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The Synthesis of 6-Azido and 6-Amino Analogues of 1-Deoxynojirimycin and their Conversion to Bicyclic Derivatives

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Abstract—1-Amino-1-deoxy-D-glucitol (**14**) was converted to the *N*-Boc-2,3;5,6-di-*O*-isopropylidene derivative **16** which was transformed further into the selectively protected 2,3-*O*-isopropylidene 6-azido piperidine **3**. The synthesis proceeded via a double inversion at C-5 involving internal attack of 4-OH to form the 4,5-epoxide **28**, and ring opening of this epoxide by 1-NH_2 to generate the piperidine **3**. This served as a valuable precursor of various target compounds, i.e. 6-azido- and 6-amino-1,6-dideoxynojirimycin **4** and **5**, and the mono- and bicyclic derivatives **6**–**12**.

Introduction

In recent years there has been considerable interest in the polyhydroxylated alkaloids 1-deoxynojirmycin[1] (**1**) and castanospermine[2] (**2**) (Fig. 1). As piperidine analogues of glucopyranose, these compounds inhibit several glucosidases and display antidiabetic and antiviral, including anti-HIV, activities. These properties have stimulated synthetic efforts directed at structural modification of **1** and **2** such as the introduction of lipophilic (fluoro,[3,4] alkyl,[5] and acyl[6]), 2- 3- or 6-amino,[7] and glucosyl[8] groups at specific positions of the piperidine and indolizidine ring systems. The synthesis of bicyclic diazasugars has also been reported.[9]

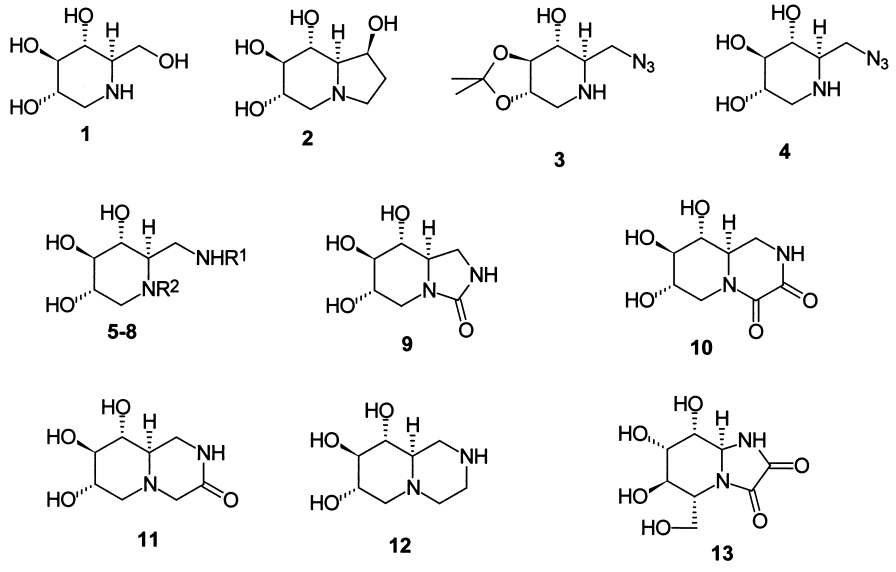

Figure 1.

Keywords: acetals; amines; azides; carbohydrates.

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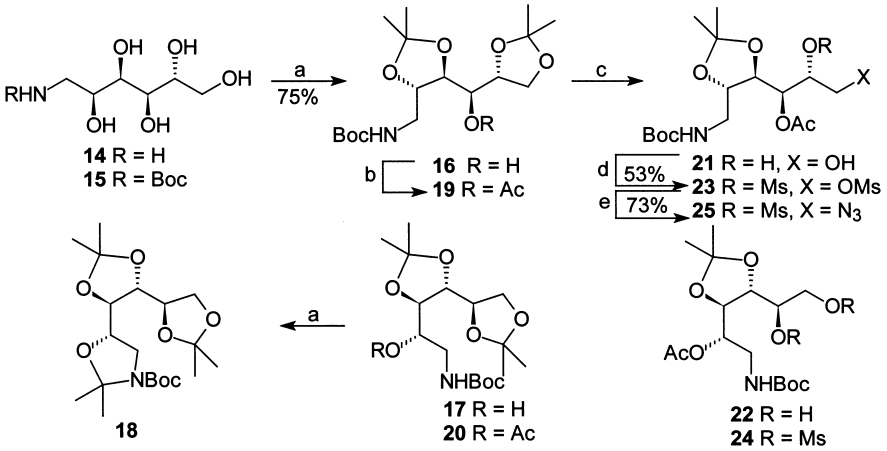
In connection with our ongoing program about the conversion of 1-amino-1-deoxy-D-glucitol to various polyhydroxylated piperidines,[10] we now report the synthesis of the azide synthon **3** and its transformation to target compounds **4**–**12**. The monocyclic 2,3,4-trihydroxy compounds **4**–**8** are analogues of 1-deoxynojirimycin in which the 6-OH group is replaced with an amino or azido group. Since apolar substituents located at the 6-*O*-position of **1** were shown to have a beneficial influence on the activity as inhibitors of α-glucosidase,[11] similar *N*-substituents such as the *p*-fluorobenzoyl group were introduced also at the 6-amino position. The bicyclic target molecules **9**–**12** show analogy to the alkaloids castanospermine and kifunensine **13**. The latter compound, isolated from *Kitasatosporia kifunense*, is a mannosidase I inhibitor exhibiting anti-influenza activity.[12] Part of this work has appeared in a preliminary form.[13]

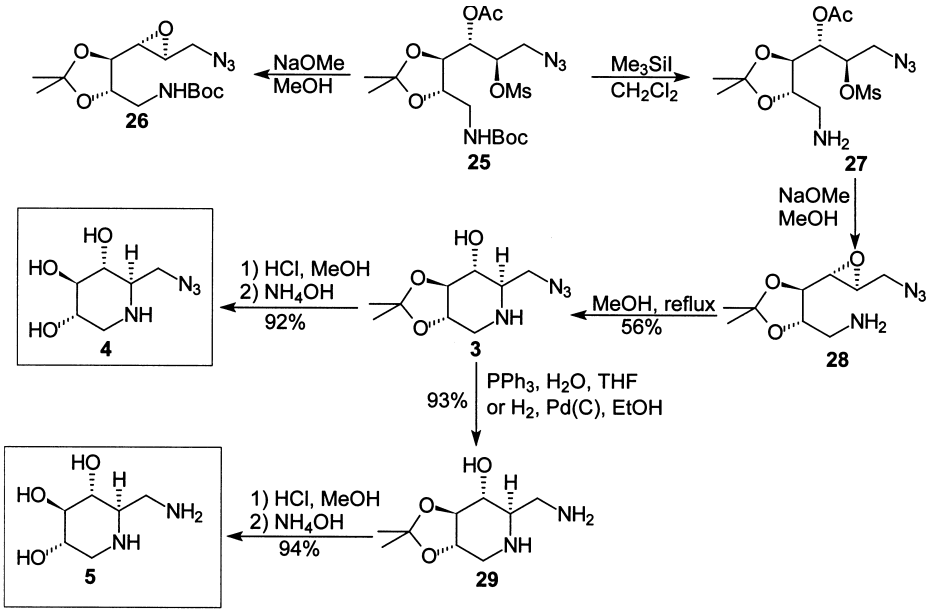
Results and Discussion

Our synthesis started with the protection of 1-amino-1-deoxy-D-glucitol (**14**) as the *N*-Boc-2,3;5,6-di-*O*-isopropylidene derivative **16** (Scheme 1). Regioselective acetal formation was accomplished by subjecting the *N*-Boc compound **15** to a brief treatment with acetone, 2,2-dimethoxypropane and *p*-toluenesulfonic acid. After 10 min, NMR analysis revealed a 9:1 ratio of the regiomeric 2,3;5,6- and 3,4;5,6-di-*O*-isopropylidene compounds **16** and **17**. An increased relative amount of diacetonide **17**, and partial conversion to the triacetonide **18** were observed on prolonged reaction. Hence, following chromatographic isolation, the 9:1 mixture of **16** and **17** was used as such for further transformation, starting with acetylation of the free OH-group. Without further purification, the mixture of acetates **19** and **20** was subjected to acidic hydrolysis (pyridinium *p*-toluenesulfonate in MeOH/H_2O at 60°), which effected a selective deprotection of the 5,6-diol moiety. To minimise complete removal of the acetal groups, the hydrolysis was interrupted when polar tetraol products firstly were detected on TLC. At this stage the 5,6-diols were separated from the starting diacetonides by successive extraction of the acidic solution with hexanes and dichloromethane. The latter extract contained the desired 5,6-diol **21**, whereas the diacetonides isolated from the hexanes were again subjected to the acid hydrolysis to give a second 5,6-diol fraction. Upon complete evaporation of the dichloromethane solutions, the 5,6-diol **21** readily underwent migration of the 4-*O*-acetyl group to form the less polar 6-*O*-acetylated compound. To avoid this conversion, the solutions were evaporated to only half their original volumes, and without further delay a reagent mixture consisting of MsCl, DMAP and Et_3N was added. The resulting 5,6-*O*-dimesylated products were combined and subjected to column chromatography. NMR analysis indicated that the dimesylate fraction consisted of a 19:1 mixture of the two regioisomers **23** and **24** (53% overall yield from the mixture of **16** and **17**). Selective substitution of the primary mesylate group was achieved by heating this mixture with sodium azide in DMF which led to chromatographic isolation of the 6-azido compound **25** as a single regioisomer in 73% yield.

To transform **25** into the acetal protected deoxynojirimycin analogue **3**, we envisaged a double inversion at C-5. In sequential order this would involve (a) internal attack of 4-OH to form the 4,5-epoxide, and (b) ring opening of this epoxide by 1-NH_2 to generate the piperidine. Two different ways were used to implement this double inversion strategy (Scheme 2). As expected, base promoted deprotection of the 4-*O*-acetate group using NaOMe in methanol led to further conversion of the intermediate alcohol to the *N*-protected epoxide **26**. However, subsequent deprotection of the amino group using trimethylsilyl iodide afforded a complex reaction mixture, probably due to reaction of the epoxide group with the Me_3SiI reagent.[14] In the alternative approach, the foregoing sequence of reactions was reversed: the amino function was deprotected first (Me_3SiI in dichloromethane) to give the amino mesylate **27**, and next the epoxide **28** was generated by treatment with NaOMe in methanol. The polar primary amine **28** was not isolated but was converted directly into the less polar piperidine **3** in boiling methanol (56% yield from **25**). Apparently, the regioselective opening of the 4,5-epoxide at the C-5 position is governed by the *trans*-fused character of the bicyclic system generated, which allows for intramolecular attack of the amine to form the six-membered but not the five-membered ring.



Scheme 1. Reagents: (a) $Me_2CO/Me_2C(OMe)_2$ (4:1), *p*-$MeC_6H_4SO_3H$ (0.5 equiv.), room temperature, 10 min; (b) Ac_2O–pyridine, DMAP; (c) PPTS, MeOH–H_2O (9:1), 60°C; (d) CH_2Cl_2, MsCl, DMAP, Et_3N; (e) NaN_3 (1.1 equiv.), DMF, 80°C.

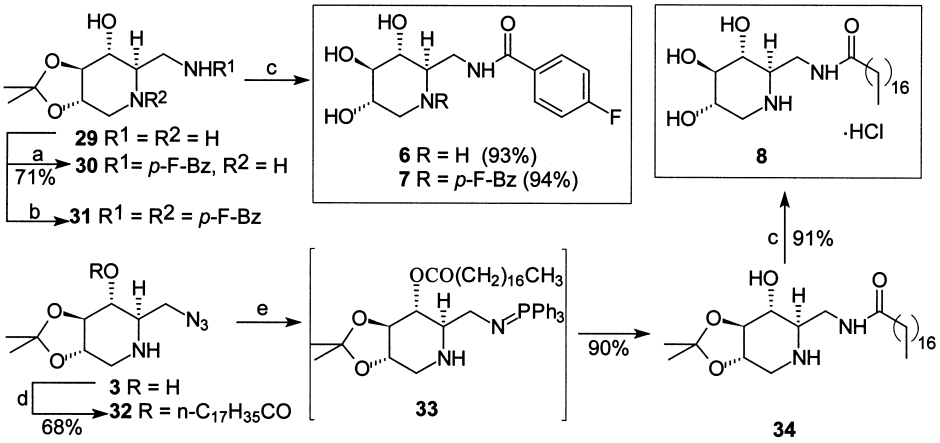


Scheme 2.

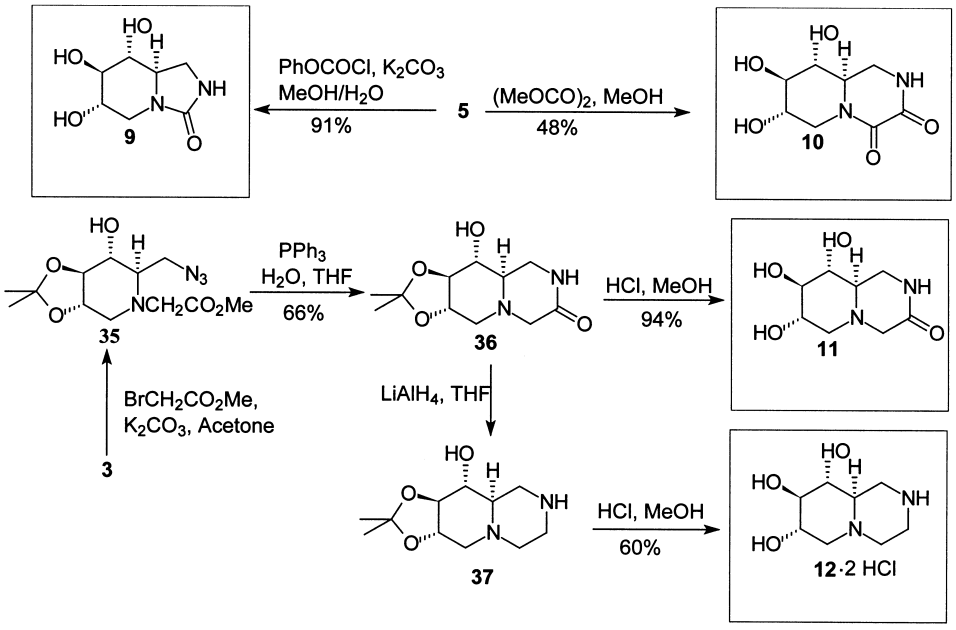
The synthetic potential of synthon **3** was confirmed by its conversion to various target compounds. The 6-azido-6-deoxy analogue of deoxynojirimycin (**4**) was prepared by treatment of **3** with HCl in MeOH, followed by chromatographic purification (silica gel; $NH_4OH/H_2O/MeOH/CHCl_3$, 1:1:28:70) and crystallisation in Et_2O/MeOH. Reduction of the azido function of **3** with triphenyl phosphine and water was carried out according to the method of Knouzi et al.[15] The resulting water-soluble 2,3-*O*-isopropylidene protected diamine **29** was purified by partitioning the reaction mixture between water and toluene. Final deprotection using HCl in MeOH yielded the 6-amino analogue of deoxynojirimycin (**5**). The ^1H NMR spectra of **4** and **5** uniformly displayed coupling constant values ^3J=9 Hz for the axial hydrogen atoms H-2 to H-5, confirming their all-*trans* stereochemical relationship and the $^4C_1$ conformation of the piperidine iminosugar.

Our next goal was to functionalise the two amino groups in a differential way by exploiting the greater reactivity of the primary amine or, conversely, by keeping it in the protected form as the 6-azide. Treatment of diamine **29** with 1 or 2 equiv. of *p*-fluorobenzoyl chloride and an excess of Et_3N in methanol gave the mono- and disubstituted amides **30** and **31**, respectively (Scheme 3). Subsequent acidic deprotection furnished the corresponding *N*-*p*-fluorobenzoyl compounds **6** and **7** in crystalline form.

In contrast to the ready *N*-acylation observed for both amino groups of diamine **29**, benzoylation of the ring amino group failed for the 6-azido compound **3**. In a similar way the octadecanoyl group could be introduced only under forcing conditions using stearic acid, EDCI and DMAP in dichloromethane. However, the resulting product proved to be the 4-*O*-esterified derivative **32**, as shown by an IR absorption at 1740 cm^{-1} and the low-field chemical shift value (δ=5.08) for proton H-4. Upon reduction of the azide function (characterised by a strong IR absorption at 2105 cm^{-1}) of **32** to the primary amine with Ph_3P/H_2O, the 4-*O*-acyl diamine generated by hydrolysis of the intermediate



Scheme 3. Reagents: (a) *p*-F-BzCl (1 equiv.), Et_3N, MeOH; (b) *p*-F-BzCl (2 equiv.), Et_3N, MeOH; (c) HCl–MeOH; (d) n-$C_{17}H_{35}CO_2H$, EDCI, DMAP; CH_2Cl_2; (e) PPh_3, H_2O, THF.



Scheme 4.

iminophosphorane **33** underwent rearrangement to form the 6-*N*-octadecanoyl amide **34**. This was characterised as the triol amide **8** following acidic removal of the acetal group. The lack of reactivity observed for ring *N*-acylation of azide **3** may be ascribed to the repulsion developed between the equatorial azidomethyl side chain and the *N*-acyl substituent, which are coplanar in the chair conformation of the *N*-acyl product. This effect may be alleviated when going from the *N*-monoacyl intermediate **30** to the *N*,*N*′-diacyl product **31**, possibly due to intramolecular hydrogen bridge formation between the two amide groups or to the generation of alternative conformations, e.g. the twist-boat form.[16]

The deprotected diamine **5** and its azido precursor **3** provide access to the fused bicyclic systems **9**–**12** (Scheme 4), which encompass an additional five- or six-membered ring similar to that found in castanospermine (**2**) and kifunensine (**13**). Treatment of **5** with phenylchloroformate and potassium carbonate in methanol/water yielded the urea derivative **9**, which was purified by column chromatography and subsequent crystallisation. The analogous diamide **10** was obtained by treating **5** with dimethyl oxalate in methanol. As opposed to the *N*-acylation of the azide **3**, *N*-alkylation with methyl bromoacetate proceeded readily to give the azido ester **35**. This was not isolated but directly reduced to form the bicyclic lactam **36** in almost quantitative yield. Acidic removal of the isopropylidene group afforded the corresponding trihydroxy lactam **11**. Alternatively, the bicyclic diamine **37** was prepared via reduction of the protected lactam **36** with $LiAlH_4$ and subjected to acidic deprotection to give the corresponding diamine salt **12**.

The structures of the bicyclic target compounds **9**–**12** were confirmed by their spectral data. Whereas the ^1H NMR spectra of **9** and **10** displayed a number of unresolved multiplets, clear cut coupling patterns were observed for the piperazine derivatives **11** and **12**. In the spectra of the latter compounds, five *trans*-1,2-diaxial interactions on six consecutive axial protons H-1ax to H-6ax (numbering according to that of the starting compound 1-amino-1-deoxy-D-glucitol) were revealed by characteristic coupling constant values in the range ^3J=9.3–11 Hz.

Conclusion

The azide synthon **3**, easily prepared from aminoglucitol **14** in seven steps, offers excellent opportunities for the synthesis of various iminosugars, as demonstrated here by its conversion to the mono- and bicyclic products **4**–**12**, which are analogues of the known glycosidase-inhibitors deoxynojirimycin, castanospermine and kifunensine. In these and other diamine target structures, the relative location of the amino nitrogens is similar to that in numerous alkaloids and piperazine or piperidine drugs. Therefore, structural features pertaining to both glucopyranose and the 1,2-diamino compounds can be accommodated via specific modification at either amino function.

Experimental

General procedures

Melting points were uncorrected. The optical rotations were measured on a Propol polarimeter fitted with a 7 cm cell. IR spectra were recorded as thin films between NaCl plates on a Perkin–Elmer 297 grating IR spectrophotometer. ^1H and ^{13}C NMR were recorded on Bruker AMX 400 and WM 250 instruments operating at 400 and 250 MHz for ^1H and 100 and 62.9 MHz for ^{13}C. ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. *J* values are reported in Hz. Mass spectra were run on Kratos MS50 and Hewlett-Packard instruments; the

ion source temperature was 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). Dry solvents were freshly distilled. Solutions were dried over $MgSO_4$. 1-Amino-1-deoxy-D-glucitol was supplied by Cerestar.

1-[(*Tert*-butoxycarbonyl)amino]-1-deoxy-D-glucitol (15).[17] To a solution of 1-amino-1-deoxy-D-glucitol **14** (6.67 g, 35 mmol) in aqueous methanol (50%, 160 mL) was added di-*tert*-butyl dicarbonate (10.80 g, 48 mmol). The mixture was stirred at rt for 4 h. After evaporation of the solvent, the residue was dissolved in a small volume of MeOH, 2-propanol was added and the precipitate was collected by filtration. The filtrate was evaporated and the residue was treated twice as above. The precipitate was dried over P_2O_5 to give compound **15** (9.43 g, 96% yield) as a white solid: mp 72–73°C (literature 86–88°C).

1-[(*Tert*-butoxycarbonyl)amino]-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-glucitol (16). Compound **15** (3.89 g, 13.84 mmol) was suspended in a 4:1 mixture (120 mL) of acetone and 2,2-dimethoxypropane. To the suspension was added *p*-TsOH·H_2O (1.32 g, 6.92 mmol). The mixture was stirred at rt for 10 min and the solution was made alkaline with aqueous Na_2CO_3. The solution was extracted with EtOAc. The organic phase was dried, evaporated and the residue was subjected to column chromatography using silica gel (hexanes–EtOAc, 7:3). This gave 3.76 g (75% yield) of an inseparable 9:1 mixture of regioisomers **16** and **17** as an oil, and triacetonide **18** (12% yield). **16**: IR: ν_{max} 2985, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 1.34 (s, 3 H), 1.40 (s, 6 H), 1.42 (s, 3 H), 1.45 (s, 9 H), 2.50 (d, 1 H, 4-OH), 3.30 (m, 1 H, H-1a), 3.43 (m, 1 H, H-1b), 3.47 (m, 1 H, H-4), 3.91 (dd, 1 H, H-3), 4.02 (m, 2 H, H-6), 4.09 (m, 1 H, H-2), 4.13 (m, 1 H, H-5), 4.98 (br s, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ 25.2 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 27.3 (CH_3), 28.3 (CH_3), 41.7 (C-1), 66.9 (C-6), 70.4 (C-4), 76.2, 76.3 (C-2, C-5), 77.8 (C-3), 79.4 (O*C*Me_3) 109.4 (Me_2CO_2), 155.8 (OCO–NH); HRMS calcd for $C_{16}H_{28}NO_7$ (M^+-CH_3) 346.1866, found 346.1863 (15%).

4-*O*-Acetyl-1-[(*tert*-butoxycarbonyl)amino]-1-deoxy-2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-D-glucitol (23). The 9:1 mixture of **16** and **17** (3.46 g, 9.59 mmol) was dissolved at in a cooled (0°C) 1:1 (v/v) mixture of pyridine and Ac_2O. DMAP (0.25 g) was added to the solution and the mixture was stirred at rt for 1 h. Water was added and the aqueous solution was extracted (3×) with an equal volume of toluene. The toluene solution was dried, and the solvent was removed by evaporation to give 4.63 g of an inseparable mixture of acetates **19** and **20** as an an oily residue (TLC hexanes–EtOAc, 7:3, R_f 0.33). Without further purification, the residue was dissolved in 90% aqueous methanol (50 mL) and PPTS (4.41 g, 9.59 mmol) was added. The solution was heated at 60°C for 6 h. The solution was diluted with water and extracted successively with hexanes (3×) and CH_2Cl_2 (2×). Evaporation of the hexanes extracts provided 1.17 g of a mixture of unreacted **19** and **20**, which was subjected again to the hydrolysis with PPTS (0.73 g, 2.90 mmol) in aqueous MeOH at 60°C for 3 h, followed by extraction as described above. To avoid the migration of the 4-*O*-acetyl group of diol **21** to the 6-*O*-position, the first CH_2Cl_2 extracts were dried immediately and then were concentrated to half their volume, and the mixture of diols **21** and **22** (TLC hexanes–EtOAc, 2:3, R_f 0.12) was sulfonylated by addition of MsCl (1.59 mL, 20.17 mmol), DMAP (0.50 g, 0.40 mmol), and Et_3N (7 mL) to this solution at 0°C. The sulfonylation was complete in less than 10 min at rt. The CH_2Cl_2 extracts of the second hydrolysis reaction were sulfonylated as described, using 6 mmol of MsCl, 3 mmol of DMAP and 2 mL of Et_3N. The CH_2Cl_2 solutions containing the products from the two sulfonylation reactions were combined and washed with an aqueous solution of K_2CO_3. The organic phase was dried and evaporated, and the residue was purified by column chromatography on silica gel (hexanes–EtOAc, 3:2) to afford 2.65 g of a 19:1 mixture of dimesylates **23** and **24** as an oily residue in 53% overall yield from the 9:1 mixture of diacetonides **16** and **17**. **23**: IR: ν_{max} 1750, 1706 1362 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 1.40 (m, 15 H, Me_2C, Me_3C), 2.15 (s, 3 H, *Me*CO), 3.10 (s, 3 H, *Me*SO_2), 3.18 (s, 3 H, *Me*SO_2), 3.34 (dt, *J*=15, 5 Hz, 1 H, H-1a), 3.41 (ddd, *J*=15, 7, 5 Hz, 1 H, H-1b), 3.75 (m, 1 H, H-2), 3.98 (br d, *J*=8.5 Hz, 1 H, H-3), 4.40 (dd, *J*=12, 6 Hz, 1 H, H-6a), 4.69 (dd, *J*=12, 2 Hz, 1 H, H-6b), 5.15 (td, *J*=6, 12 Hz, 1 H, H-5), 5.24 (br s, 1 H, NH), 5.4 (br d, *J*=6 Hz, 1 H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (*Me*CO), 26.2, 26.8 (Me_2C), 28.1 (Me_3C), 37.4, 38.4 (2 *Me*SO_2), 40.3 (C-1), 66.7 (C-6), 67.8 (C-4), 75.5 (2 C, C-2, C-3), 77.8 (C-5), 79.4 (O*C*Me_3), 109.4 (Me_2CO_2), 156.1 (N–COO), 169.6 (COO); HRMS: calcd for $C_{13}H_{22}N_1O_{12}S_2$ (M^+-CH_3, −isobutene) 448.05834, found 448.05949 (10%).

4-*O*-Acetyl-1-[(*tert*-butoxycarbonyl)amino]-6-azido-1,6-dideoxy-2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-D-glucitol (25). Compound **23** prepared according to the preceding procedure (1.96 g, 3.88 mmol) was dissolved in 10 mL of DMF. Sodium azide (0.29 g, 4.5 mmol) was added and the solution was heated at 80°C for 2 h. The reaction mixture was allowed to cool to rt, diluted with CH_2Cl_2, and the organic solution was washed with water (3×). After evaporation of the organic solvent, the residue was subjected to column chromatography (hexanes–EtOAc, 3:2) to give compound **25** (2.77 g, 73% yield) as an oil: IR: ν_{max} 2180, 1755, 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 1.40 (m,15 H, Me_2C, Me_3C), 2.16 (s, 3 H, *Me*SO_3), 3.16 (s, 3 H, CH_3CO_2), 3.33 (ddd, *J*=15, 7, 4 Hz, 1 H, H-1a), 3.36 (ddd, *J*=15, 6, 4 Hz, 1 H, H-1b), 3.53 (dd, *J*=7, 14 Hz, 1 H, H-6a), 3.74 (m, 1 H, H-2), 3.84 (br m, 1 H, H-4), 3.96 (dd, *J*=8, 2 Hz, 1 H, H-3), 4.84 (broad, 1 H, N*H*), 4.92 (m, 1 H, H-5), 5.35 (br m, 1 H, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$), δ 20.5 ($MeCO_2$), 26.52, 27.17 (Me_2C), 28.4 (Me_3C), 38.6 (*Me*SO_3), 40.7 (C-1), 51.1 (C-6), 69.5 (C-4), 76.0 (2 C, C-2, C-3), 79.0 (C-5) 79.6 (Me_3C), 109.4 (Me_2C), 156.1 (NH*C*OO), 169.3 (*C*OO); HRMS calcd for $C_{12}H_{19}N_4SO_9$ (M^+-CH_3, −isobutene) 395.0873, found 395.0878 (14%).

6-Azido-1,5-imino-2,3-*O*-isopropylidene-1,5,6-trideoxy-D-glucitol (3). To a solution of azide **25** (0.66 g, 1.42 mmol) in CH_2Cl_2 (20 mL) was added Me_3SiI (0.42 mL, 2.85 mmol). The reaction mixture was stirred for 10 min, followed by the addition of MeOH (3 mL) and Et_3N (1 mL).

The solvents and reagents were evaporated and the residue of crude primary amine **27** (TLC MeOH–EtOAc, 3:47, R_f 0.12) was treated with MeONa (0.38 g, 7.13 mmol) in MeOH (10 mL) for 1 h to form the epoxide **28** (TLC MeOH–EtOAc, 3:47, R_f 0.15). Water was added and the epoxide was extracted with EtOAc. The organic phase was dried and evaporated and the residue was heated in MeOH under reflux for 2 h. The solution was evaporated and the residue was subjected to column chromatography (EtOAc) to afford the piperidine **3** (0.184 g) as a white solid in 56% overall yield from mesylate **25**: mp 108–109.5°C; $[\alpha]_D^{20}$ +46.8 (*c* 0.45, $CHCl_3$); IR: ν_{max} 3426, 2105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 1.45 (6 H, s, *Me*$_2$C), 2.58 (1 H, m, H-5), 2.73 (1 H, m, H-1ax), 3.3-3.4 (3 H, m, H-1eq, H-2 and H-3 or H-4), 3.62 (1 H, t, *J*=9 Hz, H-3 or H-4), 3.66 (1 H, dd, *J*=5, 13 Hz, H-6a), 3.72 (1 H, dd, *J*=3.5, 13 Hz, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$), δ 26.6, 26.7 (*Me*$_2$C), 46.6 (C-1), 51.9 (C-6), 59.4 (C-5), 71.0 (C-4), 75.7, 84.2 (C-2, C-3), 110.6 (Me_2CO_2); HRMS calcd for $C_8H_{13}N_4O_3$ (M^+-CH_3) 213.0988, found 213.0987 (3%), calcd for $C_8H_{14}NO_3$ ($M^+-CH_2N_3$) 172.0974, found 172.0974 (100%).

6-Azido-1,5-imino-1,5,6-trideoxy-D-glucitol (4). Compound **3** (60 mg, 0.26 mmol) was treated with saturated methanolic HCl for 30 min. Evaporation of the solvent and column chromatography of the residue (NH_4OH–H_2O–MeOH–$CHCl_3$, 1:1:28:70, R_f 0.3) afforded, following crystallisation in Et_2O–MeOH, 45.6 mg of azide **4** (92% yield) as a white solid: mp 165–167°C; $[\alpha]_D^{20}$ +26.0 (*c* 0.054, H_2O); IR: ν_{max} 3430, 2110 cm^{-1}; ^1H NMR (400 MHz, D_2O), δ 2.85 (1 H, dd, *J*=11, 13 Hz, H-1ax.), 3.16 (1 H, ddd, *J*=3, 5, 9 Hz, H-5), 3.41 (1 H, dd, *J*=5, 13 Hz, H-1eq), 3.46 (1 H, t, *J*=9 Hz, H-3), 3.51 (1 H, t, *J*=9 Hz, H-4), 3.73 (1 H, ddd, *J*=5, 9, 11 Hz, H-2), 3.79 (1 H, dd, *J*=5, 14 Hz, H-6), 3.88 (1 H, dd, *J*=3, 14 Hz, H-6′); ^{13}C NMR (D_2O, 100 MHz), δ 46.5 (C-1), 49.2 (C-6), 57.9 (C-5), 67.6 (C-2), 69.0 (C-4), 76.3 (C-3); HRMS calcd. for $C_5H_{10}NO_3$ ($M^+-CH_2N_3$) 132.0661, found 132.0660 (100%).

6-Amino-1,5-imino-2,3-*O*-isopropylidene-1,5,6-trideoxy-D-glucitol (29). To a solution of azide **3** (103 mg, 0.51 mmol) in THF (3 mL) was added PPh_3 (135 mg, 0.51 mmol) and water (0.2 mL). The mixture was allowed to stand at rt for 7 h. Following evaporation of the solution, the residue was partitioned between water (5 mL) and toluene (5 mL). The aqueous phase was extracted further with toluene (2×5 mL). Upon evaporation of the aqueous solution, compound **29** (oil) was isolated (85 mg, 93% yield): R_f 0.36 ($CHCl_3$–MeOH–NH_4OH–H_2O, 50:45:1:5): $[\alpha]_{D20}$ −21.0 (*c* 0.072, MeOH); IR: ν_{max} 3432, 2987 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 1.40 (2 s, 6 H, Me_2C), 2.37 (ddd, *J*=9, 7, 4 Hz, 1 H, H-5), 2.60 (m, *J*=12, 10 Hz, 1 H, H-1ax), 2.74 (dd, *J*=13, 7 Hz, 1 H, H-6a), 3.08 (dd, *J*=13, 4 Hz, H-6b), 3.21 (m, *J*=12, 4 Hz, 1 H, H-1eq), 3.32–3.43 (m, 3 H, H-2, H-3, H-4); ^{13}C NMR (100 MHz, CD_3OD), δ 26.8, 27.1 (*Me*$_2$C), 43.2 (C-6), 47.6 (C-1), 63.0 (C-5), 73.5 (C-4), 77.1, 85.2 (C-2, C-3), 111.2 (Me_2CO_2); HRMS calcd for $C_9H_{15}O_3N$ (M^+-NH_3) 185.1052, found 185.1043 (15%).

6-Amino-1,5-imino-1,5,6-trideoxy-D-glucitol (5). Compound **29** (60 mg, 0.297 mmol) was treated with saturated methanolic HCl (3 mL) for 30 min. Following evaporation of the solution and twofold co-evaporation of the reagents with MeOH, the residue was treated with a solution of ammonia in methanol. Upon evaporation and crystallisation of the residue from Et_2O–MeOH compound **5** was isolated (45 mg, 94% yield) as white crystals (changing to brown on standing at rt): mp 188°C; $[\alpha]_D^{20}$ +11.5 (*c* 0.12, H_2O); IR: ν_{max} 3425 cm^{-1}; ^1H NMR (400 MHz, D_2O), δ 2.57 (1 H, dd, *J*=11, 13 Hz, H-1ax), 2.91 (1 H, m, H-5), 3.08 (1 H, dd, *J*=7.5, 13 Hz, H-6), 3.22 (1 H, dd, *J*=5, 13 Hz, H-1eq), 3.32 (1 H, t, *J*=9 Hz, H-3), 3.38 (1 H, t, *J*=9 Hz, H-4), 3.40 (1 H, dd, *J*=6.5, 13 Hz, H-6′), 3.56 (1 H, ddd, *J*=5, 9, 11 Hz, H-2); ^{13}C NMR (D_2O, 100 MHz), δ 41.0 (C-6), 48.1 (C-1), 56.4 (C-5), 69.9 (C-2), 73.3 (C-4), 77.4 (C-3); HRMS calcd for $C_6H_{15}N_2O_3$ (M^++H) 163.1083, found 163.1095 (0.2%), calcd for $C_5H_{10}NO_3$ ($M^+-CH_2NH_2$) 132.0661, found 132.0683 (100%).

6-*p*-Fluorobenzamido-2,3-*O*-isopropylidene-1,5-imino-1,5,6-trideoxy-D-glucitol (30). Compound **29** prepared from 103 mg of azide **3** (0.45 mmol) was dissolved in MeOH (5 mL). Et_3N (0.14 mL, 1 mmol) and *p*-fluorobenzoyl chloride (0.06 mL, 0.49 mmol) were added. After completion of the reaction (30 min, TLC AcOEt–MeOH, 47:3, R_f 0.2), the reaction mixture was evaporated, water (5 mL) was added, and the mixture was extracted successively with toluene and AcOEt. Upon evaporation of the AcOEt solution, 103 mg of compound **30** was isolated as a white solid (71% overall yield from **3**): mp 170–172°C; $[\alpha]_D^{20}$ +5.1 (*c* 0.2, $CHCl_3$); IR: ν_{max}^{KBr} 3340, 3280, 1645, 1600, 1550 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 1.5 (s, 6 H, *Me*$_2$C), 2.54–2.67 (m, 2 H, H-1ax, H-5), 3.21 (dd, *J*=12, 4 Hz, 1 H, H-1eq), 3.31–3.47 (m, 3 H, H-2, H-3, H-4), 3.57 (dd, *J*=14, 8 Hz, 1 H, H-6a), 3.75 (dd, *J*=14, 8 Hz, 1 H, H-6b), 7.16 (t, *J*=9 Hz, 2 H, H-3′, H-5′ arom.), 7.90 (m, 2 H, H-2′, H-6′ arom.); ^{13}C NMR: (100 MHz, CD_3OD), δ 26.9, 27.1 (*Me*$_2$C), 42.2 (C-6), 47.6 (C-1), 62.3 (C-5), 73.4 (C-4), 77.0, 84.9 (C-2, C-3), 111.4 (Me_2CO_2), 116.2, 116.4 (C′-3, C′-5 arom.), 131.0, 131.1 (C′-2, C′-6 arom.), 131.8 (C′-1 arom.), 166.2 (C′-4 arom.), 169.7 (N–CO–); HRMS calcd for $C_{16}H_{19}N_2O_3F$ (M^+-H_2O) 306.1380, found 306.1386 (6%), calcd for $C_8H_{14}NO_3$ ($M^+-CH_2NHCOC_6H_4F$) 172.0974, found 172.0975 (**31**), calcd for C_7H_4FO ($FC_6H_4CO^+$) 123.0246, found 123.0244 (100%).

6-*p*-Fluorobenzamido-1,5-imino-1,5,6-trideoxy-D-glucitol (6). Compound **30** (80 mg, 0.25 mmol) was treated with saturated methanolic HCl (3 mL) for 30 min. The mixture was evaporated and the residue was co-evaporated twice with MeOH, followed by treatment with methanolic ammonia and evaporation. Crystallisation of the residue from Et_2O–MeOH provided compound **6** (65 mg, 93% yield) as a white solid: mp 176–178°C; $[\alpha]_D^{20}$ +13.6 (*c* 0.14, H_2O); IR: ν_{max}^{KBr} 3400, 3390, 3340, 1650, 1610, 1580, 1510 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 2.49 (dd, *J*=12, 10.5 Hz, 1 H, H-1ax), 2.78 (ddd, *J*=10, 8, 3 Hz, 1 H, H-5), 3.14 (dd, *J*=12, 5 Hz, 1 H, H-1eq), 3.24 (t, *J*=10, 9 Hz, 1 H, H-4), 3.37 (t, *J*=9 Hz, 1 H, H-3), 3.52 (m, 1 H, H-6a), 3.53 (m, 1 H, H-2), 3.76 (dd, *J*=15, 3 Hz, H-6b), 7.25 (t, *J*=9 Hz, 2 H, H-3′, H-5′ arom.), 7.93 (m, 2 H, H-2′, H-6′ arom.); ^{13}C NMR (100 MHz, H_2O), δ 41.0 (C-6), 48.5 (C-1), 59.2 (C-5), 70.3 (C-2), 72.6, 77.8 (C-3, C-4), 115.4, 115.6 (C-3′, C-5′ arom.), 129.5, 129.6 (C-2′, C-6′ arom.), 129.6

(C-1′ arom.), 164.6 (C-4′ arom.), 170.2 (*C*O–NH); HRMS calcd for $C_{13}H_{15}N_2FO_3$ (M^+-H_2O) 266.1067, found 266.1069 (13%), calcd for C_8H_7NFO ($[CH_2NHCOC_6H_4F]^+$) 152.0512, found 152.0508 (8%), calcd for $C_5H_{10}NO_3$ ($M^+-CH_2NHCOC_6H_4F$) 132.0661, found 132.0663 (100%).

6-*p*-Fluorobenzamido-1,5-[(*p*-fluorobenzoyl)imino]-1,5,6-trideoxy-D-glucitol (7). Compound **29** prepared from 103 mg of azide **3** (0.45 mmol) was dissolved in MeOH (5 mL). Et_3N (0.28 mL, 2 mmol) and *p*-fluorobenzoyl chloride (0.12 mL, 0.98 mmol) was added. After completion of the reaction (30 min), the mixture was evaporated, water (5 mL) was added, and the aqueous solution was extracted (3×) with an equal volume of toluene. The organic phase was evaporated and the residue, consisting of the protected diamide **31** (TLC EtOAc–MeOH, 47:3, R_f 0.56), was treated with methanolic HCl (5 mL) for 1 h. The mixture was evaporated and the residue was distributed between water (5 mL) and toluene (5 mL). The aqueous solution was extracted with toluene (2×) and EtOAc (5×). The EtOAc solution was dried and evaporated, and the residue was crystallised from Et_2O–MeOH to give compound **7** (173 mg) as a white crystalline solid in 94% overall yield from azide **3**: mp 113–114°C; $[\alpha]_D^{20}$ +4.9 (*c* 0.2, H_2O); IR: ν_{max}^{KBr} 3380, 1710, 1640, 1600 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 3.35 (dd, *J*=16, 4 Hz, 1 H), 3.40–4.00 (m, 5 H), 4.20–4.70 (m, 2 H), 6.70–7.50 (m, 6 H), 7.70–7.90 (m, 2 H); ^{13}C NMR (100 MHz, CDO_3D), δ 40.0 (C-6), 46.3 (C-1), 57.7 (C-5), 70.2, 70.8, 71.5 (C-2, C-3, C-4), 116.0, 116.3, 116.5 (C′-3, C′-5 arom.), 130.9, 131.0 (C′-2, C′-6 arom.), 133.3 (C′-1 arom.), 164.1, 166.6 (C′-4 arom.), 174.5 (N–CO–); HRMS calcd for $C_{20}H_{20}N_2F_2O_5$ (M^+) 406.1340, found 406.1356 (0.3%), calcd for $C_{20}H_{18}N_2F_2O_4$ (M^+-H_2O) 388.1235, found 388.1251 (2%), calcd for $C_{12}H_{13}NFO_4$ ($M^+-CH_2NHCOC_6H_4F$) 254.0829, found 254.0860 (16%).

6-Azido-1,5-imino-2,3-*O*-isopropylidene-4-*O*-octadecanoyl-1,5,6-trideoxy-D-glucitol (32). To a solution of azide **3** (102 mg, 0.44 mmol) in CH_2Cl_2 (5 mL), were added stearic acid (157 mg, 0.54 mmol), EDCI (172 mg, 0.90 mmol) and DMAP (24.4 mg, 0.20 mmol). The mixture was stirred for 18 h at rt, and then was washed with water. The organic phase was dried and evaporated. The residue was purified by column chromatography (hexanes–EtOAc, 7:3) to give ester **32** (147 mg, 68% yield) as a white solid: mp 73.6–74.5°C; $[\alpha]_D^{20}$ +4.7 (*c* 0.12, $CHCl_3$); IR: ν_{max} 3426, 2105, 1740 cm^{-1}; ^1H NMR (400 MHz, C_6D_6), δ 0.95 (t, 3H, CH_3), 1.20–1.50 (m, 34 H, 14 CH_2, 2 CH_3), 1.52 (m, 2 H, C*H*$_2$CH$_2$CO), 2.15 (td, *J*=8, 1.5 Hz, 2 H, C*H*$_2$CO), 2.39 (dd, *J*=10, 11.5 Hz, 1 H, H-1ax), 2.43 (m, *J*=9, 7, 3 Hz, 1 H, H-5), 2.91 (dd, *J*=11.5, 4.5 Hz, 1 H, H-1eq), 2.99 (dd, *J*=12.5, 7 Hz, 1 H, H-6a), 3.18 (m, 2 H, H-2, H-6b), 3.42 (t, *J*=9.5, 9 Hz, 1 Hz, H-3), 5.08 (t, *J*=9.5, 9 Hz, 1 H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$), d 14.1 (CH_3), 22.7, 25.0 (CH_2), 26.7, 26.8 (*Me*$_2$C), 29.1, 29.3, 29.4, 29.5, 29.6,29.7, 32.0, 34.4 (CH_2), 46.6 (C-1), 52.1 (C-6), 58.2 (C-5), 71.8 (C-4), 76.2 (C-3), 81.5 (C-2), 110.8 (Me$_2$*C*O$_2$), 172.9 (O–CO); HRMS: calcd for $C_{26}H_{47}O_4N_4$ [M^+-CH_3] 479.3597, found 479.3592 (3%).

1,5-Imino-6-octadecanamido-1,5,6-trideoxy-D-glucitol hydrochloride (8). To a solution of amide **32** (100 mg, 0.21 mmol) in THF (5 mL), were added PPh_3 (61 mg, 0.23 mmol) and water (0.1 mL). The mixture were stirred overnight and evaporated. Column chromatography (MeOH–$CHCl_3$, 3:22) afforded 88.3 mg (90% yield) of compound **34** as a white solid. This compound (20 mg, 0.04 mmol) was treated with methanolic HCl (3 mL) for 30 min. The solution was evaporated and the residue was crystallised from Et_2O–MeOH to give 18 mg (91% yield) of **8**·HCl (white solid): mp 189.0–190.1°C; $[\alpha]_D^{20}$ +33.5 (*c* 0.86, MeOH); IR: ν_{max} 3426, 2951, 1710, 1656 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 0.88 (t, *J*=6.7 Hz, 3 H, CH_3), 1.12 (m, 2 H, C*H*$_2$–CH$_3$), 1.28 (m, 26 H, CH_2), 1.62 (m, 2 H, C*H*$_2$CH$_2$CO), 2.27 (t, *J*=7.4 Hz, 2 H, CH_2CO), 2.83 (dd, *J*=12.5, 11 Hz, 1 H, H-1ax), 3.11 (m, 1 H, H-5), 3.37 (m, 3 H, H-1eq, H-3, H-4), 3.50 (dd, *J*=15, 7 Hz, 1 H, H-6a), 3.64 (m, 2 H, H-2, H-6b); ^{13}C NMR (100 MHz, CD_3OD), δ 14.2 (CH_3), 23.6, 26.5, 30.5, 32.9, 36.9 (CH_2), 39.9 (C-6), 48.0 (C-1), 61.8 (C-5), 68.6 (C-2), 70.7 (C-4), 78.0 (C-3); HRMS: calcd for $C_{24}H_{46}O_3N_2$ [M^+-H_2O], 410.3508, found 410.3505 (19%).

(6*S*,7*R*,8*R*,8a*R*)Hexahydro-6,7,8-trihydroxyimidazo[1,5*a*]-pyridin-3(2*H*)-one (9). To a solution of diamine **5** (59.7 mg, 0.37 mmol) in 50% aqueous MeOH (5 mL), were added K_2CO_3 (276 mg, 2 mmol) and PhOCOCl (0.05 mL, 0.39 mmol). The mixture was stirred for 1 h and evaporated. The residue was dissolved in MeOH and the insoluble material was filtered off. The methanolic solution was evaporated and the residue was purified by chromatography on a silica gel column (NH_4OH–H_2O–MeOH–$CHCl_3$, 1:1:48:50) to afford, after crystallisation from Et_2O–MeOH, 63.4 mg (91% yield) of compound **9** as a white solid: mp >400°C; $[\alpha]_D^{20}$ +0.96 (*c* 0.15, H_2O); IR: ν_{max} 3426, 1655 cm^{-1}; ^1H NMR (400 MHz, D_2O), δ 2.64 (dd, *J*=12, 10 Hz, 1 H), 3.38 (m, 1 H), 3.31 (m, 3 H), 3.51 (m, 2 H), 3.78 (dd, *J*=12, 5 Hz, 1 H); ^{13}C NMR (100 MHz, D_2O), δ 43.6 (C-1), 45.9 (C-5), 60.3 (C-8a), 71.2 (C-6), 74.6 (C-8), 79.5 (C-7), 165.1 (C-3); HRMS: calcd for $C_7H_{12}O_4N_2$ [M^+], 188.0797, found 188.0801 (12%).

(7*S*,8*R*,9*R*,9a*R*)Hexahydro-7,8,9-trihydroxy-2*H*-pyrido-[1,2*a*]pyrazine-3,4(4*H*)-dione (10). Diamine **5** (69.4 mg, 0.43 mmol) was dissolved in MeOH (5 mL). $(MeOCO)_2$ (144 mg, 1.3 mmol) was added and the mixture was heated under reflux for 96 h. The mixture was evaporated and the residue was subjected to column chromatography (NH_4OH–H_2O–MeOH–$CHCl_3$, 1:1:48:50) to provide, after crystallisation from Et_2O–MeOH, 45 mg (48% yield) of compound **10** as a white solid: mp 367.2–368.4°C; $[\alpha]_D^{20}$ +0.89 (*c* 1.6, H_2O); IR: ν_{max} 3421, 1658 cm^{-1}; ^1H NMR (400 MHz, D_2O), δ 2.95 (dd, *J*=12.5, 11 Hz, 1 H), 3.45–3.70 (m, 6 H), 4.80 (dd, *J*=12.5, 5 Hz, 1 H); ^{13}C NMR (100 MHz, D_2O), δ(37.6 (C-1), 46.9 (C-6), 56.7 (C-9a), 68.1 (C-7), 70.4 (C-9), 77.2 (C-8); HRMS: calcd for $C_8H_{12}O_5N_2$ [M^+], 216.0746, found 216.0747 (26%).

(7*S*,8*R*,9*R*,9a*R*)Hexahydro-7,8-*O*-isopropylidene-7,8,9-trihydroxy-2*H*-pyrido[1,2*a*]pyrazin-3(4*H*)-one (36). To a solution of azide **3** (219.6 mg, 0.96 mmol) in acetone (5 mL) were added $BrCH_2CO_2Me$ (0.26 mL, 2.89 mmol) and K_2CO_3 (414 mg, 3 mmol). The mixture was heated under reflux and the progress of the reaction was followed

by TLC (hexanes–EtOAc, 7:3). After 24 h the solution was evaporated, and the residue was distributed between water and CH_2Cl_2. After further extraction with CH_2Cl_2, the organic phases were combined, dried, and evaporated. The residue consisting of crude compound **35** was treated overnight with PPh_3 (263 mg, 1 mmol) and water (0.2 mL) in THF (5 mL). Following evaporation and column chromatography ($CHCl_3$–MeOH, 17:3, R_f 0.35), compound **36** (245 mg) was isolated as a white solid in 66% overall yield from azide **3**: mp >400°C; $[\alpha]_D^{20}$ +78.3 (*c* 0.10, H_2O); IR: ν_{max} 3408, 1712 cm^{-1}; ^1H NMR (250 MHz, CD_3OD–$CDCl_3$), δ 2.30 (m, 2 H), 3.07 (d, *J*=17 Hz, 1 H), 3.20 (m, 2 H), 3.35–3.60 (m, 4 H), 3.64 (dd, *J*=12, 4 Hz, 1 Hz, 1 H); ^{13}C NMR (62.9 MHz, CD_3OD–$CDCl_3$), δ 26.9 (CH_3), 27.1 (CH_3), 45.6 (CH_2), 56.2 (CH_2), 57.5 (CH_2), 62.1 (CH), 72.5 (CH), 74.5 (CH), 84.1 (CH), 112.1 (C), 170.5 (CO); HRMS calcd for $C_{11}H_{18}O_4N_2$ [M^+], 242.1266, found 242.1268 (32%).

(7*S*,8*R*,9*R*,9a*R*)Hexahydro-7,8,9-trihydroxy-2*H*-pyrido-[1,2*a*]pyrazin-3(4*H*)-one (11). Compound **36** (45 mg, 0.18 mmol) was treated with methanolic HCl (3 mL) for 1 h. After evaporation, the residue was purified by chromatography on a column of silica gel (NH_4OH–H_2O–MeOH–$CHCl_3$, 1:1:48:50, R_f 0.41) to give 36 mg of compound **11** (94% yield) as a white solid: mp 296°C; $[\alpha]_D^{20}$ +52.9 (*c* 0.17, H_2O); IR: ν_{max} 3414, 1712 cm^{-1}; ^1H NMR (400 MHz, D_2O), δ 2.21 (t, *J*=11 Hz, 1 H, H-6ax), 2.53 (td, *J*=9.5, 5 Hz, 1 H, H-9a), 3.07 (dd, *J*=11, 5 Hz, 1 H, H-6eq), 3.07 (d, *J*=17 Hz, 1 H, H-4ax), 3.18 (dd, *J*=13, 10 Hz, 1 H, H-1ax), 3.24 (t, *J*=9.3 Hz, 1 H, H-9), 3.39 (t, *J*=9.3 Hz, 1 H, H-8), 3.47 (d, *J*=17 Hz, 1 H, H-4eq), 3.60 (ddd, *J*=11, 9.3, 5 Hz, 1 H, H-7), 3.66 (dd, *J*=13, 4 Hz, 1 H, H-1eq); ^{13}C NMR (100 MHz, D_2O), δ 44.1 (C-1), 54.7 (C-4), 57.2 (C-6), 58.5 (C-9a), 68.2 (C-7), 73.0 (C-9), 76.8 (C-8), 170.1 (C-3); HRMS: calcd for $C_8H_{14}O_4N_2$ [M^+], 202.0954, found 202.0959 (100%).

(7*S*,8*R*,9*R*,9a*R*)Octahydro-7,8,9-trihydroxy-2*H*-pyrido-[1,2*a*]pyrazine dihydrochloride (12). $LiAlH_4$ (71 mg, 1.85 mmol) was added to a solution of compound **36** (90 mg, 0.37 mmol) in THF (10 mL). The mixture was heated under reflux for 2 h and evaporated. The residue was applied on a column of silica gel using the solvent system NH_4OH–H_2O–MeOH–$CHCl_3$, 1:1:48:50, (R_f 0.27) to give impure compound **37** (62 mg). Without further purification, the latter material was treated directly with MeOH–HCl (3 mL) for 1 h. The solution was evaporated and the residue was crystallised from Et_2O–MeOH to afford 57.9 mg of pyrazine **12** (60% overall yield from **36**): mp >400°C; $[\alpha]_D^{20}$ +18.8 (*c* 0.19, H_2O); IR: ν_{max} 3410 cm^{-1}; ^1H NMR (400 MHz, D_2O), δ 2.99 (t, *J*=11 Hz, 1 H, H-6ax), 3.23 (dd, *J*=14, 12 Hz, 1 H, H-4ax), 3.29 (m, 1 H, H-1ax), 3.35 (m, 1 H, H-9a), 3.40 (td, *J*=14, 2 Hz, 1 H, H-3ax), 3.53 (m, 2 H, H-8, H-9), 3.55 (dd, *J*=11, 5 Hz, 1 H, H-6eq), 3.76 (m, 2 H, H-1eq, H-3eq), 3.81 (m, 1 H, H-7), 3.98 (dbrt, *J*=14 Hz, $\omega_{1/2}$=2 Hz, 1 H, H-4eq); ^{13}C NMR (100 MHz, D_2O), δ(40.9 (C-3), 43.3 (C-4), 49.6 (C-1), 55.8 (C-6), 60.2 (C-9a), 66.2 (C-7), 69.5 (C-9), 75.7 (C-8); HRMS: calcd for $C_8H_{16}O_3N_2$ [M^+], 188.1161, found 188.1157 (6%).

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