($CHCl_3$/MeOH, 23:2) to furnish compound **4** (0.299 g) as an oil in 63% overall yield from diol **12**: $[\alpha]^{18}_D = -21.3°$ ($c = 0.74$ in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, 60 °C, TMS) $\delta = 5.03$ (br t, 1 H, NHCO), 4.46 (q, $^3J_{1ax,2} = {}^3J_{1eq,2} = {}^3J_{2,3} = 2$ Hz, 1 H, H-2), 3.46 (t, $^3J_{3,4} = {}^3J_{4,5} = 9.5$ Hz, 1 H, H-4), 3.41 (m, 1 H, H-6a), 3.36 (dd, $^3J_{3,4} = 9.5$, $^3J_{2,3} = 2$ Hz, 1 H, H-3), 3.14 (ddd, $^2J_{6a,6b} = 13.7$, $^3J_{5,6b} = 7$, $^3J_{6,NH} = 5.6$ Hz, 1 H, H-6b), 3.08 (dd, $^2J_{1ax,1eq} = 14.5$, $^3J_{1eq,2} = 2$ Hz, 1 H, H-1eq), 2.73 (ddd, $^3J_{4,5} = 9.5$, $^3J_{5,6b} = 7$, $^3J_{5,6a} = 5$ Hz, 1 H, H-5), 2.65 (dd, $^2J_{1ax,1eq} = 17$, $J_{1ax,2} = 2$ Hz, 1 H, H-1ax), 2.15 (br s, 2 H, OH + NH), 1.40 (s, 9 H, 3 CH_3), 1.39 (s, 6 H, 2 CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 156.1 (OCONH), 109.1 (Me_2CO_2), 81.0 (C-3), 79.3 (Me_3CO), 74.1 (C-4), 67.4 (C-2), 59.3 (C-5), 49.8 (C-1), 43.5 (C-6), 28.4 (Me_3CO), 26.6, 26.8 (Me_2CO_2); MS (70eV) *m/z* (%) 303 (3) [MH^+], 302 (3) [M^+], 172 (32) [$M^+ - CH_2NHBoc$], 114 (48) [172 – acetone]; MS (CI, methane) *m/z* (%) 303 (60) [MH^+], 247 (80) [$MH^+ - CH_2CMe_2$], 189 (100) [$MH^+ - CH_2CMe_2$ – acetone]; HRMS calcd for $C_{14}H_{26}O_5N_2$ [M^+] 302.1842, found 302.1844 (5%).

6-Amino-1,5-imino-1,5,6-trideoxy-D-mannitol Dihydrochloride (5). Compound **4** (0.061 g, 0.02 mmol) was treated with saturated methanolic HCl for 1 h. The solution was evaporated and the residue coevaporated, with MeOH. The resulting product was crystallized from Et_2O–MeOH to give the hygroscopic hydrochloride salt of compound **5** (45.2 mg, 96% yield), which rapidly liquefied at the air. **5**; $[\alpha]^{18}_D = -75.2°$ ($c = 0.038$ in water); ^{1}H-NMR (400 MHz, D_2O, 20 °C, TMS) $\delta = 4.27$ (m, $\Sigma^3J = 7$ Hz, 1 H, H-2eq), 3.99 (t, $^3J_{4,5} = {}^3J_{4,3} = 9.5$ Hz, 1 H, H-4ax), 3.74 (dd, $^3J_{3,4} = 9.5$, $^3J_{3,2} = 3$ Hz, 1 H, H-3ax), 3.62 (dd, $^2J_{6a,6b} = 14$, $^3J_{6a,5} = 8$ Hz, 1 H, H-6a), 3.52 (dd, $^2J_{1eq,1ax} = 14$, $^3J_{1eq,2} = 3$ Hz, 1 H, H-1eq), 3.46 (m, 2 H, H-5, H-6b), 3.33 (dd, $^2J_{1ax,1eq} = 14$, $^3J_{1ax,2} = 1$ Hz, 1 H, H-1ax); ^{13}C-NMR (100 MHz, D_2O): $\delta = 72.2$ (C-3), 68.7 (C-4), 65.5 (C-2), 55.5 (C-5), 48.3 (C-1), 39.3 (C-6); MS (CI, methane) *m/z* (%) 163 (100) [MH^+], 146 (61) [$MH^+ - NH_3$], 145 (66) [$MH^+ - H_2O$]; HRMS calcd for $C_6H_{12}O_2N_2$ [$M^+ - H_2O$] 144.0899, found 144.0898 (4%).

6-[(*tert*-Butoxycarbonyl)amino]-1,5-[(*tert*-butoxycarbonyl)imino]-3,4-*O*-isopropylidene-1,5,6-trideoxy-D-mannitol (17). Compound **4** (0.485 g, 1.60 mmol) was dissolved in MeOH (5 mL). Boc_2O (0.435, 1.93 mmol) was added and the solution was stirred at rt for 4 h. After evaporation of the solvent and column chromatography (EtOAc–hexanes, 7:3) of the residue, compound **17** (0.63 g, 98% yield) was isolated as a colorless solid: mp 66.4–67.2 °C; $[\alpha]^{18}_D = -58.6°$ ($c = 0.414$ in $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, TMS) $\delta = 4.87$ (br, 1 H, NHCO), 4.40 (dd, $^2J = 14$, $^3J_{1,2} = 8$ Hz, 1 H, H-1a), 4.33 (m, $^3J = 8$, 6, and 5 Hz, 1 H, H-2), 3.95 (dt, $^3J_{4,5} = 9.5$, $^3J_{5,6} = 6$ Hz, 1 H, H-5), 3.86 (t, $^3J_{3,4} = {}^3J_{4,5} = 9.5$ Hz, 1 H, H-4), 3.46 (dd, $^3J_{3,4} = 9.5$, $^3J_{2,3} = 5$ Hz, 1 H, H-3), 3.36 (m, 2 H, H-6), 2.79 (dd, $^2J = 14$, $^3J_{1,2} = 6$ Hz, 1 H, H-1b), 2.23 (br s, 1 H, OH), 1.44 (s,12 H, 4 CH_3), 1.40 (s, 12 H, 4 CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 155.7$ and 154.9 (OCON), 113.1 (Me_2CO_2), 80.8 and 79.3 (Me_3CO), 78.0 (C-3), 73.3 (C-4), 62.5 (C-2), 58.1 (C-5), 46.2 (C-1),42.3 (C-6), 28.2 (Me_3CO), 26.4, 27.0 (Me_2CO_2); MS (CI, methane) *m/z* (%) 403 (29) [MH^+], 303 (39) [$MH^+ - CH_2CMe_2 - CO_2$], 247 (100) [$MH^+ - 2\ CH_2CMe_2 - CO_2$]; HRMS calcd for $C_{15}H_{25}N_2O_7$ [$M^+ - t$Bu], 345.1662, found 345.1662 (0.5%). Anal. Calcd for $C_{19}H_{34}N_2O_7$: C, 56.7, H, 8.5, N, 7.0. Found: C, 56.5, H, 8.5, N, 7.0.

2-Azido-6-[(*tert*-butoxycarbonyl)amino]-1,5-[(*tert*-butoxycarbonyl)imino]-3,4-*O*-isopropylidene-1,2,5,6-tetradeoxy-D-glucitol (19). To a solution of compound **17** (153 mg, 0.38 mmol) in dry CH_2Cl_2, (5 mL) were added MsCl (66 mg, 0.57 mmol), DMAP (23.5 mg, 0.19 mmol), and Et_3N (0.21 mL, 1.5 mmol). The mixture was stirred at rt for 10 min after which time the solution was washed with aqueous K_2CO_3. The organic phase was dried and evaporated. The residue was dissolved in DMF (5 mL), NaN_3 (124 mg, 1.91 mmol) was added, and the mixture was heated at 110 °C for 3 h. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). After evaporation of the organic phase, the residue was purified by column chromatography (hexanes–EtOAc, 7:3). Compound **19** (111 mg, 68% yield) was obtained as an oily residue; $[\alpha]^{18}_D = +10.3°$ ($c = 1.89$ in $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$, TMS) $\delta = 5.00$ (br, 1 H, NHCO), 4.12 (d, $^2J = 15$ Hz, 1 H, H-1a), 4.03 (m, $\Sigma J = 20$ Hz, 1 H, H-5ax), 3.72 (dd, $^3J_{3,4} = 10.5$, $^3J_{2,3} = 6$ Hz, 1 H, H-3ax), 3.62 (m, 2 H, H-6), 3.40 (m, 2 H, H-2, H-4), 3.35 (dd, $^2J = 15$, $^3J_{1,2} = 6$ Hz, 1 H, H-1b), 1.42–1.52 (m, 24 H, 8 CH_3); ^{13}C-NMR (64 MHz, $CDCl_3$) $\delta = 156.0$ and 154.6 (OCON), 113.3 (Me_2CO_2), 81.2 and 78.9 (Me_3CO), 78.3 (C-3), 75.8 (C-4), 60.2 (C-2), 56.7 (C-5), 43.8 (C-1),41.8 (C-6), 28.3, 28.2 (Me_3CO), 26.9 (Me_2CO_2); MS (CI, methane) *m/z* (%) 428 (6) [MH^+], 372 (5) [$MH^+ - CH_2CMe_2$], 316 (30) [$MH^+ - 2\ CH_2CMe_2$], 272 (100) [$MH^+ - 2\ CH_2CMe_2 - CO_2$]; HRMS calcd for $C_{11}H_{16}O_5N_5$ [$M^+ -$ Me $- CH_2CMe_2 -$ acetone], 298.1151, found 298.1160 (4%).

6-Amino-2-azido-1,5-imino-1,2,5,6-tetradeoxy-D-glucitol Dihydrochloride (7). Compound **18** (86 mg, 0.20 mmol) was treated with saturated methanolic HCl for 1 h. The solution was evaporated, and the residue coevaporated with MeOH. The resulting product was crystallized from Et_2O–MeOH to give the hygroscopic hydrochloride salt of compound **7** (49.5 mg, 95% yield): mp 146 °C dec; $[\alpha]^{18}_D = -20.0°$ ($c = 0.2$ in MeOH); ^{1}H-NMR (400 MHz, D_2O, 20 °C, TMS) $\delta = 3.80$ (ddd, $^3J_{2,1ax} = 12$, $^3J_{2,3} = 9$, $^3J_{2,1eq} = 5$ Hz, 1 H, H-2), 3.75 (t, $^3J_{4,5} = 10$, $^3J_{4,3} = 9$ Hz, 1 H, H-4), 3.68 (dd, $^2J_{1eq,1ax} = 13$, $^3J_{1eq,2} = 5$ Hz, 1 H, H-1eq), 3.65 (t, $^3J_{3,2} = {}^3J_{3,4} = 9$ Hz, 1 H, H-3), 3.58 (dd, $^2J_{6a,6b} = 13$, $^3J_{6a,5} = 6$ Hz, 1 H, H-6a), 3.50 (ddd, $^3J_{5,4} = 10$, $^3J_{5,6a} = 6$, $^3J_{5,6b} = 5$ Hz, 1 H, H-5), 3.41 (dd, $^2J_{6b,6a} = 13$, $^3J_{6b,5} = 5$ Hz, 1 H, H-6b), 3.02 (dd, $^2J_{1ax,1eq} = 13$, $^3J_{1ax,2} = 12$ Hz, 1 H, H-1ax); ^{13}C-NMR (100 MHz, D_2O): $\delta = 75.0$ (C-3), 71.1 (C-4), 58.1 (C-2), 55.2 (C-5), 44.6 (C-1), 39.3 (C-6); MS (CI, methane) *m/z* (%) 188 (59) [MH^+], 145 (100) [$MH^+ - HN_3$]; HRMS calcd for $C_5H_9O_2N_4$ [$M^+ - CH_2NH_2$] 157.0726, found 157.0729 (100%).

6-Amino-2-fluoro-1,5-imino-1,2,5,6-tetradeoxy-D-glucitol Dihydrochloride (8). Compound **17** (150 mg, 0.37 mmol) was treated with (diethylamido)sulfur trifluoride (DAST) (60.2 mg, 0.37 mmol) in dry CH_2Cl_2 (5 mL) for 10 min. Et_3N (0.1 mL) was added, and the solution was evaporated. Column chromatography of the residue (EtOAc–hexanes, 1:4) afforded compound **20** (83 mg, 55% yield) which was directly treated

with saturated methanolic HCl for 1 h. The solution was evaporated and the residue coevaporated with MeOH. The resulting product was crystallized from Et_2O–MeOH to give the hygroscopic hydrochloride salt of compound **8** (45.5 mg, 96% yield): mp = 94–95 °C; $[\alpha]^{18}_D = +4.3°$ (c = 0.1 in MeOH); ^{1}H-NMR (400 MHz, D_2O, 20 °C, TMS) δ 4.70 (dddd, $^2J_{2H,2F}$ = 46, $^3J_{2,1ax}$ = 10, $^3J_{2,3}$ = 9, $^3J_{2,1eq}$ = 5 Hz, 1 H, H-2), 3.87 (dt, $^3J_{3,2F}$ = 14, $^3J_{3,2} = {}^3J_{3,4}$ = 9 Hz, 1 H, H-3), 3.78 (ddd, $^2J_{1eq,1ax}$ = 12, $^3J_{1eq,2}$ = 5, $^3J_{1eq,2F}$ = 3 Hz, 1 H, H-1eq), 3.71 (t, $^3J_{4,5}$ = 10, $^3J_{4,3}$ = 9 Hz, 1 H, H-4), 3.57 (dd, $^2J_{6a,6b}$ = 13, $^3J_{6a,5}$ = 6 Hz, 1 H, H-6a), 3.50 (m, 1 H, H-5), 3.39 (dd, $^2J_{6b,6a}$ = 13, $^3J_{6b,5}$ = 5 Hz, 1 H, H-6b), 3.24 (ddd, $^2J_{1ax,1eq}$ = 12, $^3J_{1ax,2}$ = 10, $^3J_{1ax,2F}$ = 6 Hz, 1 H, H-1ax); ^{13}C-NMR (100 MHz, D_2O) δ = 87.0 (C-2), 73.9 (C-3), 70.3 (C-4), 55.2 (C-5), 43.7 (C-1), 39.2 (C-6); MS (CI, methane) m/z (%) 165 (100) [MH^+], 145 (56) [$MH^+ - HF$]; HRMS calcd for $C_5H_9O_2NF$ [$M^+ - CH_2NH_2$] 134.0617, found 134.0624 (100%).

2-*O*-Acetyl-6-[(*tert*-butoxycarbonyl)amino]-1,5-[(*tert*-butoxycarbonyl)imino]-3,4-*O*-isopropylidene-1,5,6-trideoxy-D-glucitol (21). To a solution of compound **17** (104 mg, 0.26 mmol) in dry THF (5 mL) were added PPh_3 (138 mg, 0.52 mmol), diethyl azodicarboxylate (91 mg), and AcOH (31 mg). The solution was stirred overnight at rt. Evaporation of the solution and colum chromatography (hexanes–EtOAc, 3:2) afforded compound **21** (92 mg) as an oily residue in 80% yield): $[\alpha]^{18}_D = +15.3°$ (c = 1.6 in $CHCl_3$); ^{1}H-NMR (400 MHz, and 250 MHz at 60 °C, $CDCl_3$, TMS) δ = 5.17 (br, 1 H, NHCO), 4.93 (dd, ^3J = 7 and 5 Hz, 1 H, H-2), 4.10 (d, ^2J = 16 Hz, 1 H, H-1a), 4.05 (dt, $^3J_{4,5}$ = 9, $^3J_{5,6}$ = 6 Hz, 1 H, H-5ax), 3.77 (dd, $^3J_{3,4}$ = 10.5, $^3J_{2,3}$ = 7 Hz, 1 H, H-3ax), 3.60 (dd, $^3J_{3,4}$ = 10.5, $^3J_{4,5}$ = 9 Hz, 1 H, H-4ax), 3.36 (m, 2 H, H-6), 3.29 (dd, ^2J = 16, $^3J_{1,2}$ = 5 Hz, 1 H, H-1b), 2.10 (s, 3 H, CH_3CO), 1.47 (s,12 H, 4 CH_3), 1.43 (s, 12 H, 4 CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 170.3 (OCOMe), 156.0 and 153.2 (OCON), 113.2 (Me_2CO_2), 80.8 and 79.2 (Me_3CO), 79.1 (C-3), 75.1 (C-4), 72.9 (C-2), 56.6 (C-5), 44.6 (C-1), 41.9 (C-6), 28.2 (Me_3CO), 26.8, 26.9 (Me_2CO_2), 20.9 ($MeCO$); MS (CI, methane) m/z (%) 445 (2) [MH^+], 389 (5) [$MH^+ - CH_2CMe_2$], 345 (7) [$MH^+ - CH_2CMe_2 - CO_2$], 333 (30) [$MH^+ - 2\ CH_2CMe_2$], 289 (58) [$MH^+ - 2\ CH_2CMe_2 - CO_2$], 275 (44) [$MH^+ - 2\ CH_2CMe_2$ – acetone]; HRMS calcd for $C_{17}H_{27}O_8N_2$ [$M^+ - t$Bu], 387.1767, found 387.1763 (0.6%).

2-O-Acetyl-6-[(*tert*-butoxycarbonyl)amino]-1,5-[(*tert*-butoxycarbonyl)imino]-3,4-*O*-isopropylidene-1,5,6-trideoxy-D-mannitol (17ac, C-2 epimer of **21).** Compound **17** (100 mg, 0.25 mmol) was treated with acetic anhydride–pyridine (1:1, 0.5 mL) for 24 h. The solution was evaporated and the residue coevaporated with toluene to afford **17ac** (100 mg, 90%): $[\alpha]^{18}_D = -17.4°$ (c = 1.9 in $CHCl_3$); ^{1}H-NMR (400 MHz and 250 MHz at 60 °C, $CDCl_3$, TMS) δ = 5.42 (ddd, ^3J = 7.8, 6.4, and 5.3 Hz, 1 H, H-2), 4.90 (br, 1 H, NHCO), 4.37 (dd, ^2J = 15, $^3J_{1,2}$ = 8 Hz, 1 H, H-1a), 3.96 (dt, $^3J_{4,5}$ = 9, $^3J_{5,6}$ = 6.5 Hz, 1 H, H-5ax), 3.90 (t, $^3J_{3,4} \mp {}^3J_{4,5}$ = 9 Hz, 1 H, H-4ax), 3.60 (dd, $^3J_{3,4}$ = 9, $^3J_{2,3}$ = 5 Hz, 1 H, H-3ax), 3.45 (t, J = 6.5 Hz, 2 H, H-6), 3.00 (dd, ^2J = 15, $^3J_{1,2}$ = 6 Hz, 1 H, H-1b), 2.08 (br s, 3 H, $MeCO$), 1.45 (m, 24 H, 8 CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 170.1 (OCOMe), 156.0 and 154.7 (OCON), 113.0 (Me_2CO_2), 81.1 and 79.2 (Me_3CO), 76.4 (C-3), 73.7 (C-4), 64.4 (C-2), 58.0 (C-5), 43.7 (C-1), 41.7 (C-6), 28.3 (Me_3CO), 26.3, 27.0 (Me_2CO_2), 20.7 (OCOMe).

Acknowledgment. The authors are indebted to the F.K.F.O. and the "Ministerie voor Wetenschapsbeleid, I.U.A.P." for financial support and to the K. U. Leuven (A.K.) for a fellowship. They wish to thank Dr. H. Röper (Cerestar, Vilvoorde, Belgium) for generous supplies of 1-amino-1-deoxy-D-glucitol, the firm Janssen Pharmaceutica for elemental analyses and biologic evaluation, and Dr. S. Toppet, Dr. P. Delbeke and Mr. R. De Boer for technical assistance.

Supporting Information Available: ^{1}H and C^{13} NMR data for **13, 4, 5, 19, 7, 8, 21** and the C-2 epimer of **21** (16 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.

JO9508255