

## A Comparison of Glucose- and Glucosamine-Related Inhibitors: Probing the Interaction of the 2-Hydroxy Group with Retaining $\beta$ -Glucosidases

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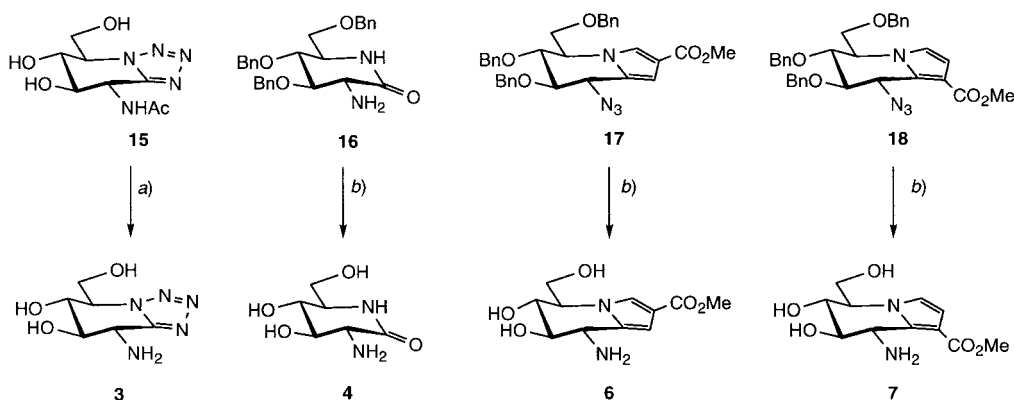
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The inhibition of the  $\beta$ -glucosidases from sweet almonds and *Caldocellum saccharolyticum* at varying pH values by the glucosamine-related inhibitors **1–7** has been compared to the inhibition by the known glucose analogues **8–14**. The amino 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  $\text{BCl}_3$  and  $\text{Bu}_4\text{NBr}$  (Schemes 3 and 4, resp.). The pH optimum for the inhibition by the amines is lower than their  $\text{p}K_{\text{HA}}$  values, evidencing that they are bound as ammonium salts and that H-bonding between  $\text{C}(2)\text{-NH}_3^+$  and the cat. base  $\text{B}^-$  contributes more strongly to binding than any possible H-bond to the  $\text{NH}_2\text{-C}(2)$  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’ ( $\Delta\Delta G(\text{OH} \rightarrow \text{NH}_3^+) = -1.5$  to  $-2.9$  kcal/mol). The increase is less pronounced for the amino derivatives **3–4**, which possess a weakly basic ‘glycosidic heteroatom’ ( $\Delta\Delta G(\text{OH} \rightarrow \text{NH}_3^+) = -0.6$  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  $\Delta\Delta G(\text{OH} \rightarrow \text{NH}_3^+)$  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  $\text{C}(2)\text{-NH}_3^+$  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  $\text{C}(2)\text{-OH}$  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  $\text{C}(2)\text{-OH}$  from a conserved Asn residue has been evidenced by crystal-structure analysis of several retaining *endo*- $\beta$ -glucosidases 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  $\text{C}(2)\text{-OH}$ . 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,  $\text{C}(2)\text{-OH}$  forms a H-bond to the catalytic nucleophile. A H-bond from  $\text{C}(2)\text{-OH}$  is expected to also contribute to the binding of transition-state-analogous inhibitors. Replacing  $\text{C}(2)\text{-OH}$  by  $\text{C}(2)\text{-NH}_3^+$

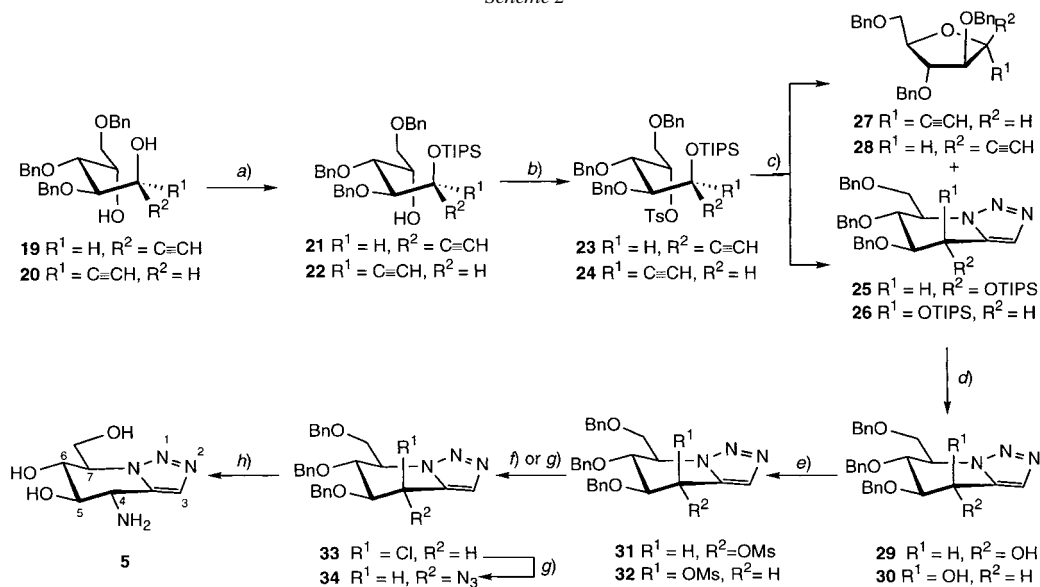


Scheme 1



a) 1M aq. HCl/THF 3 : 1; 71%. b) H<sub>2</sub>, 10% Pd/C; **4** (92%); **6** (58%); **7** (63%).

Scheme 2



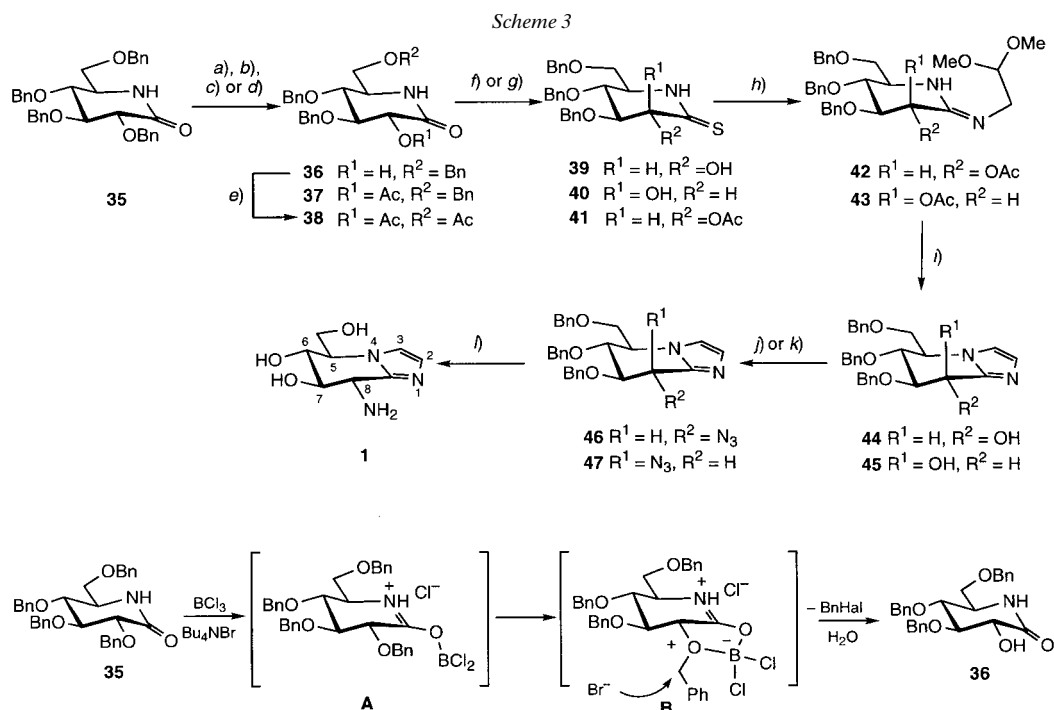
Bn = PhCH<sub>2</sub>, TIPS = <sup>i</sup>Pr<sub>3</sub>Si, Ms = MeSO<sub>2</sub>

a) BuLi, <sup>i</sup>Pr<sub>3</sub>SiCl, THF, -78 → 25°; 84%. b) TsCl, pyridine, DMAP (= *N,N*-dimethylpyridin-4-amine); 87%. c) NaN<sub>3</sub>, DMSO, 110°; 38% of **25**, 21% **26**, and 12% of **27/28** 2 : 1. d) Bu<sub>4</sub>NF, THF; 91%. e) MsCl, pyridine; 88% of **31**; 87% of **32**. f) Bu<sub>4</sub>NCl, DMF; 82%. g) NaN<sub>3</sub>, DMF, 50°; 83% from **32**; 85% from **33**. h) H<sub>2</sub>, 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<sub>4</sub>NCl in DMF. Exposure of the *manno*-

configured mesylate **32** and chloro derivative **33** to  $\text{NaN}_3$  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 debenzoylation of **35** at C(2) by treatment with  $\text{BCl}_3$  between  $-78^\circ$  and  $23^\circ$  in the presence of  $\text{Bu}_4\text{NBr}$  yielded 75–87% of **36**. To the best of our knowledge, there are only two known examples of a *Lewis*-acid-promoted regioselective debenzoylation of secondary BnO groups in carbohydrates [23][24]<sup>2)</sup>, and the regioselective *Lewis*-acid-mediated cleavage of an ether function in  $\alpha$ -position of a lactam or an amide C=O group is new. Similarly as for the known  $\text{BCl}_3$ -,  $\text{BBr}_3$ -, or  $\text{AlCl}_3$ -promoted cleavage of *peri*-MeO groups in anthraquinones [28–31], it most probably proceeds *via* coordination of  $\text{BCl}_3$  to the C=O group (**A** and **B** in Scheme 3). Coordination of  $\text{BCl}_3$  to the C=O and the



a)  $\text{BCl}_3$  (slow addition),  $\text{Bu}_4\text{NBr}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ \rightarrow 23^\circ$ ; 75–87% of **36**. b) 1.  $\text{BCl}_3$  (rapid addition),  $\text{Bu}_4\text{NBr}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ \rightarrow 23^\circ$ ; 2.  $\text{Ac}_2\text{O}$ , pyridine; **37** (33%) and **38** (48%). c) 1.  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ \rightarrow 23^\circ$ ; 2.  $\text{Ac}_2\text{O}$ , pyridine; **37** (63%) and **38** (26%). d) 1.  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ \rightarrow 23^\circ$ ; 2.  $\text{Ac}_2\text{O}$ , pyridine; **37** (51%) and **38** (32%). e)  $\text{Ac}_2\text{O}$ , 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,  $\text{Hg}(\text{OAc})_2$ , THF; **42/43** 2:1 (73%). i)  $\text{TsOH}$ , toluene/ $\text{H}_2\text{O}$  95:5; **44/45** 1:1 to 5:3 (67–71%). j)  $\text{Bu}_3\text{P}$ , 4%  $\text{HN}_3$  in toluene; **46** (72–74%). k)  $\text{Bu}_3\text{P}$ , 2.6M  $\text{HN}_3$  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,  $\text{H}_2$ ,  $\text{AcOEt/MeOH/AcOH}$  1:1:1; 79%.

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 debenzoylation 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<sub>4</sub>NBr was omitted, or when BBr<sub>3</sub> was used instead of BCl<sub>3</sub> (*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<sub>3</sub> (*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<sub>3</sub> · OEt<sub>2</sub>. According to TLC and <sup>1</sup>H-NMR spectroscopy of the acetylated crude, however, this Lewis acid led to random debenzoylation of the lactam.

Activation of the regioselectively deprotected lactam **36** by thionation with either P<sub>2</sub>S<sub>10</sub> or Lawesson's reagent failed. The hydroxy lactam **36** did not react with P<sub>2</sub>S<sub>10</sub> 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)<sub>2</sub> [32], however, led to a 2 : 1 mixture (73%) of the *gluco*- and *manno*-N-(2,2-dimethoxyethyl)amidines **42** and **43**<sup>3)</sup>. 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<sup>4)</sup> (67%) of the known [33] hydroxyimidazopyridines **44** and **45**<sup>5)</sup>. Mitsunobu reaction of pure **44**, pure **45**, or a 1 : 1 mixture **44/45** with a 4% soln. of HN<sub>3</sub> in toluene according to *Tatsuta et al.* [34] led, in agreement with their results, exclusively to the *gluco*-azido derivative **46** (72–74%)<sup>6)</sup>. Saturating the reaction mixture with HN<sub>3</sub> 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<sub>3</sub> (presaturation by HN<sub>3</sub>) lead to increased inversion of configuration (increased S<sub>N</sub>2 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<sub>N</sub>2 and S<sub>N</sub>1 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**.

<sup>3)</sup> A sample was separated by FC.

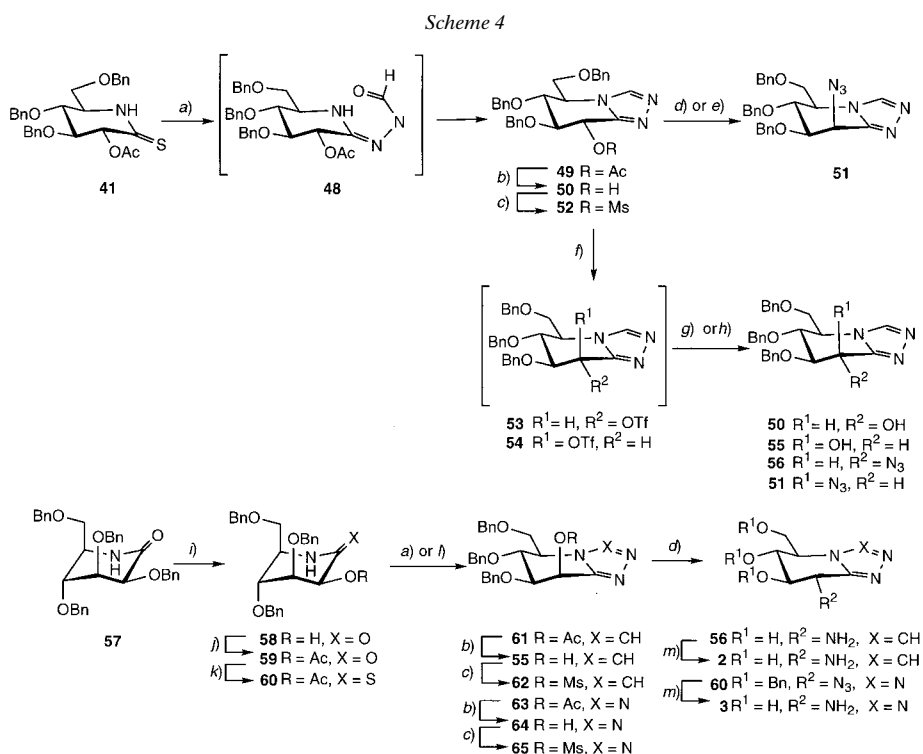
<sup>4)</sup> This is the ratio for the transformation on a 350-mg scale. On a 20-mg scale, the ratio **42/43** was 5 : 3.

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

<sup>6)</sup> 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)<sub>2</sub>, followed by NH<sub>3</sub>-mediated deacetylation. The intermediate amidrazone **48** cyclized *in situ* to the triazole **49**. While **50** proved inert to a 4% soln. of HN<sub>3</sub> under *Mitsunobu* conditions at 70°, it was partially transformed into the *manno*-azido derivative **51** (19%) when the soln. was saturated with HN<sub>3</sub>; 56% of **50** was recovered. The *gluco*-mesylate **52** (98% from **50**) led exclusively to the *manno*-azido compound **51** when exposed to NaN<sub>3</sub> in DMF (yields 46–95%), but not the diastereoselectivity depending upon the concentration of the nucleophile.

Exposure of **50** to Tf<sub>2</sub>O in pyridine/CH<sub>2</sub>Cl<sub>2</sub> 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 <sup>1</sup>H-NMR spectrum of the crude obtained by



Bn = PhCH<sub>2</sub>, Ms = MeSO<sub>2</sub>, Tf = CF<sub>3</sub>SO<sub>2</sub>

a) Formylhydrazine, Hg(OAc)<sub>2</sub>, THF; **49** (9%); **61** (86% from **60**). b) 2M NH<sub>3</sub> in MeOH; **50** (98%); **55** (quant.); **64** (99%). c) MsCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>; **52** (98%); **62** (84%); **65** (96%). d) NaN<sub>3</sub>, DMF; **51** (46–95%); **56** (92%). e) Bu<sub>3</sub>P, 2.6M HN<sub>3</sub> in THF, DEAD; 19% from **50**. f) Tf<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, pyridine, –78°; **53/54** 1:1 (90%). g) Normal workup; **50/55** 7:2 (89%). h) NaN<sub>3</sub>; **56/51** 4:1 to 1:10 (32–54%). i) BCl<sub>3</sub> (slow addition), Bu<sub>4</sub>NBr, CH<sub>2</sub>Cl<sub>2</sub>, –78° → 23°; 85%. j) Ac<sub>2</sub>O, pyridine; 98%. k) Lawesson's reagent, toluene; 92%. l) Me<sub>3</sub>SiN<sub>3</sub>, Hg(OAc)<sub>2</sub>; **63** (84% from **59**). m) MeOH/AcOH, 10% Pd/C, H<sub>2</sub>; **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<sub>3</sub> 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<sub>3</sub>SiN<sub>3</sub> and Hg(OAc)<sub>2</sub> 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 <sup>1</sup>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 <sup>13</sup>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 <sup>4</sup>C<sub>1</sub>-conformation, while the *manno*-lactams **58** and **59** and the *manno*-thiolactam **60** form a 2:1 mixture of <sup>1</sup>C<sub>4</sub>- and <sup>4</sup>C<sub>1</sub>-conformers. Remarkably, the *manno*-amidine **43** neither adopts the conformation of the known [19] 2,3,4,6-tetra-*O*-benzylated analogue (flattened <sup>5</sup>S<sub>3</sub>) nor of the *manno*-lactams **58** or **59** (<sup>1</sup>C<sub>4</sub>/<sup>4</sup>C<sub>1</sub> 2:1), but a <sup>4</sup>H<sub>3</sub>-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<sup>7)</sup>, 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,

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

HCl being required for the second protonation, indicating that the  $pK_{\text{HA}}$  of the azole moiety is considerably lowered by the ammonium group<sup>8</sup>). The coupling constants (Table 2) evidence that the unprotonated glucosamine derivatives **1**, **2**, and **4–7**, and the protonated glucosamine-derived tetrazole **3**·H<sup>+</sup> and pyrrole **6**·H<sup>+</sup> adopt a conformation close to <sup>4</sup>H<sub>3</sub>. The 1,3-interaction between the amino group and the methoxycarbonyl group forces the 1-(methoxycarbonyl)pyrrole glucosamine analogues **7** (like the *gluco*-analogue **14** [20]) to adopt a conformation between <sup>4</sup>H<sub>3</sub> and a sofa, with C(3) below the plane of the tetrahydropyrrolopyridine. A slight deviation from the <sup>4</sup>H<sub>3</sub>-conformation is also observed for the diprotonated aminoimidazole **1**·2H<sup>+</sup>, where the somewhat smaller *J*(H,H) value indicates a small percentage of the <sup>3</sup>H<sub>4</sub>-conformer. Signal overlap prevented an assignment of the conformation of the unprotonated tetrazole glucosamine analogue **2** and of the protonated **1**·H<sup>+</sup>, **2**·H<sup>+</sup>, **4**·H<sup>+</sup>, **5**·H<sup>+</sup>, and **7**·H<sup>+</sup>. 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<sub>2</sub>O) of Protonated and Unprotonated Glucosamine Analogues **1–7**

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

<sup>a)</sup> Conventional carbohydrate numbering used. <sup>b)</sup> Azolopyridine numbering used. <sup>c)</sup> Hidden by HDO signal.

**Enzymatic Tests and Discussion.** – The glucosamine derivatives **1–7** and their glucose analogues **8–14** were tested against  $\beta$ -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  $\beta$ -glucosidases, and E–H for the *C. saccharolyticum*  $\beta$ -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-

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



Table 2. *Coupling Constants (D<sub>2</sub>O) 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 <sup>a)</sup>
<b>1</b>	b)	9.6	9.6	b)	b)	about <sup>4</sup> H <sub>3</sub>
<b>1</b> ·H <sup>+</sup>	7.8	b)	b)	b)	b)	b)
<b>1</b> ·2H <sup>+</sup>	7.9	7.9	8.6	4.1	7.1	<sup>4</sup> H <sub>3</sub> / <sup>β</sup> H <sub>4</sub>
<b>2</b>	9.6	9.7	9.7	2.5	4.1	<sup>4</sup> H <sub>3</sub>
<b>2</b> ·H <sup>+</sup>	8.5	b)	b)	b)	b)	b)
<b>2</b> ·2H <sup>+</sup>	8.6	b)	b)	b)	b)	b)
<b>3</b>	b)	b)	b)	b)	b)	b)
<b>3</b> ·H <sup>+</sup>	9.5	9.5	9.6	2.5	b)	<sup>4</sup> H <sub>3</sub>
<b>4</b>	9.4	9.6	9.5	2.8	4.5	<sup>4</sup> H <sub>3</sub>
<b>4</b> ·H <sup>+</sup>	b)	b)	b)	b)	b)	b)
<b>5</b>	9.3	9.5	9.5	2.2	2.5	<sup>4</sup> H <sub>3</sub>
<b>5</b> ·H <sup>+</sup>	b)	b)	b)	b)	b)	b)
<b>6</b>	9.3	9.3	9.3	2.2	b)	<sup>4</sup> H <sub>3</sub>
<b>6</b> ·H <sup>+</sup>	9.0	9.0	9.3	3.4	b)	<sup>4</sup> H <sub>3</sub>
<b>7</b>	6.9	8.7	7.5	b)	3.7	<sup>4</sup> H <sub>3</sub> / <sup>S</sup> <sub>3</sub>
<b>7</b> ·H <sup>+</sup>	6.9	b)	b)	2.2	b)	b)

<sup>a)</sup> Conventional carbohydrate numbering used. <sup>b)</sup> Not determined.

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

<sup>a)</sup> 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<sub>2</sub> 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<sup>7)</sup> **8–11**, which possess a ‘glycosidic heteroatom’<sup>9)</sup> 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-

<sup>9)</sup> A heteroatom corresponding to the glycosidic O-atom of the substrate.

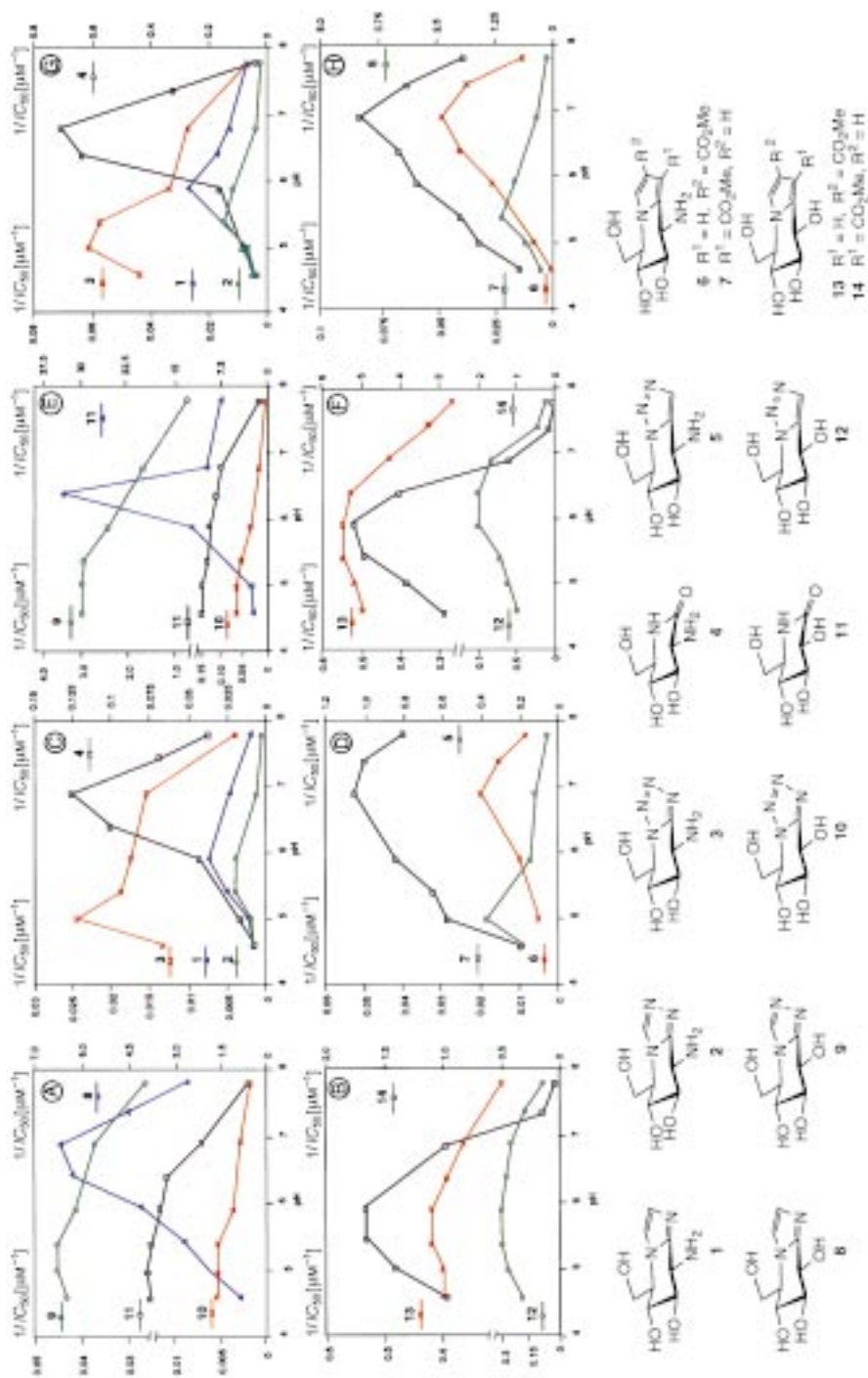


Fig. 1.  $1/IC_{50}$  vs. pH Plots of **1–14** for  $\beta$ -glucosidases from sweet almonds (A–D) and from *Caldocellum saccharolyticum* (E–H). Note the two scales on the right and left side of each graphic

Table 4. pH Dependence of  $IC_{50}$  Values [ $\mu\text{M}$ ] of **1–14** against  $\beta$ -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
<b>1</b>	241	161	77	41	63	85	a)	165
<b>2</b>	210	143	75	96	a)	274	a)	411
<b>3</b>	17	12	13	22	a)	27	a)	115
<b>4</b>	21	11	8	6	a)	1.4	3.2	23
<b>5</b>	3500	1700	900	1200	a)	2800	a)	7200
<b>6</b>	711	121	a)	38	25	21	27	76
<b>7</b>	69	31	25	17	15	12	16	26
<b>8</b>	0.41	0.35	a)	0.08	0.03	0.05	a)	0.13
<b>9</b>	0.30	0.30	0.33	0.4	a)	0.6	a)	1.3
<b>10</b>	30	30	34	52	a)	120	a)	208
<b>11</b>	7	7	7.5	8	9	10	a)	45
<b>12</b>	20000	16000	14000	10000	10000	12000	40000	80000
<b>13</b>	2000	1900	1800	1800	1900	2300	3000	6000
<b>14</b>	360	270	210	200	260	820	4000	10000

a) Not determined.

dependence of their activity. They inhibit the tested  $\beta$ -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<sup>10</sup>) 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<sup>-</sup>, 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<sup>-</sup> is either so weak that its loss by protonation of B<sup>-</sup> has no significant influence, or is compensated by effects of unknown nature. The partial protonation of the inhibitor by AH should reduce the  $pK_{\text{HA}}$  value of C(2)–OH and strengthen the presumed H-bond between C(2)–OH and B<sup>-</sup>. This H-bond and the interaction of B<sup>-</sup> with the (partially) positively charged anomeric carbon are expected to reduce the basicity of B<sup>-</sup>; 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  $pK_{\text{HA}} = 2.4$  [36]), tetrazole **10** (estimated  $pK_{\text{HA}} = -4.0$  [36]), and lactam **11** (estimated  $pK_{\text{HA}} = -0.5^{11}$ ) will not be protonated by the buffer. The glucose-related imidazole **8** ( $pK_{\text{HA}} = 6.12$  [36]), however, exists predominantly in its protonated form below pH 6.12. This is expressed by its

<sup>10)</sup> The  $pK_{\text{HA}}$  values of AH and the protonated catalytic nucleophile BH of the two  $\beta$ -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  $\beta$ -glucosidases tested here, has its activity optimum at a pH close to 6 [38].

<sup>11)</sup> The  $pK_{\text{HA}}$  value of valerolactam is *ca.* 0.6 [39]. As evident from comparing the  $pK_{\text{HA}}$  value of **8** with that of 1,5-dimethylimidazole [40], the OH groups of the carbohydrate moiety reduce the  $pK_{\text{HA}}$  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  $\beta$ -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 glucosidase 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**<sup>12</sup>) (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).

<sup>12</sup>) 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  $\beta$ -glucosidase and the inhibitor during 30–60 min before starting the enzymatic reaction by addition of the substrate.

Table 5. Inhibition of  $\beta$ -Glucosidases from Sweet Almonds and *Caldocellum saccharolyticum* by Glucosamine-Derived Inhibitors **1–7** Compared to Their Inhibition by the Glucose-Derived Inhibitors **8–14**

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

<sup>a</sup>) Difference in dissociation energy between glucosamine and glucose analogue calculated on the basis of  $K_{\text{i}}$  at  $\text{pH}_{\text{opt}}$ . <sup>b</sup>) pH corresponding to optimal inhibition;  $\text{p}K_{\text{HA}} - \text{pH}_{\text{opt}}$  in parenthesis. Same values for  $\beta$ -glucosidases from sweet almonds and *C. saccharolyticum*. <sup>c</sup>) pH corresponding to optimal inhibition. <sup>d</sup>)  $IC_{50}/2$ .

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  $\text{B}^-$  of either the OH or the  $\text{NH}_3^+$  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  $\text{NH}_3^+$  group, whether under the influence of the stronger  $\sigma$ -acceptor on the basic properties of the methoxycarbonyl group, or by a competing intramolecular H-bond from the  $\text{NH}_3^+$  to the methoxycarbonyl group is difficult to decide on the basis of

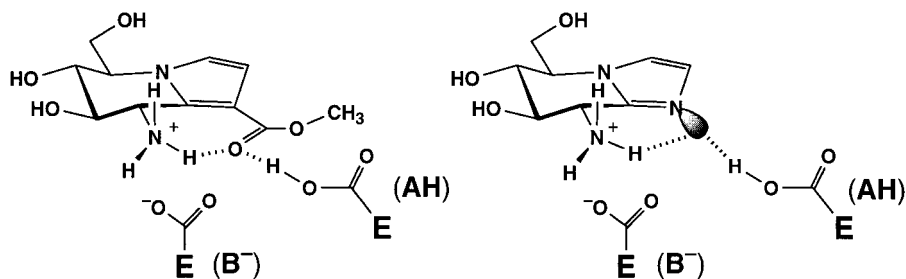


Fig. 2. Double competition between H-bond donors and acceptors involving  $\text{B}^-$ ,  $\text{NH}_3^+ - \text{C}(2)$ , the 'glycosidic heteroatom', and AH

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  $\text{NH}_3^+$  and  $\text{B}^-$  (cf. Fig. 2) also explains the much lower activity of the aminoimidazole **1** ( $\Delta\Delta G = 4.3\text{--}4.7$  kcal/mol) and aminotriazole **2** ( $\Delta\Delta G = 2.3\text{--}2.8$  kcal/mol), as compared to the corresponding alcohols<sup>13</sup>). The effects of replacing the OH by an  $\text{NH}_3^+$  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  $\text{B}^-$  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  $\text{B}^-$ .

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### Experimental Part

*General.* Solvents were distilled before use. Normal workup implies distribution of the crude product between  $\text{Et}_2\text{O}$  and sat. aq.  $\text{NH}_4\text{Cl}$  soln. and ice, unless indicated otherwise, drying of the org. layer ( $\text{Na}_2\text{SO}_4$ ), filtration, and evaporation of the filtrate. TLC: Merck silica gel 60F-254 plates; detection by heating with ‘mostain’ (400 ml of 10%  $\text{H}_2\text{SO}_4$  soln., 20 g of  $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 6\text{H}_2\text{O}$ , 0.4 g of  $\text{Ce}(\text{SO}_4)_2$ ). Flash chromatography (FC): silica gel Fluka 60 (0.04–0.063 mm). IR Spectra: KBr of 2%  $\text{CH}_2\text{Cl}_2$  soln.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR: at 300 and 75 MHz, resp., if not indicated otherwise; chemical shifts  $\delta$  in ppm, coupling constants  $J$  in Hz. FAB-MS: 3-nitrobenzyl alcohol, unless indicated otherwise.

(5R,6R,7S,8S)-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 ( $\text{NH}_4^+$  form), 0.01M  $\text{NH}_4\text{OH}$ ) 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

- <sup>13</sup>) The unfavourable influence of C(2)– $\text{NH}_3^+$  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  $\text{NH}_3^+$  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**.

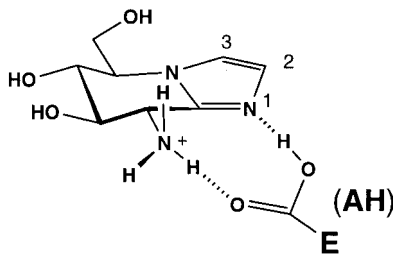


Fig. 3. Illustration of the interactions expected between the catalytic acid (AH) and the protonated glucosamine-derived imidazole **1** if the carbonyl group of AH were oriented correctly to accept a H-bond from  $\text{NH}_3^+ - \text{C}(2)$

chromatography (*Amberlite CG-120* (H<sup>+</sup> form), 1M NH<sub>4</sub>OH) gave **3** (40 mg, 76%). Colourless solid. *R*<sub>f</sub> (AcOEt/MeOH/H<sub>2</sub>O 5 : 1 : 0.1) 0.05. <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O): 3.72–3.75 (br. *m*, H–C(7)); 4.12–4.15 (br. *m*, irradi. at 4.36 → *d*, *J* ≈ 12.5, CH–C(5)); 4.34–4.35 (*m*, irradi. at 4.49 → change, H–C(5)); 4.49 (br. *d*, *J* = 12.8, irradi. at 4.36 → change, CH–C(5)). <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O, 2 equiv. of CF<sub>3</sub>COOH): 4.07 (*t*, *J* = 9.6, irradi. at 4.91 → *d*, *J* = 9.5, H–C(7)); 4.12–4.20 (*m*, irradi. 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, irradi. at 4.07 → *s*, H–C(8)). <sup>13</sup>C-NMR (75 MHz, D<sub>2</sub>O): 50.02 (*d*, C(8)); 60.46 (*t*, CH<sub>2</sub>–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<sub>3</sub>): 202 (100, [M + 1]<sup>+</sup>), 91 (100). Anal. calc. for C<sub>6</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub> · 0.5 H<sub>2</sub>O (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<sup>+</sup> form), 0.1M aq. NH<sub>4</sub>OH) gave **4** (28 mg, 92%). Colourless foam, which turned yellowish upon standing. *R*<sub>f</sub> (AcOEt/MeOH 5 : 1) 0.03. <sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O): 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)). <sup>13</sup>C-NMR (125 MHz, D<sub>2</sub>O): 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]<sup>+</sup>). Anal. calc. for C<sub>6</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub> (176.17): C 40.91, H 6.87, N 15.90; found: C 41.04, H 6.79, N 15.76.

**Methyl (5R,6R,7R,8S)-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<sub>4</sub><sup>+</sup> form), 0.1M NH<sub>4</sub>OH) gave **6** (7 mg, 58%). Colourless, hygroscopic foam. *R*<sub>f</sub> (AcOEt/MeOH/H<sub>2</sub>O 5 : 1 : 0.1) 0.08. <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O): 3.59 (*t*, *J* = 9.3, H–C(7)); 3.84 (*s*, MeO); 3.90 (*d*, *J* = 9.3, irradi. at 3.59 → *s*, H–C(8)); 3.94 (*t*, *J* = 9.3, irradi. 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)). <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O, 2 equiv. of CF<sub>3</sub>COOH): 3.80 (*s*, MeO); 3.88 (*t*, *J* = 9.0, irradi. 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, irradi. at 4.73 → *d*, *J* = 1.6, H–C(1)); 7.69 (*d*, *J* = 1.6, H–C(3)). <sup>13</sup>C-NMR (75 MHz, D<sub>2</sub>O): 53.33 (*d*, C(8)); 54.75 (*q*, MeO); 62.03 (*t*, CH<sub>2</sub>–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]<sup>+</sup>). Anal. calc. for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub> · 1.5 H<sub>2</sub>O (283.28): C 46.64, H 6.76, N 9.89; found: C 46.93, H 6.77, N 9.59.

**Methyl (5R,6R,7R,8S)-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<sub>4</sub><sup>+</sup> form), 0.1M NH<sub>4</sub>OH) gave **7** (73 mg, 63%). Colourless, hygroscopic foam which turned yellowish upon standing. *R*<sub>f</sub> (AcOEt/MeOH/H<sub>2</sub>O 5 : 1 : 0.1) 0.05. <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O): 3.83 (*dd*, *J* = 8.7, 6.9, irradi. at 4.25 → *d*, *J* ≈ 8.7, irradi. 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*, irradi. 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, irradi. 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)). <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O + 2 equiv. of CF<sub>3</sub>COOH): 3.89 (*s*, MeO); 4.05–4.18 (*m*, irradi. 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)). <sup>13</sup>C-NMR (75 MHz, D<sub>2</sub>O, 3 equiv. of HCl): 52.97 (*d*, C(8)); 55.12 (*q*, MeO); 61.75 (*t*, CH<sub>2</sub>–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]<sup>+</sup>). Anal. calc. for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub> · 0.25 H<sub>2</sub>O (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 <sup>1</sup>Pr<sub>3</sub>SiCl (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*<sub>f</sub> (AcOEt/hexane 1 : 5) 0.52, 0.56. IR (CH<sub>2</sub>Cl<sub>2</sub>): 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*. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 0.95–1.36 (*m*, (Me<sub>2</sub>CH)<sub>3</sub>Si); 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).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ; numbering of **22**): 12.22, 12.59 (2*d*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 17.99, 17.99 (2*q*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 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  $\text{PhCH}_2$ ); 74.96, 75.02 (2*d*, C(3)); 79.08, 79.62 (2*d*, C(4)); 80.99, 82.20 (2*d*,  $\text{C}\equiv\text{CH}$ ); 82.87, 84.23 (2*s*,  $\text{C}\equiv\text{CH}$ ); 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,  $[\text{M} + \text{H}]^+$ ), 603 (36,  $\text{M}^+$ ), 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  $\text{TsCl}$  (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.  $\text{NaHCO}_3$  soln., and stirred at 25° for an additional hour. After evaporation of pyridine, the residue was distributed between  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$ , the aq. layer extracted with  $\text{Et}_2\text{O}$  ( $2 \times 150$  ml), and the combined org. phase washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), 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 ( $\text{CH}_2\text{Cl}_2$ ): 3306*s*, 3010*m*, 2967*m*, 2867*m*, 1956*w*, 1604*m*, 1497*m*, 1454*s*, 1398*m*, 1176*s*, 1094*s*, 1027*s*.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 0.88–1.18 (*m*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 2.34 (*s*, 0.5 Me); 2.43 (*d*,  $J = 2.1$ , 0.5  $\text{C}\equiv\text{CH}$ ); 2.45 (*s*, 0.5 Me); 2.48 (*d*,  $J = 2.1$ , 0.5  $\text{C}\equiv\text{CH}$ ); 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).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ; numbering of **24**): 12.47, 12.49 (2*d*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 18.15, 18.21 (2*q*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 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  $\text{PhCH}_2$ ); 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*,  $\text{C}\equiv\text{CH}$ ); 82.99, 83.35 (2*s*,  $\text{C}\equiv\text{CH}$ ); 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,  $[\text{M} + 1]^+$ ), 757 (31,  $\text{M}^+$ ), 181 (74), 91 (100).

Treatment of **23/24** with  $\text{NaN}_3$ . A soln. of **23/24** 1:1 (2.56 g, 3.4 mmol) in DMSO (120 ml) was treated with  $\text{NaN}_3$  and stirred at 110° for 15 h. The solvent was evaporated, the residue distributed between  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$ , the aq. layer extracted with  $\text{Et}_2\text{O}$  ( $2 \times 150$  ml), and the combined org. layer washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), 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 ( $\text{CH}_2\text{Cl}_2$ ): 3301*s*, 3089*m*, 2925*m*, 1586*w*, 1425*m*, 1362*s*, 1288*m*, 1207*s*, 1093*s*, 1028*s*, 910*m*.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 2.59 (*d*,  $J = 2.5$ , irradi. at 4.75  $\rightarrow$  *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*,  $J = 3.4$ , irradi. at 4.75  $\rightarrow$  *d*,  $J = 3.1$ , irradi. at 4.05  $\rightarrow$  *d*,  $J = 3.4$ , H–C(4)); 4.29 (*q*,  $J \approx 5.3$ , irradi. at 4.05  $\rightarrow$  *t*,  $J \approx 4.9$ , H–C(6)); 4.52–4.62 (*m*, 5  $\text{PhCH}$ ); 4.65 (*d*,  $J = 11.8$ ,  $\text{PhCH}$ ); 4.75 (br. *t*,  $J \approx 2.8$ , H–C(3)); 7.26–7.41 (*m*, 15 arom. H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 69.78 (*t*, C(7)); 72.16 (*d*, C(3)); 72.24 (*t*, 2  $\text{PhCH}_2$ ); 73.55 (*t*,  $\text{PhCH}_2$ ); 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,  $\text{M}^+$ ), 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 ( $\text{CH}_2\text{Cl}_2$ ): 3302*m*, 3088*m*, 2924*m*, 1585*w*, 1428*m*, 1362*s*, 1290*m*, 1207*s*, 1096*s*, 1027*s*, 910*m*.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 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).  $^1\text{H-NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ ): 2.12 (*d*,  $J = 2.4$ , irradi. at 4.71  $\rightarrow$  *s*, H–C(1)); 3.63–3.73 (*m*, 2 H–C(7)); 3.86 (*dd*,  $J = 4.8$ , 2.7, irradi. at 4.71  $\rightarrow$  *d*,  $J = 2.2$ , irradi. at 4.12  $\rightarrow$  *d*,  $J = 4.0$ , H–C(4)); 4.12 (br. *t*,  $J \approx 3.0$ , irradi. at 3.86  $\rightarrow$  *d*,  $J = 3.4$ , H–C(5)); 4.21–4.38 (*m*, irradi. at 4.12  $\rightarrow$  change, 5  $\text{PhCH}$ , H–C(6)); 4.53 (*d*,  $J = 11.7$ ,  $\text{PhCH}$ ), 4.71 (*dd*,  $J = 4.5$ , 2.4, H–C(3)); 7.03–7.32 (*m*, 15 arom. H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 70.50 (*t*, C(7)); 71.07 (*d*, C(3)); 71.87, 72.44, 73.52 (3*t*, 3  $\text{PhCH}_2$ ); 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,  $\text{M}^+$ ), 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-[(triisopropylsilyloxy)[1,2,3]triazolo[1,5-*a*]pyridine (**25**):  $R_f$  (AcOEt/hexane 1:3) 0.40.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 0.84–1.33 (*m*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 3.84 (*t*,  $J = 7.2$ , irradi. at 5.10  $\rightarrow$  *d*,  $J = 7.2$ , H–C(5)); 3.97 (*dd*,  $J = 10.3$ , 2.8, CH–C(7)); 4.25–4.33 (*m*, irradi. at 3.84  $\rightarrow$  change, irradi. at 3.97  $\rightarrow$  change, H–C(6), CH–C(7)); 4.43 (*d*,  $J = 11.8$ ,  $\text{PhCH}$ ); 4.49 (*d*,  $J = 11.8$ ,  $\text{PhCH}$ ); 4.57–4.60 (*m*, irradi. at 3.97  $\rightarrow$  change, 3  $\text{PhCH}$ , H–C(7)); 4.73 (*d*,  $J = 11.8$ ,  $\text{PhCH}$ ); 5.10 (*d*,  $J = 6.9$ , irradi. at 3.84  $\rightarrow$  *s*, H–C(4)); 7.15–7.35 (*m*, 15 arom. H); 7.70 (*s*, H–C(3)).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 12.89 (*d*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 18.12 (*q*,  $(\text{Me}_2\text{CH})_3\text{Si}$ ), 60.99 (*d*, C(7)); 67.22 (*d*, C(4)); 67.51 (*t*,  $\text{CH}_2$ –C(7)); 73.67, 74.34, 74.43 (3*t*, 3  $\text{PhCH}_2$ ); 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,  $[\text{M} + \text{H}]^+$ ), 628 (100,  $\text{M}^+$ ), 91 (47).



Data of (4R,5S,6R,7R)-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.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 1.02–1.13 ( $m$ ,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 3.86 ( $dd$ ,  $J = 6.9$ , 2.8, irradi. at 5.33  $\rightarrow d$ ,  $J = 6.9$ ,  $\text{H-C}(5)$ ); 4.04 ( $dd$ ,  $J = 9.7$ , 6.9,  $\text{CH-C}(7)$ ); 4.10 ( $dd$ ,  $J = 9.7$ , 4.1,  $\text{CH-C}(7)$ ); 4.45 (br.  $s$ , 2  $\text{PhCH}_2$ ); 4.60–4.75 ( $m$ , irradi. at 4.04  $\rightarrow$  change, 4  $\text{PhCH}$ ,  $\text{H-C}(6)$ ,  $\text{H-C}(7)$ ); 5.33 ( $d$ ,  $J = 2.8$ ,  $\text{H-C}(4)$ ); 7.20–7.34 ( $m$ , 15 arom. H); 7.65 ( $s$ ,  $\text{H-C}(3)$ ).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 12.45 ( $d$ ,  $(\text{Me}_2\text{CH})_3\text{Si}$ ), 18.06 ( $q$ ,  $(\text{Me}_2\text{CH})_3\text{Si}$ ); 60.82 ( $d$ ,  $\text{C}(7)$ ); 68.87 ( $t$ ,  $\text{CH}_2\text{-C}(7)$ ); 71.71, 71.75, 72.81 ( $3t$ , 3  $\text{PhCH}_2$ ); 73.10, 73.29 ( $2d$ ,  $\text{C}(4)$ ,  $\text{C}(5)$ ); 79.24 ( $d$ ,  $\text{C}(6)$ ); 127.66–128.91 (several  $d$ ); 131.29 ( $d$ ,  $\text{C}(3)$ ); 135.96 ( $s$ ,  $\text{C}(3a)$ ); 137.51, 137.66, 137.76 ( $3s$ ). FAB-MS: 629 (45,  $[M + \text{H}]^+$ ), 628 (100,  $M^+$ ), 91 (78).

(4R,5S,6R,7R)-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  $\text{Bu}_4\text{NF}$  (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.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 3.10 (br.  $d$ ,  $J \approx 4.0$ , irradi. at 5.09  $\rightarrow s$ , exchange with  $\text{D}_2\text{O}$ ,  $\text{HO-C}(4)$ ); 3.93–4.02 ( $m$ , irradi. at 5.09  $\rightarrow$  change, irradi. at 4.70  $\rightarrow$  change,  $\text{H-C}(5)$ ,  $\text{CH-C}(7)$ ); 4.11 ( $dd$ ,  $J = 9.7$ , 4.4, irradi. at 4.70  $\rightarrow d$ ,  $J = 9.7$ ,  $\text{CH-C}(7)$ ); 4.44–4.66 ( $m$ , 6  $\text{PhCH}$ ,  $\text{H-C}(6)$ ); 4.67–4.71 ( $m$ , irradi. at 4.11  $\rightarrow$  change,  $\text{H-C}(7)$ ); 5.09 ( $dd$ ,  $J = 8.4$ , 3.7, irradi. at 3.96  $\rightarrow d$ ,  $J = 3.7$ ,  $\text{H-C}(4)$ ); 7.18–7.36 ( $m$ , 15 arom. H), 7.72 ( $s$ ,  $\text{H-C}(3)$ ).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 59.69 ( $d$ ,  $\text{C}(7)$ ); 61.73 ( $t$ ,  $\text{CH}_2\text{-C}(7)$ ); 69.17 ( $d$ ,  $\text{C}(4)$ ); 71.77 ( $d$ ,  $\text{C}(5)$ ); 73.08, 73.18, 73.59 ( $3t$ , 3  $\text{PhCH}_2$ ); 77.61 ( $d$ ,  $\text{C}(6)$ ); 128.06–128.91 (several  $d$ ); 132.29 ( $d$ ,  $\text{C}(3)$ ); 135.14 ( $s$ ,  $\text{C}(3a)$ ); 136.97, 137.41, 137.72 ( $3s$ ). FAB-MS: 472 (56,  $[M + \text{H}]^+$ ), 471 (45,  $M^+$ ), 91 (100).

(4R,5S,6R,7R)-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  $\text{MsCl}$  (80  $\mu\text{l}$ , 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.  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 2.76 ( $s$ ,  $\text{MsO}$ ); 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 ( $d$ ,  $J = 3.3$ ,  $\text{H-C}(4)$ ); 7.18–7.82 ( $m$ , 15 arom. H); 8.20 ( $s$ ,  $\text{H-C}(3)$ ).

(4S,5S,6R,7R)-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.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 3.34 (br.  $s$ , exchange with  $\text{D}_2\text{O}$ ,  $\text{HO-C}(4)$ ); 3.96 ( $dd$ ,  $J = 6.5$ , 5.0,  $\text{H-C}(5)$ ); 4.05 ( $dd$ ,  $J = 9.7$ , 4.1,  $\text{CH-C}(7)$ ); 4.13 ( $dd$ ,  $J = 9.7$ , 6.9,  $\text{CH-C}(7)$ ); 4.44 ( $dd$ ,  $J = 6.5$ , 4.7, irradi. at 3.96  $\rightarrow$  change,  $\text{H-C}(6)$ ); 4.47 ( $s$ ,  $\text{PhCH}_2$ ); 4.64 ( $d$ ,  $J = 11.5$ ,  $\text{PhCH}$ ); 4.66 ( $d$ ,  $J = 11.8$ ,  $\text{PhCH}$ ); 4.71–4.85 ( $m$ ,  $\text{PhCH}_2$ ,  $\text{H-C}(7)$ ); 4.87 (br.  $t$ ,  $J \approx 5.0$ , irradi. at 3.96  $\rightarrow$  br.  $d$ ,  $J = 6.6$ ,  $\text{H-C}(4)$ ); 7.22–7.36 ( $m$ , 15 arom. H); 7.75 ( $s$ ,  $\text{H-C}(3)$ ).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 60.01 ( $d$ ,  $\text{C}(7)$ ); 64.44 ( $d$ ,  $\text{C}(4)$ ); 68.53 ( $t$ ,  $\text{CH}_2\text{-C}(7)$ ); 73.61, 73.82, 73.94 ( $3t$ , 3  $\text{PhCH}_2$ ); 74.00 ( $d$ ,  $\text{C}(5)$ ); 79.34 ( $d$ ,  $\text{C}(6)$ ); 128.00–128.91 (several  $d$ ); 132.58 ( $d$ ,  $\text{C}(3)$ ); 135.12 ( $s$ ,  $\text{C}(3a)$ ); 136.93, 137.55, 137.82 ( $3s$ ).

(4S,5R,6R,7R)-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.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 2.93 ( $s$ ,  $\text{MsO}$ ); 3.99 ( $dd$ ,  $J = 10.3$ , 2.8, irradi. at 4.58  $\rightarrow d$ ,  $J = 10.3$ ,  $\text{CH-C}(7)$ ); 4.10 ( $dd$ ,  $J = 8.4$ , 7.2,  $\text{H-C}(5)$ ); 4.33–4.42 ( $m$ , irradi. at 3.99  $\rightarrow$  change, irradi. at 4.58  $\rightarrow$  change,  $\text{PhCH}$ ,  $\text{H-C}(6)$ ,  $\text{CH-C}(7)$ ); 4.46 ( $d$ ,  $J = 11.8$ ,  $\text{PhCH}$ ); 4.54–4.63 ( $m$ , irradi. at 3.99  $\rightarrow$  change, 2  $\text{PhCH}$ ,  $\text{H-C}(7)$ ); 4.78 ( $d$ ,  $J = 11.2$ ,  $\text{PhCH}$ ); 4.85 ( $d$ ,  $J = 10.9$ ,  $\text{PhCH}$ ); 5.73 ( $d$ ,  $J = 7.2$ , irradi. at 4.10  $\rightarrow s$ ,  $\text{H-C}(4)$ ); 7.18–7.38 ( $m$ , 15 arom. H); 7.85 ( $s$ ,  $\text{H-C}(3)$ ).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 38.42 ( $q$ ,  $\text{MsO}$ ); 61.10 ( $d$ ,  $\text{C}(7)$ ); 66.52 ( $t$ ,  $\text{CH}_2\text{-C}(7)$ ); 71.71 ( $d$ ,  $\text{C}(4)$ ); 73.46 ( $t$ ,  $\text{PhCH}_2$ ); 74.69 ( $d$ ,  $\text{C}(5)$ ); 74.78, 75.12 ( $2t$ , 2  $\text{PhCH}_2$ ); 79.52 ( $d$ ,  $\text{C}(6)$ ); 127.00–128.89 (several  $d$ ); 133.61 ( $d$ ,  $\text{C}(3)$ ); 136.99 ( $s$ ,  $\text{C}(3a)$ ); 137.07, 137.38, 137.38 ( $3s$ ). FAB-MS: 551 (25,  $[M + \text{H}]^+$ ), 550 (100,  $M^+$ ), 454 (46), 91 (100).

(4R,5S,6R,7R)-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  $\text{Bu}_4\text{NCl}$  (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.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 4.03 ( $dd$ ,  $J = 6.6$ , 3.4,  $\text{H-C}(5)$ ); 4.05–4.15 ( $m$ , 2 H); 4.47 (br.  $s$ ,  $\text{PhCH}_2$ ); 4.57–4.78 ( $m$ , 6 H); 5.41 ( $d$ ,  $J = 3.3$ , irradi. at 4.03  $\rightarrow s$ ,  $\text{H-C}(4)$ ); 7.22–7.38 ( $m$ , 15 arom. H); 7.72 ( $s$ ,  $\text{H-C}(3)$ ).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 48.52 ( $d$ ,  $\text{C}(4)$ ); 60.42 ( $d$ ,  $\text{C}(7)$ ); 68.27 ( $t$ ,  $\text{CH}_2\text{-C}(7)$ ); 72.23 ( $d$ ,  $\text{C}(5)$ ); 73.12, 73.34, 73.57 ( $3t$ , 3  $\text{PhCH}_2$ ); 76.90 ( $d$ ,  $\text{C}(6)$ ); 127.72–128.61 (several  $d$ ); 132.67 ( $s$ ,  $\text{C}(3)$ ); 133.05 ( $s$ ,  $\text{C}(3a)$ ); 136.86, 137.14, 137.68 ( $3s$ ). FAB-MS: 492 (32), 491 (25), 490 (100,  $M^+$ ), 454 (15), 91 (51).

(4S,5R,6R,7R)-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  $\text{NaN}_3$  (108 mg, 1.66 mmol) and stirred at 50° for 3 h. DMF was evaporated, the residue distributed between  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$  (3  $\times$

50 ml), and the combined org. phase washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), 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  $\text{NaN}_3$  (125 mg, 1.92 mmol) and stirred at  $50^\circ$  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 ( $\text{CH}_2\text{Cl}_2$ ): 3033m, 2929m, 2871m, 2109s, 1497m, 1454m, 1363m, 1326m, 1215m, 1145s, 1109s, 1019s.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 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).  $^1\text{H-NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ ): 3.38 (t,  $J=8.7$ , irradi. at 3.93  $\rightarrow$  d,  $J=8.5$ , H–C(5)); 3.67 (dd,  $J=10.3$ , 2.2, irradi. at 3.93  $\rightarrow$  d,  $J=10.3$ , CH–C(7)); 3.93 (br. d,  $J=8.7$ , irradi. at 3.38  $\rightarrow$  change, H–C(4)); 3.92–3.98 (m, irradi. at 3.67  $\rightarrow$  change, irradi. at 4.31  $\rightarrow$  change, H–C(7)); 4.05 (d,  $J=11.5$ , PhCH); 4.07 (t,  $J=8.4$ , irradi. at 3.38  $\rightarrow$  change, H–C(6)); 4.16 (d,  $J=11.8$ , PhCH); 4.31 (dd,  $J=10.3$ , 3.4, irradi. at 3.67  $\rightarrow$  change, irradi. at 3.93  $\rightarrow$  d,  $J=10.3$ , CH'–C(7)); 4.44 (d,  $J=11.5$ , PhCH); 4.57 (d,  $J=1.3$ , PhCH); 4.63 (d,  $J=11.6$ , PhCH); 4.69 (d,  $J=11.5$ , PhCH); 6.99–7.29 (m, 15 arom. H); 7.59 (d,  $J=0.8$ , irradi. at 3.93  $\rightarrow$  s, H–C(3)).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 57.10 (d, C(4)); 61.56 (d, C(7)); 66.71 (t,  $\text{CH}_2$ –C(7)); 73.60, 75.26, 75.54 (3t, 3 PhCH<sub>2</sub>); 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 (3s). 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* ( $\text{NH}_4^+$  form), 0.1M  $\text{NH}_4\text{OH}$ ) gave **5** (29 mg, 81%).  $R_f$  (MeOH/AcOEt 1:9) 0.30.  $^1\text{H-NMR}$  (300 MHz,  $\text{D}_2\text{O}$ ): 3.71 (t,  $J\approx 9.5$ , H–C(5)); 3.99 (d,  $J=9.3$ , irradi. at 3.71  $\rightarrow$  d,  $J=3.2$ , H–C(4)); 4.12 (t,  $J\approx 9.5$ , irradi. at 4.42  $\rightarrow$  d,  $J=9.7$ , irradi. at 3.71  $\rightarrow$  dd,  $J=9.7$ , 3.2, H–C(6)); 4.24 (dd,  $J=12.8$ , 2.2, irradi. at 4.42  $\rightarrow$  d,  $J=12.8$ , CH–C(7)); 4.42 (br. dt,  $J\approx 9.3$ , 2.4, H–C(7)); 4.60 (dd,  $J=12.8$ , 2.5, irradi. at 4.42  $\rightarrow$  d,  $J=12.8$ , CH'–C(7)); 7.84 (s, H–C(3)).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{D}_2\text{O}$ ): 51.16 (d, C(4)); 61.06 (t,  $\text{CH}_2$ –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  $\text{Bu}_4\text{NBr}$  (320 mg, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 ml) was cooled to  $-78^\circ$ , treated with 1M  $\text{BCl}_3$  in  $\text{CH}_2\text{Cl}_2$  (1 ml) for 15 min, and allowed to warm to  $-10^\circ$  within 3 h (TLC: ca. 50% conversion). After addition of  $\text{Bu}_4\text{NBr}$  (160 mg, 0.5 mmol), the soln. was cooled to  $-78^\circ$ , treated dropwise with  $\text{BCl}_3$  (1 ml) for 15 min, and allowed to warm to  $+23^\circ$  within 3 h (TLC: complete consumption of **35**). The soln. was cooled to  $-30^\circ$  and treated with a sat. aq.  $\text{K}_2\text{CO}_3$  soln. and ice and warmed to  $23^\circ$ . The org. layer was separated and the aq. layer extracted with  $\text{Et}_2\text{O}$  ( $3\times$ ). The combined org. layers were dried ( $\text{MgSO}_4$ ) and evaporated. The residue was dissolved in  $\text{Et}_2\text{O}$ , the soln. washed with brine, dried ( $\text{MgSO}_4$ ), and evaporated. FC ( $\text{CH}_2\text{Cl}_2/\text{AcOEt}$  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.  $95^\circ$ .  $R_f$  ( $\text{CH}_2\text{Cl}_2/\text{AcOEt}$  7:3) 0.41.  $[\alpha]_D^{20} = +51.1$  ( $c=0.95$ ,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ ): 3511w (br.), 3388m, 3067w, 3008w, 2867m, 1678s, 1497w, 1454m, 1362w, 1304m, 1116m, 1028m.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 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  $\text{CD}_3\text{OD}$ , OH); 4.14 (d,  $J=9.3$ , H–C(2)); 4.45 (d,  $J=12.1$ , PhCH); 4.49 (d,  $J=12.1$ , PhCH); 4.55 (d,  $J=11.2$ , PhCH); 4.84 (d,  $J=11.2$ , PhCH); 4.93 (d,  $J=11.2$ , PhCH); 5.07 (d,  $J=11.2$ , PhCH); 6.52 (br. s, exchange with  $\text{CD}_3\text{OD}$ , NH); 7.22–7.69 (m, 15 arom. H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 55.11 (d, C(5)); 70.43 (t, C(6)); 72.17 (d, C(2)); 73.50, 74.75, 75.04 (3t, 3 PhCH<sub>2</sub>); 76.11, 82.62 (2d, C(3), C(4)); 127.97–128.81 (several s); 137.61, 137.67, 138.68 (3s); 172.30 (s, C=O). CI-MS ( $\text{NH}_3$ ): 448 (21,  $[M+1]^+$ ). Anal. calc. for  $\text{C}_{27}\text{H}_{29}\text{NO}_5$  (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  $23^\circ$  with  $\text{Ac}_2\text{O}$  (0.15 ml, 1.6 mmol) and stirred for 2 h. Evaporation of the solvent at reduced pressure and  $40^\circ$  (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 ( $\text{CHCl}_3$ ): 3390w, 3038w, 2927w, 2857w, 1749m, 1689s, 1602m, 1455m, 1374w, 1318w, 1118w, 910w, 649w, 607w, 556w.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 2.05 (s, AcO); 3.26–3.32 (m, H–C(5)); 3.54–3.65 (m, C(6)); 3.67 (t,  $J=9.0$ , irradi. at 4.02  $\rightarrow$  d,  $J\approx 9.0$ , 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<sub>2</sub>); 4.75 (d,  $J=11.2$ , PhCH); 4.83 (d,  $J=11.5$ , PhCH); 4.89 (d,  $J=11.2$ , PhCH); 4.93 (d,  $J=10.9$ , PhCH); 5.32 (d,  $J=9.3$ , irradi. at 4.02  $\rightarrow$  s, H–C(2)); 6.30 (br. s, NH); 7.19–7.45 (m, 15 arom. H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 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 (3t, 3 PhCH<sub>2</sub>); 77.69 (d); 80.55 (d); 128.04–128.80 (several d); 137.57, 137.68, 138.10 (3s); 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  $\text{BCl}_3$  within 2 min. The crude product was dissolved in pyridine (5 ml), treated with  $\text{Ac}_2\text{O}$  (0.1 ml, 1.1 mmol), stirred for 2 h at  $23^\circ$ , and evaporated at  $40^\circ$  (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  $\text{Bu}_4\text{NBr}$ . For completion of the reaction, a third equiv. of  $\text{BCl}_3$  had to be added. The crude product was dissolved in pyridine (1 ml), the soln. treated with  $\text{Ac}_2\text{O}$  (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  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  instead of 1M  $\text{BCl}_3$ . FC gave **37** (69 mg, 51%) and **38** (26 mg, 32%).

*Data of 38*:  $R_f$  (AcOEt/hexane 1:1) 0.13. IR ( $\text{CHCl}_3$ ): 3390w, 3008w, 2908w, 1747s, 1692s, 1603w, 1454m, 1371m, 1316w, 1111m, 1047s, 909w, 604w.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 2.04, 2.06 (2s, 2 AcO); 3.59 (ddd,  $J = 9.0, 6.2, 2.8$ , H-C(5)); 3.69 (t,  $J = 9.0$ , irradiat. at 4.01  $\rightarrow$  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,  $J = 10.9$ , PhCH); 4.74 (d,  $J = 11.5$ , PhCH); 4.87 (d,  $J = 11.5$ , PhCH); 4.91 (d,  $J = 10.9$ , PhCH); 5.28 (d,  $J = 9.3$ , irradiat. at 4.01  $\rightarrow$  s, H-C(2)); 6.39 (br. s, NH); 7.26–7.39 (m, 10 arom. H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 20.69 (br. q, 2 Me); 54.88 (d, C(5)); 63.66 (t, C(6)); 72.11 (d); 74.94, 75.12 (2t, 2 PhCH<sub>2</sub>); 76.28 (d); 80.36 (d); 128.20–128.85 (several d); 137.39, 137.92 (2s); 167.67 (s, NC=O); 170.34, 170.91 (2s, 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  $80^\circ$  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.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 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 PhCH); 4.25 (d,  $J = 11.7$ , 0.5 H, PhCH); 4.35–4.58 (m, H-C(2), OH, 3 PhCH); 4.65 (d,  $J = 11.5$ , 0.5 H, PhCH); 4.81 (d,  $J = 11.3$ , 0.5 H, PhCH); 4.89 (d,  $J = 11.5$ , 0.5 H, PhCH); 4.90 (d,  $J = 11.7$ , 0.5 H, PhCH); 5.09 (d,  $J = 11.7$ , 0.5 H, PhCH); 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  $25^\circ$  for 20 h. Normal workup, FC (AcOEt/hexane 1:2), and crystallization from  $\text{Et}_2\text{O}$ /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  $80^\circ$ : **41** (600 mg, 92%).  $R_f$  ( $\text{Et}_2\text{O}$ /hexane 2:1) 0.51. M.p.  $91^\circ$ . IR ( $\text{CHCl}_3$ ): 3361w, 3007m, 2978w, 2878m, 2867m, 1747s, 1597m, 1514s, 1454m, 1370m, 1313m, 1070s, 1028w, 910w.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 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<sub>2</sub>); 4.47 (d,  $J = 10.9$ , PhCH); 4.76 (s, PhCH<sub>2</sub>); 4.78 (d,  $J = 10.9$ , PhCH); 5.59 (d,  $J = 8.1$ , H-C(2)); 7.16–7.40 (m, 15 arom. H); 8.11 (br. s, exchange with  $\text{CD}_3\text{OD}$ , NH).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 20.69 (q, Me); 58.09 (d, C(5)); 68.26 (t, C(6)); 73.04, 74.06, 74.12 (3t, 3 PhCH<sub>2</sub>); 75.65, 76.15, 79.45 (3d, C(2), C(3), C(4)); 127.61–128.22 (several d); 136.66, 136.82, 137.23 (3s), 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  $\text{C}_{29}\text{H}_{31}\text{NO}_5\text{S}$  (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  $\text{Hg}(\text{OAc})_2$  (300 mg, 0.941 mmol) in THF (5 ml) was treated at  $0^\circ$  with aminoacetaldehyde dimethyl acetal (0.5 ml, 4.6 mmol) and stirred at  $0^\circ$  for 1 h. Normal workup, filtration of the org. layer through *Celite*, drying ( $\text{MgSO}_4$ ), 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 ( $\text{CHCl}_3$ ): 3440m, 3370w, 3050w, 3010m, 2925s, 2870s, 1750s, 1649s, 1497s, 1453s, 1361m, 1261w, 1090m.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 1.99 (s, AcO); 3.25–3.41 (m, irradiat. at 4.45  $\rightarrow$  change, NCH<sub>2</sub>); 3.25 (br. s, 2 MeO); 3.55–3.58 (m, H-C(5)); 3.68–3.81 (m, irradiat. at 3.55  $\rightarrow$  change, 2 H-C(6)); 3.78 (t,  $J = 9.0$ , irradiat. at 3.55  $\rightarrow$  d,  $J \approx 8.5$ , H-C(4)); 3.89 (dd,  $J = 9.0, 7.8$ , irradiat. at 5.39  $\rightarrow$  d,  $J \approx 9.0$ , H-C(3)); 4.45 (t,  $J = 5.3$ , irradiat. at 3.30  $\rightarrow$  s, NCH<sub>2</sub>CH); 4.51–4.60 (m, 4 PhCH, NH); 4.80 (d,  $J = 11.5$ , PhCH); 4.82 (d,  $J = 11.5$ , PhCH); 5.39 (d,  $J = 7.8$ , irradiat. at 3.89  $\rightarrow$  s, H-C(2)); 7.25–7.39 (m, 15 arom. H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 20.89 (q, Me); 42.52 (t, CH<sub>2</sub>N); 54.05 (q, MeO); 54.33 (q, MeO); 61.51 (d, C(5)); 71.38 (t, C(6)); 72.69, 73.40, 74.75 (3t, 3 PhCH<sub>2</sub>); 74.44 (d, C(2)); 78.31, 82.06 (2d, C(3), C(4)); 102.62 (d, CH(OMe)<sub>2</sub>); 127.65–128.67 (several d); 137.51, 138.03, 138.51 (3s); 154.10 (s, C(1)); 171.50 (s, C=O).

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

(5R,6R,7R,8S)- and (5R,6R,7R,8R)-6,7-Bis(benzyloxy)-5-[ (benzyloxy)methyl]-5,6,7,8-tetrahydroimida-zo[1,2-a]pyridin-8-ol (**44** and **45**). *a*) A soln. of **42/43** 2:1 (350 mg, 0.61 mmol) and TsOH·H<sub>2</sub>O (500 mg) in toluene (25 ml) was treated with H<sub>2</sub>O (0.5 ml) and stirred at 80° for 12 h. Workup (Et<sub>2</sub>O, sat. aq. K<sub>2</sub>CO<sub>3</sub> 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. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 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, irradi. at 4.96 →  $d$ ,  $J\approx 8.5$ , H–C(7)); 4.17 (ddd,  $J=7.5$ , 5.0, 2.8, H–C(5)); 4.44 (s, PhCH<sub>2</sub>); 4.57 (d,  $J=11.8$ , PhCH); 4.89 (d,  $J=11.2$ , PhCH); 4.95 (d,  $J=11.2$ , PhCH); 4.96 (d,  $J=7.3$ , irradi. at 4.06 → s, H–C(8)); 5.15 (d,  $J=11.5$ , PhCH); 7.04, 7.11 (2d,  $J=1.3$ , H–C(2), H–C(3)); 7.20–7.47 (m, 15 arom. H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 58.71 (d, C(5)); 68.02 (d, C(8)); 68.83 (t, CH<sub>2</sub>–C(5)); 73.40, 73.92, 74.99 (3t, 3 PhCH<sub>2</sub>); 75.47, 82.95 (2d, 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 (3s); 147.48 (s, C(8a)). FAB-MS: 497 (100, [M+1]<sup>+</sup>).

*Data of 45:*  $R_f$  (AcOEt/hexane 1:1) 0.10. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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<sub>2</sub>); 4.61 (d,  $J=11.2$ , PhCH); 4.73 (d,  $J=11.8$ , PhCH); 4.85 (d,  $J=11.8$ , PhCH); 4.94 (d,  $J=11.5$ , PhCH); 5.16 (d,  $J=3.43$ , H–C(8)); 7.02, 7.11 (2d,  $J=1.3$ , H–C(2), H–C(3)); 7.21–7.39 (m, 15 arom. H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 59.39, 62.65 (2d, C(5), C(8)); 71.03 (t, CH<sub>2</sub>–C(5)); 72.56, 73.42, 74.65 (3t, 3 PhCH<sub>2</sub>); 73.79, 79.37 (2d, 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)).

(5R,6R,7R,8S)- and (5R,6R,7R,8R)-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<sub>3</sub>P (62 μl, 0.25 mmol) in THF (10 ml) was cooled to 0°, treated with 4% HN<sub>3</sub> 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<sub>3</sub><sup>14</sup> 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<sub>3</sub>): 3004m, 2872w, 2108s, 1743w, 1605w, 1535m, 1496m, 1454m, 1367w, 1110s, 1034w, 931w. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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,  $J=12.1$ , PhCH); 4.44 (d,  $J=12.1$ , PhCH); 4.55 (d,  $J=11.2$ , PhCH); 4.73 (d,  $J=6.5$ , H–C(8)); 4.79 (d,  $J=11.2$ , PhCH); 4.87 (d,  $J=10.9$ , PhCH); 4.88 (d,  $J=11.5$ , PhCH); 7.02, 7.12 (2d,  $J=1.3$ , H–C(2), H–C(3)); 7.13–7.36 (m, 15 arom. H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): 58.84, 59.09 (2d, C(5), C(8)); 68.78 (t, CH<sub>2</sub>–C(5)); 73.42, 74.65, 74.92 (3t, 3 PhCH<sub>2</sub>); 75.36, 80.84 (2d, 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)).

<sup>14</sup>) Carried out by treating NaN<sub>3</sub> with conc. H<sub>2</sub>SO<sub>4</sub> and passing the HN<sub>3</sub> gas by means of a Teflon tube through the reaction mixture at 0° during 30 min. A HN<sub>3</sub> concentration of 2.6M was determined by titration (NaOH/phenolphthaleine).

*Data of 47:*  $R_f$  (AcOEt/hexane 1:1) 0.35. IR (CHCl<sub>3</sub>): 3008m, 2869w, 2106s, 1739w, 1602w, 1549w, 1496m, 1454m, 1366w, 1100s, 1038w, 931w. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 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, irradi. at 4.91 →  $d$ ,  $J \approx 8.0$ , H–C(7)); 4.09–4.15 (m, irradi. at 4.00 → change, H–C(5), H–C(6)); 4.43 ( $d$ ,  $J = 11.8$ , PhCH); 4.48 ( $d$ ,  $J = 11.8$ , PhCH); 4.59 ( $d$ ,  $J = 11.2$ , PhCH); 4.71 ( $d$ ,  $J = 11.8$ , PhCH); 4.79 ( $d$ ,  $J = 11.8$ , PhCH); 4.88 ( $d$ ,  $J = 11.5$ , PhCH); 4.91 ( $d$ ,  $J = 3.7$ , irradi. at 4.00 →  $s$ , H–C(8)); 7.09, 7.11 (2d,  $J = 1.3$ , H–C(2), H–C(3)); 7.21–7.39 (m, 15 arom. H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 55.75 ( $d$ , C(5)); 59.17 ( $d$ , C(8)); 70.31 ( $t$ , CH<sub>2</sub>–C(5)); 73.11, 73.42, 74.65 (3 $t$ , 3 PhCH<sub>2</sub>); 77.35, 78.60 (2d, 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 (3s); 140.77 ( $s$ , C(8a)). FAB-MS: 497 (100, [M + 1]<sup>+</sup>).

(5R,6R,7R,8S)-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<sub>4</sub><sup>+</sup> form), 0.1M NH<sub>4</sub>OH) gave **1** (27 mg, 79%). Colourless, highly hygroscopic solid, which turned yellow upon standing.  $R_f$  (AcOEt/MeOH/H<sub>2</sub>O 5:5:1) 0.05. <sup>1</sup>H-NMR (D<sub>2</sub>O): 3.90 ( $t$ ,  $J = 9.3$ , H–C(6)); 3.98–4.31 (m, H–C(5), H–C(7), H–C(8), CH<sub>2</sub>–C(5)); 7.15, 7.35 (2d,  $J = 1.6$ , H–C(2), H–C(3)). <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O, 1 equiv. of CF<sub>3</sub>CO<sub>2</sub>H): 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 (2d,  $J = 2.0$ , H–C(2), H–C(3)). <sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O, 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 ( $t$ ,  $J \approx 7.9$ , 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 (2d,  $J = 2.0$ , H–C(2), H–C(3)). <sup>13</sup>C-NMR (125 MHz, D<sub>2</sub>O): 50.70 ( $d$ , C(8)); 61.53 ( $t$ , CH<sub>2</sub>–C(5)); 65.47 ( $d$ , C(5)); 69.63, 71.54 (2d, C(6), C(7)); 124.01, 125.10 (2d, C(2), C(3)); 140.23 ( $s$ , C(8a)). CI-MS: 200 (11, [M + 1]<sup>+</sup>), 177 (100). Anal. calc. for C<sub>8</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub> · 1.5 H<sub>2</sub>O (226.24): C 42.47, H 7.12, N 18.57; found: C 42.12, H 6.82, N 18.67.

(5R,6R,7S,8S)-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)<sub>2</sub> (80 mg, 0.25 mmol) in THF (2 ml) was cooled to 0°, treated with formylhydrazine<sup>15</sup> (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<sub>3</sub>): 3008w, 2870m, 1742s, 1455m, 1428m, 1100s, 1029m, 909m. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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, irradi. at 6.21 →  $d$ ,  $J \approx 6.0$ , H–C(7)); 4.36–4.41 (m, H–C(5)); 4.41 ( $d$ ,  $J = 11.8$ , PhCH); 4.47 ( $d$ ,  $J = 11.8$ , PhCH); 4.48 ( $d$ ,  $J = 11.5$ , PhCH); 4.69 ( $d$ ,  $J = 11.5$ , PhCH); 4.73 ( $d$ ,  $J = 12.1$ , PhCH); 4.81 ( $d$ ,  $J = 11.5$ , PhCH); 6.21 ( $d$ ,  $J = 5.0$ , H–C(8)); 7.16–7.38 (m, 15 arom. H); 8.32 ( $s$ , H–C(3)). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 20.89 ( $s$ , Me); 58.08 ( $d$ , C(5)); 64.80 ( $d$ , C(8)); 69.46 ( $t$ , CH<sub>2</sub>–C(5)); 73.63, 73.65, 73.84 (3 $t$ , 3 PhCH<sub>2</sub>); 74.73, 76.93 (2d, C(6), C(7)); 128.12–128.91 (several  $d$ ); 137.05, 137.10, 137.29 (3s); 142.71 ( $d$ , C(3)); 147.90 ( $s$ , C(8a)); 170.31 ( $s$ , C=O). FAB-MS: 514 (100, [M + 1]<sup>+</sup>).

(5R,6R,7R,8S)-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<sub>3</sub> 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<sub>3</sub>): 3533m, 3324m (br.), 3090m, 3007s, 2870m, 1498m, 1454m, 1364m, 1104s, 1028m, 911w. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 1.83 (br.  $s$ , exchange with CD<sub>3</sub>OD, 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, irradi. at 5.09 →  $d$ ,  $J \approx 7.0$ , H–C(7)); 4.33–4.37 (m, H–C(5)); 4.40 ( $d$ ,  $J = 11.8$ , PhCH); 4.47 ( $d$ ,  $J = 11.8$ , PhCH); 4.56 ( $d$ ,  $J = 11.5$ , PhCH); 4.71 ( $d$ ,  $J = 11.6$ , PhCH); 4.80 ( $d$ ,  $J = 11.5$ , PhCH); 4.92 ( $d$ ,  $J = 11.5$ , PhCH); 5.09 (br.  $d$ ,  $J = 5.6$ , H–C(8)); 7.19–7.39 (m, 15 arom. H); 8.30 ( $s$ , H–C(3)). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 57.84 ( $d$ , C(5)); 65.25 (C(8)); 69.60 ( $t$ , CH<sub>2</sub>–C(5)); 73.65 ( $t$ , PhCH<sub>2</sub>); 74.13 (br.  $t$ , 2 PhCH<sub>2</sub>); 74.75, 79.76 (2d, C(6), C(7)); 128.21–128.91 (several  $d$ ); 136.93, 137.13, 137.71 (3s); 142.21 ( $d$ , C(3)); 152.04 ( $s$ , C(8a)). CI-MS (NH<sub>3</sub>): 472 (15, [M + 1]<sup>+</sup>), 380 (23), 91 (100).

(5R,6R,7R,8R)-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<sub>3</sub>): 3572w, 3321w (br.), 3008m, 2927m, 2869m, 1953w, 1811w, 1604w, 1497m, 1454m, 1364m, 1307w, 1265m, 1098s, 1028m, 1010w, 911w. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 3.67 ( $d$ ,  $J = 6.2$ , CH<sub>2</sub>–C(5)); 4.00 (dd,  $J = 6.9$ , 4.4, H–C(6)); 4.08 (dd,  $J = 6.9$ , 3.4, irradi. at 5.33 →  $d$ ,  $J = 6.9$ , H–C(7)); 4.29 ( $td$ ,  $J = 6.2$ , 4.4, H–C(5)); 4.42 ( $d$ ,  $J = 11.8$ , PhCH); 4.50 ( $d$ ,  $J = 11.8$ , PhCH); 4.55 ( $d$ ,  $J = 11.8$ , PhCH); 4.71 ( $d$ ,  $J = 12.5$ , PhCH); 4.75 ( $d$ ,  $J = 12.4$ , PhCH);

<sup>15</sup>) Fluka purum, recrystallized from toluene.

4.90 (*d*, *J* = 12.1, PhCH); 5.33 (*d*, *J* = 3.1, H–C(8)); 5.33 (br. *s*, exchange with CD<sub>3</sub>OD, OH); 7.17–7.40 (*m*, 15 arom. H); 8.36 (*s*, H–C(3)). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, 5% CD<sub>3</sub>OD): 3.62–3.66 (*m*, CH<sub>2</sub>–C(5)); 3.98–3.99 (*m*, C(6), C(7)); 4.20–4.28 (*m*, C(5)); 4.41 (*d*, *J* = 11.8, PhCH); 4.48 (*d*, *J* = 11.8, PhCH); 4.54 (*d*, *J* = 11.5, PhCH); 4.66 (*d*, *J* = 11.8, PhCH); 4.76 (*d*, *J* = 11.8, PhCH); 4.84 (*d*, *J* = 11.8, PhCH); 5.22 (br. *s*, H–C(8)); 7.14–7.38 (*m*, 15 arom. H); 8.35 (*s*, H–C(3)). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 58.49 (*d*, C(5)); 62.08 (*d*, C(8)); 71.09 (*t*, CH<sub>2</sub>–C(5)); 73.65 (br. *t*, 3 PhCH<sub>2</sub>); 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<sub>2</sub>Cl<sub>2</sub> (2 ml) containing 100 μl of pyridine was treated with Tf<sub>2</sub>O (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<sub>2</sub> stream through the mixture. The resulting reddish solid (23 mg) contained the triflates **53/54** in a ratio of 1 : 1 (by <sup>1</sup>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%).

(5R,6R,7S,8S)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-8-[(methylsulfonyl)oxy]-[1,2,4]triazolo[4,3-*a*]pyridine (**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<sub>2</sub>O, normal workup gave **52** (59 mg, 98%), which was used for the next step without further purification. *R*<sub>f</sub> (AcOEt) 0.31. IR (CHCl<sub>3</sub>): 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*. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 3.41 (*s*, MeSO<sub>2</sub>); 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, irradi. at 5.96 → *d*, *J* = 5.9, H–C(7)); 4.39 (*d*, *J* = 11.8, PhCH); 4.37–4.42 (*m*, H–C(5)); 4.44 (*d*, *J* = 11.5, PhCH); 4.46 (*d*, *J* = 12.1, PhCH); 4.68 (*d*, *J* = 11.5, PhCH); 4.77 (*d*, *J* = 11.5, PhCH); 4.90 (*d*, *J* = 11.2, PhCH); 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)). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 39.90 (*q*, MeSO<sub>2</sub>); 58.70 (*d*, C(5)); 69.46 (*t*, CH<sub>2</sub>–C(5)); 70.99 (*d*, C(8)); 73.58, 73.68, 74.29 (3*t*, 3 PhCH<sub>2</sub>); 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)).

(5R,6R,7R,8S)-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<sub>3</sub> (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<sub>3</sub> (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<sub>3</sub>P (16 μl, 0.065 mmol) in THF (3 ml) was saturated at 0° with HN<sub>3</sub>, 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*<sub>f</sub> (AcOEt) 0.31. IR (CHCl<sub>3</sub>): 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*. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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, irradi. at 4.93 → *d*, *J* = 7.5, H–C(7)); 4.23–4.27 (*m*, H–C(5)); 4.41 (*d*, *J* = 11.8, PhCH); 4.50 (*d*, *J* = 11.8, PhCH); 4.58 (*d*, *J* = 11.5, PhCH); 4.67 (*d*, *J* = 11.5, PhCH); 4.75 (*d*, *J* = 11.8, PhCH); 4.78 (*d*, *J* = 11.8, PhCH); 4.93 (*d*, *J* = 3.7, H–C(8)); 7.17–7.41 (*m*, 15 arom. H); 8.39 (*s*, H–C(3)). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 53.49 (*d*, C(5)); 58.16 (*d*, C(8)); 70.34 (*t*, CH<sub>2</sub>–C(5)); 73.13 (*d*); 73.68, 73.79, 74.08 (3*t*, 3 PhCH<sub>2</sub>); 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<sub>3</sub>): 497 (6, [M + 1]<sup>+</sup>), 239 (22), 91 (100).

(5R,6R,7R,8R)-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<sub>3</sub> (12 mg, 0.185 mmol): **56** (10 mg, 92%). *R*<sub>f</sub> (AcOEt) 0.45. IR (CHCl<sub>3</sub>): 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*. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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, irradi. at 3.95 → *d*, *J* ≈ 6.2, H–C(6)); 3.95 (*dd*, *J* = 7.2, 6.2, irradi. 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, PhCH); 4.46 (*d*, *J* = 12.1, PhCH); 4.53 (*d*, *J* = 11.5, PhCH); 4.56 (*d*, *J* = 11.8, PhCH); 4.84 (*d*, *J* = 11.8, 2 PhCH); 4.85 (*d*, *J* = 6.2, irradi. at 3.95 → *s*, H–C(8)); 7.14–7.43 (*m*, 15 arom. H); 8.31 (*s*, H–C(3)). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 56.09 (br. *d*, C(5), C(8)); 68.84 (*t*, CH<sub>2</sub>–C(5)); 73.65, 74.31, 74.78 (3*t*, 3 PhCH<sub>2</sub>); 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<sub>2</sub>Cl<sub>2</sub> (2 ml) was cooled to –78°, treated with Tf<sub>2</sub>O (16 μl, 0.1 mmol), allowed to reach 0° within 1 h, cooled to –78°, and treated with a suspension of NaN<sub>3</sub> (6.3 mg, 0.098 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>): 3453w (br.), 3394m, 3089w, 3066w, 2868m, 1496s, 1454w, 1361m, 1310m, 1262m, 1093m, 1073s, 1028m, 909w. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 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,  $J=3.1$ , irradi. at 4.44 →  $d$ ,  $J\approx 3.0$ , H-C(3)); 4.31 (d,  $J=11.5$ , PhCH); 4.44 (d,  $J=11.5$ , PhCH); 4.44 (d,  $J=3.1$ , irradi. at 4.11 →  $s$ , H-C(2)); 4.45 (br. s, exchange with CD<sub>3</sub>OD, OH); 4.47 (s, PhCH<sub>2</sub>); 4.63 (d,  $J=12.1$ , PhCH); 4.83 (d,  $J=12.1$ , PhCH); 6.19 (s, exchange with CD<sub>3</sub>OD, NH); 7.17–7.20 (m, 2 arom. H); 7.21–7.42 (m, 13 arom. H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 55.15 (d, C(5)); 69.06 (d, C(2)); 70.58 (t, C(6)); 71.63, 73.32, 73.80 (3t, 3 PhCH<sub>2</sub>); 75.63, 77.07 (2d, C(3), C(4)); 127.87–128.58 (several d); 137.06, 137.32, 138.06 (3s); 171.83 (s, C=O). FAB-MS: 448 (100, [M + 1]<sup>+</sup>).

*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<sub>3</sub>): 3393m, 3089w, 3067m, 3008m, 2920m, 2867m, 1749s, 1687s, 1496w, 1454m, 1371m, 1318w, 1094s, 1028m, 909m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 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, irradi. at 5.65 →  $d$ ,  $J=4.1$ , H-C(3)); 4.41 (d,  $J=11.8$ , PhCH); 4.44 (d,  $J=11.5$ , PhCH); 4.49 (d,  $J=11.8$ , PhCH); 4.54 (d,  $J=11.8$ , 2 PhCH); 4.70 (d,  $J=12.1$ , PhCH); 5.65 (d,  $J=3.1$ , H-C(2)); 6.01 (br. s, exchange with CD<sub>3</sub>OD, NH); 7.19–7.39 (m, 15 arom. H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 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 (3t, 3 PhCH<sub>2</sub>); 77.69, 80.55 (2d, C(3), C(4)); 128.10–129.95 (several d); 137.29, 137.63, 137.70 (3s); 166.98 (s, NC=O); 170.29 (s, OC=O). FAB-MS: 490 (21, [M + 1]<sup>+</sup>), 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<sub>3</sub>): 3362m, 3069w, 3067w, 3008m, 2916m, 2868m, 1953w, 1748s, 1599w, 1520s, 1497s, 1454m, 1370m, 1316m, 1096s, 910m. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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, irradi. at 5.83 →  $d$ ,  $J=4.0$ , H-C(3)); 4.39 (d,  $J=11.5$ , PhCH); 4.46 (d,  $J=11.8$ , PhCH); 4.51 (d,  $J=11.8$ , PhCH); 4.56 (d,  $J=11.8$ , PhCH); 4.58 (d,  $J=11.8$ , PhCH); 4.77 (d,  $J=12.1$ , PhCH); 5.83 (d,  $J=3.1$ , H-C(2)); 7.18–7.40 (m, 15 arom. H); 8.20 (br. s, exchange with CD<sub>3</sub>OD, NH). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 21.18 (q, Me); 58.49 (d, C(5)); 69.73 (t, C(6)); 72.58, 73.05, 73.50 (3t, 3 PhCH<sub>2</sub>); 73.84, 74.41, 76.35 (3d, C(2), C(3), C(4)); 128.17–128.83 (several d); 137.21, 137.32, 137.69 (3s); 170.08 (s, C=O); 197.81 (s, C=S).

*(5R,6R,7S,8R)-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)<sub>2</sub> (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<sub>3</sub>): 3008m, 2870w, 1749s, 1498m, 1454m, 1371m, 1112s, 1071s, 1045m, 946w, 910w, 836w. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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, irradi. at 6.61 →  $d$ ,  $J\approx 8.1$ , H-C(7)); 4.25 (ddd,  $J=8.0$ , 5.3, 3.4, H-C(5)); 4.44 (d,  $J=11.8$ , PhCH); 4.50 (d,  $J=12.5$ , PhCH); 4.54 (d,  $J=11.5$ , PhCH); 4.57 (d,  $J=11.5$ , PhCH); 4.78 (d,  $J=11.2$ , PhCH); 4.84 (d,  $J=11.5$ , PhCH); 6.61 (d,  $J=3.7$ , H-C(8)); 7.21–7.39 (m, 15 arom. H); 8.40 (s, H-C(3)). <sup>1</sup>H-NMR (75 MHz, CDCl<sub>3</sub>): 20.91 (q, Me); 58.39 (d, C(5)); 61.11 (d, C(8)); 70.33 (t, CH<sub>2</sub>-C(5)); 73.10, 76.80 (2d, C(6), C(7)); 73.16, 73.64, 74.28, (3t, 3 PhCH<sub>2</sub>); 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).

*(5R,6R,7S,8R)-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  $\mu$ l, 0.386 mmol) in pyridine (1 ml): **62** (57 mg, 84%).  $R_f$  (AcOEt) 0.26. IR (CHCl<sub>3</sub>): 3150w, 3066m, 3008m, 2928m, 2869m, 1952w, 1869w, 1810w, 1734w, 1604w, 1496m, 1412w, 1368s, 1337m, 1261m, 1217s, 1117s, 1110s, 1028m, 972m, 910m. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 3.29 (s, MeSO<sub>2</sub>); 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, irradi. 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,  $J=11.5$ , PhCH); 4.49 (d,  $J=11.8$ , PhCH); 4.57 (d,  $J=11.5$ , PhCH); 4.64 (d,  $J=11.5$ , PhCH); 4.84 (d,  $J=11.5$ , PhCH); 4.95 (d,  $J=11.5$ , PhCH); 6.15 (d,  $J=3.4$ , H-C(8)); 7.17–7.41 (m, 15 arom. H); 8.43 (s, H-C(3)). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 39.75 (q, MeSO<sub>2</sub>); 58.54 (d, C(5)); 69.70 (d, C(8)); 69.99 (t, CH<sub>2</sub>-C(5)); 72.95 (d); 73.34, 73.66, 74.54 (3t, 3 PhCH<sub>2</sub>); 76.74 (d); 128.20–128.94 (several d); 136.93, 137.00, 137.06 (3s); 138.02 (d, C(3)); 147.31 (s, C(8a)).

*(5R,6R,7S,8S)-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<sub>4</sub><sup>+</sup> form), 0.01M aq. NH<sub>4</sub>OH) gave **2** (32 mg, 61%). *R<sub>f</sub>* (AcOEt/MeOH 5:1) 0.12. <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O): 3.75 (*t*, *J* = 9.6, irradi. at 3.94 → *d*, *J* ≈ 9.5, H-C(7)); 3.94 (*t*, *J* = 9.7, irradi. 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, irradi. at 3.75 → change, H-C(8)); 4.10–4.16 (*m*, irradi. at 3.94 → change, H-C(5)); 4.26 (*dd*, *J* = 12.8, 2.5, CH-C(5)); 8.66 (*s*, H-C(3)). <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O + 2 equiv. of CF<sub>3</sub>COOH): 4.00–4.12 (*m*, irradi. 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)). <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O, 2 equiv. of CF<sub>3</sub>COOH and 5 equiv. of HCl): 3.99–4.12 (*m*, irradi. 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)). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 49.59 (*d*, C(8)); 59.69 (*t*, CH<sub>2</sub>-C(5)); 60.21 (*d*, C(5)); 68.38, 74.40 (*2d*, H-C(6), H-C(7)); 143.02 (*d*, C(3)); 154.38 (*s*, C(8a)).

(**5R,6R,7S,8R**)-8-Acetoxy-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-1,5-a]pyridine (**63**). A soln. of **60** (50 mg, 0.1 mmol) and Hg(OAc)<sub>2</sub> (32 mg, 0.1 mmol) in THF (1 ml) was treated with Me<sub>3</sub>SiN<sub>3</sub> (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<sub>f</sub>* (AcOEt/hexane 1:2) 0.41. IR (CHCl<sub>3</sub>): 3067w, 3008m, 2929w, 2872m, 1953w, 1755s, 1497m, 1455s, 1370s, 1092s, 1028m, 911w. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 2.17 (*s*, AcO); 4.04 (*d*, *J* = 5.6, CH<sub>2</sub>-C(5)); 4.15 (*dd*, *J* = 6.5, 3.4, H-C(7)); 4.43 (*d*, *J* = 11.8, PhCH); 4.45–4.47 (*m*, H-C(6)); 4.49 (*d*, *J* = 11.8, PhCH); 4.50 (*d*, *J* = 12.1, PhCH); 4.61 (*d*, *J* = 12.1, 2 PhCH); 4.64 (*td*, *J* = 5.4, 4.4, H-C(5)); 4.74 (*d*, *J* = 11.8, PhCH); 6.55 (*d*, *J* = 3.4, H-C(8)); 7.18–7.37 (*m*, 15 arom. H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 20.72 (*q*, Me); 60.29, 62.05 (*2d*, C(5), C(8)); 67.78 (*t*, CH<sub>2</sub>-C(5)); 71.69, 75.63 (*2d*, C(6), C(7)); 73.23, 73.41, 73.49 (*3t*, 3 PhCH<sub>2</sub>); 127.74–128.64 (several *d*); 136.64, 136.74, 137.30 (*3s*); 149.97 (*s*, C(8a)); 169.48 (*s*, C=O). CI-MS (NH<sub>3</sub>): 515 (67, M<sup>+</sup>), 91 (100).

(**5R,6R,7R,8R**)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-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<sub>f</sub>* (AcOEt/hexane 1:2) 0.26. IR (CHCl<sub>3</sub>): 3559m, 3324m (*br.*), 3067w, 3008m, 2926m, 2871m, 1953w, 1878w, 1810w, 1676w, 1062w, 1429w, 1455s, 1397w, 1364w, 1340w, 1097s, 1028m, 910m. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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, irradi. 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, PhCH); 4.53 (*d*, *J* = 11.8, PhCH); 4.59 (*d*, *J* = 11.8, PhCH); 4.61 (*d*, *J* = 11.8, PhCH); 4.64 (*d*, *J* = 11.8, PhCH); 4.70 (*d*, *J* = 11.8, PhCH); 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). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 59.99 (*d*, C(5)); 68.73 (*d*, C(8)); 68.72 (*t*, CH<sub>2</sub>-C(5)); 72.08, 76.70 (*2d*, C(6), C(7)); 72.92, 73.66, 73.82 (*3t*, 3 PhCH<sub>2</sub>); 128.08–128.89 (several *d*); 136.93, 137.18, 137.53 (*3s*); 153.55 (*s*, C(8a)). CI-MS: 473 (7, [M + 1]<sup>+</sup>), 381 (7), 91 (100).

(**5R,6R,7S,8R**)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-8-[(methylsulfonyl)oxy]-5,6,7,8-tetrahydro-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<sub>f</sub>* (AcOEt/hexane 1:2) 0.53. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 3.29 (*s*, MeSO<sub>2</sub>); 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<sub>2</sub>); 4.46 (*dd*, *J* = 6.9, 3.7, H-C(6)); 4.59 (*d*, *J* = 11.5, PhCH); 4.60 (*d*, *J* = 11.8, PhCH); 4.61–4.66 (*m*, H-C(5)); 4.70 (*d*, *J* = 11.5, PhCH); 4.80 (*d*, *J* = 11.5, PhCH); 6.19 (*d*, *J* = 3.7, H-C(8)); 7.17–7.38 (*m*, 15 arom. H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 39.70 (*q*, MeSO<sub>2</sub>); 60.51 (*d*, C(5)); 67.87 (*t*, CH<sub>2</sub>-C(5)); 69.05 (*d*, C(8)); 72.06 (*d*); 73.58, 73.66, 74.00 (*3t*, 3 PhCH<sub>2</sub>); 76.23 (*d*); 127.99–128.94 (several *d*); 136.64 (*br. s*); 137.49 (*s*); 150.45 (*s*, C(8a)).

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

*Inhibition Studies.* Determination of the inhibition constants (*K<sub>i</sub>*) or the *IC*<sub>50</sub> values were performed with a range of inhibitor concentrations (typically 4–8 concentrations) which bracket the *K<sub>i</sub>* or *IC*<sub>50</sub> value.

*a) Inhibition of Sweet Almonds β-Glucosidases.* Inhibition constants (*K<sub>i</sub>*) and *IC*<sub>50</sub> were determined at 37°, using *McIlvaine's* Na<sub>2</sub>PO<sub>4</sub>/citric acid buffer solutions [42][43] (0.1M, 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  $\beta$ -Glucosidase.* Similarly as described in *a*). The inhibition constants and  $IC_{50}$  values were determined at 55°.

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