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A novel approach to the 1-deoxynojirimycin system: synthesis from sucrose of 2-acetamido-1,2-dideoxynojirimycin, as well as some 2-*N*-modified derivatives

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Abstract

6-Azido-1,3,4-tri-*O*-benzyl-6-deoxy-D-fructofuranose can be easily obtained in two steps from the known 6,6′-diazido-6,6′-dideoxysucrose (available in two steps from sucrose) and cyclized by controlled hydrogenation and concomitant intramolecular reductive amination to give 3,4,6-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-mannitol, a partially protected derivative of 1-deoxymannojirimycin. After *N*-protection, position 2 is regio-specifically available to modification. This novel approach was taken advantage of in a synthesis of 2-acetamido-1,2-dideoxynojirimycin and new analogues thereof. Results of inhibition studies conducted with these new compounds employing *N*-acetylhexosaminidases of various sources are discussed. © 1996 Elsevier Science Ltd.

Keywords: 1-Deoxynojirimycin; 2-Acetamido-1,2-dideoxynojirimycin; Glycosidase inhibitors; Sucrose

1. Introduction

Over the past decade, sugars with nitrogen instead of oxygen in the ring (sometimes referred to as aza-sugars) have emerged as the most important class of reversible glycosidase inhibitors [1]. Spurred by biochemical and medicinal research, glycosidases involved in the modification of glycoproteins and glycolipids have become of eminent

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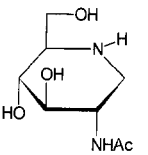
interest due to their crucial roles in a wide variety of biological processes. In this context, inhibitors of hexosaminidases are interesting compounds as a large number of glycoconjugates contain *N*-acetyl-D-glucosamine or *N*-acetyl-D-galactosamine residues. One of the most powerful reversible inhibitors of hexosaminidases is 2-acetamido-1,2-dideoxynojirimycin (**1**, 2-acetamido-1,2,5-trideoxy-1,5-imino-D-glucitol), which has been synthesized from D-glucose [2,3] as well as methyl α-D-mannopyranoside [4] and *N*-acetyl-D-glucosamine [5].



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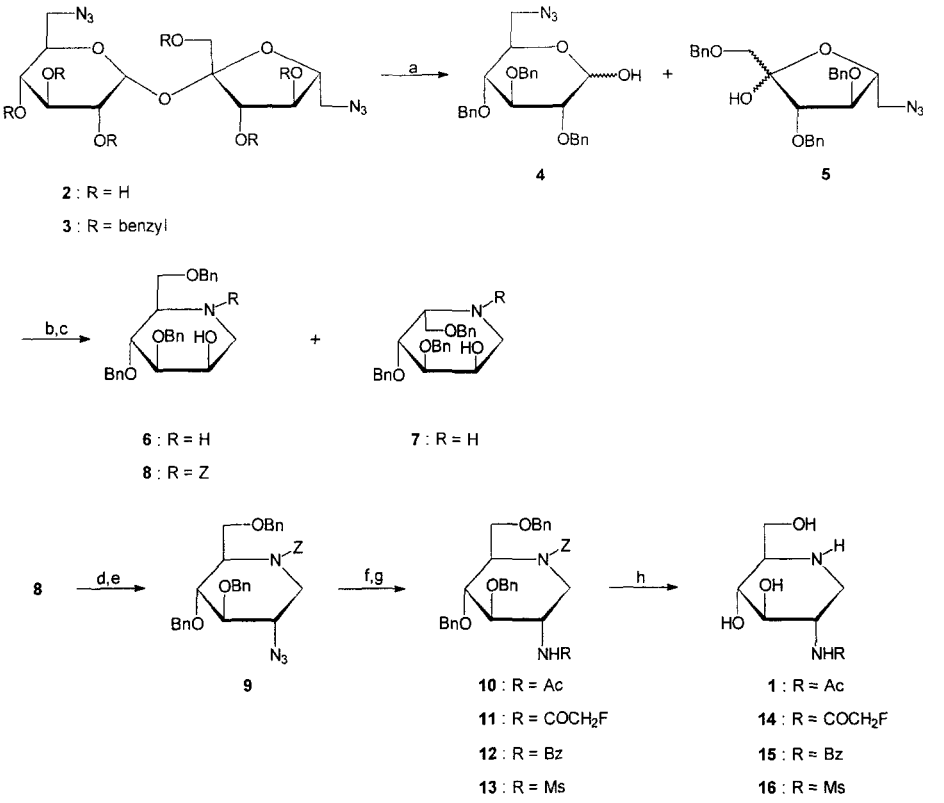
Other approaches have taken advantage of 1-deoxynojirimycin as the starting material [6,7]. A synthesis of compound **1** has also been achieved with the aid of an aldolase-catalyzed key step [8]. The most efficient access to compound **1** to date was recently reported by Furneaux and co-workers [9].

In connection with a project concerned with the synthesis and biological evaluation of glycosidase inhibitors of the structural type under consideration, we have become interested in analogues of compound **1** modified in the *N*-acyl group. Such derivatives could be interesting for the purpose of the isolation and purification of hexosaminidases by affinity chromatography [10], as well as for NMR spectroscopic studies of the respective inhibitor–enzyme complex [11].

2. Results and discussion

Following our synthesis [12] of the mannosidase inhibitor 1-deoxymannojirimycin [13] from sucrose, which was based on the highly stereoselective intramolecular reductive amination of 6-aminodeoxy-D-fructofuranose, a common approach in this series of compounds ([12] and references cited there), we reasoned that 6,6′-diazido-6,6′-dideoxysucrose (**2**) [14] could be an interesting intermediate, allowing a quite general access to 1-deoxynojirimycin as well as 1-deoxymannojirimycin derivatives modified at position 2. From compound **2**, upon per-*O*-benzylation (to give fully protected derivative **3**) and subsequent hydrolysis of the glycosidic bond, a 1:1 mixture of 6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-D-glucopyranose (**4**) and the desired intermediate, 6-azido-1,3,4-tri-*O*-benzyl-6-deoxy-D-fructofuranose (**5**), was obtained in high overall yield (Scheme 1). By hydrogenolysis of the latter over Raney nickel under controlled conditions and concomitant intramolecular reductive amination, 3,4,6-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-mannitol (**6**) was formed in over 70% yield, together with 7% of the corresponding L-*gulo*-epimer **7**, which could easily be separated by chromatography on silica gel after in situ *N*-protection with the aid of benzyloxycarbonyl chloride. In the



Scheme 1. (a) Amberlite IR 120 [H^+], MeCN–H_2O; (b) H_2, Raney Ni, MeOH; (c) CbzCl; (d) Tf_2O, Pyr; (e) NaN_3, DMF; (f) Ph_3P, H_2O; (g) *N*-acylation or *N*-sulfonylation; (h) H_2, Pd–C, MeOH.

resulting *N*-benzyloxycarbonyl-3,4,6-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-mannitol (**8**), position 2 is regio-specifically available for any kind of modification compatible with the protecting groups employed. Activation of C-2 by *O*-trifluoromethanesulfonylation and subsequent nucleophilic displacement of the leaving group with azide yielded 2-azido-*N*-benzyloxycarbonyl-3,4,6-tri-*O*-benzyl-1,2,5-trideoxy-1,5-imino-D-glucitol (**9**). Reduction of the azido group with the aid of triphenylphosphine [15] in tetrahydrofuran, followed by *N*-acetylation with acetic anhydride in pyridine, gave fully protected 2-acetamido-1,2-dideoxynojirimycin (**10**), which, upon hydrogenolytic removal of the benzyl protecting groups, was converted into the title compound. By variation of the *N*-acylating reagent, the corresponding fully protected *N*-(2′-fluoroacetyl)-, *N*-benzoyl-, as well as *N*-methylsulfonyl derivatives (**11–13**) of compound **1**, were obtained that, by *N*-, and *O*-deprotection, gave free inhibitors **14–16**.

Interestingly, NMR spectra of the protected compounds point to the fact that in some cases the $^1C_4$ conformation is preferred and that in some others the spectra exhibit doubled signals suggesting two different stable conformations. Very pronounced is the retardation of signals of the ring carbons in ^{13}C NMR experiments with fully protected

Table 1
Inhibition of *N*-acetylglucosaminidases by 2-acetamido-1,2-dideoxynojirimycin and some derivatives modified in the 2-*N*-acyl group (K_i values in mM)

Inhibitor	Enzyme source		
	Bovine kidney	*Helix pomatia*	Jack beans
2-*N*-Acetyl-dNM (**1**)	0.6	80	0.14
2-*N*-Fluoroacetyl-dNM (**14**)	20	n.d. [a]	4.3
2-*N*-Benzoyl-dNM (**15**)	100	(1000)	n.d. [a]
2-*N*-Mesyl-dNM (**16**)	3000	(5000)	n.d. [a]

[a] n.d., not determined.

iminodeoxy glucitol and mannitol derivatives. Similar observations have been made by Hasegawa and co-workers, as well as by Fleet and his group in this series of compounds [16].

This reported approach comprises 11 simple synthetic steps from sucrose. The formation of the partially protected 1-deoxymannojirimycin derivative **6** and its *N*-protection, as well as the reduction of the 2-azido group in compound **9** and its subsequent *N*-acylation, can be performed as one-pot procedures. A route to utilize the isomeric ballast of the sequence, glucose derivative **4**, as an intermediate in the synthesis of 1,5-dideoxy-1,5-imino-D-arabinitol, recently demonstrated to be a useful inhibitor of α-L-fucosidase [17], is currently under investigation.

Clearly, a wide variety of new derivatives of glycosidase inhibitors 1-deoxynojirimycin, 1-deoxymannojirimycin, as well as of the title compound, are potentially available by the reported approach, taking advantage of sucrose as the cheapest available D-fructofuranoside, as well as the synthetic versatility of intermediate **6**.

Inhibition studies with *N*-acetylglucosaminidases of mammalian, molluscan, and plant origin (Table 1) demonstrate the great specificity of these enzymes with respect to the 2-*N*-acetyl group. Even the small structural alteration of the displacement of a hydrogen atom by fluorine in this moiety caused a dramatic impairment of the affinity. This cannot be accounted for by different steric requirements for hydrogen and fluorine, because these are very similar. A possible explanation might be a larger energy of desolvation relative to the less polar acetyl group. This is supported by partition experiments between *n*-octanol and water where the aqueous phase is favored 5.4-fold by the fluoromethyl over the methyl group [18] and by the solubilities of CH_3F and CH_4 in water which are 166 mL and 3.5 mL/100 mL, respectively [19]. An interesting finding was the (almost) complete loss of inhibitory power caused by the introduction of the 2-*N*-mesyl group, which is distinctly less voluminous than the *N*-benzoyl group. This effect demonstrates the close complementarity of the glycon binding sites to the planar geometry and the hydrogen-bonding properties of the acetyl group. The tetrahedral mesyl substituent interferes strongly with this region of the active site.

Kinetic studies [20] with *N*-acetylglucosaminides in which the acetyl group had been replaced by the benzoyl and tosyl groups showed that these are not hydrolyzed by *N*-acetylglucosaminidases. Phenyl *N*-fluoroacetylglucosaminide, however, was reported to be a good substrate. The latter finding is puzzling because structural variations in the

substrate generally have much smaller effects on binding per se as exemplified by the K_i values of substrate-related inhibitors than on the kinetic properties of substrates with the same structural modifications [1].

3. Experimental

General methods.—Melting points were recorded on a Tottoli apparatus and are uncorrected. Optical rotations were measured on a JASCO digital polarimeter with a path length of 10 cm. NMR spectra were recorded at 200 and 300 MHz (^{1}H), and at 50.29 and 75.47 MHz (^{13}C), in $CDCl_3$ for protected compounds and in D_2O or CD_3OD for free inhibitors. The signals of the *O*-benzyl as well as *N*-benzoxycarbonyl protecting groups were found in the expected regions and are not listed explicitly. TLC was performed on precoated aluminum sheets (E. Merck 5554). For column chromatography Silica Gel-60 (E. Merck) was used.

N-Acetylglucosaminidases from bovine kidney, *Helix pomatia*, and jack beans were from Sigma Chemical Co., St. Louis, MO (USA). Activities and inhibition constants were determined with 4-methylumbelliferyl *N*-acetyl-β-D-glucosaminide as described in ref. [5].

*6,6′-Diazido-1,3,4,2′,3′,4′-hexa-*O*-benzyl-6,6′-dideoxysucrose* (**3**).—Sodium hydride (9.1 g, 380 mmol) and benzyl bromide (36 mL, 300 mmol) were subsequently added to a solution of 6,6′-diazido-6,6′-dideoxysucrose (**2** [12,14], 15 g, 38 mmol) in 1:3 *N*,*N*-dimethylformamide–tetrahydrofuran, and the reaction was monitored by TLC. Upon completion of the reaction, methanol (50 mL) was carefully added to the mixture to destroy excess sodium hydride. After concentration under reduced pressure, the residue was partitioned between dichloromethane and 5% hydrochloric acid, and the organic layer was washed with sodium bicarbonate, dried (sodium sulfate) and concentrated under reduced pressure. Chromatographic purification yielded the per-*O*-benzylated derivative **3** (29.0 g, 81%) as a slightly yellow syrup: $[\alpha]_D^{20}$ +57° (*c* 1.1, $CHCl_3$); ^{1}H NMR: 5.88 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.17–5.07 (m, 8 H), 4.99–4.60 (m, 12 H), 4.37–4.25 (m, 2 H), 4.18 (t, 1 H), 3.97–3.31 (m, 8 H); ^{13}C NMR (δ in ppm): 105.0 (C-2′), 90.0 (C-1), 83.9, 82.6, 81.5, 80.1, 79.4, 78.4 (C-2, C-3, C-4, C-3′, C-4′, C-5′), 75.4, 74.8, 73.5, 73.0, 72.6, 72.1, 71.3, 70.6 (6 benzyl, C-5, C-1′), 53.5 (C-6′), 51.6 (C-6). Anal. Calcd for $C_{54}H_{56}N_6O_9$: C, 69.51; H, 6.05. Found: C, 69.29; H, 6.13.

*6-Azido-1,3,4-tri-*O*-benzyl-6-deoxy-*D*-fructofuranose* (**4**) *and 6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-*D*-glucopyranose* (**5**).—To a 10% solution of compound **3** (20.0 g, 21.4 mmol) in 10:1 acetonitrile–water, trifluoroacetic acid (16 mL, 210 mmol) was added, and the reaction mixture kept at 45 °C for 24 h. Dichloromethane was added, and the mixture was washed sequentially with satd aq sodium bicarbonate and water, and dried (sodium sulfate). After removal of the drying agent and concentration under reduced pressure, the residue was chromatographically purified to give partially protected fructose derivative **4** [7.8 g, 76%; mp 66–68 °C, $[\alpha]_D^{20}$ +30° (*c* 1.1, $CHCl_3$)] and glucose derivative **5** [8.3 g, 82%; mp, $[\alpha]_D^{20}$ +59° (*c* 1.2, $CHCl_3$)]. **4**: ^{13}C NMR: 105.7, 102.8 (C-2α/β), 87.1, 84.0, 83.6, 83.5, 81.6, 79.5 (C-3α/β, C-4α/β, C-5α/β), 72.4, 71.4 (C-1α/β), 53.4, 52.4 (C-6α/β). Anal. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.19; H, 6.15.

Found: C, 68.32; H, 6.23. **5**: ^{13}C NMR: 97.7 (C-1β), 91.4 (C-1α), 84.7, 83.5, 81.8, 80.5, 78.5, 75.4, 70.3 (C-2,3,4α/β), 51.6 (C-6α/β). Anal. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.19; H, 6.15. Found: C, 67.98; H, 6.15.

*3,4,6-Tri-*O*-benzyl-1,5-dideoxy-1,5-imino-*D*-mannitol* (**6**) *and 3,4,6-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-*L*-gulitol* (**7**).—To a 5% solution of compound **4** (5.0 g, 10.5 mmol) in dry methanol, Raney nickel (5 g) (caution: pyrophoric) was added, and the mixture was stirred under an atmosphere of hydrogen at ambient pressure until TLC indicated completion of the reaction. After filtration, the solvent was removed under reduced pressure to give an inseparable mixture of partially protected iminoalditols **6** and **7**, which was immediately used in the next step.

*3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-*D*-mannitol* (**8**).—To a 5% solution of the crude mixture of intermediates **6** and **7** (3.50 g, 8.1 mmol) in 5:1 dichloromethane–methanol, solid sodium bicarbonate (2 g) and benzyloxycarbonyl chloride (1.4 mL, 1.2 equiv) were added, and the mixture was stirred at ambient temperature for 30 min. Dichloromethane (100 mL) was added, and the mixture was washed with water, the aqueous layer was once extracted with dichloromethane (100 mL), and the combined organic layers were dried (sodium sulfate). Removal of the solvent under reduced pressure and chromatography of the residue gave compound **8** (3.40 g, 74%) as a colorless syrup: $[\alpha]_D^{20}$ −25.3° (*c* 1.8, $CHCl_3$); ^{1}H NMR: 4.92–4.52 (m, 3 H, H-5, 2 benzyl), 4.21 (bs, 1 H, H-1e), 4.08–3.94 (m, 2 H, H-2, H-4), 3.82 (bs, 1 H, H-3), 3.75 (m, 2 H, H-6, H-6′), 2.95 (dd, 1 H, $J_{1a,1e}$ 12.1 Hz, H-1a), 2.50 (bs, 1 H, OH-2); despite all efforts, spectra of this compound did not resolve due to the presence of rotamers as previously observed [16]; ^{13}C NMR: 156.2 (CO), 77.5 (C-3), 72.3 (broad signal, C-4), 67.5 (broad signal, C-6), 64.8 (C-2), 53.0 (broad signal, C-5), 41.6 (C-1). Anal. Calcd for $C_{35}H_{37}NO_6$: C, 74.05; H, 6.57. Found: C, 73.73; H, 6.79.

Further fractions yielded the corresponding L-*gulo* epimer as a colorless syrup: $[\alpha]_D^{20}$ −15° (*c* 0.9, $CHCl_3$); ^{1}H NMR: 4.81–4.45 (m, 7 H, H-5, 3 benzyl), 4.35 (bm, 1 H, H-1e), 4.08–3.71 (m, 5 H, H-2,3,4,6,6′), 3.25 (bm, 1 H, H-1a), 2.53 (bs, 1 H, OH-2); ^{13}C NMR: 156.6 (CO), 78.9 (C-3), 75.7 (C-4), 67.6 (C-6), 66.9 (C-2), 53.3 (bs, C-5), 44.5 (C-1). Anal. Calcd for $C_{35}H_{37}NO_6$: C, 74.05; H, 6.57. Found: C, 73.82; H, 6.80.

*2-Azido-3,4,6-tri-*O*-benzyl-*N*-benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino-*D*-glucitol* (**9**).—To a 5% solution of compound **8** (1.0 g, 1.76 mmol) in dry dichloromethane containing pyridine (0.28 mL, 2 equiv), trifluoromethylsulfonyl anhydride (0.35 mL, 2.11 mmol) was added at 0 °C. Upon completion of the reaction (15 min), dichloromethane was added, and the mixture was washed consecutively with 5% aq HCl and freshly prepared satd aq sodium bicarbonate. Drying (sodium sulfate) and concentration of the filtrate under reduced pressure furnished a slightly yellow syrup that was immediately used in the next step. To a 5% solution of the triflate in dry *N,N*-dimethylformamide, sodium azide (600 mg, 9.2 mmol) was added, and the mixture was stirred at ambient temperature for 1 h. Dichloromethane was added, and after filtration the solution was concentrated under reduced pressure. The oily residue was chromatographically purified to yield compound **9** (830 mg, 79%): $[\alpha]_D^{20}$ +28° (*c* 2.1, $CHCl_3$); ^{1}H NMR: 4.52 (m, 1 H, C-5), 4.05 (broad dd, 1 H, $J_{1e,2}$ 2.9 Hz, H-1e), 3.95 (bt, 1 H, $J_{3,4} = J_{4,5}$ 4.3 Hz, H-4), 3.61–3.70 (m, 4 H, H-2, H-3, H-6, H-6′), 3.47 (dd, 1 H, $J_{1a,1e}$ 14.3 Hz, $J_{1a,2}$ 3.8 Hz, H-1a); ^{13}C NMR: 155.9 (CO), 78.8 (C-3), 73.4 (C-4), 68.2 (C-6),

59.4 (C-2), 54.7 (C-5), 41.3 (C-1). Anal. Calcd for $C_{35}H_{36}N_4O_5$: C, 70.93; H, 6.12. Found: C, 71.28; H, 5.88.

2-Acetamido-3,4,6-tri-O-*benzyl*-N-*benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino*-D-*glucitol* (**10**).—To a 1% solution of compound **9** (100 mg) in dry tetrahydrofuran, triphenylphosphine (53 mg, 1.2 equiv) was added, and the mixture stirred at ambient temperature for 10 h. Two equiv of water were added, and the solution was stirred for a further 10 h. The solvent was removed under reduced pressure, the residue was dissolved in pyridine, and excess acetic anhydride was added. After 30 min the reaction mixture was diluted with dichloromethane and washed consecutively with 5% aq HCl and satd aq sodium bicarbonate. Chromatography of the residue obtained after drying (sodium sulfate) and concentration under reduced pressure gave **10** as a colorless syrup (78 mg, 76%): $[\alpha]_D^{20}$ −12° (*c* 1.1, $CHCl_3$); ^{1}H NMR: 6.77, 6.62 (2 d, 1 H, NH-2), 4.45 (m, 1-H, H-5), 4.20–4.07 (bm, 2 H, H-1e, H-4), 3.87–3.56 (m, 4 H, H-2,3,6,6′), 3.25 (bd, 1 H, H-1a), 1.78, 1.58 (bs, Me); ^{13}C NMR: 169.4 (CO, acetyl), 156.7 (CO, Z), 77.3 (C-3), 74.4, 74.0 (C-4), 67.3 (C-6), 53.8, 52.2 (C-5), 45.5, 45.3 (C-2), 39.6 (C-1). Anal. Calcd for $C_{37}H_{40}N_2O_6$: C, 73.01; H, 6.62. Found: C, 72.76; H, 6.80.

3,4,6-Tri-O-*benzyl*-N-*benzyloxycarbonyl-1,2,5-trideoxy-2-fluoroacetamido-1,5-imino*-D-*glucitol* (**11**).—Analoguously to the procedure for preparation of compound **10**, but employing fluoroacetyl chloride (2 equiv) as the acylating agent, intermediate **11** (70 mg, 74%) was obtained: $[\alpha]_D^{20}$ −2.8° (*c* 0.9, $CHCl_3$); ^{1}H NMR: 7.72 (bs, 1 H, NH-2), 4.50 (m, 1 H, H-5), 4.28–4.14 (m, 2 H, H-1e, H-4), 3.90–3.56 (m, 4 H, H-2,3,6,6′), 3.29 (bt, 1 H, H-1a); ^{13}C NMR: 167.5 (d, $J_{C,F}$ 17.7 Hz, CO of fluoroacetyl), 156.7 (bs, CO of Z), 80.2, 79.7 (2 d, $J_{C,F}$ 185 Hz, CH_2F), 74.4, 74.2 (C-3), 72.9, 72.7 (C-4), 67.4, 67.2 (C-6), 53.4, 52.1 (C-5), 45.5, 45.3 (C-2), 39.5, 39.3 (C-1). Anal. Calcd for $C_{37}H_{39}FN_2O_6$: C, 70.91; H, 6.27. Found: C, 71.42; H, 6.02.

3,4,6-Tri-O-*benzyl*-N-*benzyloxycarbonyl-2-benzamido-1,2,5-trideoxy-1,5-imino*-D-*glucitol* (**12**).—Employing benzoyl chloride (2 equiv) instead of acetic anhydride in the same procedure as for the synthesis of compound **10**, product **12** was obtained as a colorless syrup (100 mg, 88%): [a] −0.3° (*c* 1.2, $CHCl_3$); ^{1}H NMR: 4.50 (m, 1 H, H-5), 4.38–4.28 (m, 2 H, H-1e, H-4), 4.02–3.75 (m, H-2,3,6,6′), 3.40 (bd, 1 H, H-1a); ^{13}C NMR: 166.6, 166.3 (CO of Bz), 156.9 (CO of Z), 74.9, 74.5 (C-3), 74.1, 73.9 (C-4), 67.1 (C-6), 53.6, 52.0 (C-5), 46.1, 45.7 (C-2), 39.7 (C-1). Anal. Calcd for $C_{41}H_{42}N_2O_6$: C, 74.75; H, 6.43. Found: C, 74.31; H, 6.66.

3,4,6-Tri-O-*benzyl*-N-*benzyloxycarbonyl-1,2,5-trideoxy-1,5-imino-2-methylsulfonylamido*-D-*glucitol* (**13**).—In analogy to the preparation of compound **10**, mesylamido derivative **13** (51 mg, 47%) was obtained by substitution of acetic anhydride with methanesulfonyl chloride (2 equiv): $[\alpha]_D^{20}$ −15.5° (*c* 1.1, $CHCl_3$); ^{1}H NMR: 4.41 (m, 1 H, H-5), 4.25–4.05 (bm, 1 H, H-1e), 3.86–3.61 (bm, 5 H, H-2,3,4,6,6′), 3.27 (bt, 1 H, H-1a), 2.95, 2.64 (bs, 3 H, SO_2Me); ^{13}C NMR: 156.4 (CO), 74.7 (C-3), 72.6 (bs, C-4), 67.0 (C-6), 54.5, 52.1 (bs, C-5), 49.7 (SO_2Me), 42.7 (bs, C-2), 39.7 (bs, C-1). Anal. Calcd for $C_{36}H_{40}N_2O_7S$: C, 67.06; H, 6.25. Found: C, 67.41; H, 6.31.

2-Acetamido-1,2,5-trideoxy-1,5-imino-D-*glucitol* (**1**).—A solution of compound **10** (50 mg, 0.082 mmol) in ethanol (10 mL) was hydrogenated over Pearlman's catalyst [$Pd(OH)_2$-on-charcoal, 10%] under an atmosphere of hydrogen at ambient pressure. Filtration of the catalyst, removal of the solvent under reduced pressure, followed by

ion-pair chromatography of the crude product on Amberlite CG 50 gave compound **1** (12 mg, 70%) as a white powder: mp 203 °C; $[\alpha]_D^{20}$ +18° (*c* 0.5, MeOH). NMR data were identical with values reported in the literature and matched signals of an authentic sample.

1,2,5-Trideoxy-2-fluoroacetamido-1,5-imino-D-*glucitol* (**14**).—In analogy to the procedure employed for the deprotection of compound **10**, intermediate **11** gave product **14** (12 mg, 85%) as a colorless glass: $[\alpha]_D^{20}$ +19° (*c* 0.5, MeOH); ^{1}H NMR (MeOH-d_4): 4.85 (d, 2 H, $J_{C,F}$ 47.0 Hz, CH_2F), 3.88 (m, 1 H, H-2), 3.85 (dd, 1 H, $J_{5,6}$ 3.1 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.67 (dd, 1 H, $J_{5,6'}$ 6.1 Hz, H-6'), 3.43 (dd, 1 H, $J_{2,3}$ 10.1 Hz, $J_{3,4}$ 8.8 Hz, H-3), 3.27 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 3.13 (dd, 1 H, $J_{1a,1e'}$ 12.3 Hz, $J_{1e,2}$ 4.9 Hz, H-1e), 2.54 (dd, 1 H, $J_{1a,2}$ 11.5 Hz, H-1a), 2.50 (m, 1 H, H-5); ^{13}C NMR: 170.8 (d, $J_{C,F}$ 17.7 Hz, CO), 81.1 (d, $J_{C,F}$ 183 Hz, CH_2F), 77.6 (C-3), 74.3 (C-4), 63.2 (C-6), 62.9 (C-5), 53.8 (C-2), 48.2 (C-1). Anal. Calcd for $C_8H_{15}FN_2O_4$: C, 43.24; H, 6.80. Found: C, 43.75; H, 6.95.

2-Benzamido-1,2,5-trideoxy-1,5-imino-D-*glucitol* (**15**).—Employing the same procedure as for compound **1** for the deprotection of compound **12**, product **15** (17 mg, 89%) was obtained: $[\alpha]_D^{20}$ +13° (*c* 0.5, MeOH); ^{1}H NMR (D_2O): 4.08 (m, 1 H, H-2), 3.92 (dd, 1 H, $J_{5,6}$ 2.9 Hz, $J_{6,6'}$ 11.7 Hz, H-6), 3.77 (dd, 1 H, $J_{5,6'}$ 5.8 Hz, H-6'), 3.65 (dd, 1 H, $J_{2,3}$ 10.1 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.47 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.28 (dd, 1 H, $J_{1a,1e}$ 12.1 Hz, $J_{1e,2}$ 4.9 Hz, H-1e), 2.74 (m, 1 H, H-5), 2.69 (dd, 1 H, H-1a); ^{13}C NMR: 172.3 (CO), 76.7 (C-3), 73.0 (C-4), 62.1 (C-6), 61.5 (C-5), 53.6 (C-2), 47.8 (C-1). Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81. Found: C, 58.40; H, 6.99.

1,2,5-Trideoxy-1,5-imino-2-methanesulfonylamido-D-*glucitol* (**16**).—Following the same procedure as for the deprotection of acetamido derivative **10**, compound **13** gave product **16** (11 mg, 73%) as a colorless glass: $[\alpha]_D^{20}$ +11° (*c* 1.0, MeOH); ^{1}H NMR (MeOH-d_4): 3.85 (m, 1 H, H-2), 3.81 (dd, 1 H, $J_{5,6}$ 3.0 Hz, $J_{6,6'}$ 11.3 Hz, H-6), 3.59 (dd, 1 H, $J_{5,6'}$ 5.9 Hz, H-6'), 3.46 (dd, 1 H, $J_{2,3} = J_{3,4}$ 9 Hz, H-3), 3.30 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.03 (dd, 1 H, $J_{1a,1e}$ 12.4 Hz, $J_{1e,2}$ 4.5 Hz, H-1e), 2.85 (s, 3 H, SO_2Me), 2.59 (dd, 1 H, $J_{1a,1e} = J_{1a,2}$ 12 Hz, H-1a), 2.56 (m, 1 H, H-5); ^{13}C NMR: 77.8 (C-3), 73.7 (C-4), 65.3 (C-6), 60.3 (C-5), 57.5 (C-2), 51.2 (C-1), 41.5 (SO_2Me). Anal. Calcd for $C_7H_{16}N_2O_5S$: C, 34.99; H, 6.88. Found: C, 34.85; H, 7.00.

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