A Comparison of Glucose- and Glucosamine-Related Inhibitors: Probing the Interaction of the 2-Hydroxy Group with Retaining β-Glucosidases

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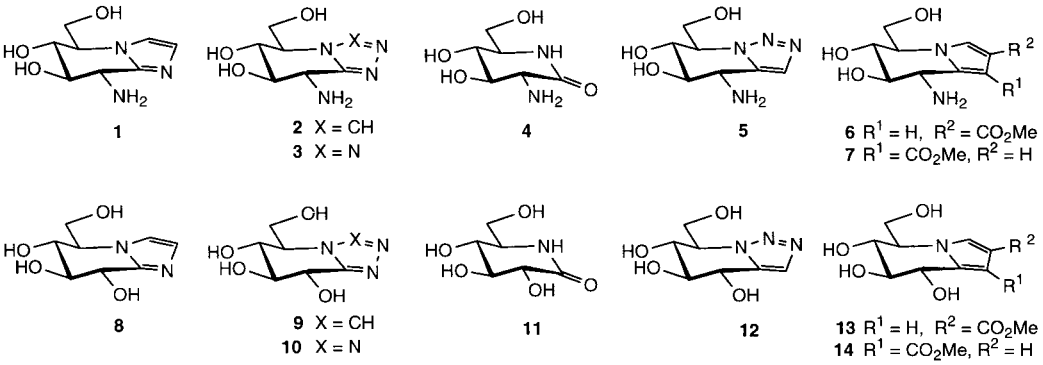
The inhibition of the β-glucosidases from sweet almonds and *Caldocellum saccharolyticum* at varying pH values by the glucosamine-related inhibitors **1**–**7** has been compared to the inhibition by the known glucose analogues **8**–**14**. The amino derivatives **3**, **4**, **6**, and **7** were prepared in one step from the known **15**–**18** (*Scheme 1*), and the amino-1,2,3-triazole **5** by a variant of the synthesis leading to the glucose analogue **12** (*Scheme 2*). The key step for the preparation of the aminoimidazole **1** and of the amino-1,2,4-triazole **2** is the regioselective cleavage of the benzyloxy group at C(2) of the gluconolactam **35** and the mannonolactam **57**, respectively, by BCl_3 and Bu_4NBr (*Schemes 3* and *4*, resp.). The pH optimum for the inhibition by the amines is lower than their pK_{HA} values, evidencing that they are bound as ammonium salts and that H-bonding between C(2)–NH_3^+ and the cat. base B^- contributes more strongly to binding than any possible H-bond to the NH_2–C(2) group. The influence of the ammonium group on the inhibitory strength correlates with the basicity of the 'glycosidic heteroatom'. The strongest increase of the inhibitory strength is observed for the amines lacking a 'glycosidic heteroatom' ($\Delta\Delta G(OH \rightarrow NH_3^+) = -1.5$ to -2.9 kcal/mol). The increase is less pronounced for the amino derivatives **3**–**4**, which possess a weakly basic 'glycosidic heteroatom' ($\Delta\Delta G(OH \rightarrow NH_3^+) = -0.6$ to -1.1 kcal/mol); the amino compounds **1** and **2**, which possess a strongly basic 'glycosidic heteroatom', are weaker inhibitors than the corresponding hydroxy compounds, as expressed by $\Delta\Delta G(OH \rightarrow NH_3^+)$ between $+4.3$ and $+4.7$ kcal/mol for the amino-imidazole **1**, and between $+2.3$ and 2.8 kcal/mol for the amino-1,2,4-triazole **2**, denoting the dominant detrimental influence of a C(2)–NH_3^+ group on the H-bond acceptor properties of a sufficiently basic 'glycosidic heteroatom'.

Introduction. – During glycoside hydrolysis, the OH groups of the glycon moiety interact with the active site of the glycosidase and thereby contribute to stabilizing the transition state. The contribution of each OH group has been determined by analysing the steady-state and pre-steady-state kinetics of the hydrolysis of aryl glycosides in which each hydroxy group of the glycon had been substituted by a H- or F-atom [1–4]. According to these studies, the interaction of C(2)–OH stabilizes the transition state by at least 10 kcal/mol, *i.e.*, about two to three times more than any other glycon hydroxy group. Formation of a H-bond to C(2)–OH from a conserved Asn residue has been evidenced by crystal-structure analysis of several retaining *endo*-β-glycosidases in complex with the substrate or a substrate analogue [5–8]. However, the strength of a H-bond between two uncharged residues is expected below 10 kcal/mol [9]; thus, the large value suggests the participation of a charged residue in H-bonding with C(2)–OH. Indeed, the crystal structure of *exo*-xylanase/cellulase from *Cellulomonas fimi* [8] and of its H205N/E127A mutant [10], covalently bonded *via* the catalytic nucleophile to 2-deoxy-2-fluorocellobiose and cellobiose (hence corresponding to a reactive intermediate), respectively, strongly suggest [10][11] that, in addition to, or instead of, the H-bond to the conserved Asn residue, C(2)–OH forms a H-bond to the catalytic nucleophile. A H-bond from C(2)–OH is expected to also contribute to the binding of transition-state-analogous inhibitors. Replacing C(2)–OH by C(2)–NH_3^+

should lead to a stronger H-bond[1]) but not necessarily to stronger inhibition, as the ammonium group may impair other binding interactions between the inhibitor and the enzyme. The enhanced σ-acceptor strength of an NH_3^+ as compared to an OH group is expected to lower the basicity of the azole moiety of inhibitors of the azolopyridine type, such as **1**–**3**; the NH_3^+ group may also compete with the catalytic acid as H-bond donor to N(1) of **1**–**3**. The replacement of C(2)–OH by an ammonium group is expected to have an opposite effect on the inhibition if C(2)–OH should function as H-bond acceptor, *e.g.*, from the conserved Asn residue particularly if such an interaction should be strengthened on the way to the transition state by partial deprotonation of C(2)–OH by the catalytic nucleophile.



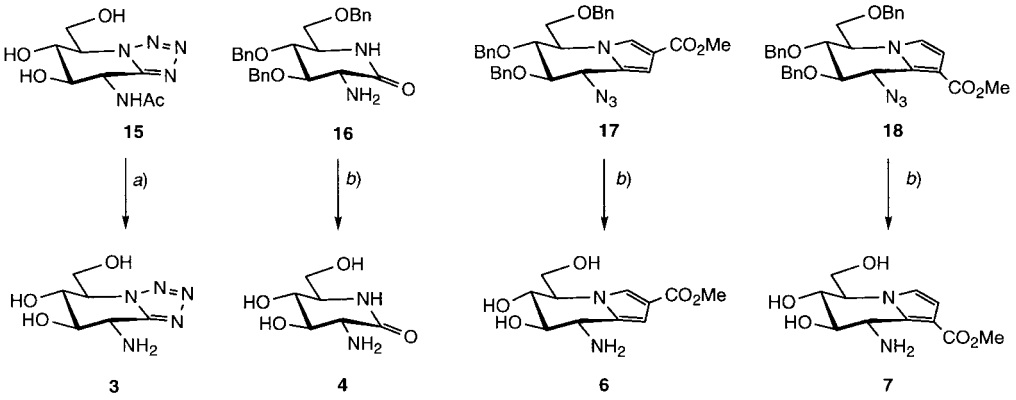
We have prepared the glucosamine-derived inhibitors **1**–**7**, determined their pK_{HA} values, and compared their inhibition at varying pH values with those of the glucose-derived inhibitors **8**–**14** to probe the interaction of C(2)–OH with the catalytic nucleophile and the conserved Asn residue, and the effect of the ammonium group on the interaction of the inhibitor with the catalytic acid.

Synthesis. – The glucosamine-related tetrazole **3**, lactam **4**, and pyrroles **6** and **7** were prepared in one step from the acetamidotetrazole **15** [13], the tri-*O*-benzyl-glucosaminolactam **16** [14], and the 8-azidopyrrolopyridines **17** and **18** [15] (*Scheme 1*). Acidic hydrolysis (1M aq. HCl/THF 1:3) of **15** yielded 71% of **3**, and hydrogenation of **16**–**18** yielded 92% of **4**, 58% of **6**, and 63% of **7**.

The amino-1,2,3-triazole **5** was prepared from a 1:1 mixture of the L-*ido*- and D-*gluco*-acetyleno-diols **19** and **20** (*Scheme 2*) that have been used for the preparation of the glucose-related **12** and its *manno*-analogue [16]. Regioselective monosilylation with $^iPr_3SiCl$ led to 84% of a 1:1 mixture **21**/**22**, which was tosylated to yield 87% of **23**/**24** 1:1. Nucleophilic displacement of the TsO group with azide at 110° followed by *in situ* cycloaddition yielded, after flash chromatography (FC), 38% of the *gluco*-triazolopyridine **25**, 21% of the *manno*-analogue **26**, and 12% of a 2:1 mixture of the known α-D- and β-D-1-deoxy-1-*C*-ethynyl-arabinoses **27** and **28** [17]. Neighbouring-group participations of BnO substituents leading to furanose derivatives such as **27** and **28** are well precedented ([18][19] and refs. cited therein). The configuration of **25** and

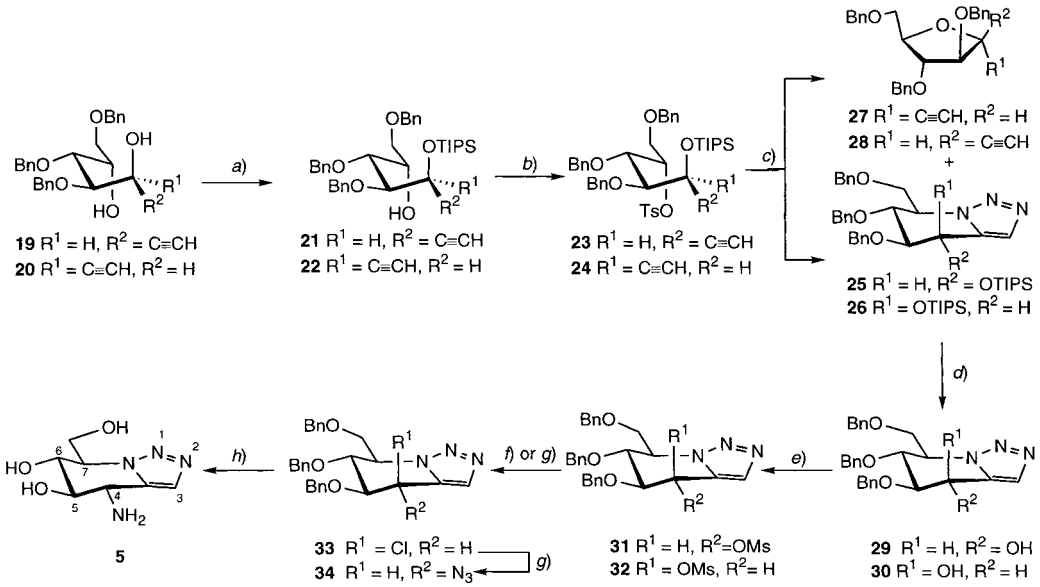
[1]) This assumption is supported by the *ca.* 20-fold stronger inhibition at pH 6.2 of β-glucosidases from almonds by glucosamine than by glucose [12].

Scheme 1



a) 1M aq. HCl/THF 3:1; 71%. *b*) H_2, 10% Pd/C; **4** (92%); **6** (58%); **7** (63%).

Scheme 2



Bn = $PhCH_2$, TIPS = $^iPr_3Si$, Ms = $MeSO_2$

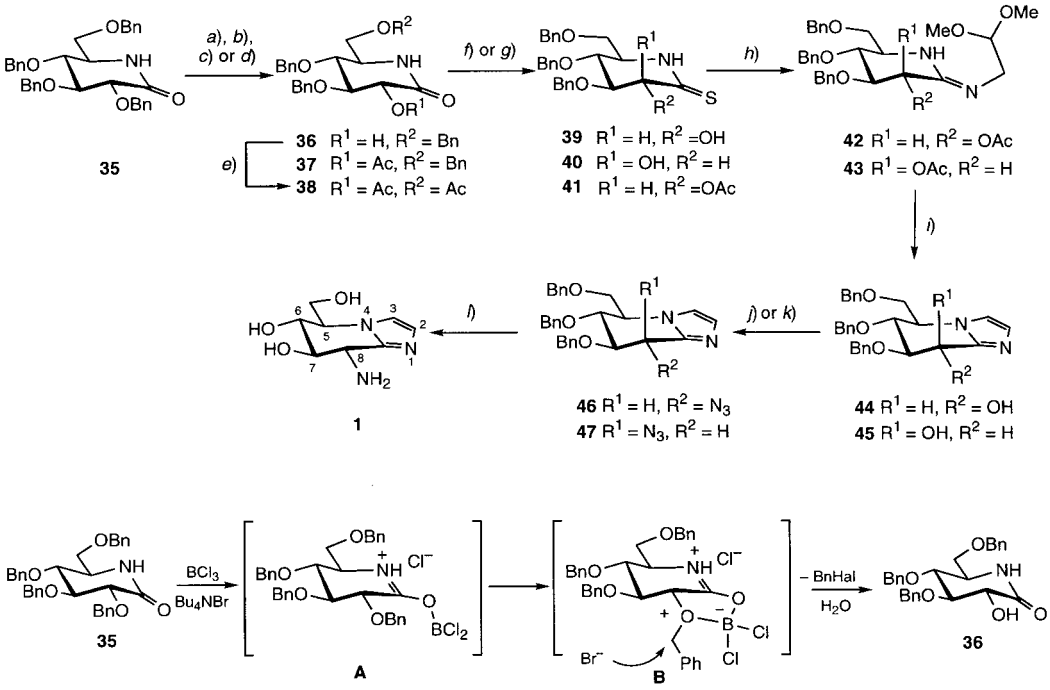
a) BuLi, $^iPr_3SiCl$, THF, $-78 \rightarrow 25°$; 84%. *b*) TsCl, pyridine, DMAP (= *N*,*N*-dimethylpyridin-4-amine); 87%. *c*) NaN_3, DMSO, 110°; 38% of **25**, 21% **26**, and 12% of **27**/**28** 2:1. *d*) Bu_4NF, THF; 91%. *e*) MsCl, pyridine; 88% of **31**; 87% of **32**. *f*) Bu_4NCl, DMF; 82%. *g*) NaN_3, DMF, 50°; 83% from **32**; 85% from **33**. *h*) H_2, Pd/C, AcOH; 81%.

26 was evidenced by the large and small $J(7,8)$ values, respectively, similarly as for the corresponding tetra-*O*-benzyl ethers [16]. Desilylation of **25** and **26**, leading to 91% of **29** and **30**, respectively, followed by mesylation, yielded **31** and **32** (88 and 87%, resp.), of which the *gluco*-configured mesylate **31** was converted to the *manno*-chloro derivative **33** (82%) by treatment with Bu_4NCl in DMF. Exposure of the *manno*-

configured mesylate **32** and chloro derivative **33** to NaN_3 in DMF led in over 80% yield to the *gluco*-azido compound **34**. Hydrogenolysis in the presence of Pd/C yielded 81% of the desired aminotriazole **5**.

The aminoimidazole **1** was prepared in seven steps from the benzylated gluconolactam **35** [20–22] (*Scheme 3*). Regioselective debenzylation of **35** at C(2) by treatment with BCl_3 between $-78°$ and 23° in the presence of Bu_4NBr yielded 75–87% of **36**. To the best of our knowledge, there are only two known examples of a *Lewis*-acid-promoted regioselective debenzylation of secondary BnO groups in carbohydrates [23][24][2]), and the regioselective *Lewis*-acid-mediated cleavage of an ether function in α-position of a lactam or an amide C=O group is new. Similarly as for the known BCl_3-, BBr_3-, or $AlCl_3$-promoted cleavage of *peri*-MeO groups in anthraquinones [28–31], it most probably proceeds *via* coordination of BCl_3 to the C=O group (**A** and **B** in *Scheme 3*). Coordination of BCl_3 to the C=O and the

Scheme 3



a) BCl_3 (slow addition), Bu_4NBr, CH_2Cl_2, $-78° \rightarrow 23°$; 75–87% of **36**. *b*) 1. BCl_3 (rapid addition), Bu_4NBr, CH_2Cl_2, $-78° \rightarrow 23°$; 2. Ac_2O, pyridine; **37** (33%) and **38** (48%). *c*) 1. BCl_3, CH_2Cl_2, $-78° \rightarrow 23°$; 2. Ac_2O, pyridine; **37** (63%) and **38** (26%). *d*) 1. BBr_3, CH_2Cl_2, $-78° \rightarrow 23°$; 2. Ac_2O, pyridine; **37** (51%) and **38** (32%). *e*) Ac_2O, pyridine, 98%. *f*) **36**, *Lawesson*'s reagent, toluene; **39**/**40** 1:1 (8%). *g*) **37**, *Lawesson*'s reagent, toluene; 92% of **41**. *h*) Aminoacetaldehyde dimethyl acetal, $Hg(OAc)_2$, THF; **42**/**43** 2:1 (73%). *i*) TsOH, toluene/H_2O 95:5; **44**/**45** 1:1 to 5:3 (67–71%). *j*) Bu_3P, 4% HN_3 in toluene; **46** (72–74%). *k*) Bu_3P, 2.6M HN_3 in THF; **46**/**47** 1:1 (72%) from **44**; **46**/**47** 6:4 (68%) from **45**; **46**/**47** 5:4 (75%) from **44**/**45** 1:1. *l*) 10% Pd/C, H_2, AcOEt/MeOH/AcOH 1:1:1; 79%.

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[2]) Examples of hydrogenolytic regioselective debenzylations are found in [25–27].

C(2)–OBn groups leads to the immonium derivatives **A** and **B**, followed by debenzylation and formation of the benzyl halides (presumably mostly the bromide) and the complexed hydroxy lactam. The mono-alcohol **36** was still obtained in reasonable yields when Bu_4NBr was omitted, or when BBr_3 was used instead of BCl_3 (*cf. Exper. Part*); it was, however, accompanied by considerable amounts of the 2,6-dihydroxy derivative, as evidenced by acetylation of the crude, yielding the mono-acetate **37** (51–63%) and the diacetate **38** (26–32%). Rapid addition of BCl_3 (*cf. Exper. Part*) also led to substantial amounts of the diol, as evidenced by isolation of 48% **38** and 33% **37** after acetylation of the crude. The regioselective deprotection at C(2) was also attempted with $BF_3 \cdot OEt_2$. According to TLC and ^{1}H-NMR spectroscopy of the acetylated crude, however, this *Lewis* acid led to random debenzylation of the lactam.

Activation of the regioselectively deprotected lactam **36** by thionation with either P_2S_{10} or *Lawesson*'s reagent failed. The hydroxy lactam **36** did not react with P_2S_{10} in toluene under reflux. Treatment with *Lawesson*'s reagent led to a complex mixture of highly polar compounds, from which only 8% of a 1:1 mixture of the *gluco*- and *manno*-configured thiolactams **39** and **40** was isolated. However, the acetylated lactam **37**, obtained in 98% from **36**, was readily thionated by *Lawesson*'s reagent at 23°, leading, within 20 h, to 92% of the thiolactam **41**. At 80°, this conversion was completed within 2 h. In contrast to the thionation of the tetrabenzylated lactam **35** at this temperature [21], thionation of the acetoxy lactam **37** was not accompanied by epimerization at C(2). Treatment of **41** with aminoacetaldehyde dimethyl acetal in the presence of $Hg(OAc)_2$ [32], however, led to a 2:1 mixture (73%) of the *gluco*- and *manno*-*N*-(2,2-dimethoxyethyl)amidines **42** and **43**[3]). The TsOH-promoted cyclization of **42**/**43** 2:1 was accompanied by deacetylation and further epimerization at C(2), leading to a 1:1 mixture[4]) (67%) of the known [33] hydroxyimidazopyridines **44** and **45**[5]). *Mitsunobu* reaction of pure **44**, pure **45**, or a 1:1 mixture **44**/**45** with a 4% soln. of HN_3 in toluene according to *Tatsuta et al.* [34] led, in agreement with their results, exclusively to the *gluco*-azido derivative **46** (72–74%)[6]). Saturating the reaction mixture with HN_3 prior to the addition of diethyl diazenedicarboxylate (DEAD), however, led to a *ca.* 1:1 mixture (72%) of the *gluco*- and *manno*-azido compounds **46**/**47** from the *gluco*-alcohol **44**, to a *ca.* 6:4 mixture (68%) **46**/**47** from the *manno*-alcohol **45**, and to a *ca.* 5:4 mixture (75%) **46**/**47** from the 1:1 mixture **44**/**45**. The slight dependence of the ratio of *gluco*- and *manno*-azido derivatives on the ratio of *gluco*- and *manno*-alcohol indicates that elevated concentrations of HN_3 (presaturation by HN_3) lead to increased inversion of configuration (increased S_N2 character), although the elimination-addition process *via* an azafulvenium cation (*cf.* [15][34]) still prevails. The results show that not only the relative contribution of the S_N2 and S_N1 character, but also the diastereoselectivity of the addition to the azafulvenium cation depend on the concentration of the nucleophile. Hydrogenation of the *gluco*-configured azidoimidazole **46** yielded 79% of the desired amine **1**.

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[3]) A sample was separated by FC.

[4]) This is the ratio for the transformation on a 350-mg scale. On a 20-mg scale, the ratio **42**/**43** was 5:3.

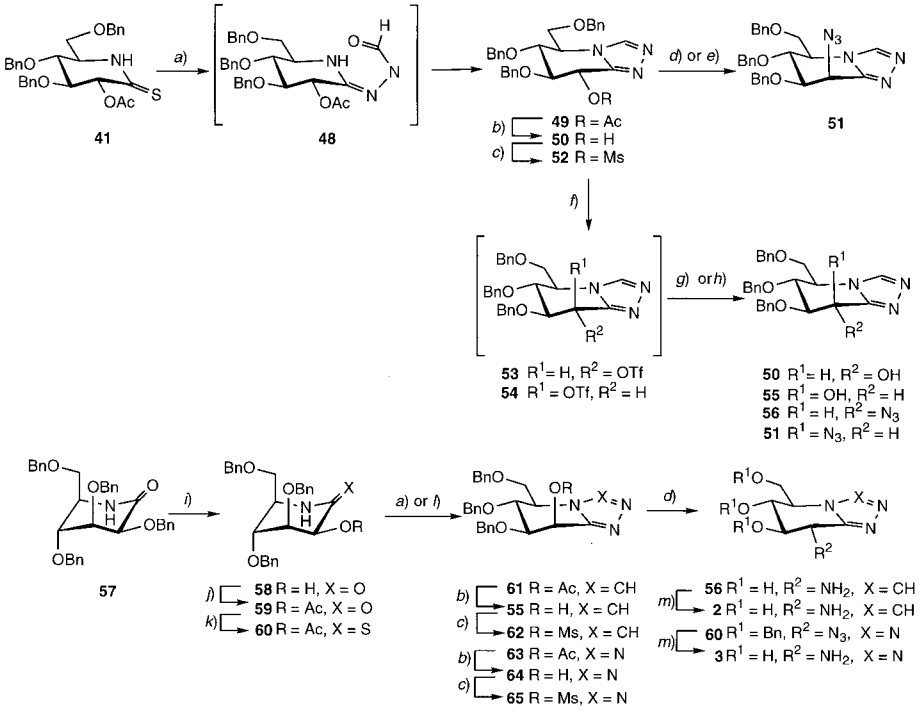
[5]) The preparation of the imidazoles **44**–**46** has been reported by *Tatsuta et al.* [33][34]; we report IR of **46**, and ^{1}H- and ^{13}C-NMR data of **44**–**46** in the *Exper. Part.*

[6]) This diastereoselectivity has been rationalized by a preferred pseudoaxial attack on an azafulvenium intermediate [15][34].

In view of the preparation of the aminotriazole **2** (*Scheme 4*), we wondered if C(8)–OH of the *gluco*-triazole **50** will also be substituted with retention of configuration. We obtained **50** (*Scheme 4*) in 87% yield by treating the thiolactam **41** with formylhydrazine in the presence of $Hg(OAc)_2$, followed by NH_3-mediated deacetylation. The intermediate amidrazone **48** cyclized *in situ* to the triazole **49**. While **50** proved inert to a 4% soln. of HN_3 under *Mitsunobu* conditions at 70°, it was partially transformed into the *manno*-azido derivative **51** (19%) when the soln. was saturated with HN_3; 56% of **50** was recovered. The *gluco*-mesylate **52** (98% from **50**) led exclusively to the *manno*-azido compound **51** when exposed to NaN_3 in DMF (yields 46–95%), but not the diastereoselectivity depending upon the concentration of the nucleophile.

Exposure of **50** to Tf_2O in pyridine/CH_2Cl_2 at −78° led to a 1:1 mixture of the *gluco*- and *manno*-triflates **53** and **54** (*ca.* 90%). They could not be separated due to their instability, but were identified in the ^{1}H-NMR spectrum of the crude obtained by

Scheme 4



Bn = $PhCH_2$, Ms = $MeSO_2$, Tf = CF_3SO_2

a) Formylhydrazine, $Hg(OAc)_2$, THF; **49** (9%); **61** (86% from **60**). *b*) 2M NH_3 in MeOH; **50** (98%); **55** (quant.); **64** (99%). *c*) MsCl, pyridine, CH_2Cl_2; **52** (98%); **62** (84%); **65** (96%). *d*) NaN_3, DMF; **51** (46–95%); **56** (92%). *e*) Bu_3P, 2.6M HN_3 in THF, DEAD; 19% from **50**. *f*) Tf_2O, CH_2Cl_2, pyridine, −78°; **53**/**54** 1:1 (90%). *g*) Normal workup; **50**/**55** 7:2 (89%). *h*) NaN_3; **56**/**51** 4:1 to 1:10 (32–54%). *i*) BCl_3 (slow addition), Bu_4NBr, CH_2Cl_2, −78° → 23°; 85%. *j*) Ac_2O, pyridine; 98%. *k*) *Lawesson*'s reagent, toluene; 92%. *l*) Me_3SiN_3, $Hg(OAc)_2$; **63** (84% from **59**). *m*) MeOH/AcOH, 10% Pd/C, H_2; **2** (61%); **3** (76%).

evaporating the solvent at 0° (H–C(8) at 6.01 and 6.24 ppm). The triflates were hydrolysed during aqueous workup at 0°, leading to a 7:2 mixture (89%) of the *gluco*- and *manno*-alcohols **50** and **55**. The change of the *gluco*/*manno* ratio from 1:1 to 7:2 evidences that hydrolysis proceeds at least partially *via* a triazafulvenium cation that is preferentially attacked from the *si*-side. To prepare the required *gluco*-configured 8-azido-1,2,4-triazole **51** we treated the 1:1 mixture of the triflates **53**/**54** *in situ* with NaN_3 and obtained the *gluco*- and *manno*-azido compounds **51** and **56** in ratios ranging from 1:10 to 4:1 (32–54%). This conversion, however, suffered from low reproducibility of yield and stereoselectivity (*cf. Exper. Part*). Therefore, we planned to prepare the *gluco*-azidotriazole **56** from tetra-*O*-benzyl mannonolactam **57** [35], similarly as the *manno*-azidotriazole **51** from the tetra-*O*-benzyl gluconolactam **35**. To our delight, the conditions for the monodebenzylation of **35** worked equally well for the mannonolactam **57**, leading in 85% yield to the alcohol **58**. As for the *gluco*-hydroxy lactam **36**, attempted thionation of **58** with *Lawesson*'s reagent gave a complex mixture consisting mainly of highly polar compounds, while thionation of the acetate **59** at 80° yielded 92% of the thiolactam **60**. This thiolactam was transformed to the acetoxytriazole **61** and hence to the alcohol **55** that was mesylated to **62** and converted to the *gluco*-azidotriazole **56** (66% from **60**). Hydrogenolysis of **56** in the presence of Pd/C yielded 61% of the aminotriazole **2**. We also transformed the thiolactam **60** into the aminotetrazole **3** (*Scheme 3*) that we had previously synthesized from the tetrazole GlcNAc analogue **15** (*Scheme 1*). Treatment of **60** with Me_3SiN_3 and $Hg(OAc)_2$ yielded 84% of the tetrazole **63** that was transformed into the amine **3**, similarly to the transformation of the triazole **61** into **2**, by deacetylation to **64** (99%), mesylation to **65** (96%), substitution to **66** (96%), and hydrogenolysis to **3** (76%).

The monodebenzylated *gluco*- and *manno*-lactams **36** and **58** were identified on the basis of the disappearance of the signals of one benzyl group in the NMR spectra and the strong downfield shift of the H–C(2) signal ($\Delta\delta = 1.18$ ppm) in the ^{1}H-NMR spectrum of the acetates **37** and **59**. The constitution of the 2,6-di-*O*-acetyl-3,4-di-*O*-benzyl lactam **38** was deduced in an analogous manner. The *gluco*- and *manno*-thiolactams **41** and **60** were characterized by the $^{13}C{=}S$ signal at 197.49 and 197.81 ppm. According to their J(H,H) values, which closely match those of the known tetrabenzylated *gluco*- and *manno*-lactams **35** and **57**, respectively, the *gluco*-lactams **36**–**38**, the *gluco*-thiolactam **41**, and the *gluco*-amidine **42** adopt the $^4C_1$-conformation, while the *manno*-lactams **58** and **59** and the *manno*-thiolactam **60** form a 2:1 mixture of $^1C_4$- and $^4C_1$-confomers. Remarkably, the *manno*-amidine **43** neither adopts the conformation of the known [19] 2,3,4,6-tetra-*O*-benzylated analogue (flattened $^5S_3$) nor of the *manno*-lactams **58** or **59** ($^1C_4/^4C_1$ 2:1), but a $^4H_3$-conformation, as evidenced by the rather large J(3,4) and J(4,5) values. The protected *gluco*- and *manno*-azoles **25**, **26**, **29**–**34**, **44**–**47**, **49**–**56**, and **61**–**66** were identified by comparing their NMR data with those of the tetra-*O*-benzylated *gluco*- and *manno*-azoles [15][16][18–20][32].

The glucosamine analogues **1**–**7** reacted with ninhydrin at 300° on the TLC plate to give rise to an intense yellow to reddish colouration. Protonation affected the chemical shifts, particularly of the H–C(2) signal[7]), which was shifted downfield by 0.6–0.9 ppm (*Table 1*). The aminoimidazole **1** and the amino-1,2,4-triazole **2** were protonated twice,

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[7]) Conventional carbohydrate numbering is used to facilitate the discussion.

HCl being required for the second protonation, indicating that the pK_{HA} of the azole moiety is considerably lowered by the ammonium group[8]). The coupling constants (*Table 2*) evidence that the unprotonated glucosamine derivatives **1**, **2**, and **4**–**7**, and the protonated glucosamine-derived tetrazole **3**·H^+ and pyrrole **6**·H^+ adopt a conformation close to $^4H_3$. The 1,3-interaction between the amino group and the methoxycarbonyl group forces the 1-(methoxycarbonyl)pyrrole glucosamino analogues **7** (like the *gluco*-analogue **14** [20]) to adopt a conformation between $^4H_3$ and a sofa, with C(3) below the plane of the tetrahydropyrrolopyridine. A slight deviation from the $^4H_3$-conformation is also observed for the diprotonated aminoimidazole **1**·2 H^+, where the somewhat smaller J(H,H) value indicates a small percentage of the $^3H_4$-conformer. Signal overlap prevented an assignment of the conformation of the unprotonated tetrazole glucosamine analogue **2** and of the protonated **1**·H^+, **2**·H^+, **4**·H^+, **5**·H^+, and **7**·H^+. The small influence of diprotonation on the conformation of the aminoimidazole **1** and the absence of a conformational change upon protonation of the tetrazole **3** and the pyrrole **6** mean that protonation-induced conformational changes should not significantly influence the inhibition properties.

Table 1. *Selected Chemical Shifts* (D_2O) *of Protonated and Unprotonated Glucosamine Analogues* **1**–**7**

	H–C(2)[a])	H–C(3)[a])	H–C(4)[a])	H–C(5)[a])	H–C(6)[a])	H′–C(6)[a])	H–C(1)[b])	H–C(2)[b])	H–C(3)[b])
1	3.98–4.31	3.98–4.31	3.90	3.98–4.31	3.98–4.31	3.98–4.31	–	7.15	7.35
1·H^+	4.65	4.05–4.15	4.05–4.15	4.12–4.28	4.05–4.15	4.12–4.28	–	7.45	7.60
1·2 H^+	4.82	4.23	4.18	4.38	4.10	4.26	–	7.62	7.77
2	4.09	3.75	3.94	4.10–4.16	4.04	4.26	–	–	8.66
2·H^+	4.65	4.00–4.12	4.00–4.12	4.22–4.24	4.00–4.12	4.25–4.31	–	–	9.02
2·2 H^+	4.70	3.99–4.12	3.99–4.12	4.28–4.32	3.99–4.12	4.25–4.29	–	–	9.38
3	4.14	3.74	4.14	4.36	4.14	4.49	–	–	–
3·H^+	4.91	4.07	4.12–4.20	4.43–4.47	4.12–4.20	4.49	–	–	–
4	3.49	3.77	3.73	3.38–3.41	3.78	3.85	–	–	–
4·H^+	3.72–4.03	3.72–4.03	3.72–4.03	3.39–3.41	3.72–4.03	3.72–4.03	–	–	–
5	3.99	3.71	4.12	4.42	4.24	4.60	7.84	–	–
5·H^+	*ca.* 4.9[c])	3.92–4.06	3.92–4.06	4.45–4.61	3.92–4.06	4.45–4.61	7.95	–	–
6	3.90	3.59	3.94	4.01–4.11	4.01–4.11	4.26	6.60	–	7.65
6·H^+	4.73	3.88	3.99	4.05–4.10	4.05–4.10	4.24	6.67	–	7.69
7	4.25	3.83	4.00	4.07–4.12	4.07–4.12	4.23	–	6.75	6.95
7·H^+	4.74	4.05–4.18	4.05–4.18	4.05–4.18	4.05–4.18	4.26	–	6.82	7.09

[a]) Conventional carbohydrate numbering used. [b]) Azolopyridine numbering used. [c]) Hidden by HDO signal.

Enzymatic Tests and Discussion. – The glucosamine derivatives **1**–**7** and their glucose analogues **8**–**14** were tested against β-glucosidases from sweet almonds (activity optimum at pH 5.6 [12]) and *Caldocellum saccharolyticum* (activity optimum at pH 6.2 [37]) at pH values ranging from 4.6 to 7.8 (*Tables 3* and *4*). The pH-dependence of the inhibition is represented by $1/IC_{50}$ *vs.* pH plots A–H in *Fig. 1*.

The plots have been grouped into four families; A–D for the almond β-glucosidases, and E–H for the *C. saccharolyticum* β-glucosidase, the plots in family A and B (E and F) grouping the glucose-related inhibitors, and C and D (G and H) the glucosamine-

[8]) Only one pK_{HA} value could be determined for aqueous solutions of the aminoimidazole **1** ($pK_{HA} = 6.33$) and the 1,2,4-triazole **2** ($pK_{HA} = 5.82$), the second being lower than 3.0. This compares to a pK_{HA} of 6.12 for the imidazole **8** and to an extrapolated pK_{HA} of 2.4 for the 1,2,4-triazole **9** [36].

Table 2. *Coupling Constants* (D_2O) *of Protonated and Unprotonated Glucosamine Analogues* **1**–**7** *and Deduced Conformations*

	$J(2,3)$[a])	$J(3,4)$[a])	$J(4,5)$[a])	$J(5,6)$[a])	$J(5,6')$[a])	Conformation[a])
1	[b])	9.6	9.6	[b])	[b])	about $^4H_3$
1·H$^+$	7.8	[b])	[b])	[b])	[b])	[b])
1·2H$^+$	7.9	7.9	8.6	4.1	7.1	$^4H_3/^3H_4$
2	9.6	9.7	9.7	2.5	4.1	$^4H_3$
2·H$^+$	8.5	[b])	[b])	[b])	[b])	[b])
2·2H$^+$	8.6	[b])	[b])	[b])	[b])	[b])
3	[b])	[b])	[b])	[b])	[b])	[b])
3·H$^+$	9.5	9.5	9.6	2.5	[b])	$^4H_3$
4	9.4	9.6	9.5	2.8	4.5	$^4H_3$
4·H$^+$	[b])	[b])	[b])	[b])	[b])	[b])
5	9.3	9.5	9.5	2.2	2.5	$^4H_3$
5·H$^+$	[b])	[b])	[b])	[b])	[b])	[b])
6	9.3	9.3	9.3	2.2	[b])	$^4H_3$
6·H$^+$	9.0	9.0	9.3	3.4	[b])	$^4H_3$
7	6.9	8.7	7.5	[b])	3.7	$^4H_3/S_3$
7·H$^+$	6.9	[b])	[b])	2.2	[b])	[b])

[a]) Conventional carbohydrate numbering used. [b]) Not determined.

Table 3. *pH Dependence of* IC_{50} *Values* [μM] *of* **1**–**14** *against β-Glucosidases from Sweet Almonds*

	pH 4.6	pH 5.0	pH 5.4	pH 5.9	pH 6.4	pH 6.8	pH 7.4	pH 7.8
1	593	456	200	136	[a])	213	[a])	510
2	595	490	250	260	[a])	830	[a])	2000
3	75	41	53	57	[a])	65	[a])	250
4	129	56	[a])	23	10	8	14	27
5	5600	2700	3800	7200	[a])	8700	[a])	18700
6	[a])	200	[a])	102	[a])	50	66	120
7	102	35	31	24	[a])	19	20	25
8	0.71	0.41	0.31	0.23	0.16	0.15	0.21	0.33
9	23	22	22	24	[a])	27	[a])	38
10	186	190	188	270	[a])	340	[a])	550
11	79	77	80	87	93	138	[a])	500
12	45000	33000	30000	29000	32000	35000	50000	100000
13	5000	5000	4500	4500	[a])	6000	[a])	20000
14	1000	700	600	600	[a])	1000	5000	10000

[a]) Not determined.

related inhibitors. Families A (E) and B (F), respectively, correspond to C(2)–OH inhibitors either possessing a glycosidic heteroatom, or not. Similarly, the C(2)–NH_2 inhibitors grouped in families C (G) and D (H) either possess such a heteroatom, or not. The plots for the almond and the *C. saccharolyticum* enzymes are very similar.

The plots A and E for the C(2)–OH inhibitors[7]) **8**–**11**, which possess a 'glycosidic heteroatom'[9]) are essentially determined by the potential of the inhibitors to accept a proton from the catalytic acid AH. Thus, the 1,2,4-triazole **9**, tetrazole **10**, and lactam **11**, which possess a weakly basic 'glycosidic heteroatom', show a very similar pH-

[9]) A heteroatom corresponding to the glycosidic O-atom of the substrate.

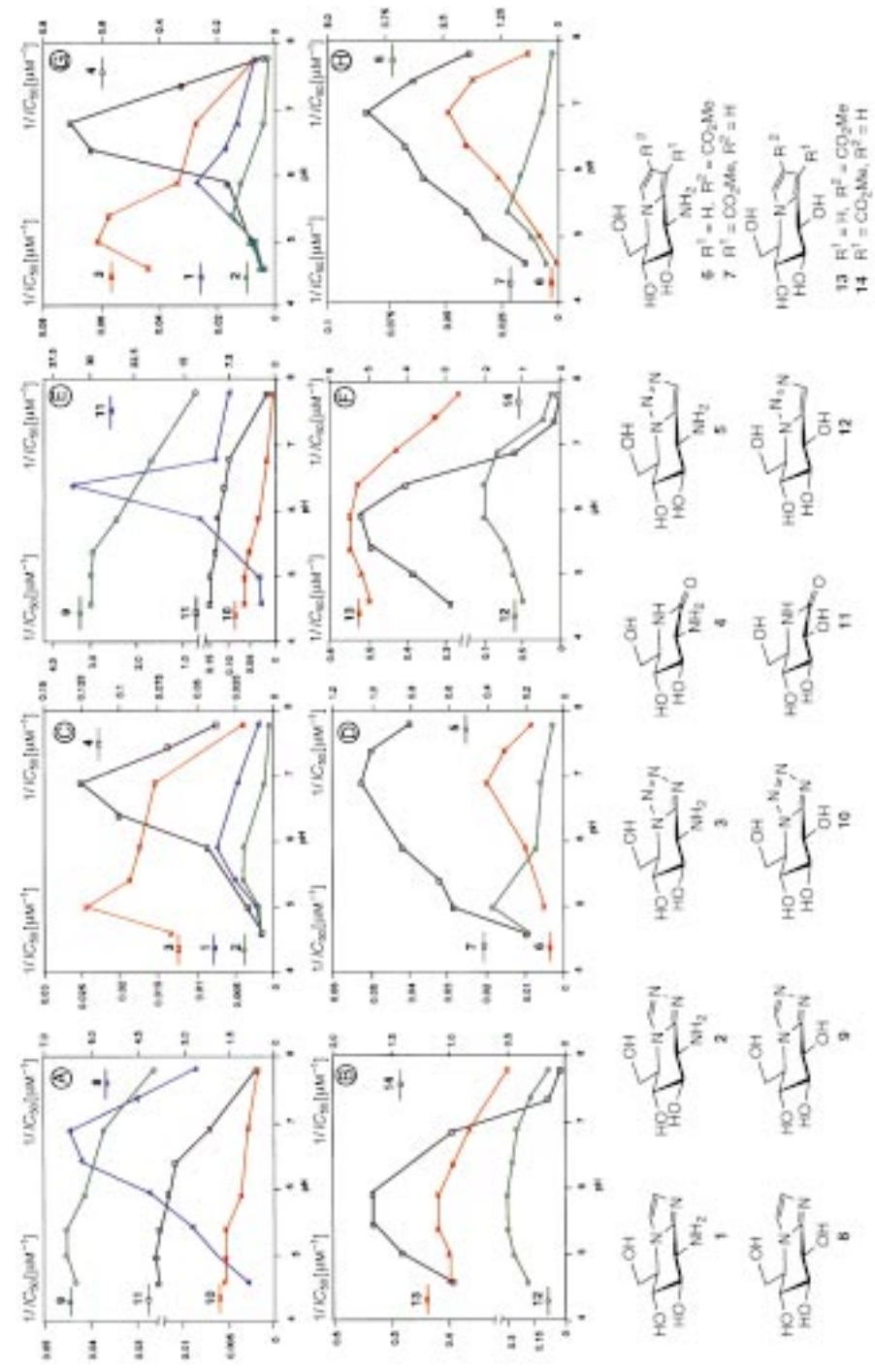

Fig. 1. *$1/IC_{50}$ vs. pH Plots of* **1**–**14** *for β-glucosidases from sweet almonds* (A–D) *and from* Caldocellum saccharolyticum (E–H). Note the two scales on the right and left side of each graphic

Table 4. *pH Dependence of* IC_{50} *Values* [μM] *of* **1**–**14** *against β-Glucosidase from* Caldocellum saccharolyticum

	pH 4.6	pH 5.0	pH 5.4	pH 5.9	pH 6.4	pH 6.8	pH 7.4	pH 7.8
1	241	161	77	41	63	85	[a])	165
2	210	143	75	96	[a])	274	[a])	411
3	17	12	13	22	[a])	27	[a])	115
4	21	11	8	6	[a])	1.4	3.2	23
5	3500	1700	900	1200	[a])	2800	[a])	7200
6	711	121	[a])	38	25	21	27	76
7	69	31	25	17	15	12	16	26
8	0.41	0.35	[a])	0.08	0.03	0.05	[a])	0.13
9	0.30	0.30	0.33	0.4	[a])	0.6	[a])	1.3
10	30	30	34	52	[a])	120	[a])	208
11	7	7	7.5	8	9	10	[a])	45
12	20000	16000	14000	10000	10000	12000	40000	80000
13	2000	1900	1800	1800	1900	2300	3000	6000
14	360	270	210	200	260	820	4000	10000

[a]) Not determined.

dependence of their activity. They inhibit the tested *β*-glucosidases optimally between pH 4.6 and *ca.* 5.4–5.9, with the inhibition gradually decreasing at higher pH. This decrease is rationalized by the progressive deprotonation of the catalytic acid AH[10]) and concomitant loss of the H-bond from AH to the inhibitor. The deprotonated catalytic acid may interact repulsively with the inhibitor and also with the catalytic nucleophile B^-, possibly inducing a conformational change of the active site which further lowers its affinity for the inhibitor.

The pH-dependence of the inhibition by **9**–**11** differs markedly from the pH-dependence of the enzymic activity [12][37] in that **9**–**11** show no decrease of their inhibitory strength at low pH. The interaction of the inhibitor with B^- is either so weak that its loss by protonation of B^- has no significant influence, or is compensated by effects of unknown nature. The partial protonation of the inhibitor by AH should reduce the pK_{HA} value of C(2)–OH and strengthen the presumed H-bond between C(2)–OH and B^-. This H-bond and the interacton of B^- with the (partially) positively charged anomeric carbon are expected to reduce the basicity of B^-; it may thus remain unprotonated at pH 4.6, below which the activity of the enzyme was too weak to allow a reproducible determination of IC_{50} values.

The H-bond formation between AH and the glycosidic heteroatom is prevented by deprotonation of AH (higher pH values) and by protonation of the glycosidic heteroatom by an alternative acid. Even at the lowest pH value (4.6) used for the IC_{50} determinations, the weakly basic 1,2,4-triazole **9** (estimated $pK_{HA} = 2.4$ [36]), tetrazole **10** (estimated $pK_{HA} = -4.0$ [36]), and lactam **11** (estimated $pK_{HA} = -0.5$[11])) will not be protonated by the buffer. The glucose-related imidazole **8** ($pK_{HA} = 6.12$ [36]), however, exists predominantly in its protonated form below pH 6.12. This is expressed by its

[10]) The pK_{HA} values of AH and the protonated catalytic nucleophile BH of the two *β*-glucosidases are not known. They have been determined to 4.6 and 6.7 for a xylanase from *Bacillus subtilis* which, like to the two *β*-glucosidases tested here, has its activity optimum at a pH close to 6 [38].

[11]) The pK_{HA} value of valerolactam is *ca.* 0.6 [39]. As evident from comparing the pK_{HA} value of **8** with that of 1,5-dimethylimidazole [40], the OH groups of the carbohydrate moiety reduce the pK_{HA} value by *ca.* 1 unit.

$1/IC_{50}$ *vs.* pH plots (A and E) which differ markedly from the one of **9**–**11**, showing a pronounced pH optimum for the inhibition activity that is strongest at pH 6.4 (almonds) and 6.4–6.8 (*C. saccharolyticum*) and falls off at higher and lower pH. This pH dependence expresses the requirement, for optimal inhibition, of AH forming a H-bond to the otherwise unprotonated imidazole, and of B^- interacting with the (partially) protonated imidazole; the strong inhibition by imidazoles is thus paralleled by a similar pH dependence of inhibition and enzyme activity, satisfying one of the conditions for an inhibitor to act as a transition-state analogue.

According to plots B and F, the C(2)–OH inhibitors lacking a 'glycosidic heteroatom' (**12**–**14**) inhibit the tested β-glucosidases optimally between pH 5.4 and 5.9 (almonds) or pH 5.4 and 6.4 (*C. saccharolyticum*). The 1,2,3-triazole **12** and the (methoxycarbonyl)pyrrole **13**, both possessing a =C–H group at the glycosidic position and thus unable to accept a H-bond from AH, are very weak inhibitors and show rather flat $1/IC_{50}$ *vs.* pH plots. The slight decrease of the inhibition at higher pH may reflect the above-postulated repulsive interaction of A^- with the inhibitor (C(2)–OH H-bonded to B^-?) and possibly a conformational change of the active site. The inhibitory activity of **12** and **13** decreases at lower pH, unlike the activity of **9**–**11**, in keeping with the above-postulated effect on the basicity of B^- of the partially protonated **9**–**11** (*i.e.*, B^- is protonated more readily when the glycosidase is complexed with **12** and **13** than with **9**–**11**).

The pyrrole **14**, which possesses a =C–COOMe group at the glycosidic position, is a stronger inhibitor than **12** and **13**, and its activity is marked by a clear pH optimum, thus resembling the $1/IC_{50}$ *vs.* pH plot of the imidazole **8**. This analogy suggests that the methoxycarbonyl group of **14** interacts with AH similarly as N(1) of the imidazole, and that its protonation induces an analogous interaction of B^- with the (alkoxycarbonyl)pyrrole of **14** and with the imidazole of **8**, the lower inhibitory activity of **14** reflecting the lower basicity of **14** and the cost of the required positional adjustment.

The IC_{50} values (*Table 5*) and the $1/IC_{50}$ *vs.* pH profiles of the glucosamine-related **1**–**7**[12]) (plots C, D, G, and H) show a pronounced influence of the amino group on the strength and pH dependence of the inhibition. On the basis of their activity at optimal pH, the amines **1**–**7** form two groups, one comprising the amines **3**, **4**, and **5**–**7** that are stronger inhibitors than the corresponding alcohols (**10**, **11**, and **12**–**14**), and the other the amines **1** and **2** that are weaker than the corresponding alcohols (**8** and **9**). The inhibitors of the first group are either weak or no H-bond acceptors for AH, those of the second group are, in principle, good H-bond acceptors.

The introduction of the amino group consistently raises the pK_{HA} value of the inhibitors, and the pH-optimum for the inhibition by all amines is below their pK_{HA} values (*cf. Table 5*), indicating that they are bound as ammonium salts and that the H-bond between C(2)–NH_3^+ and B^- contributes more strongly to binding than any possible H-bond to the C(2)–NH_2 group. The difference between pK_{HA} and the pH of optimal inhibition is larger (0.5 to 1.0 units; *cf. Table 5*) for the amines lacking a basic 'glycosidic heteroatom' (**5**–**7**, plots C and G), than for those (**1**–**4**, 0.2 to 0.4 units) possessing such a heteroatom (plots C and G).

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[12]) For the tetrazole **3**, the lactam **4**, and pyrroles **6** and **7**, a slow onset of the inhibition was observed, requiring a preincubation of the β-glucosidase and the inhibitor during 30–60 min before starting the enzymatic reaction by addition of the substrate.

Table 5. *Inhibition of β-Glucosidases from Sweet Almonds and* Caldocellum saccharolyticum *by Glucosamine-Derived Inhibitors* **1**–**7** *Compared to Their Inhibition by the Glucose-Derived Inhibitors*

Compounds compared	Enzyme	$\Delta\Delta G_{diss.}$ [a]) [kcal/mol]	Data of the glucosamine-derived inhibitors **1**–**7**				Data of the glucose-derived inhibitors **8**–**14**		
			pK_{HA}	pH_{opt} [b])	K_i [μM] (pH 6.8)	K_i [μM] (pH_{opt})	K_i [μM] (pH 6.8)	K_i [μM] (pH_{opt})	pH_{opt} [c])
1 with **8**	Almonds	+ 4.7	6.33	5.9 (0.43)	107 [c])	68 [c])	0.1	0.05	6.4
	C. sacch.	+ 4.3			43 [d])	20	0.02 [d])	0.015	6.4–6.8
2 with **9**	Almonds	+ 2.3	5.82	5.4 (0.42)	450	210	19	6	4.6–5.4
	C. sacch.	+ 2.8			137 [d])	12	0.3 [d])	0.15	4.6–5.4
3 with **10**	Almonds	− 0.9	5.29	5.0 (0.29)	28	20 [d])	150	93 [d])	4.6–5.4
	C. sacch.	− 0.6			13 [d])	6 [d])	60 [d])	15 [d])	4.6–5.4
4 with **11**	Almonds	− 1.1	7.04	6.8 (0.24)	6.6	6.6	125	38 [d])	4.6–5.4
	C. sacch.	− 1.1			0.7 [d])	0.7 [d])	5 [d])	3.5 [d])	4.6–5.4
5 with **12**	Almonds	− 1.5	6.01	5.0 (0.99)	4350 [d])	1350 [d])	17500 [d])	14500 [d])	5.4–5.9
	C. sacch.	− 1.6			1400 [d])	450 [d])	6000 [d])	5000 [d])	5.9–6.4
6 with **13**	Almonds	− 2.8	7.31	6.8 (0.51)	26 [d])	26	6000	2250 [d])	5.4–5.9
	C. sacch.	− 2.9			11 [d])	11 [d])	1150 [d])	900 [d])	5.4–6.4
7 with **14**	Almonds	− 2.2	7.84	6.8 (1.04)	9	9	300	300 [d])	5.4–5.9
	C. sacch.	− 1.8			6 [d])	6 [d])	410 [d])	100 [d])	5.9

[a]) Difference in dissociation energy between glucosamine and glucose analogue calculated on the basis of K_i at pH_{opt}. [b]) pH corresponding to optimal inhibition; $pK_{HA} - pH_{opt}$ in parenthesis. Same values for β-glucosidases from sweet almonds and *C. saccharolyticum*. [c]) pH corresponding to optimal inhibition. [d]) $IC_{50}/2$.

The strongest increase of inhibitory activity (corresponding to 2.8 kcal/mol for almonds and 2.9 kcal/mol for *C. saccharolyticum*) is observed for the pyrrole **6** that cannot act as H-bond acceptor for AH; thus, these values correspond to the maximal strengthening, for inhibitors of this type, of the H-bond to B^- of either the OH or the NH_3^+ group. The increase of inhibitor strength is smaller for the isomeric ester **7**, and this to the extent (0.6 and 1.1 kcal/mol) by which the corresponding hydroxy ester **14** is a better inhibitor than the isomeric hydroxy ester **13**. This correlation is in keeping with the above-formulated hypothesis that the methoxycarbonyl group of **14** but not of **13** acts as H-bond acceptor for AH. This interaction is lost upon replacement of the OH group by an NH_3^+ group, whether under the influence of the stronger σ-acceptor on the basic properties of the methoxycarbonyl group, or by a competing intramolecular H-bond from the NH_3^+ to the methoxycarbonyl group is difficult to decide on the basis of

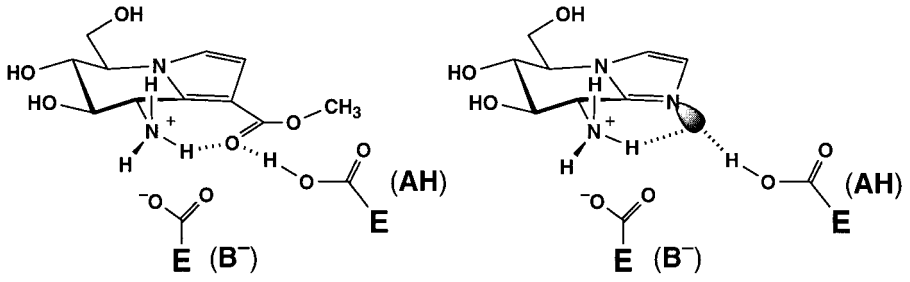

Fig. 2. *Double competition between H-bond donors and acceptors involving B^-, $NH_3^+ - C(2)$, the 'glycosidic heteroatom', and AH*

these data alone. Evidence for the effect of such an intramolecular H-bond has been discussed [41]. Partial or complete loss of the H-bond-acceptor properties of the 'glycosidic heteroatom' and concomitant weakening of the H-bond between NH_3^+ and B^- (*cf. Fig. 2*) also explains the much lower activity of the aminoimidazole **1** ($\Delta\Delta G =$ 4.3–4.7 kcal/mol) and aminotriazole **2** ($\Delta\Delta G = 2.3–2.8$ kcal/mol), as compared to the corresponding alcohols[13]). The effects of replacing the OH by an NH_3^+ group on the inhibition by the analogues possessing a weakly basic 'glycosidic heteroatom' correlate with the basicity of this heteroatom and denote the competition between strengthening of the H-bond to B^- and weakening of the H-bond from AH. That the weakening effect (up to 4.3–4.7 kcal/mol) is more pronounced than the strengthening one (up to 2.8–2.9 kcal/mol) is in keeping with the anticipated (on the basis of the mechanism of action of the glycosidases and the lateral protonation of these inhibitors) stronger influence of the H-bond from AH to the 'glycosidic heteroatom' than of the H-bond between C(2)–OH and B^-.

We thank Dr. *B. Bernet* for checking the *Exper. Part*, *J. Schneider* and *D. Manser* for the pK_{HA} determinations, and the *Swiss National Science Foundation* and *Oxford Glycosciences Ltd.*, Abingdon (UK), for generous support.

Experimental Part

General. Solvents were distilled before use. Normal workup implies distribution of the crude product between Et_2O and sat. aq. NH_4Cl soln. and ice, unless indicated otherwise, drying of the org. layer (Na_2SO_4), filtration, and evaporation of the filtrate. TLC: *Merck* silica gel *60F-254* plates; detection by heating with 'mostain' (400 ml of 10% H_2SO_4 soln., 20 g of $(NH_4)_6Mo_7O_{24}\cdot 6\,H_2O$, 0.4 g of $Ce(SO_4)_2$). Flash chromatography (FC): silica gel *Fluka 60* (0.04–0.063 mm). IR Spectra: KBr of 2% CH_2Cl_2 soln. ^{1}H- and ^{13}C-NMR: at 300 and 75 MHz, resp., if not indicated otherwise; chemical shifts δ in ppm, coupling constants J in Hz. FAB-MS: 3-nitrobenzyl alcohol, unless indicated otherwise.

*(5*R*,6*R*,7*S*,8*S*)-8-Amino-5,6,7,8-tetrahydro-5-(hydroxymethyl)tetrazolo[1,5-*a*]pyridine-6,7-diol* (**3**). a) *From* **15**. A soln. of **15** (5 mg, 0.021 mmol) in THF/1M aq. HCl 3:1 (4 ml) was refluxed during 13 h. Evaporation of the solvent and ion-exchange chromatography (*Amberlite CG-120* (NH_4^+ form), 0.01M NH_4OH) gave **2** (3 mg, 71%).

b) *From* **66**. A soln. of **66** (60 mg, 0.26 mmol) in MeOH/AcOH 5:1 (5 ml) was treated with 10% Pd/C (20 mg) and hydrogenated at 6 bar during 24 h. Filtration, evaporation of the solvent, and ion-exchange

[13]) The unfavourable influence of C(2)–NH_3^+ on the inhibition indicates, in keeping with crystal structures for most retaining *exo*- and *endo*-glycosidases, that the catalytic acid (AH) is not correctly oriented to interact, by H-bonding, with both the NH_3^+ group and with the 'glycosidic heteroatom'. As illustrated in *Fig. 3*, such a cooperative interaction should be favourable and strengthen the inhibition by **1** and **2**.

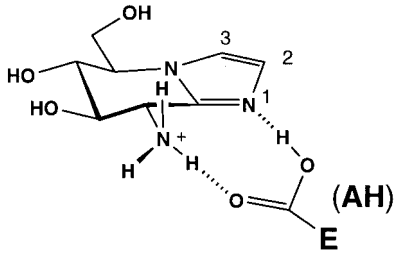

Fig. 3. *Illustration of the interactions expected between the catalytic acid* (AH) *and the protonated glucosamine-derived imidazole* **1** *if the carbonyl group of AH were oriented correctly to accept a H-bond from* NH_3^+–*C(2)*

chromatography (*Amberlite CG-120* (H^+ form), 1M NH_4OH) gave **3** (40 mg, 76%). Colourless solid. R_f (AcOEt/MeOH/H_2O 5:1:0.1) 0.05. ^{1}H-NMR (300 MHz, D_2O): 3.72–3.75 (br. *m*, H–C(7)); 4.12–4.15 (br. *m*, irrad. at 3.74 → change, irrad. at 4.36 → change, H–C(6), H–C(8)); 4.14 (*dd*, *J* = 12.8, 1.9, irrad. at 4.49 → br. *s*, irrad. at 4.36 → *d*, *J* ≈ 12.5, CH–C(5)); 4.34–4.35 (*m*, irrad. at 4.49 → change, H–C(5)); 4.49 (br. *d*, *J* = 12.8, irrad. at 4.36 → change, CH–C(5)). ^{1}H-NMR (300 MHz, D_2O, 2 equiv. of CF_3COOH): 4.07 (*t*, *J* = 9.6, irrad. at 4.91 → *d*, *J* = 9.5, H–C(7)); 4.12–4.20 (*m*, irrad. at 4.07 → change, H–C(6), CH–C(5)); 4.43–4.47 (*m*, H–C(5)); 4.49 (*dd*, *J* = 12.5, 2.5, CH–C(5)); 4.91 (*d*, *J* = 9.5, irrad. at 4.07 → *s*, H–C(8)). ^{13}C-NMR (75 MHz, D_2O): 50.02 (*d*, C(8)); 60.46 (*t*, *C*H_2–C(5)); 65.70 (*d*, C(5)); 70.08, 73.03 (2*d*, C(6), C(7)); 153.05 (*s*, C(8a)). CI-MS (NH_3): 202 (100, $[M+1]^+$), 91 (100). Anal. calc. for $C_6H_{11}N_5O_3 \cdot 0.5\ H_2O$ (210.78): C 34.19, H 5.74, N 33.32; found: C 34.42, H 5.77, N 33.38.

2,5-Diamino-2,5-dideoxy-D-*gluconolactam* (**4**). A soln. of **16** (80 mg, 0.173 mmol) in MeOH/AcOH 1:1 (2 ml) was hydrogenated at 1 bar during 6 h. Filtration, evaporation, and ion-exchange chromatography (*Amberlite CG-120* (H^+ form), 0.1M aq. NH_4OH) gave **4** (28 mg, 92%). Colourless foam, which turned yellowish upon standing. R_f (AcOEt/MeOH 5:1) 0.03. ^{1}H-NMR (500 MHz, D_2O): 3.38–3.41 (*m*, H–C(5)); 3.49 (*d*, *J* = 9.4, H–C(2)); 3.73 (*t*, *J* = 9.6, H–C(4)); 3.77 (*t*, *J* ≈ 9.4, H–C(3)); 3.78 (*dd*, *J* = 12.1, 4.5, H–C(6)); 3.85 (*dd*, *J* = 12.1, 2.8, H–C(6)). ^{13}C-NMR (125 MHz, D_2O): 55.56 (*d*, C(2)); 56.86 (*d*, C(5)); 60.27 (*t*, C(6)); 67.96, 72.90 (2*d*, C(3), C(4)); 172.65 (*d*, C(1)). FAB-MS: 177 (100, $[M+1]^+$). Anal. calc. for $C_6H_{12}N_2O_4$ (176.17): C 40.91, H 6.87, N 15.90; found: C 41.04, H 6.79, N 15.76.

*Methyl (5*R,*6*R,*7*R,*8*S*)-8-Amino-5,6,7,8-tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)indolizine-2-carboxylate* (**6**). A soln. of **17** (26 mg, 0.047 mmol) in AcOH (2 ml) was treated with 10% Pd/C (30 mg) and hydrogenated at atmospheric pressure during 19 h. After filtration and evaporation, the crude was dissolved in 0.01M HCl (3 ml), treated with activated charcoal (5 mg), filtered, and evaporated. Ion-exchange chromatography (*Amberlite CG-120* (NH_4^+ form), 0.1M NH_4OH) gave **6** (7 mg, 58%). Colourless, hygroscopic foam. R_f (AcOEt/MeOH/H_2O 5:1:0.1) 0.08. ^{1}H-NMR (300 MHz, D_2O): 3.59 (*t*, *J* = 9.3, H–C(7)); 3.84 (*s*, MeO); 3.90 (*d*, *J* = 9.3, irrad. at 3.59 → *s*, H–C(8)); 3.94 (*t*, *J* = 9.3, irrad. at 3.59 → *d*, *J* = 9.0, H–C(6)); 4.01–4.11 (*m*, H–C(5), CH–C(5)); 4.26 (*dd*, *J* = 12.5, 2.2, CH–C(5)); 6.60 (br. *s*, H–C(1)); 7.65 (*d*, *J* = 1.6, H–C(3)). ^{1}H-NMR (300 MHz, D_2O, 2 equiv. of CF_3COOH): 3.80 (*s*, MeO); 3.88 (*t*, *J* = 9.0, irrad. at 4.73 → *d*, *J* = 9.0, H–C(7)); 3.99 (*t*, *J* = 9.3, H–C(6)); 4.05–4.10 (*m*, H–C(5), CH–C(5)); 4.24 (*dd*, *J* = 13.4, 3.4, CH–C(5)); 4.73 (*dd*, *J* = 9.3, 1.2, H–C(8)); 6.67 (*dd*, *J* = 1.6, 1.2, irrad. at 4.73 → *d*, *J* = 1.6, H–C(1)); 7.69 (*d*, *J* = 1.6, H–C(3)). ^{13}C-NMR (75 MHz, D_2O): 53.33 (*d*, *C*(8)); 54.75 (*q*, MeO); 62.03 (*t*, *C*H_2–C(5)); 64.63 (*d*, C(5)); 70.80, 73.60 (2*d*, C(6), C(7)); 109.93 (*d*, C(1)); 119.09 (*s*, C(8a)); 128.71 (*s*, C(2)); 128.76 (*d*, C(3)); 170.32 (*s*, C=O). FAB-MS: 257 (100, $[M+1]^+$). Anal. calc. for $C_{11}H_{16}N_2O_5 \cdot 1.5\ H_2O$ (283.28): C 46.64, H 6.76, N 9.89; found: C 46.93, H 6.77, N 9.59.

*Methyl (5*R,*6*R,*7*R,*8*S*)-8-Amino-5,6,7,8-tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)indolizine-1-carboxylate* (**7**). A soln. of **18** (240 mg, 0.45 mmol) in AcOH (10 ml) was treated with 10% Pd/C (120 mg) and hydrogenated at atmospheric pressure during 19 h. After filtration and evaporation, the crude was dissolved in 0.01M HCl (3 ml), treated with activated charcoal (5 mg), filtered, and evaporated. Ion-exchange chromatography (*Amberlite CG-120* (NH_4^+ form), 0.1M NH_4OH) gave **7** (73 mg, 63%). Colourless, hygroscopic foam which turned yellowish upon standing. R_f (AcOEt/MeOH/H_2O 5:1:0.1) 0.05. ^{1}H-NMR (300 MHz, D_2O): 3.83 (*dd*, *J* = 8.7, 6.9, irrad. at 4.25 → *d*, *J* ≈ 8.7, irrad. at 4.00 → *d*, *J* ≈ 6.9, H–C(7)); 3.86 (*s*, MeO); 4.00 (*dd*, *J* = 8.4, 7.5, H–C(6)); 4.07–4.12 (*m*, irrad. at 4.00 → change, H–C(5), CH–C(5)); 4.23 (*dd*, *J* = 9.7, 3.7, CH–C(5)); 4.25 (*d*, *J* = 6.9, irrad. at 3.83 → *s*, H–C(8)); 6.75 (*d*, *J* = 3.1, H–C(2)); 6.95 (*d*, *J* = 3.1, H–C(3)). ^{1}H-NMR (300 MHz, D_2O + 2 equiv. of CF_3COOH): 3.89 (*s*, MeO); 4.05–4.18 (*m*, irrad. at 4.74 → change, H–C(5), H–C(6), H–C(7), CH–C(5)); 4.26 (*dd*, *J* = 12.4, 2.2, CH–C(5)); 4.74 (*d*, *J* = 6.9, H–C(8)); 6.82 (*d*, *J* = 3.4, H–C(2)); 7.09 (*d*, *J* = 3.4, H–C(3)). ^{13}C-NMR (75 MHz, D_2O, 3 equiv. of HCl): 52.97 (*d*, C(8)); 55.12 (*q*, MeO); 61.75 (*t*, *C*H_2–C(5)); 64.41 (*d*, C(5)); 70.08, 73.08 (2*d*, C(6), C(7)); 114.99 (*d*, C(1)); 116.03 (*s*, C(8a)); 123.97 (*d*, C(3)); 131.33 (*s*, C(1)); 170.81 (*s*, C=O). FAB-MS: 257 (100, $[M+1]^+$). Anal. calc. for $C_{11}H_{16}N_2O_5 \cdot 0.25\ H_2O$ (260.76): C 50.66, H 6.28, N 10.74; found: C 50.57, H 6.33, N 10.51.

4,5,7-Tri-O-*benzyl-1,2-dideoxy-3*-O-*(triisopropylsilyl)*-L-ido-*hept-1-ynitol* (**21**) *and 1,3,4-Tri*-O-*benzyl-6,7-dideoxy-5*-O-*(triisopropylsilyl)*-D-gluco-*hept-6-ynitol* (**22**). A soln. of **19**/**20** 1:1 (2.68 g, 6.0 mmol) in THF (54 ml) was cooled to −78°, treated with 2.5M BuLi in heptane (2.3 ml, 5.75 mmol), stirred for 15 min, treated with ^{i}Pr_3SiCl (1.22 ml, 5.75 mmol), and allowed to reach 25° within 9 h. Normal workup and FC (AcOEt/hexane 1:5) gave **21**/**22** 1:1 (3.031 g, 84%). R_f (AcOEt/hexane 1:5) 0.52, 0.56. IR (CH_2Cl_2): 3569*m*, 3315*m*, 3090*m*, 3064*m*, 3008*s*, 2923*m*, 2864*m*, 1952*w*, 1875*w*, 1811*w*, 1605*w*, 1497*m*, 1450*s*, 1396*m*, 1349*m*, 1243*m*, 1070*s*, 1027*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95–1.36 (*m*, $(Me_2CH)_3Si$); 2.46 (br. *d*, *J* = 4.9, 0.5 H); 2.51 (*d*, *J* = 2.5, 0.5 C≡CH), 2.52 (*d*, *J* = 2.1, 0.5 C≡CH); 2.68 (br. *s*, 0.5 H); 3.48–3.50 (*m*, 1 H); 3.79 (*dd*, *J* = 5.9, 5.3, 0.5 H); 3.82–

3.94 (*m*, 1 H); 3.98 (*dd*, *J* = 7.1, 3.0, 0.5 H); 4.04 (*dd*, *J* = 5.8, 3.3, 0.5 H); 4.13–4.44 (*m*, 1.5 H); 4.46–5.05 (*m*, 7 H); 7.28–7.34 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$; numbering of **22**): 12.22, 12.59 (2*d*, $(Me_2CH)_3Si$); 17.99, 17.99 (2*q*, $(Me_2CH)_3Si$); 62.73, 64.65 (2*d*, C(5)); 70.31, 71.67 (2*d*, C(2)); 71.09, 72.19 (2*t*, C(1)); 73.24, 73.44, 74.57, 74.70, 75.17, 75.52 (6*t*, 3 Ph*C*H_2); 74.96, 75.02 (2*d*, C(3)); 79.08, 79.62 (2*d*, C(4)); 80.99, 82.20 (2*d*, C≡*C*H); 82.87, 84.23 (2*s*, *C*≡CH); 127.68–128.68 (several *d*); 138.01 (0.5 *s*); 138.49 (*s*); 138.57 (0.5 *s*); 138.875 (*s*). FAB-MS: 604 (23, $[M+H]^+$), 603 (36, M^+), 571 (100), 181 (92).

4,5,7-Tri-O-*benzyl-1,2-dideoxy-2*-O-*(4-tolylsulfonyl)-3*-O-*(triisopropylsilyl)*-L-ido-*hept-1-ynitol* (**23**) *and 1,3,4-Tri*-O-*benzyl-6,7-dideoxy-2*-O-*(4-tolylsulfonyl)-5*-O-*(triisopropylsilyl)*-D-gluco-*hept-6-ynitol* (**24**). A soln. of **21**/**22** 1:1 (2.93 g, 4.9 mmol) in pyridine (50 ml) was treated with TsCl (9.3 g, 49 mmol) and DMAP (*N*,*N*-dimethylpyridin-4-amine; 150 mg), stirred at 50° for 12 h, cooled to 0°, treated with sat. aq. $NaHCO_3$ soln., and stirred at 25° for an additional hour. After evaporation of pyridine, the residue was distributed between H_2O and Et_2O, the aq. layer extracted with Et_2O (2 × 150 ml), and the combined org. phase washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:7) afforded **23**/**24** 1:1 (3.21 g, 87%). R_f (AcOEt/hexane 1:5) 0.63. IR (CH_2Cl_2): 3306*s*, 3010*m*, 2967*m*, 2867*m*, 1956*w*, 1604*m*, 1497*m*, 1454*s*, 1398*m*, 1176*s*, 1094*s*, 1027*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88–1.18 (*m*, $(Me_2CH)_3Si$); 2.34 (*s*, 0.5 Me); 2.43 (*d*, *J* = 2.1, 0.5 C≡CH); 2.45 (*s*, 0.5 Me); 2.48 (*d*, *J* = 2.1, 0.5 C≡CH); 3.21 (*dd*, *J* = 11.6, 4.6, 0.5 H); 3.45–3.86 (*m*, 2.5 H); 4.07–4.20 (*m*, 1.5 H); 4.27–4.41 (*m*, 1.5 H); 4.42–5.05 (*m*, 6 H); 7.13–7.31 (*m*, 17 arom. H); 7.72 (*m*, *J* = 8.3, 1 H); 7.76 (*d*, *J* = 8.3, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$; numbering of **24**): 12.47, 12.49 (2*d*, $(Me_2CH)_3Si$); 18.15, 18.21 (2*q*, $(Me_2CH)_3Si$); 21.68 (*q*, Me); 65.10, 65.57 (2*d*, C(5)); 68.53, 69.31 (2*t*, C(1)); 71.13, 73.10 (2 C), 74.46, 74.56, 75.26 (5*t*, 3 Ph*C*H_2); 75.26, 75.71, 76.11, 77.25 (4*d*, C(2), C(3)); 80.78, 80.63 (2*d*, C(4)); 82.39, 82.62 (2*d*, C≡*C*H); 82.99, 83.35 (2*s*, *C*≡CH); 127.70–129.80 (several *d*); 134.39 (0.5 *s*); 135.01 (0.5 *s*); 136.35 (0.5 *s*); 137.86 (0.5 *s*); 138.04 (*s*); 138.61 (*s*); 144.55 (*s*). FAB-MS: 758 (43, $[M+1]^+$), 757 (31, M^+), 181 (74), 91 (100).

Treatment of **23**/**24** *with* NaN_3. A soln. of **23**/**24** 1:1 (2.56 g, 3.4 mmol) in DMSO (120 ml) was treated with NaN_3 and stirred at 110° for 15 h. The solvent was evaporated, the residue distributed between H_2O and Et_2O, the aq. layer extracted with Et_2O (2 × 150 ml), and the combined org. layer washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:5) gave **27**/**28** 2:1 (0.174 g, 12%), **25** (0.993 g, 38%), and **26** (0.275 g, 21%). The mixture **27**/**28** was separated by FC (AcOEt/hexane 1:9).

Data of 3,6-Anhydro-4,5,7-tri-O-*benzyl*-D-manno-*hept-1-ynitol* (**27**): R_f (AcOEt/hexane 1:9) 0.28. IR (CH_2Cl_2): 3301*s*, 3089*m*, 2925*m*, 1586*w*, 1425*m*, 1362*s*, 1288*m*, 1207*s*, 1093*s*, 1028*s*, 910*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.59 (*d*, *J* = 2.5, irrad. at 4.75 → *s*, H–C(1)); 3.58–3.68 (*m*, 2 H–C(7)); 4.05 (*dd*, *J* = 5.9, 3.1, H–C(5)); 4.26 (*t*, *J* = 3.4, irrad. at 4.75 → *d*, *J* = 3.1, irrad. at 4.05 → *d*, *J* = 3.4, H–C(4)); 4.29 (*q*, *J* ≈ 5.3, irrad. at 4.05 → *t*, *J* ≈ 4.9, H–C(6)); 4.52–4.62 (*m*, 5 PhC*H*); 4.65 (*d*, *J* = 11.8, PhC*H*); 4.75 (br. *t*, *J* ≈ 2.8, H–C(3)); 7.26–7.41 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 69.78 (*t*, C(7)); 72.16 (*d*, C(3)); 72.24 (*t*, 2 Ph*C*H_2); 73.55 (*t*, Ph*C*H_2); 75.20 (*s*, C(2)); 81.40 (*d*, C(1)); 81.75, 84.36, 89.07 (3*d*, C(4), C(5), C(6)); 127.8–128.72 (several *d*); 137.60, 138.04, 138.34 (3*s*). FAB-MS: 428 (8, M^+), 427 (21), 391 (86), 149 (58), 91 (100).

Data of 3,6-Anhydro-4,5,7-tri-O-*benzyl*-D-gluco-*hept-1-ynitol* (**28**; *cf.* [18]): R_f (AcOEt/hexane 1:9) 0.20. IR (CH_2Cl_2): 3302*m*, 3088*m*, 2924*m*, 1585*w*, 1428*m*, 1362*s*, 1290*m*, 1207*s*, 1096*s*, 1027*s*, 910*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.56 (*d*, *J* = 2.0, H–C(1)); 3.57–3.78 (*m*, 2 H–C(7)); 3.99–4.14 (*m*, 3 H); 4.50–4.75 (*m*, 7 H); 7.25–7.40 (*m*, 15 arom. H). ^{1}H-NMR (300 MHz, C_6D_6): 2.12 (*d*, *J* = 2.4, irrad. at 4.71 → *s*, H–C(1)); 3.63–3.73 (*m*, 2 H–C(7)); 3.86 (*dd*, *J* = 4.8, 2.7, irrad. at 4.71 → *d*, *J* = 2.2, irrad. at 4.12 → *d*, *J* = 4.0, H–C(4)); 4.12 (br. *t*, *J* ≈ 3.0, irrad. at 3.86 → *d*, *J* = 3.4, H–C(5)); 4.21–4.38 (*m*, irrad. at 4.12 → change, 5 PhC*H*, H–C(6)); 4.53 (*d*, *J* = 11.7, PhC*H*), 4.71 (*dd*, *J* = 4.5, 2.4, H–C(3)); 7.03–7.32 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 70.50 (*t*, C(7)); 71.07 (*d*, C(3)); 71.87, 72.44, 73.52 (3*t*, 3 Ph*C*H_2); 76.31 (*s*, C(2)), 79.04 (*d*, C(1)); 82.44, 83.39, 84.21 (3*d*, C(4), C(5), C(6)); 127.82–128.65 (several *d*); 137.89 (2*s*); 138.40 (*s*). FAB-MS: 428 (8, M^+), 427 (23), 391 (100), 149 (36), 91 (50).

*Data of (4*S*,5*S*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]-4,5,6,7-tetrahydro-4-[(triisopropylsilyl)-oxy][1,2,3]triazolo[1,5-*a*]pyridine* (**25**): R_f (AcOEt/hexane 1:3) 0.40. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84–1.33 (*m*, $(Me_2CH)_3Si$)); 3.84 (*t*, *J* = 7.2, irrad. at 5.10 → *d*, *J* = 7.2, H–C(5)); 3.97 (*dd*, *J* = 10.3, 2.8, CH–C(7)); 4.25–4.33 (*m*, irrad. at 3.84 → change, irrad. at 3.97 → change, H–C(6), CH′–C(7)); 4.43 (*d*, *J* = 11.8, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.57–4.60 (*m*, irrad. at 3.97 → change, 3 PhC*H*, H–C(7)); 4.73 (*d*, *J* = 11.8, PhC*H*); 5.10 (*d*, *J* = 6.9, irrad. at 3.84 → *s*, H–C(4)); 7.15–7.35 (*m*, 15 arom. H); 7.70 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 12.89 (*d*, $(Me_2CH)_3Si$); 18.12 (*q*, $(Me_2CH)_3Si$), 60.99 (*d*, C(7)); 67.22 (*d*, C(4)); 67.51 (*t*, CH_2–C(7)); 73.67, 74.34, 74.43 (3*t*, 3 Ph*C*H_2); 76.20 (*d*, C(5)); 83.51 (*d*, C(6)); 127.40–128.71 (several *d*); 132.06 (*d*, C(3)); 137.30 (*s*, C(3a)); 137.77, 137.87, 138.26 (3 *s*). FAB-MS: 629 (47, $[M+H]^+$), 628 (100, M^+), 91 (47).

*Data of (4*R*,5*S*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]-4,5,6,7-tetrahydro-4-(triisopropylsilyloxy)[1,2,3]triazolo[1,5-*a*]pyridine* (**26**): R_f (AcOEt/hexane 1:3) 0.23. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.02–1.13 (*m*, $(Me_2CH)_3Si$); 3.86 (*dd*, *J* = 6.9, 2.8, irrad. at 5.33 → *d*, *J* = 6.9, H–C(5)); 4.04 (*dd*, *J* = 9.7, 6.9, CH–C(7)); 4.10 (*dd*, *J* = 9.7, 4.1, CH′–C(7)); 4.45 (br. *s*, 2 PhC*H*$_2$); 4.60–4.75 (*m*, irrad. at 4.04 → change, 4 PhC*H*, H–C(6), H–C(7)); 5.33 (*d*, *J* = 2.8, H–C(4)); 7.20–7.34 (*m*, 15 arom. H); 7.65 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 12.45 (*d*, $(Me_2CH)_3Si$), 18.06 (*q*, $(Me_2CH)_3Si$); 60.82 (*d*, C(7)); 68.87 (*t*, CH_2–C(7)); 71.71, 71.75, 72.81 (3*t*, 3 PhCH_2); 73.10, 73.29 (2*d*, C(4), C(5)); 79.24 (*d*, C(6)); 127.66–128.91 (several *d*); 131.29 (*d*, C(3)); 135.96 (*s*, C(3a)); 137.51, 137.66, 137.76 (3*s*). FAB-MS: 629 (45, $[M+H]^+$), 628 (100, M^+), 91 (78).

*(4*R*,5*S*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridin-4-ol* (**30**). A soln. of **26** (155 mg, 0.25 mmol) in THF (2 ml) was treated with 1M Bu_4NF (0.35 ml, 0.35 mmol) and stirred at 25° for 1 h. Evaporation and FC (AcOEt/hexane 2:3) gave **30** (106 mg, 91%). R_f (AcOEt/hexane 3:2) 0.43. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.10 (br. *d*, *J* ≈ 4.0, irrad. at 5.09 → *s*, exchange with D_2O, HO–C(4)); 3.93–4.02 (*m*, irrad. at 5.09 → change, irrad. at 4.70 → change, H–C(5), CH–C(7)); 4.11 (*dd*, *J* = 9.7, 4.4, irrad. at 4.70 → *d*, *J* = 9.7, CH′–C(7)); 4.44–4.66 (*m*, 6 PhC*H*, H–C(6)); 4.67–4.71 (*m*, irrad. at 4.11 → change, H–C(7)); 5.09 (*dd*, *J* = 8.4, 3.7, irrad. at 3.96 → *d*, *J* = 3.7, H–C(4)); 7.18–7.36 (*m*, 15 arom. H), 7.72 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 59.69 (*d*, C(7)); 61.73 (*t*, CH_2–C(7)); 69.17 (*d*, C(4)); 71.77 (*d*, C(5)); 73.08, 73.18, 73.59 (3*t*, 3 PhCH_2); 77.61 (*d*, C(6)); 128.06–128.91 (several *d*); 132.29 (*d*, C(3)); 135.14 (*s*, C(3a)); 136.97, 137.41, 137.72 (3*s*). FAB-MS: 472 (56, $[M+H]^+$), 471 (45, M^+), 91 (100).

*(4*R*,5*S*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridin-4-yl Methanesulfonate* (**32**). A soln. of **30** (95 mg, 0.2 mmol) in pyridine (2 ml) was treated at 0° with MsCl (80 µl, 1.03 mmol) and stirred for 5 h. Normal workup gave **32** (97.4 mg, 88%) which was used for the next step without purification. R_f (AcOEt/hexane 2:3) 0.4. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.76 (*s*, MsO); 3.94–4.05 (*m*, 2 H); 4.29–4.58 (*m*, 3 H); 4.62–4.75 (*m*, 2 H); 4.81–4.95 (*m*, 4 H); 6.16 (*d*, *J* = 3.3, H–C(4)); 7.18–7.82 (*m*, 15 arom. H); 8.20 (*s*, H–C(3)).

*(4*S*,5*S*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridin-4-ol* (**29**). As described for **26**, with **25** (450 mg, 0.72 mmol). FC (AcOEt/hexane 2:3) afforded **29** (306 mg, 91%). R_f (AcOEt/hexane 3:2) 0.45. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.34 (br. *s*, exchange with D_2 O, HO–C(4)); 3.96 (*dd*, *J* = 6.5, 5.0, H–C(5)); 4.05 (*dd*, *J* = 9.7, 4.1, CH–C(7)); 4.13 (*dd*, *J* = 9.7, 6.9, CH′–C(7)); 4.44 (*dd* , *J* = 6.5, 4.7, irrad. at 3.96 → change, H–C(6)); 4.47 (*s*, PhCH_2); 4.64 (*d*, *J* = 11.5, PhC*H*); 4.66 (*d*, *J* = 11.8, PhC*H*); 4.71–4.85 (*m*, PhCH_2, H–C(7)); 4.87 (br. *t*, *J* ≈ 5.0, irrad. at 3.96 → br. *d*, *J* = 6.6, H–C(4)); 7.22–7.36 (*m*, 15 arom. H); 7.75 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 60.01 (*d*, C(7)); 64.44 (*d*, C(4)); 68.53 (*t*, CH_2–C(7)); 73.61, 73.82, 73.94 (3*t*, 3 PhCH_2); 74.00 (*d*, C(5)); 79.34 (*d*, C(6)); 128.00–128.91 (several *d*); 132.58 (*d*, C(3)); 135.12 (*s*, C(3a)); 136.93, 137.55, 137.82 (3*s*).

*(4*S*,5*R*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridin-4-yl Methanesulfonate* (**31**). As described for **30**, with **29** (190 mg, 0.4 mmol). Crude **31** (193 mg, 87%) was used for the next step. R_f (AcOEt/hexane 2:3) 0.51. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.93 (*s*, MsO); 3.99 (*dd*, *J* = 10.3, 2.8, irrad. at. 4.58 → *d*, *J* = 10.3, CH–C(7)); 4.10 (*dd*, *J* = 8.4, 7.2, H–C(5)); 4.33–4.42 (*m*, irrad. at 3.99 → change, irrad. at 4.58 → change, PhC*H*, H–C(6), CH′–C(7)); 4.46 (*d*, *J* = 11.8, PhC*H*); 4.54–4.63 (*m*, irrad. at 3.99 → change, 2 PhC*H*, H–C(7)); 4.78 (*d*, *J* = 11.2, PhC*H*); 4.85 (*d*, *J* = 10.9, PhC*H*): 5.73 (*d*, *J* = 7.2, irrad. at 4.10 → *s*, H–C(4)); 7.18–7.38 (*m*, 15 arom. H); 7.85 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.42 (*q*, MsO); 61.10 (*d*, C(7)); 66.52 (*t*, CH_2–C(7)); 71.71 (*d*, C(4)); 73.46 (*t*, PhCH_2); 74.69 (*d*, C(5)); 74.78, 75.12 (2*t*, 2 PhCH_2); 79.52 (*d*, C(6)); 127.00–128.89 (several *d*); 133.61 (*d*, C(3)); 136.99 (*s*, C(3a)); 137.07, 137.38, 137.38 (3*s*). FAB-MS: 551 (25, $[M+H]^+$), 550 (100, M^+), 454 (46), 91 (100).

*(4*R*,5*S*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]-4-chloro-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5*a*]-pyridine* (**33**). A soln. of **31** (150 mg, 0.27 mmol) in DMF (2 ml) was treated with Bu_4NCl (750 mg, 2.7 mmol) and stirred at 25° for 1 d. Evaporation of DMF at 20 mbar and normal workup afforded **33** (115 mg, 82%) which was used without purification for the next step. R_f (AcOEt/hexane 2:3) 0.41. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.03 (*dd*, *J* = 6.6, 3.4, H–C(5)); 4.05–4.15 (*m*, 2 H); 4.47 (br. *s*, PhCH_2); 4.57–4.78 (*m*, 6 H); 5.41 (*d*, *J* = 3.3, irrad. at 4.03 → *s*, H–C(4)); 7.22–7.38 (*m*, 15 arom. H); 7.72 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 48.52 (*d*, C(4)); 60.42 (*d*, C(7)); 68.27 (*t*, CH_2–C(7)); 72.23 (*d*, C(5)); 73.12, 73.34, 73.57 (3*t*, 3 PhCH_2); 76.90 (*d*, C(6)); 127.72–128.61 (several *d*); 132.67 (*s*, C(3)); 133.05 (*s*, C(3a)); 136.86, 137.14, 137.68 (3*s*). FAB-MS: 492 (32), 491 (25), 490 (100, M^+), 454 (15), 91 (51).

*(4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6-bis(benzyloxy)-7-[(benzyloxy)methyl]-4,5,6,7-tetrahydro[1,2,3]-triazolo[1,5-*a*]pyridine* (**34**). *a*) A soln. of **32** (90 mg, 0.164 mmol) in DMF (2 ml) was treated with NaN_3 (108 mg, 1.66 mmol) and stirred at 50° for 3 h. DMF was evaporated, the residue distributed between H_2O and Et_2O (3 ×

50 ml), and the combined org. phase washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:3) gave **34** (67.5 mg, 83%).

b) A soln. of **33** (95 mg, 0.19 mmol) in DMF (1 ml) was treated with NaN_3 (125 mg, 1.92 mmol) and stirred at 50° for 10 h. After evaporation of DMF, normal workup and FC (AcOEt/hexane 1:3) afforded **34** (83 mg, 85%). R_f (AcOEt/hexane 2:3) 0.75. IR (CH_2Cl_2): 3033*m*, 2929*m*, 2871*m*, 2109*s*, 1497*m*, 1454*m*, 1363*m*, 1326*m*, 1215*m*, 1145*s*, 1109*s*, 1019*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.82–4.00 (*m*, 2 H); 4.30–4.54 (*m*, 5 H); 4.57–4.73 (*m*, 2 H); 4.82–4.98 (*m*, 3 H). ^{1}H-NMR (300 MHz, C_6D_6): 3.38 (*t*, *J* = 8.7, irrad. at 3.93 → *d*, *J* = 8.5, H–C(5)); 3.67 (*dd*, *J* = 10.3, 2.2, irrad. at 3.93 → *d*, *J* = 10.3, CH–C(7)); 3.93 (br. *d*, *J* = 8.7, irrad. at 3.38 → change, H–C(4)); 3.92–3.98 (*m*, irrad. at 3.67 → change, irrad. at 4.31 → change, H–C(7)); 4.05 (*d*, *J* = 11.5, PhC*H*); 4.07 (*t*, *J* = 8.4, irrad. at 3.38 → change, H–C(6)); 4.16 (*d*, *J* = 11.8, PhC*H*); 4.31 (*dd*, *J* = 10.3, 3.4, irrad. at 3.67 → change, irrad. at 3.93 → *d*, *J* = 10.3, CH′–C(7)); 4.44 (*d*, *J* = 11.5, PhC*H*); 4.57 (*d*, *J* = 1.3, PhC*H*); 4.63 (*d*, *J* = 11.6, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 6.99–7.29 (*m*, 15 arom. H); 7.59 (*d*, *J* = 0.8, irrad. at 3.93 → *s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 57.10 (*d*, C(4)); 61.56 (*d*, C(7)); 66.71 (*t*, CH_2–C(7)); 73.60, 75.26, 75.54, (3*t*, 3 PhCH_2); 75.54 (*d*, C(5)); 81.69 (*d*, C(6)); 128.08–128.86 (several *d*); 132.10 (*d*, C(3)); 132.68 (*s*, C(3a)); 132.27, 137.52, 137.68 (3*s*). FAB-MS: 497 (48, $[M+H]^+$), 91 (100).

*(4*S*,5*R*,6*R*,7*R*)-4-Amino-4,5,6,7-tetrahydro-7-(hydroxymethyl)[1,2,3]triazolo[1,5-*a*]pyridine-5,6-diol* (**5**). A suspension of **34** (90 mg, 0.18 mmol) and 10% Pd/C (50 mg) in AcOH (1 ml) was hydrogenated at 7 bar for 5 d. Filtration through *Celite*, evaporation, and ion-exchange chromatography (*Amberlite CG 120* (NH_4^+ form), 0.1M NH_4OH) gave **5** (29 mg, 81%). R_f (MeOH/AcOEt 1:9) 0.30. ^{1}H-NMR (300 MHz, D_2O): 3.71 (*t*, *J* ≈ 9.5, H–C(5)); 3.99 (*d*, *J* = 9.3, irrad. at 3.71 → *d*, *J* = 3.2, H–C(4)); 4.12 (*t*, *J* ≈ 9.5, irrad. at 4.42 → *d*, *J* = 9.7, irrad. at 3.71 → *dd*, *J* = 9.7, 3.2, H–C(6)); 4.24 (*dd*, *J* = 12.8, 2.2, irrad., at 4.42 → *d*, *J* = 12.8, CH–C(7)); 4.42 (br. *dt*, *J* ≈ 9.3, 2.4, H–C(7)); 4.60 (*dd*, *J* = 12.8, 2.5, irrad. at 4.42 → *d*, *J* = 12.8, CH′–C(7)); 7.84 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, D_2O): 51.16 (*d*, C(4)); 61.06 (*t*, CH_2–C(7)); 66.19 (*d*, C(7)); 70.51 (*d*, C(5)); 77.62 (*d*, C(6)); 134.12 (*d*, C(3)); 141.57 (*s*, C(3a)). FAB-MS: 201 (36, $[M+H]^+$).

*5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-*D*-gluconolactam* (**36**). A soln. of **35** (500 mg, 0.93 mmol) and dry Bu_4NBr (320 mg, 1 mmol) in CH_2Cl_2 (30 ml) was cooled to −78°, treated with 1M BCl_3 in CH_2Cl_2 (1 ml) for 15 min, and allowed to warm to −10° within 3 h (TLC: *ca.* 50% conversion). After addition of Bu_4NBr (160 mg, 0.5 mmol), the soln. was cooled to −78°, treated dropwise with BCl_3 (1 ml) for 15 min, and allowed to warm to +23° within 3 h (TLC: complete consumption of **35**). The soln. was cooled to −30° and treated with a sat. aq. K_2CO_3 soln. and ice and warmed to 23°. The org. layer was separated and the aq. layer extracted with Et_2O (3×). The combined org. layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in Et_2O, the soln. washed with brine, dried ($MgSO_4$), and evaporated FC (CH_2Cl_2/AcOEt 3:7) gave **36** (362 mg, 87%) as a colourless oil which crystallized upon standing. The same procedure was performed on a 5-g scale. The crude **36** was directly crystallized from AcOEt/hexane yielding pure **36** (2.6 g, 62%). An additional crop (0.5 g, 13%) was obtained by FC of the mother liquor. M.p. 95°. R_f (CH_2Cl_2/AcOEt 7:3) 0.41. $[\alpha]_D^{20} = +51.1$ (*c* = 0.95, $CHCl_3$). IR ($CHCl_3$): 3511*w* (br.), 3388*m*, 3067*w*, 3008*w*, 2867*m*, 1678*s*, 1497*w*, 1454*m*, 1362*w*, 1304*m*, 1116*m*, 1028*m*. ^{1}H-NMR ($CDCl_3$): 3.27–3.32 (*m*, H–C(5)); 3.53–3.66 (*m*, H–C(4), 2 H–C(6)); 3.85 (*t*, *J* = 9.0, H–C(3)); 3.87 (br. *s*, exchange with CD_3OD, OH); 4.14 (*d*, *J* = 9.3, H–C(2)); 4.45 (*d*, *J* = 12.1, PhC*H*); 4.49 (*d*, *J* = 12.1, PhC*H*); 4.55 (*d*, *J* = 11.2, PhC*H*); 4.84 (*d*, *J* = 11.2, PhC*H*); 4.93 (*d*, *J* = 11.2, PhC*H*); 5.07 (*d*, *J* = 11.2, PhC*H*); 6.52 (br. *s*, exchange with CD_3OD, NH); 7.22–7.69 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 55.11 (*d*, C(5)); 70.43 (*t*, C(6)); 72.17 (*d*, C(2)); 73.50, 74.75, 75.04 (3*t*, 3 PhCH_2); 76.11, 82.62 (2*d*, C(3), C(4)); 127.97–128.81 (several *s*); 137.61, 137.67, 138.68 (3*s*); 172.30 (*s*, C=O). CI-MS (NH_3): 448 (21, $[M+1]^+$). Anal. calc. for $C_{27}H_{29}NO_5$ (447.53): C 72.46, H 6.53, N 3.13; found: C 72.44, H 6.62, N 3.13.

*2-*O*-Acetyl-5-amino-3,4,6-tri-*O*-benzyl-5-deoxy-*D*-gluconolactam* (**37**). A soln. of **36** (500 mg, 1.12 mmol) in pyridine (5 ml) was treated at 23° with Ac_2O (0.15 ml, 1.6 mmol) and stirred for 2 h. Evaporation of the solvent at reduced pressure and 40° (within *ca.* 1 h) gave **37** (548 mg, 98%) which was used for the next reaction without further purification. R_f (AcOEt/hexane 1:1) 0.16. IR ($CHCl_3$): 3390*w*, 3038*w*, 2927*w*, 2857*w*, 1749*m*, 1689*s*, 1602*m*, 1455*m*, 1374*w*, 1318*w*, 1118*w*, 910*w*, 649*w*, 607*w*, 556*w*. ^{1}H-NMR ($CDCl_3$): 2.05 (*s*, AcO); 3.26–3.32 (*m*, H–C(5)); 3.54–3.65 (*m*, C(6)); 3.67 (*t*, *J* = 9.0, irrad. at 4.02 → *d*, *J* ≈ 9.0, H–C(4)); 3.91 (*dd*, *J* = 11.5, 6.2, H–C(6)); 4.02 (*t*, *J* = 9.0, H–C(3)); 4.54 (*s*, PhCH_2); 4.75 (*d*, *J* = 11.2, PhC*H*); 4.83 (*d*, *J* = 11.5, PhC*H*); 4.89 (*d*, *J* = 11.2, PhC*H*); 4.93 (*d*, *J* = 10.9, PhC*H*); 5.32 (*d*, *J* = 9.3, irrad. at 4.02 → *s*, H–C(2)); 6.30 (br. *s*, NH); 7.19–7.45 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 20.81 (*q*, Me); 54.44 (*d*, C(5)); 72.17 (*t*, C(6)); 73.53 (*d*, C(2)); 74.97, 75.15, 77.04 (3*t*, 3 PhCH_2); 77.69 (*d*); 80.55 (*d*); 128.04–128.80 (several *d*); 137.57, 137.68, 138.10 (3*s*); 167.32 (*s*, NC=O); 170.37 (*s*, OC=O). FAB-MS: 490 (39, $[M+1]^+$), 327 (44), 281 (76), 147 (100), 91 (83), 73 (89).

2,6-Di-O-*acetyl-5-amino-3,4-di*-O-*benzyl-5-deoxy*-D-*gluconolactam* (**38**). *a*) As described for the conversion of **35** to **36**, but on a 100-mg scale (0.186 mmol) and addition of BCl_3 within 2 min. The crude product was dissolved in pyridine (5 ml), treated with Ac_2O (0.1 ml, 1.1 mmol), stirred for 2 h at 23°, and evaporated at 40° (within *ca.* 1 h). FC (AcOEt/hexane 1:1) gave **37** (30 mg, 33%) and **38** (39 mg, 48%).

b) As described for the conversion of **35** to **36**, but on a 100-mg scale (0.186 mmol) in the absence of Bu_4NBr. For completion of the reaction, a third equiv. of BCl_3 had to be added. The crude product was dissolved in pyridine (1 ml), the soln. treated with Ac_2O (0.1 ml, 1.1 mmol) and stirred for 2 h, and the solvent evaporated as described in *a*). FC of the residue (AcOEt/hexane 1:1) gave **37** (57 mg, 63%) and **38** (21 mg, 26%).

c) As described in *b*), but using 1M BBr_3 in CH_2Cl_2 instead of 1M BCl_3. FC gave **37** (69 mg, 51%) and **38** (26 mg, 32%).

Data of **38**: R_f (AcOEt/hexane 1:1) 0.13. IR ($CHCl_3$): 3390*w*, 3008*w*, 2908*w*, 1747*s*, 1692*s*, 1603*w*, 1454*m*, 1371*m*, 1316*w*, 1111*m*, 1047*s*, 909*w*, 604*w*. ^{1}H-NMR ($CDCl_3$): 2.04, 2.06 (2*s*, 2 AcO); 3.59 (*ddd*, $J = 9.0, 6.2, 2.8$, H–C(5)); 3.69 (*t*, $J = 9.0$, irrad. at 4.01 → *d*, $J \approx 9.0$, H–C(4)); 3.91 (*dd*, $J = 11.5, 6.2$, H–C(6)); 4.01 (*t*, $J = 9.0$, H–C(3)); 4.32 (*dd*, $J = 11.5, 6.2$, H–C(6)); 4.63 (*d*, $J = 10.9$, PhC*H*); 4.74 (*d*, $J = 11.5$, PhC*H*); 4.87 (*d*, $J = 11.5$, PhC*H*); 4.91 (*d*, $J = 10.9$, PhC*H*); 5.28 (*d*, $J = 9.3$, irrad. at 4.01 → *s*, H–C(2)); 6.39 (br. *s*, NH); 7.26–7.39 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 20.69 (br. *q*, 2 Me); 54.88 (*d*, C(5)); 63.66 (*t*, C(6)); 72.11 (*d*); 74.94, 75.12 (2*t*, 2 PhCH_2); 76.28 (*d*); 80.36 (*d*); 128.20–128.85 (several *d*); 137.39, 137.92 (2*s*); 167.67 (*s*, NC=O); 170.34, 170.91 (2*s*, 2 OC=O).

5-Amino-3,4,6-tri-O-*benzyl-5-deoxy*-D-*gluconothiolactam* (**39**) *and 5-Amino-3,4-tri*-O-*benzyl-5-deoxy*-D-*mannonothiolactam* (**40**). A soln. of **36** (50 mg, 0.11 mmol) in toluene (4 ml) was treated with *Lawesson*'s reagent and stirred at r.t. for 13 h (TLC: no conversion of **36**) and at 80° for 2 h (TLC: complete conversion of **36**), leading mainly to polar compounds. Normal workup and FC (AcOEt/hexane 1:2) gave **39**/**40** 1:1 (4 mg, 8%). R_f (AcOEt/hexane 2:1) 0.78. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.14–3.21 (*m*, 0.5 H, H–C(5) of **39**); 3.41–3.69 (*m*, 4 H, H–C(4), 2 H–C(6), H–C(5), and H–C(3) of **40**); 3.78 (*t*, $J = 9.1$, 0.5 H, H–C(3) of **39**); 4.09–4.13 (*m*, 1.5 H, 3 PhC*H*); 4.25 (*d*, $J = 11.7$, 0.5 H, PhC*H*); 4.35–4.58 (*m*, H–C(2), OH, 3 PhC*H*); 4.65 (*d*, $J = 11.5$, 0.5 H, PhC*H*); 4.81 (*d*, $J = 11.3$, 0.5 H, PhC*H*); 4.89 (*d*, $J = 11.5$, 0.5 H, PhC*H*); 4.90 (*d*, $J = 11.7$, 0.5 H, PhC*H*); 5.09 (*d*, $J = 11.7$, 0.5 H, PhC*H*); 7.13–7.42 (*m*, 15 arom. H); 8.09 (*s*, 0.5 H, NH); 8.14 (*s*, 0.5 H, NH).

2-O-*Acetyl-5-amino-3,4,6-tri*-O-*benzyl-5-deoxy*-D-*gluconothiolactam* (**41**). *a*) A soln. of **37** (1.2 g, 2.45 mmol) in toluene (10 ml) was treated with *Lawesson*'s reagent (990 mg, 2.45 mmol) and stirred at 25° for 20 h. Normal workup, FC (AcOEt/hexane 1:2), and crystallization from Et_2O/hexane gave **41** (1.14 g, 92%). Colourless needles.

b) As described in *a*), but on a 631-mg scale and stirring for 2 h at 80°: **41** (600 mg, 92%). R_f (Et_2O/hexane 2:1) 0.51. M.p. 91°. IR ($CHCl_3$): 3361*w*, 3007*m*, 2978*w*, 2878*m*, 2867*m*, 1747*s*, 1597*m*, 1514*s*, 1454*m*, 1370*m*, 1313*m*, 1070*s*, 1028*w*, 910*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.10 (*s*, AcO); 3.27–3.32 (*m*, H–C(5)); 3.56–3.71 (*m*, H–C(4), 2 H–C(6)); 3.93 (*t*, $J = 8.0$, H–C(3)); 4.47 (*s*, PhCH_2); 4.47 (*d*, $J = 10.9$, PhC*H*); 4.76 (*s*, PhCH_2); 4.78 (*d*, $J = 10.9$, PhC*H*); 5.59 (*d*, $J = 8.1$, H–C(2)); 7.16–7.40 (*m*, 15 arom. H); 8.11 (br. *s*, exchange with CD_3OD, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.69 (*q*, Me); 58.09 (*d*, C(5)); 68.26 (*t*, C(6)); 73.04, 74.06, 74.12 (3*t*, 3 PhCH_2); 75.65, 76.15, 79.45 (3*d*, C(2), C(3), C(4)); 127.61–128.22 (several *d*); 136.66, 136.82, 137.23 (3*s*), 169.49 (*s*, C=O); 197.49 (*s*, C=S). CI-MS: 506 (3, $[M+1]$), 340 (3), 258 (4), 108 (86), 91 (100). Anal. calc. for $C_{29}H_{31}NO_5S$ (505.63): C 68.89, H 6.18, N 2.77; found: C 68.80, H 6.26, N 2.85.

2-O-*Acetyl-3,4,6-tri*-O-*benzyl-1,5-dideoxy-1-[(2,2-dimethoxyethyl)imino]-1,5-imino*-D-*glucitol and* -D-*mannitol* (**42** and **43**). A soln. of **41** (420 mg, 0.881 mmol) and $Hg(OAc)_2$ (300 mg, 0.941 mmol) in THF (5 ml) was treated at 0° with aminoacetaldehyde dimethyl acetal (0.5 ml, 4.6 mmol) and stirred at 0° for 1 h. Normal workup, filtration of the org. layer through *Celite*, drying ($MgSO_4$), and evaporation gave **42**/**43** 2:1 (371 mg, 73%). For characterization, 20 mg of this mixture was separated by FC (AcOEt/MeOH 20:1) to yield **42** (12 mg) and **43** (5 mg).

Data of **42**: R_f (AcOEt) 0.03. IR ($CHCl_3$): 3440*m*, 3370*w*, 3050*w*, 3010*m*, 2925*s*, 2870*s*, 1750*s*, 1649*s*, 1497*s*, 1453*s*, 1361*m*, 1261*w*, 1090*m*. ^{1}H-NMR ($CDCl_3$): 1.99 (*s*, AcO); 3.25–3.41 (*m*, irrad. at 4.45 → change, NCH_2); 3.25 (br. *s*, 2 MeO); 3.55–3.58 (*m*, H–C(5)); 3.68–3.81 (*m*, irrad. at 3.55 → change, 2 H–C(6)); 3.78 (*t*, $J = 9.0$, irrad. at 3.55 → *d*, $J \approx 8.5$, H–C(4)); 3.89 (*dd*, $J = 9.0$, 7.8, irrad. at 5.39 → *d*, $J \approx 9.0$, H–C(3)); 4.45 (*t*, $J = 5.3$, irrad. at 3.30 → *s*, NCH_2CH); 4.51–4.60 (*m*, 4 PhC*H*, NH); 4.80 (*d*, $J = 11.5$, PhC*H*); 4.82 (*d*, $J = 11.5$, PhC*H*); 5.39 (*d*, $J = 7.8$, irrad. at 3.89 → *s*, H–C(2)); 7.25–7.39 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.89 (*q*, Me); 42.52 (*t*, CH_2N); 54.05 (*q*, MeO); 54.33 (*q*, MeO); 61.51 (*d*, C(5)); 71.38 (*t*, C(6)); 72.69, 73.40, 74.75 (3*t*, 3 PhCH_2); 74.44 (*d*, C(2)); 78.31, 82.06 (2*d*, C(3), C(4)); 102.62 (*d*, $CH(OMe)_2$); 127.65–128.67 (several *d*); 137.51, 138.03, 138.51 (3*s*); 154.10 (*s*, C(1)); 171.50 (*s*, C=O).

Data of **43**: R_f (AcOEt) 0.01. IR ($CHCl_3$): 3445*m*, 3068*w*, 3002*m*, 2928*s*, 2868*s*, 1745*s*, 1645*s*, 1516*s*, 1497*s*, 1398*s*, 1360*m*, 1070*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.00 (*s*, AcO); 3.32–3.43 (*m*, irrad. at 4.46 → change, NCH_2); 3.33 (*s*, MeO); 3.35 (*s*, MeO); 3.55–3.60 (*m*, irrad. at 3.94 → change, H–C(5)); 3.66 (*dd*, *J* = 9.4, 4.4, irrad. at 3.58 → *d*, *J* = 9.5, H–C(6)); 3.71–3.79 (*m*, irrad. at 3.58 → change, H–C(6)); 3.87 (*dd*, *J* = 7.5, 3.4, irrad. at 5.52 → *d*, *J* ≈ 7.5, H–C(3)); 3.94 (br. *t*, *J* ≈ 7.5, irrad. at 3.58 → *d*, *J* ≈ 7.0, H–C(4)); 4.46 (*t*, *J* = 5.6, irrad. at 3.40 → *s*, C*H*$(OMe)_2$); 4.49–4.61 (*m*, 5 PhC*H*); 4.78 (*d*, *J* = 11.2, PhC*H*); 5.52 (*d*, *J* = 3.4, H–C(2)); 7.25–7.39 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.44 (*q*, Me); 42.09 (*t*, CH_2N); 53.55 (*q*, Me); 53.83 (*q*, Me); 60.91 (*d*, C(5)); 66.91 (*t*, C(6)); 71.61 (br. *t*, 2 Ph*C*H_2); 72.69 (*t*, Ph*C*H_2); 73.23, 74.08, 77.04 (3*d*, C(2), C(3), C(4)); 102.48 (*d*, *C*H$(OMe)_2$); 127.03–128.11 (several *d*); 137.57, 138.14, 138.61 (3*s*); 153.03 (*s*, C(1)); 171.51 (*s*, C=O).

*(5*R*,6*R*,7*R*,8*S*)- and (5*R*,6*R*,7*R*,8*R*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6-7,8-tetrahydroimidazo[1,2-*a*]pyridin-8-ol* (**44** and **45**). *a*) A soln. of **42**/**43** 2:1 (350 mg, 0.61 mmol) and $TsOH \cdot H_2O$ (500 mg) in toluene (25 ml) was treated with H_2O (0.5 ml) and stirred at 80° for 12 h. Workup (Et_2O, sat. aq. K_2CO_3 soln.) and FC (AcOEt) gave **44**/**45** 1:1 (212 mg, 67%). A sample (100 mg) of this mixture was separated by FC (AcOEt/hexane 3:1) to yield **44** (47 mg) and **45** (45 mg).

b) As described in *a*), but on a smaller scale (20 mg of **42**/**43** 2:1): **44**/**45** 5:3 (12 mg, 71%).

Data of **44**: R_f (AcOEt/hexane 1:1) 0.12. ^{1}H-NMR ($CDCl_3$): 3.73 (*dd*, *J* = 10.6, 5.3, CH–C(5)); 3.85 (*dd*, *J* = 10.3, 2.8, CH–C(5)); 3.95 (*dd*, *J* = 8.7, 7.5, H–C(6)); 4.06 (*dd*, *J* = 8.7, 7.2, irrad. at 4.96 → *d*, *J* ≈ 8.5, H–C(7)); 4.17 (*ddd*, *J* = 7.5, 5.0, 2.8, H–C(5)); 4.44 (*s*, PhCH_2); 4.57 (*d*, *J* = 11.8, PhC*H*); 4.89 (*d*, *J* = 11.2, PhC*H*); 4.95 (*d*, *J* = 11.2, PhC*H*); 4.96 (*d*, *J* = 7.3, irrad. at 4.06 → *s*, H–C(8)); 5.15 (*d*, *J* = 11.5, PhC*H*); 7.04, 7.11 (2*d*, *J* = 1.3, H–C(2), H–C(3)); 7.20–7.47 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 58.71 (*d*, C(5)); 68.02 (*d*, C(8)); 68.83 (*t*, *C*H_2–C(5)); 73.40, 73.92, 74.99 (3*t*, 3 Ph*C*H_2); 75.47, 82.95 (2*d*, C(6), C(7)); 117.25 (*d*, C(3)); 127.99–128.27 (several *d*); 129.27 (*d*, C(2)); 137.65, 137.95, 138.84 (3*s*); 147.48 (*s*, C(8a)). FAB-MS: 497 (100, $[M+1]^+$).

Data of **45**: R_f (AcOEt/hexane 1:1) 0.10. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.70 (*dd*, *J* = 10.0, 6.5, CH–C(5)); 3.80 (*dd*, *J* = 10.0, 3.1, CH–C(5)); 3.97 (*dd*, *J* = 8.1, 3.4, H–C(7)); 4.16 (*ddd*, *J* = 7.8, 6.5, 3.4, H–C(5)); 4.22 (*dd*, *J* = 7.8, 6.5, H–C(6)); 4.44 (*s*, PhCH_2); 4.61 (*d*, *J* = 11.2, PhC*H*); 4.73 (*d*, *J* = 11.8, PhC*H*); 4.85 (*d*, *J* = 11.8, PhC*H*); 4.94 (*d*, *J* = 11.5, PhC*H*); 5.16 (*d*, *J* = 3.43, H–C(8)); 7.02, 7.11 (2*d*, *J* = 1.3, H–C(2), H–C(3)); 7.21–7.39 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 59.39, 62.65 (2*d*, C(5), C(8)); 71.03 (*t*, *C*H_2–C(5)); 72.56, 73.42, 74.65 (3*t*, 3 Ph*C*H_2); 73.79, 79.37 (2*d*, C(6), C(7)); 118.57 (*m*, C(3)); 128.04–128.73 (several *d*); 129.25 (*d*, C(2)); 137.73 (*s*); 138.07 (br. *s*); 145.40 (*s*, C(8a)).

*(5*R*,6*R*,7*R*,8*S*)- and (5*R*,6*R*,7*R*,8*R*)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**46** and **47**). *a*) According to [34], a soln. of **44** (100 mg, 0.21 mmol) and Bu_3P (62 µl, 0.25 mmol) in THF (10 ml) was cooled to 0°, treated with 4% HN_3 in toluene (310 µl, 0.208 mmol) and DEAD (39 µl, 0.25 mmol), and stirred at 23° for 2 h. Normal workup and FC (AcOEt/hexane 1:3 → 1:1) gave **46** (82 mg, 78%). Colourless oil.

b) As described in *a*), but with **44**/**45** 1:1: **46** (78 mg, 74%).

c) As described in *a*), but with **45** (20 mg, 0.0426 mmol): **46** (19 mg, 72%).

d) As described in *a*), but saturating the mixture with HN_3[14]) instead of adding a 4% soln. in toluene: **46**/**47** *ca.* 1:1 (76 mg, 72%).

e) As described in *d*), but with **44**/**45** 1:1: **46**/**47** 5:4 (79 mg, 75%).

f) As described in *d*), but with **45** (20 mg, 0.043 mmol): **46**/**47** 6:4 (18 mg, 68%).

Data of **46**: R_f (AcOEt/hexane 1:1) 0.38. IR ($CHCl_3$): 3004*m*, 2872*w*, 2108*s*, 1743*w*, 1605*w*, 1535*m*, 1496*m*, 1454*m*, 1367*w*, 1110*s*, 1034*w*, 931*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.68 (*dd*, *J* = 10.3, 5.0, CH–C(5)); 3.79 (*dd*, *J* = 10.3, 3.1, CH–C(5)); 3.89 (*dd*, *J* = 8.1, 6.9, H–C(7)); 3.96 (*dd*, *J* = 8.1, 7.2, H–C(6)); 4.13–4.18 (*m*, H–C(5)); 4.39 (*d*, *J* = 12.1, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*), 4.55 (*d*, *J* = 11.2, PhC*H*); 4.73 (*d*, *J* = 6.5, H–C(8)); 4.79 (*d*, *J* = 11.2, PhC*H*); 4.87 (*d*, *J* = 10.9, PhC*H*); 4.88 (*d*, *J* = 11.5, PhC*H*); 7.02, 7.12 (2*d*, *J* = 1.3, H–C(2), H–C(3)); 7.13–7.36 (*m*, 15 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 58.84, 59.09 (2*d*, C(5), C(8)); 68.78 (*t*, *C*H_2–C(5)); 73.42, 74.65, 74.92 (3*t*, 3 Ph*C*H_2); 75.36, 80.84 (2*d*, C(6), C(7)); 118.18 (*d*, C(3)); 127.87–128.81 (several *d*); 130.24 (*d*, C(2)); 137.48 (*s*); 137.55 (br. *s*); 141.30 (*s*, C(8a)).

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[14]) Carried out by treating NaN_3 with conc. H_2SO_4 and passing the HN_3 gas by means of a *Teflon* tube through the reaction mixture at 0° during 30 min. A HN_3 concentration of 2.6M was determined by titration (NaOH/phenolphthaleine).

Data of **47**: R_f (AcOEt/hexane 1:1) 0.35. IR ($CHCl_3$): 3008*m*, 2869*w*, 2106*s*, 1739*w*, 1602*w*, 1549*w*, 1496*m*, 1454*m*, 1366*w*, 1100*s*, 1038*w*, 931*w*. ^{1}H-NMR ($CDCl_3$): 3.66 (*dd*, *J* = 10.3, 6.2, CH−C(5)); 3.75 (*dd*, *J* = 10.3, 3.4, CH−C(5)); 4.00 (*dd*, *J* = 8.4, 4.1, irrad. at 4.91 → *d*, *J* ≈ 8.0, H−C(7)); 4.09–4.15 (*m*, irrad. at 4.00 → change, H−C(5), H−C(6)); 4.43 (*d*, *J* = 11.8, PhC*H*); 4.48 (*d*, *J* = 11.8, PhC*H*); 4.59 (*d*, *J* = 11.2, PhC*H*); 4.71 (*d*, *J* = 11.8, PhC*H*); 4.79 (*d*, *J* = 11.8, PhC*H*); 4.88 (*d*, *J* = 11.5, PhC*H*); 4.91 (*d*, *J* = 3.7, irrad. at 4.00 → *s*, H−C(8)); 7.09, 7.11 (2*d*, *J* = 1.3, H−C(2), H−C(3)); 7.21–7.39 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 55.75 (*d*, C(5)); 59.17 (*d*, C(8)); 70.31 (*t*, *C*H_2−C(5)); 73.11, 73.42, 74.65 (3*t*, 3 Ph*C*H_2); 77.35, 78.60 (2*d*, C(6), C(7)); 119.12 (*d*, C(3)); 128.02–128.88 (several *d*); 130.22 (*d*, C(2)); 137.34, 137.70, 137.71 (3*s*); 140.77 (*s*, C(8a)). FAB-MS: 497 (100, $[M+1]^+$).

*(5*R*,6*R*,7*R*,8*S*)-8-Amino-5,6,7,8-tetrahydro-5-(hydroxymethyl)imidazo[1,2-*a*]pyridine-6,7-diol* (**1**). A soln. of **46** (72 mg, 0.145 mmol) in AcOEt/MeOH/AcOH 1:1:1 (2 ml) was hydrogenated in the presence of 10% Pd/C (31 mg) at 6 bar during 24 h. After filtration and evaporation, the crude was dissolved in 0.01M HCl (3 ml) and treated with activated charcoal (5 mg). Filtration, lyophilization, and ion-exchange chromatography (*Amberlite CG-120* (NH_4^+ form), 0.1M NH_4OH) gave **1** (27 mg, 79%). Colourless, highly hygroscopic solid, which turned yellow upon standing. R_f (AcOEt/MeOH/H_2O 5:5:1) 0.05. ^{1}H-NMR (D_2O): 3.90 (*t*, *J* = 9.3, H−C(6)); 3.98–4.31 (*m*, H−C(5), H−C(7), H−C(8), CH_2−C(5)); 7.15, 7.35 (2*d*, *J* = 1.6, H−C(2), H−C(3)). ^{1}H-NMR (300 MHz, D_2O, 1 equiv. of CF_3CO_2H): 4.05–4.15 (*m*, CH−C(5), H−C(6), H−C(7)); 4.12–4.28 (*m*, H−C(5), CH−C(5)); 4.67 (br. *d*, *J* = 7.5, H−C(8)); 7.45, 7.60 (2*d*, *J* = 2.0, H−C(2), H−C(3)). ^{1}H-NMR (500 MHz, D_2O, 5 equiv. of HCl): 4.10 (*dd*, *J* = 13.0, 4.1, CH−C(5)); 4.18 (*dd*, *J* = 8.6, 7.1, H−C(6)); 4.23 (*t*, *J* ≈ 7.9, H−C(7)); 4.26 (*dd*, *J* = 13.0, 2.9, CH−C(5)); 4.36–4.39 (*m*, H−C(5)); 4.82 (*d*, *J* = 7.9, H−C(8)); 7.62, 7.77 (2*d*, *J* = 2.0, H−C(2), H−C(3)). ^{13}C-NMR (125 MHz, D_2O): 50.70 (*d*, C(8)); 61.53 (*t*, *C*H_2−C(5)); 65.47 (*d*, C(5)); 69.63, 71.54 (2*d*, C(6), C(7)); 124.01, 125.10 (2*d*, C(2), C(3)); 140.23 (*s*, C(8a)). CI-MS: 200 (11, $[M+1]^+$), 177 (100). Anal. calc. for $C_8H_{13}N_3O_3 \cdot 1.5\,H_2O$ (226.24): C 42.47, H 7.12, N 18.57; found: C 42.12, H 6.82, N 18.67.

*(5*R*,6*R*,7*S*,8*S*)-8-Acetoxy-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro[1,2,4]triazolo[1,2-*a*]pyridine* (**49**). A soln. of **41** (100 mg, 0.198 mmol) and $Hg(OAc)_2$ (80 mg, 0.25 mmol) in THF (2 ml) was cooled to 0°, treated with formylhydrazine[15]) (120 mg, 1.99 mmol), and stirred at 23° for 3 h. Filtration through *Celite*, normal workup, and FC (AcOEt) gave **49** (91 mg, 89%). Colourless oil that crystallized upon standing. R_f (AcOEt) 0.30. IR ($CHCl_3$): 3008*w*, 2870*m*, 1742*s*, 1455*m*, 1428*m*, 1100*s*, 1029*m*, 909*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.06 (*s*, AcO); 3.62 (*dd*, *J* = 10.0, 7.5, CH−C(5)); 3.73 (*dd*, *J* = 9.6, 2.8, CH−C(5)); 3.86 (*dd*, *J* = 6.0, 5.6, H−C(6)); 4.14 (*dd*, *J* = 6.2, 5.0, irrad. at 6.21 → *d*, *J* ≈ 6.0, H−C(7)); 4.36–4.41 (*m*, H−C(5)); 4.41 (*d*, *J* = 11.8, PhC*H*); 4.47 (*d*, *J* = 11.8, PhC*H*); 4.48 (*d*, *J* = 11.5, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.73 (*d*, *J* = 12.1, PhC*H*); 4.81 (*d*, *J* = 11.5, PhC*H*); 6.21 (*d*, *J* = 5.0, H−C(8)); 7.16–7.38 (*m*, 15 arom. H); 8.32 (*s*, H−C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.89 (*s*, Me); 58.08 (*d*, C(5)); 64.80 (*d*, C(8)); 69.46 (*t*, *C*H_2−C(5)); 73.63, 73.65, 73.84 (3*t*, 3 Ph*C*H_2); 74.73, 76.93 (2*d*, C(6), C(7)); 128.12–128.91 (several *d*); 137.05, 137.10, 137.29 (3*s*); 142.71 (*d*, C(3)); 147.90 (*s*, C(8a)); 170.31 (*s*, C=O). FAB-MS: 514 (100, $[M+1]^+$).

*(5*R*,6*R*,7*R*,8*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-8-ol* (**50**). A soln. of **49** (60 mg, 0.12 mmol) in THF (1 ml) was treated with 2M NH_3 in MeOH (1 ml) and kept at 40° in a stoppered flask for 30 min. Evaporation and normal workup gave **50** (55 mg, 98%), which was used for the next step without further purification. R_f (AcOEt) 0.12. IR ($CHCl_3$): 3533*m*, 3324*m* (br.), 3090*m*, 3007*s*, 2870*m*, 1498*m*, 1454*m*, 1364*m*, 1104*s*, 1028*m*, 911*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.83 (br. *s*, exchange with CD_3OD, OH); 3.60 (*dd*, *J* = 10.0, 7.5, CH−C(5)); 3.71 (*dd*, *J* = 10.3, 3.4, CH−C(5)); 3.88 (*dd*, *J* = 6.8, 5.6, H−C(6)); 4.10 (*dd*, *J* = 6.8, 5.6, irrad. at 5.09 → *d*, *J* ≈ 7.0, H−C(7)); 4.33–4.37 (*m*, H−C(5)); 4.40 (*d*, *J* = 11.8, PhC*H*); 4.47 (*d*, *J* = 11.8, PhC*H*); 4.56 (*d*, *J* = 11.5, PhC*H*); 4.71 (*d*, *J* = 11.6, PhC*H*); 4.80 (*d*, *J* = 11.5, PhC*H*); 4.92 (*d*, *J* = 11.5, PhC*H*); 5.09 (br. *d*, *J* = 5.6, H−C(8)); 7.19–7.39 (*m*, 15 arom. H); 8.30 (*s*, H−C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 57.84 (*d*, C(5)); 65.25 (C(8)); 69.60 (*t*, *C*H_2−C(5)); 73.65 (*t*, Ph*C*H_2); 74.13 (br. *t*, 2 Ph*C*H_2); 74.75, 79.76 (2*d*, C(6), C(7)); 128.21–128.91 (several *d*); 136.93, 137.13, 137.71 (3*s*); 142.21 (*d*, C(3)); 152.04 (*s*, C(8a)). CI-MS (NH_3): 472 (15, $[M+1]^+$), 380 (23), 91 (100).

*(5*R*,6*R*,7*R*,8*R*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-8-ol* (**55**). As described for **49**, with **61** (63 mg, 0.123 mmol): **55** (58 mg, quant.). R_f (AcOEt) 0.10. IR ($CHCl_3$): 3572*w*, 3321*w* (br.), 3008*m*, 2927*m*, 2869*m*, 1953*w*, 1811*w*, 1604*w*, 1497*m*, 1454*m*, 1364*m*, 1307*w*, 1265*m*, 1098*s*, 1028*m*, 1010*w*, 911*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.67 (*d*, *J* = 6.2, CH_2−C(5)); 4.00 (*dd*, *J* = 6.9, 4.4, H−C(6)); 4.08 (*dd*, *J* = 6.9, 3.4, irrad. at 5.33 → *d*, *J* = 6.9, H−C(7)); 4.29 (*td*, *J* = 6.2, 4.4, H−C(5)); 4.42 (*d*, *J* = 11.8, PhC*H*), 4.50 (*d*, *J* = 11.8, PhC*H*); 4.55 (*d*, *J* = 11.8, PhC*H*); 4.71 (*d*, *J* = 12.5, PhC*H*); 4.75 (*d*, *J* = 12.4, PhC*H*);

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[15]) *Fluka purum*, recrystallized from toluene.

4.90 (*d*, *J* = 12.1, PhC*H*); 5.33 (*d*, *J* = 3.1, H–C(8)); 5.33 (br. *s*, exchange with CD_3OD, OH); 7.17–7.40 (*m*, 15 arom. H); 8.36 (*s*, H–C(3)). ^{1}H-NMR (300 MHz, $CDCl_3$, 5% CD_3OD): 3.62–3.66 (*m*, CH_2–C(5)); 3.98–3.99 (*m*, C(6), C(7)); 4.20–4.28 (*m*, C(5)); 4.41 (*d*, *J* = 11.8, PhC*H*); 4.48 (*d*, *J* = 11.8, PhC*H*); 4.54 (*d*, *J* = 11.5, PhC*H*); 4.66 (*d*, *J* = 11.8, PhC*H*); 4.76 (*d*, *J* = 11.8, PhC*H*); 4.84 (*d*, *J* = 11.8, PhC*H*); 5.22 (br. *s*, H–C(8)); 7.14–7.38 (*m*, 15 arom. H); 8.35 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 58.49 (*d*, C(5)); 62.08 (*d*, C(8)); 71.09 (*t*, CH_2–C(5)); 73.65 (br. *t*, 3 Ph*C*H_2); 73.87, 76.78 (2*d*, C(6), C(7)); 128.20–128.89 (several *d*); 137.27, 137.27, 137.82 (3*s*); 142.84 (*d*, C(3)); 152.04 (*s*, C(8a)).

Trifluoromethanesulfonation of **50**: A soln. of **50** (20 mg, 0.0424 mmol) in CH_2Cl_2 (2 ml) containing 100 µl of pyridine was treated with Tf_2O (10 µl, 0.0636 mmol) at −78°. The mixture was allowed to reach 0° within 1 h and the solvent evaporated at 0° by passing a N_2 stream through the mixture. The resulting reddish solid (23 mg) contained the triflates **53**/**54** in a ratio of 1:1 (by ^{1}H-NMR: integration of H–C(8) signals at 6.01 and 6.24 ppm). Normal workup of this solid gave **50**/**55** 7:2 (16 mg, 89%).

*(5*R*,6*R*,7*S*,8*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro-8-[(methylsulfonyl)oxy]-[1,2,4]triazolo[4,3-*a*]pyridin* (**52**). At 0°, a soln. of **50** (50 mg, 0.11 mmol) in pyridine (0.5 ml) was treated with MsCl (40 µl, 0.5 mmol) and stirred for 30 min. After treatment with ice and H_2O, normal workup gave **52** (59 mg, 98%), which was used for the next step without further purification. R_f (AcOEt) 0.31. IR ($CHCl_3$): 3067*m*, 3008*m*, 2936*m*, 2870*m*, 1953*w*, 1811*w*, 1732*w*, 1603*w*, 1498*m*, 1454*m*, 1367*s*, 1336*m*, 1177*s*, 1099*s*, 1016*m*, 973*m*, 949*s*, 842*m*, 528*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.41 (*s*, $MeSO_2$); 3.58 (*dd*, *J* = 10.0, 7.8, CH–C(5)); 3.69 (*dd*, *J* = 10.0, 3.1, CH–C(5)); 3.84 (*dd*, *J* = 5.9, 5.0, H–C(6)); 4.29 (*dd*, *J* = 5.9, 4.4, irrad. at 5.96 → *d*, *J* = 5.9, H–C(7)); 4.39 (*d*, *J* = 11.8, PhC*H*); 4.37–4.42 (*m*, H–C(5)); 4.44 (*d*, *J* = 11.5, PhC*H*); 4.46 (*d*, *J* = 12.1, PhC*H*); 4.68 (*d*, *J* = 11.5, PhC*H*); 4.77 (*d*, *J* = 11.5, PhC*H*); 4.90 (*d*, *J* = 11.2, PhC*H*); 5.96 (*d*, *J* = 4.7, H–C(8)); 7.18–7.24 (*m*, 4 arom. H); 7.25–7.36 (*m*, 11 arom. H); 8.35 (*s*, H–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 39.90 (*q*, $MeSO_2$); 58.70 (*d*, C(5)); 69.46 (*t*, CH_2–C(5)); 70.99 (*d*, C(8)); 73.58, 73.68, 74.29 (3*t*, 3 Ph*C*H_2); 73.74, 77.09 (2*d*, C(6), C(7)); 128.21–128.93 (several *d*); 136.66, 136.82, 137.00 (3*s*); 143.10 (*d*, C(3)); 146.71 (*s*, C(8a)).

*(5*R*,6*R*,7*R*,8*S*)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine* (**51**). *a*) A soln. of **52** (36 mg, 0.066 mmol) in DMF (1 ml) was treated with NaN_3 (50 mg, 0.72 equiv.) and stirred at 70° for 2 h. After addition of toluene (5 ml), the mixture was filtered through *Celite*. Evaporation and FC (AcOEt) gave **51** (31 mg, 95%).

b) As described in *a*), with NaN_3 (5 mg, 0.078 mmol), DMF (20 ml), and stirring during 24 h at 100°: **51** (5 mg, 46%) and recovered **52** (3 mg, 25%).

c) A soln. of **50** (25 mg, 0.053 mmol) and Bu_3P (16 µl 0.065 mmol) in THF (3 ml) was saturated at 0° with HN_3, treated with DEAD (10 µl, 0.064 mmol), and stirred at 70° for 4 h (stoppered flask). Normal workup and FC gave **51** (5 mg, 19%) and recovered **50** (14 mg, 56%). **51**: R_f (AcOEt) 0.31. IR ($CHCl_3$): 3067*m*, 3008*m*, 2927*m*, 2668*m*, 2112*s*, 1667*w*, 1602*w*, 1498*m*, 1454*m*, 1363*m*, 1305*w*, 1102*s*, 1028*w*, 929*w*, 912*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.58 (*dd*, *J* = 10.0, 8.1, CH–C(5)); 3.64 (*dd*, *J* = 10.0, 3.7, CH–C(5)); 3.96 (*dd*, *J* = 7.5, 5.0, H–C(6)); 4.03 (*dd*, *J* = 7.2, 3.7, irrad. at 4.93 → *d*, *J* = 7.5, H–C(7)); 4.23–4.27 (*m*, H–C(5)); 4.41 (*d*, *J* = 11.8, PhC*H*); 4.50 (*d*, *J* = 11.8, PhC*H*); 4.58 (*d*, *J* = 11.5, PhC*H*); 4.67 (*d*, *J* = 11.5, PhC*H*); 4.75 (*d*, *J* = 11.8, PhC*H*); 4.78 (*d*, *J* = 11.8, PhC*H*); 4.93 (*d*, *J* = 3.7, H–C(8)); 7.17–7.41 (*m*, 15 arom. H); 8.39 (*s*, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 53.49 (*d*, C(5)); 58.16 (*d*, C(8)); 70.34 (*t*, CH_2–C(5)); 73.13 (*d*); 73.68, 73.79, 74.08 (3*t*, 3 Ph*C*H_2); 76.75 (*d*); 128.20–129.01 (several *d*); 136.98, 137.04, 137.10 (3*s*); 143.29 (*d*, C(3)); 147.56 (*s*, C(8a)). CI-MS (NH_3): 497 (6, $[M+1]^+$), 239 (22), 91 (100).

*(5*R*,6*R*,7*R*,8*R*)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine* (**56**). As described for **52**, with **62** (12 mg, 0.0218 mmol), DMF (0.5 ml), and NaN_3 (12 mg, 0.185 mmol): **56** (10 mg, 92%). R_f (AcOEt) 0.45. IR ($CHCl_3$): 3068*w*, 3008*m*, 2927*m*, 2869*m*, 2111*s*, 1694*w*, 1497*m*, 1455*m*, 1362*m*, 1261*m*, 1097*s*, 1013*m*, 909*m*, 602*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.59 (*dd*, *J* = 10.3, 6.9, CH–C(5)); 3.72 (*dd*, *J* = 10.3, 2.8, CH–C(5)); 3.86 (*dd*, *J* = 7.5, 6.2, irrad. at 3.95 → *d*, *J* ≈ 6.2, H–C(6)); 3.95 (*dd*, *J* = 7.2, 6.2, irrad. at 4.85 → *d*, *J* ≈ 7.5, H–C(7)); 4.27 (*td*, *J* = 6.5, 2.8, H–C(5)); 4.39 (*d*, *J* = 11.8, PhC*H*); 4.46 (*d*, *J* = 12.1, PhC*H*); 4.53 (*d*, *J* = 11.5, PhC*H*); 4.56 (*d*, *J* = 11.8, PhC*H*); 4.84 (*d*, *J* = 11.8, 2 PhC*H*); 4.85 (*d*, *J* = 6.2, irrad. at 3.95 → *s*, H–C(8)); 7.14–7.43 (*m*, 15 arom. H); 8.31 (*s*, H–C(3)). ^{13}C-NMR ($CDCl_3$): 56.09 (br. *d*, C(5), C(8)); 68.84 (*t*, CH_2–C(5)); 73.65, 74.31, 74.78 (3*t*, 3 Ph*C*H_2); 74.76, 79.39 (2*d*, C(6), C(7)); 128.23–128.93 (several *d*); 136.97 (br. *s*); 142.53 (*d*, C(3)); 147.92 (*s*, C(8a)).

Transformation of **50** *to Azides* **51**/**56**. A soln. of **50** (23 mg, 0.0488 mmol) and pyridine (20 µl) in CH_2Cl_2 (2 ml) was cooled to −78°, treated with Tf_2O (16 µl, 0.1 mmol), allowed to reach 0° within 1 h, cooled to −78°, and treated with a suspension of NaN_3 (6.3 mg, 0.098 mmol) in CH_2Cl_2 (2 ml). The mixture was allowed to reach 23° within *ca.* 2 h. Normal workup gave **56**/**51** 4:1 (13 mg, 54%). The same procedure was repeated twice, leading to **56**/**51** 1:10 (48%) and 3:7 (32%).

5-Amino-3,4,6-tri-O-*benzyl-5-deoxy*-D-*mannonolactam* (**58**). As described for **36**, with **57** (600 mg, 0.558 mmol): **58** (424 mg, 85%). Colourless oil. R_f (AcOEt/hexane 2:1) 0.51. IR ($CHCl_3$): 3453*w* (br.), 3394*m*, 3089*w*, 3066*w*, 2868*m*, 1496*s*, 1454*w*, 1361*m*, 1310*m*, 1262*m*, 1093*m*, 1073*s*, 1028*m*, 909*w*. ^{1}H-NMR ($CDCl_3$): 3.45 (*t*, *J* = 9.0, H–C(6)); 3.49 (*dd*, *J* = 4.1, 3.1, H–C(4)); 3.51 (*dd*, *J* = 9.3, 4.1, H–C(6)); 3.61–3.66 (*m*, H–C(5)); 4.11 (*t*, *J* = 3.1, irrad. at 4.44 → *d*, *J* ≈ 3.0, H–C(3)); 4.31 (*d*, *J* = 11.5, PhC*H*); 4.44 (*d*, *J* = 11.5, PhC*H*); 4.44 (*d*, *J* = 3.1, irrad. at 4.11 → *s*, H–C(2)); 4.45 (br. *s*, exchange with CD_3OD, OH); 4.47 (*s*, PhCH_2); 4.63 (*d*, *J* = 12.1, PhC*H*); 4.83 (*d*, *J* = 12.1, PhC*H*); 6.19 (*s*, exchange with CD_3OD, NH); 7.17–7.20 (*m*, 2 arom. H); 7.21–7.42 (*m*, 13 arom. H). ^{13}C-NMR ($CDCl_3$): 55.15 (*d*, C(5)); 69.06 (*d*, C(2)); 70.58 (*t*, C(6)); 71.63, 73.32, 73.80 (3*t*, 3 Ph*C*H$_2$); 75.63, 77.07 (2*d*, C(3), C(4)); 127.87–128.58 (several *d*); 137.06, 137.32, 138.06 (3*s*); 171.83 (*s*, C=O). FAB-MS: 448 (100, $[M+1]^+$).

2-O-*Acetyl-5-amino-3,4,6-tri*-O-*benzyl-5-deoxy*-D-*mannonolactam* (**59**). As described for **37**, with **58** (872 mg, 1.86 mmol): **59** (950 mg, 98%) which was used for the next reaction without further purification. R_f (AcOEt/hexane 2:1) 0.53. IR ($CHCl_3$): 3393*m*, 3089*w*, 3067*m*, 3008*m*, 2920*m*, 2867*m*, 1749*s*, 1687*s*, 1496*w*, 1454*m*, 1371*m*, 1318*w*, 1094*s*, 1028*m*, 909*m*. ^{1}H-NMR ($CDCl_3$): 2.21 (*s*, AcO); 3.44 (*t*, *J* = 9.0, H–C(6)); 3.51 (*dd*, *J* = 9.3, 4.7, H–C(6)); 3.57 (br. *t*, *J* = 4.1, H–C(4)); 3.66–3.71 (*m*, H–C(5)); 4.04 (*dd*, *J* = 4.1, 3.1, irrad. at 5.65 → *d*, *J* = 4.1, H–C(3)); 4.41 (*d*, *J* = 11.8, PhC*H*); 4.44 (*d*, *J* = 11.5, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.54 (*d*, *J* = 11.8, 2 PhC*H*); 4.70 (*d*, *J* = 12.1, PhC*H*); 5.65 (*d*, *J* = 3.1, H–C(2)); 6.01 (br. *s*, exchange with CD_3OD, NH); 7.19–7.39 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 20.95 (*q*, Me); 55.46 (*d*, C(5)); 69.70 (*d*, C(2)); 70.99 (*t*, C(6)); 72.16, 73.10, 73.44 (3*t*, 3 Ph*C*H$_2$); 77.69, 80.55 (2*d*, C(3), C(4)); 128.10–129.95 (several *d*); 137.29, 137.63, 137.70 (3*s*); 166.98 (*s*, NC=O); 170.29 (*s*, OC=O). FAB-MS: 490 (21, $[M+1]^+$), 281 (76), 147 (100), 91 (83), 73 (89).

2-O-*Acetyl-5-amino-3,4,6-tri*-O-*benzyl-5-deoxy*-D-*mannonothiolactam* (**60**). As described for **41**, the conversion of **59** (480 mg, 1.073 mmol) with *Lawesson*'s reagent (240 mg, 2.45 mmol) in toluene (5 ml) gave **60** (458 mg, 92%). Yellowish oil. R_f (AcOEt/hexane 1:3) 0.52. IR ($CHCl_3$): 3362*m*, 3069*w*, 3067*w*, 3008*m*, 2916*m*, 2868*m*, 1953*w*, 1748*s*, 1599*w*, 1520*s*, 1497*s*, 1454*m*, 1370*m*, 1316*m*, 1096*s*, 910*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.24 (*s*, AcO); 3.44 (*t*, *J* = 9.3, H–C(6)); 3.52 (*dd*, *J* = 9.3, 3.7, H–C(6)); 3.57–3.64 (*m*, H–C(4), H–C(5)); 3.99 (*dd*, *J* = 4.0, 3.1, irrad. at 5.83 → *d*, *J* = 4.0, H–C(3)); 4.39 (*d*, *J* = 11.5, PhC*H*); 4.46 (*d*, *J* = 11.8, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 4.56 (*d*, *J* = 11.8, PhC*H*); 4.58 (*d*, *J* = 11.8, PhC*H*); 4.77 (*d*, *J* = 12.1, PhC*H*); 5.83 (*d*, *J* = 3.1, H–C(2)); 7.18–7.40 (*m*, 15 arom. H); 8.20 (br. *s*, exchange with CD_3OD, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.18 (*q*, Me); 58.49 (*d*, C(5)); 69.73 (*t*, C(6)); 72.58, 73.05, 73.50 (3*t*, 3 Ph*C*H$_2$); 73.84, 74.41, 76.35 (3*d*, C(2), C(3), C(4)); 128.17–128.83 (several *d*); 137.21, 137.32, 137.69 (3*s*); 170.08 (*s*, C=O); 197.81 (*s*, C=S).

*(5*R*,6*R*,7*S*,8*R*)-8-Acetoxy-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine* (**61**). As described for **49**, the reaction of **60** (100 mg, 0.198 mmol) with $Hg(OAc)_2$ (90 mg, 0.245 mmol) and formylhydrazine (60 mg, 1.0 mmol) in THF (2 ml) gave **61** (73 mg, 76%). R_f (AcOEt) 0.21. IR ($CHCl_3$): 3008*m*, 2870*w*, 1749*s*, 1498*m*, 1454*m*, 1371*m*, 1112*s*, 1071*s*, 1045*m*, 946*w*, 910*w*, 836*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.16 (*s*, AcO); 3.62 (*dd*, *J* = 9.7, 7.8, CH–C(5)); 3.73 (*dd*, *J* = 10.0, 3.4, CH–C(5)); 3.87 (*dd*, *J* = 7.8, 5.6, H–C(6)); 4.08 (*dd*, *J* = 8.1, 3.7, irrad. at 6.61 → *d*, *J* ≈ 8.1, H–C(7)); 4.25 (*ddd*, *J* = 8.0, 5.3, 3.4, H–C(5)); 4.44 (*d*, *J* = 11.8, PhC*H*); 4.50 (*d*, *J* = 12.5, PhC*H*); 4.54 (*d*, *J* = 11.5, PhC*H*); 4.57 (*d*, *J* = 11.5, PhC*H*); 4.78 (*d*, *J* = 11.2, PhC*H*); 4.84 (*d*, *J* = 11.5, PhC*H*); 6.61 (*d*, *J* = 3.7, H–C(8)); 7.21–7.39 (*m*, 15 arom. H); 8.40 (*s*, H–C(3)). ^{1}H-NMR (75 MHz, $CDCl_3$): 20.91 (*q*, Me); 58.39 (*d*, C(5)); 61.11 (*d*, C(8)); 70.33 (*t*, *C*H$_2$–C(5)); 73.10, 76.80 (2*d*, C(6), C(7)); 73.16, 73.64, 74.28, (3*t*, 3 PhCH_2); 128.15–129.30 (several *d*); 137.16 (*s*); 137.18 (br. *s*); 143.08 (*d*, C(3)); 148.05 (*s*, C(8a)); 169.81 (*s*, C=O).

*(5*R*,6*R*,7*S*,8*R*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydro-8-[(methylsulfonyl)oxy][1,2,4]-triazolo[4,3-*a*]pyridine* (**62**). As described for **52**, with **55** (58 mg, 0.123 mmol) and MsCl (30 µl, 0.386 mmol) in pyridine (1 ml): **62** (57 mg, 84%). R_f (AcOEt) 0.26. IR ($CHCl_3$): 3150*w*, 3066*m*, 3008*m*, 2928*m*, 2869*m*, 1952*w*, 1869*w*, 1810*w*, 1734*w*, 1604*w*, 1496*m*, 1412*w*, 1368*s*, 1337*m*, 1261*m*, 1177*s*, 1110*s*, 1028*m*, 972*m*, 910*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.29 (*s*, $MeSO_2$); 3.60 (*dd*, *J* = 9.7, 8.1, CH–C(5)); 3.70 (*dd*, *J* = 10.0, 3.1, CH–C(5)); 3.98 (*dd*, *J* = 7.8, 5.9, H–C(6)); 4.10 (*dd*, *J* = 8.1, 3.7, irrad. at 6.15 → *d*, *J* = 8.1, H–C(7)); 4.23 (*ddd*, *J* = 8.1, 5.9, 2.8, H–C(5)); 4.43 (*d*, *J* = 11.5, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.57 (*d*, *J* = 11.5, PhC*H*); 4.64 (*d*, *J* = 11.5, PhC*H*); 4.84 (*d*, *J* = 11.5, PhC*H*); 4.95 (*d*, *J* = 11.5, PhC*H*); 6.15 (*d*, *J* = 3.4, H–C(8)); 7.17–7.41 (*m*, 15 arom. H); 8.43 (*s*, H–C(3)). ^{13}C-NMR ($CDCl_3$): 39.75 (*q*, $MeSO_2$); 58.54 (*d*, C(5)); 69.70 (*d*, C(8)); 69.99 (*t*, *C*H$_2$–C(5)); 72.95 (*d*); 73.34, 73.66, 74.54 (3*t*, 3 Ph*C*H$_2$); 76.74 (*d*); 128.20–128.94 (several *d*); 136.93, 137.00, 137.06 (3*s*); 138.02 (*d*, C(3)); 147.31 (*s*, C(8a)).

*(5*R*,6*R*,7*S*,8*S*)-8-Amino-5,6,7,8-tetrahydro-5-(hydroxymethyl)[1,2,4]triazolo[4,3-*a*]pyridine-6,7-diol* (**2**). A soln. of **56** (60 mg, 0.26 mmol) in MeOH/AcOH 5:1 (5 ml) was treated with 10% Pd/C (30 mg) and

hydrogenated at 6 bar during 24 h. After filtration and evaporation, the crude was dissolved in 0.01M HCl and evaporated. Ion-exchange chromatography (*Amberlite CG-120* (NH_4^+ form), 0.01M aq. NH_4OH) gave **2** (32 mg, 61%). R_f (AcOEt/MeOH 5:1) 0.12. ^{1}H-NMR (300 MHz, D_2O): 3.75 (*t*, *J* = 9.6, irrad. at 3.94 → *d*, *J* ≈ 9.5, H–C(7)); 3.94 (*t*, *J* = 9.7, irrad. at 3.75 → *d*, *J* ≈ 9.5, H–C(6)); 4.04 (*dd*, *J* = 12.7, 4.0, CH–C(5)); 4.09 (*d*, *J* = 9.7, irrad. at 3.75 → change, H–C(8)); 4.10–4.16 (*m*, irrad. at 3.94 → change, H–C(5)); 4.26 (*dd*, *J* = 12.8, 2.5, CH–C(5)); 8.66 (*s*, H–C(3)). ^{1}H-NMR (300 MHz, D_2O + 2 equiv. of CF_3COOH): 4.00–4.12 (*m*, irrad. at 4.65 → change, H–C(6), H–C(7), CH–C(5)); 4.22–4.24 (*m*, H–C(5)); 4.25–4.31 (*m*, CH–C(5)); 4.65 (*d*, *J* = 8.5, H–C(8)); 9.02 (*s*, H–C(3)). ^{1}H-NMR (300 MHz, D_2O, 2 equiv. of CF_3COOH and 5 equiv. of HCl): 3.99–4.12 (*m*, irrad. at 4.70 → change, H–C(6), H–C(7), CH–C(5)); 4.25–4.29 (*m*, CH–C(5)); 4.28–4.32 (*m*, H–C(5)); 4.70 (*d*, *J* = 8.6, H–C(8)); 9.38 (br. *s*, H–C(3)). ^{13}C-NMR ($CDCl_3$): 49.59 (*d*, C(8)); 59.69 (*t*, *C*H_2–C(5)); 60.21 (*d*, C(5)); 68.38, 74.40 (2*d*, H–C(6), H–C(7)); 143.02 (*d*, C(3)); 154.38 (*s*, C(8a)).

*(5*R*,6*R*,7*S*,8*R*)-8-Acetoxy-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine* (**63**). A soln. of **60** (50 mg, 0.1 mmol) and $Hg(OAc)_2$ (32 mg, 0.1 mmol) in THF (1 ml) was treated with Me_3SiN_3 (0.1 ml, 0.067 mmol) and stirred at r.t. for 8 h. Normal workup and FC (AcOEt/hexane 1:2) gave **63** (43 mg, 84%). R_f (AcOEt/hexane 1:2) 0.41. IR ($CHCl_3$): 3067*w*, 3008*m*, 2929*w*, 2872*m*, 1953*w*, 1755*s*, 1497*m*, 1455*s*, 1370*s*, 1092*s*, 1028*m*, 911*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.17 (*s*, AcO); 4.04 (*d*, *J* = 5.6, CH_2–C(5)); 4.15 (*dd*, *J* = 6.5, 3.4, H–C(7)); 4.43 (*d*, *J* = 11.8, PhC*H*); 4.45–4.47 (*m*, H–C(6)); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.50 (*d*, *J* = 12.1, PhC*H*); 4.61 (*d*, *J* = 12.1, 2 PhC*H*); 4.64 (*td*, *J* = 5.4, 4.4, H–C(5)); 4.74 (*d*, *J* = 11.8, PhC*H*); 6.55 (*d*, *J* = 3.4, H–C(8)); 7.18–7.37 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.72 (*q*, Me); 60.29, 62.05 (2*d*, C(5), C(8)); 67.78 (*t*, *C*H_2–C(5)); 71.69, 75.63 (2*d*, C(6), C(7)); 73.23, 73.41, 73.49 (3*t*, 3 PhCH_2); 127.74–128.64 (several *d*); 136.64, 136.74, 137.30 (3*s*); 149.97 (*s*, C(8a)); 169.48 (*s*, C=O). CI-MS (NH_3): 515 (67, M^+), 91 (100).

*(5*R*,6*R*,7*R*,8*R*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridin-8-ol* (**64**). As described for **50**, with **63** (43 mg, 0.0836 mmol) in 2M methanolic ammonia (2 ml): **64** (39 mg, 99%). R_f (AcOEt/hexane 1:2) 0.26. IR ($CHCl_3$): 3559*m*, 3324*m* (br.), 3067*w*, 3008*m*, 2926*m*, 2871*m*, 1953*w*, 1878*w*, 1810*w*, 1676*w*, 1062*w*, 1429*w*, 1455*s*, 1397*w*, 1364*w*, 1340*w*, 1097*s*, 1028*m*, 910*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.93 (*t*, *J* = 9.0, CH–C(5)); 4.06 (*dd*, *J* = 9.3, 4.7, CH–C(5)); 4.15 (*d*, *J* = 5.6, 3.7, irrad. at 5.35 → *d*, *J* ≈ 5.6, H–C(7)); 4.44–4.48 (*m*, *J* = 5.6, 3.1, H–C(6), OH); 4.47 (*d*, *J* = 11.8, PhC*H*); 4.53 (*d*, *J* = 11.8, PhC*H*); 4.59 (*d*, *J* = 11.8, PhC*H*); 4.61 (*d*, *J* = 11.8, PhC*H*); 4.64 (*d*, *J* = 11.8, PhC*H*); 4.70 (*d*, *J* = 11.8, PhC*H*); 4.70–4.74 (*m*, H–C(5)); 5.35 (*d*, *J* = 3.7, H–C(8)); 7.18–7.39 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 59.99 (*d*, C(5)); 68.73 (*d*, C(8)); 68.72 (*t*, *C*H_2–C(5)); 72.08, 76.70 (2*d*, C(6), C(7)); 72.92, 73.66, 73.82 (3*t*, 3 PhCH_2); 128.08–128.89 (several *d*); 136.93, 137.18, 137.53 (3*s*); 153.55 (*s*, C(8a)). CI-MS: 473 (7, $[M+1]^+$), 381 (7), 91 (100).

*(5*R*,6*R*,7*S*,8*R*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl)]-8-[(methylsulfonyl)oxy]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine* (**65**). As described for **52**, with **64** (40 mg, 0.073 mmol) and MsCl (20 µl, 0.257 mmol) in pyridine (1 ml): **65** (37 mg, 96%). R_f (AcOEt/hexane 1:2) 0.53. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.29 (*s*, $MeSO_2$); 3.98 (*dd*, *J* = 9.3, 4.7, CH–C(5)); 4.04 (*dd*, *J* = 9.7, 6.9, CH–C(5)); 4.20 (*dd*, *J* = 6.8, 3.7, H–C(7)); 4.43 (*s*, PhCH_2); 4.46 (*dd*, *J* = 6.9, 3.7, H–C(6)); 4.59 (*d*, *J* = 11.5, PhC*H*); 4.60 (*d*, *J* = 11.8, PhC*H*); 4.61–4.66 (*m*, H–C(5)); 4.70 (*d*, *J* = 11.5, PhC*H*); 4.80 (*d*, *J* = 11.5, PhC*H*); 6.19 (*d*, *J* = 3.7, H–C(8)); 7.17–7.38 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 39.70 (*q*, $MeSO_2$); 60.51 (*d*, C(5)); 67.87 (*t*, *C*H_2–C(5)); 69.05 (*d*, C(8)); 72.06 (*d*); 73.58, 73.66, 74.00 (3*t*, 3 PhCH_2); 76.23 (*d*); 127.99–128.94 (several *d*); 136.64 (br. *s*); 137.49 (*s*); 150.45 (*s*, C(8a)).

*(5*R*,6*R*,7*R*,8*R*)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl)]-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine* (**66**). As described for **51**, with **65** (40 mg, 0.073 mmol) and NaN_3 (50 mg, 0.77 mmol) in DMF (0.5 ml). FC (AcOEt/hexane 1:4) gave **66** (35 mg, 96%). R_f (AcOEt/hexane 1:4) 0.45. IR ($CHCl_3$): 3067*w*, 3008*m*, 2999*m*, 2872*m*, 2113*s*, 1603*w*, 1496*w*, 1455*m*, 1374*m*, 1325*w*, 1111*m*, 1046*m*, 909*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.89 (*dd*, *J* = 10.3, 2.8, CH–C(5)); 3.93 (*dd*, *J* = 8.4, 7.5, irrad. at 4.32 → *d*, *J* ≈ 7.5, H–C(6)); 4.23 (*dd*, *J* = 10.3, 3.7, CH–C(5)); 4.32 (*dd*, *J* = 8.7, 7.5, irrad. at 4.88 → *d*, *J* ≈ 8.7, H–C(7)); 4.34 (*d*, *J* = 11.8, PhC*H*); 4.40 (*d*, *J* = 11.5, PhC*H*); 4.46–4.50 (*m*, H–C(5)); 4.58 (*d*, *J* = 11.5, PhC*H*); 4.87 (*s*, PhCH_2); 4.87 (*d*, *J* = 6.8, H–C(8)); 4.88 (*d*, *J* = 11.8, PhC*H*); 7.14–7.40 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 56.08 (*d*, C(8)); 60.56 (*d*, C(5)); 65.93 (*t*, *C*H_2–C(5)); 73.61 (*t*, PhCH_2); 74.46 (*d*); 75.23, 75.57 (2*t*, 2 PhCH_2); 80.62 (*d*); 128.15–128.93 (several *d*); 136.92, 137.11, 137.13 (3*s*); 150.91 (*s*, C(8a)). CI-MS: 497 (6, $[M+1]^+$), 239 (25), 108 (95), 91 (100).

Inhibition Studies. Determination of the inhibition constants (K_i) or the IC_{50} values were performed with a range of inhibitor concentrations (typically 4–8 concentrations) which bracket the K_i or IC_{50} value.

a) *Inhibition of Sweet Almonds β-Glucosidases.* Inhibition constants (K_i) and IC_{50} were determined at 37°, using *McIllvaine*'s Na_2PO_4/citric acid buffer solutions [42][43] (0.11M, pH 4.6, 5.0, 5.4, 5.9, 6.4, 6.8, 7.4, and 7.8) and 4-nitrophenyl β-D-glucopyranoside as the substrate. The enzymatic reaction was started after incubation of

the enzyme in presence of the inhibitor during 30 min or 1 h by the addition of the substrate. The increase of absorption per min at 400 nm was taken as velocity for the hydrolysis of the substrate. The increase was linear during all measurements (2 min). IC_{50} Values were determined by plotting the velocity of substrate hydrolysis *vs.* the inhibitor concentration. Determination of the inhibitor concentration corresponding to half the velocity measured in absence of the inhibitor gave the appropriate IC_{50} value. K_i Values were determined by taking the slopes from the *Lineweaver-Burk* plots [44] and plotting them *vs.* the inhibitor concentrations [45]. After fitting a straight line to the data by linear regression, the negative [I] intercept of this plot gave the appropriate K_i. Slow-binding inhibitors (**3**, **4**, **6**, and **7**) were identified by the significantly larger IC_{50} values determined when the enzymatic reaction was started by adding the enzyme to an inhibitor/substrate soln. instead of adding the substrate to a preincubated (30 min – 1 h) soln. of enzyme and inhibitor.

b) *Inhibition of* Caldocellum saccharolyticum *β-Glucosidase.* Similarly as described in *a*). The inhibition constants and IC_{50} values were determined at 55°.

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