

Synthesis and Evaluation of Indolizine-Type Inhibitors of *N*-Acetyl- β -D-Glucosaminidases

by Narendra Panday, Thierry Granier, and Andrea Vasella*

Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

To check if the strong inhibition of *N*-acetyl- β -D-glucosaminidase by the tetrazole **8** and the imidazoles **9** and **10** correlates with the presence of a heteroatom corresponding to the glycosidic O-atom, we prepared the GlcNAc-derived pyrroles (tetrahydroindolizines) **18**, **19**, **27**, **28**, **34**, and **35**, lacking such a heteroatom. For this, the glucose-derived pyrroles **11**–**13** were treated with a *Lewis* acid in the presence of trimethylsilyl azide. Conditions of kinetic control favored the formation of the *gluco*-azides **14**, **23**, and **30**, while thermodynamic control favoured the *manno*-azides **20**, **29**, and **36**. Reduction of the azides **14**, **20**, **23**, **30**, and **36** by Pd/C-catalyzed hydrogenolysis or, better, with propanedithiol and Et₃N, followed by acetylation or trifluoroacetylation and hydrogenolytic debenzoylation, gave the deprotected acetamido- and trifluoroacetamido-pyrroles **18**, **19**, **22**, **27**, **28**, **34**, **35**, **40**, and **41**. As compared to the tetrazole **8** and the imidazole **9**, the pyrroles **18**, **19**, **27**, **28**, **34**, and **35** are only modest inhibitors of *N*-acetyl- β -D-glucosaminidase from bovine kidney (*K_i* values between 10 and 75 μ M), indicating the necessity of a heteroatom at the glycosidic position. *K_i* Values between 100 and 160 μ M for the inhibition of *N*-acetyl- β -D-glucosaminidase from jack beans were determined for the pyrroles **19**, **34**, and **35**. The trifluoroacetamides inhibited both enzymes about twice as strongly as the corresponding acetamides.

Introduction. – There is good evidence that the catalytically active carboxy group of lysozyme does not protonate the glycosidic O-atom from above, *i.e.*, perpendicularly to the plane of the pyranosidic ring, as depicted in *Koshland's* mechanism [1]. Rather, this protonation occurs 'laterally', *i.e.*, in the plane of the pyranosidic ring [2], as deduced from an X-ray structure of lysozyme in complex with the trisaccharide 2-acetamido-2-deoxy-D-muramic acid- β -(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-D-glucose- β -(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-D-muramic acid [3]. The lateral orientation of the protonating carboxy group appears also to be a feature of several retaining β -glycosidases, as deduced from a comparison of inhibitors either possessing an sp²-hybridized heteroatom corresponding to the glycosidic O-atom or not [4], and from the X-ray structure of an endocellulase from *Acidothermus cellulolyticus* in complex with cellotetraose [5]. Thus, the tetrazole **1** [6], the triazole **2** [7], and the imidazole **3** [8] are good inhibitors of β -glycosidases, while the triazole **4** [4] and the pyrroles **5**–**7** [9] are not (*Fig. 1*).

Although the *N*-acetyl- β -D-glucosaminidase from bovine kidney is strongly inhibited by the tetrazole **8** [10] and the imidazoles **9** [8] and **10** [11] (*Fig. 2*), this finding is not considered sufficient evidence for or against a lateral protonation of the substrate by this enzyme¹⁾ as long as analogues lacking a heteroatom at the glycosidic position have not

¹⁾ This hexosaminidase and the above mentioned β -glycosidases belong to different families according to *Henrissat's* classification of glycosyl hydrolases [12][13]. An extrapolation of the results observed with β -glycosidases to hexosaminidases appears particularly problematic in view of the reaction mechanism of these enzymes, differing considerably with regard to the catalytic nucleophile [14] [15].

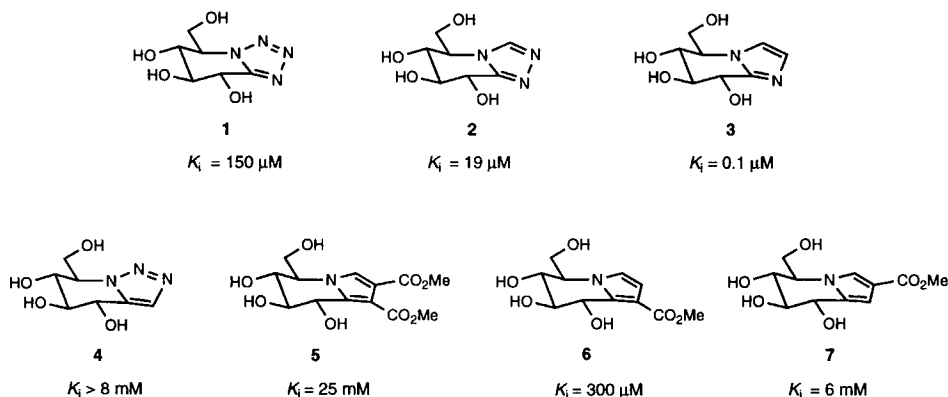


Fig. 1. K_i Values of gluco-configured tetrahydropyridozoles against sweet-almonds β -glucosidases

been tested. As the pyrroles (tetrahydroindolizines) **11**–**13** are readily available²⁾, we considered to transform them into the corresponding *N*-acetylglucosamine derivatives. A similar transformation has been described by *Tatsuta et al.* [18], who converted analogous imidazopyridines into the corresponding azides by substituting the HO–C(8) group under *Mitsunobu* conditions. Presumably, this reaction proceeds by an elimination/addition; hence, acid promoted elimination of a C(8)-(benzyloxy) group of the tetrahydroindolizines **11**–**13** in the presence of a suitable azide donor should also lead to the desired products and obviate the necessity of a selective protection.

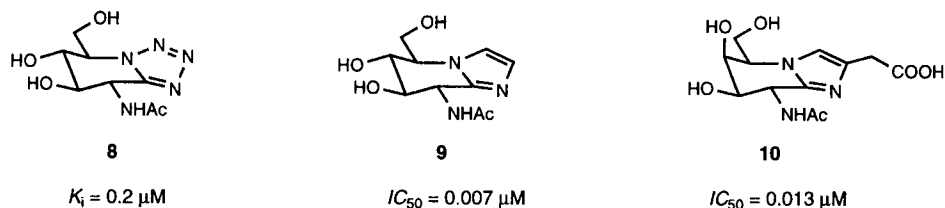


Fig. 2. K_i and IC_{50} Values of three strong tetrahydropyridazole-type hexosaminidase inhibitors against *N*-acetyl- β -D-glucosaminidase from bovine kidney

The acetamido group is expected to contribute significantly to the binding of inhibitors to *N*-acetyl- β -D-glucosaminidases³⁾. This contribution is due to H-donation from the N–H, H-bonding to the carbonyl O-atom, and to hydrophobic interactions involving the Me moiety. Several examples are known where the enhanced acidity of a trifluoroacetamido function (as compared to the one of an acetamido group) leads to stronger binding. *N*-(Trifluoroacetyl)- α -D-glucosamine binds about twice as well to

²⁾ We have prepared these compounds from the 2,3,4,6-tetra-*O*-benzyl-D-gluconolactam [7][16][17] in three steps, the key step being a 1,3-dipolar cycloaddition of a *Münchnone* to dimethyl acetylenedicarboxylate or methyl propiolate [9]. This procedure yields **11** in 91% and **12/13** (4:3) in 73% overall yield from the lactam.

³⁾ The contribution of the acetamido group to the binding of *N*-acetylglucal to *N*-acetyl- β -D-glucosaminidase from jack beans has been estimated to 4.2 kcal/mol [19].

lysozyme than *N*-acetyl- α -D-glucosamine [20]. The trifluoroacetamido analogue of *N*-acetyl-2,3-didehydro-2-deoxyneuraminic acid inhibits the neuraminidase from *Vibrio cholerae* 12 times better than the parent compound [21]. Similarly, the trifluoroacetamido analogue of siastatin B inhibits β -glucuronidase from bovine liver 2400 times more strongly than the acetamido analogue [22]. To the best of our knowledge, the effect of an analogous substitution has not been investigated for inhibitors of *N*-acetyl- β -D-glucosaminidases.

Synthesis. – Treatment of the diester **11** (*Scheme 1*) with trimethylsilyl azide and $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 at -7° ⁴⁾ gave a *ca.* 3:1 mixture⁵⁾ of the azides **14/20** (82%), from which the *gluco*-configured azide **14** was isolated in 75% yield by flash chromatography. Running the reaction in toluene between 23 and 90° led to a 1:4 mixture **14/20** (85%), from which the *manno*-configured azide **20** was isolated in 65% yield.

Treatment of the more reactive monoester **12** with trimethylsilyl azide and $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 at -78° gave a 2:3 mixture of the *gluco*- and *manno*-azides **23/29** (76%). In the presence of the milder *Lewis* acids $\text{TiCl}(\text{O}^i\text{Pr})_3$ or ZnCl_2 in MeCN at 0° , however, we obtained a 4:1 mixture **23/29** (81%). Similarly, treatment of the regioisomeric monoester **13** with trimethylsilyl azide and $\text{TiCl}(\text{O}^i\text{Pr})_3$ in MeCN or CH_2Cl_2 at 0° yielded 86% of a 7:3 mixture of the *gluco*- and *manno*-azides **30/36** that were separated by HPLC.

Depending on the *Lewis* acid, solvent, temperature, and reaction time, different ratios of the *gluco*- and *manno*-azides were obtained; longer reaction times and higher temperatures leading predominantly to the *manno*-configured azides **20**, **29**, and **36**, while shorter reaction times and lower temperatures gave mainly the *gluco*-configured azides **14**, **23**, and **30** (*cf.* *Table 1*). This result suggests that the *gluco*-azides are formed under kinetic control, that the *manno*-epimers are more stable and that they equilibrate under harsher conditions. This was confirmed by treating the pure *gluco*-azides **14**, **23**, and **30** and their *manno*-analogues **20**, **29**, and **36** with $\text{BF}_3 \cdot \text{OEt}_2$ in the presence of trimethylsilyl azide at 23° . Under these conditions, as shown by monitoring the reaction in CD_2Cl_2 by ^1H -NMR spectroscopy, the equilibrium for **23/29** and **30/36** was reached within a few minutes, and for the less reactive diester pair **14/20** after 64 h. The *manno*-azides are favoured, with solvent-dependent *gluco/manno* ratios of 1:7 for **14/20**, between 1:9 and 1:11 for **23/29**, and between 1:3 and 3:7 for **30/36** (*Table 2*).

Under the conditions tested, the diastereoselectivities are not high and – as far as kinetic control operates – presumably the result of a stereoelectronic control, *viz.* a (pseudo)axial attack on the *bona fide* intermediates, as illustrated for the transformation of **12** via the azoniafulvene⁶⁾ **A** (*Scheme 2*) to **23** and **29**.

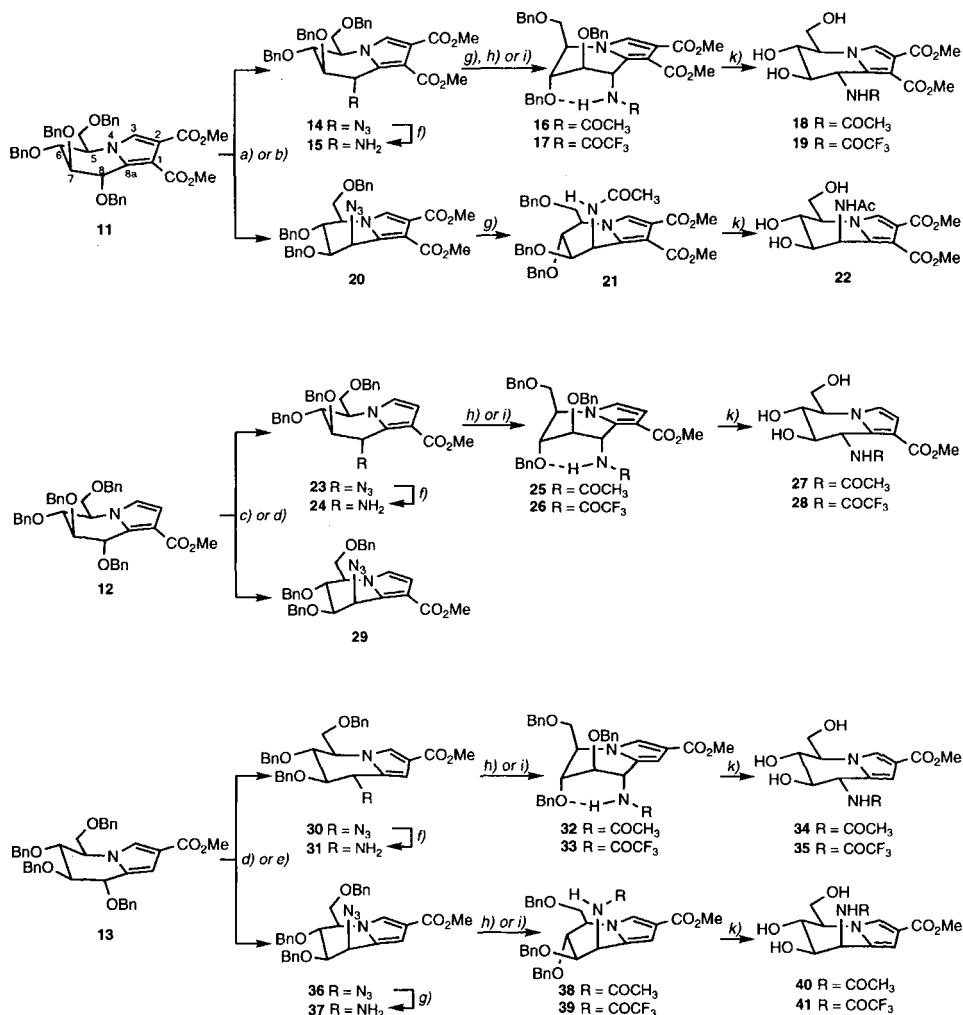
Comparison of the equilibrium ratios in *Table 2* shows that the energy difference between the *gluco*- and *manno*-configured azides is higher for the C(1)-substituted pyrroles **14/20** and **23/29**, than for the C(1)-unsubstituted pyrroles **30/36**, reflecting the unfavourable 1,5-interaction between the COOMe substituent at C(1) and the N_3 group

⁴⁾ Running the reaction at lower temperatures considerably protracted the reaction without modifying the ratio **14/20**.

⁵⁾ As determined by integration of the H–C(8) signals in the ^1H -NMR spectrum of the crude.

⁶⁾ Azoniafulvene intermediates are known. Leading references are given in [18] and [23–46].

Scheme 1



a) Trimethylsilyl azide, BF₃ · OEt₂, CH₂Cl₂, -7°; **14/20** 3:1, 82%. b) Trimethylsilyl azide, BF₃ · OEt₂, toluene, 90°; **14/20** 1:4, 85%. c) Trimethylsilyl azide, TiCl(OⁱPr)₃ or ZnCl₂, MeCN, 0°; **23/29** 4:1, 81%. d) Trimethylsilyl azide, BF₃ · OEt₂, CH₂Cl₂, -78°; **23/29** 2:3, 76%; **30/36** 1:2, 85%. e) Trimethylsilyl azide, TiCl(OⁱPr)₃, MeCN or CH₂Cl₂, 0°; **30/36** 7:3, 81–86%. f) HS(CH₂)₃SH, Et₃N, MeOH, 23°; **15**, 99%; **24**, 97%; **31**, 95%; **37**, 93%. g) 1. H₂, Pd/C, AcOEt, MeOH. 2. Ac₂O, pyridine; **16**, 70% from **14**; **21**, 70%. h) Ac₂O, pyridine; **16**, 97%; **25**, 98%; **32**, 97%; **38**, 97%. i) (CF₃O)₂O, pyridine; **17**, 95%; **26**, 98%; **33**, 95%; **39**, 89%. k) H₂, 10% Pd/C; **18**, 70%; **19**, 83%; **22**, 72%; **27**, 88%; **28**, 84%; **34**, 92%; **35**, 80%; **40**, 88%; **41**, 93%.

at C(8) that forces the *gluco*-azides **14** and **23** into a somewhat distorted ^{5,8}B-conformation.

The protected acetamido-pyrroles **16** and **21** were obtained from **14** and **20**, respectively, by Pd-catalyzed reduction of the N₃ group and acetylation (70%). To improve the yields, we reduced **14** with propane-1,3-dithiol and Et₃N [47]. This yielded 99% of the

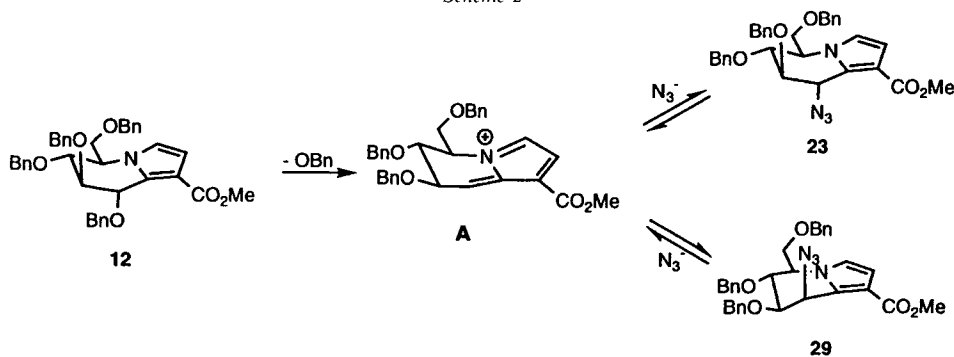
Table 1. Ratio of gluco/manno-8-Azidopyrrolopyridines Depending on the Reaction Conditions as Determined by ¹H-NMR Spectroscopy

Starting material	Lewis acid	Solvent	Temperature [°]	Reaction time [min]	gluco/manno
11	BF ₃ · OEt ₂	CH ₂ Cl ₂	–7	210	3:1
11	BF ₃ · OEt ₂	toluene	90	15	1:4
12	BF ₃ · OEt ₂	CH ₂ Cl ₂	–78	15	2:3
12	BF ₃ · OEt ₂	CH ₂ Cl ₂	0	15	1:7
12	BF ₃ · OEt ₂	CH ₂ Cl ₂	23	15	1:10
12	TiCl(O ⁱ Pr) ₃	MeCN	0	560	4:1
12	TiCl(O ⁱ Pr) ₃	MeCN	–10	720	4:1 ^{a)}
12	TiCl(O ⁱ Pr) ₃	CH ₂ Cl ₂	0	480	7:3
12	TiCl(O ⁱ Pr) ₃	CH ₂ Cl ₂	–10	560	7:3 ^{a)}
12	ZnCl ₂	MeCN	–10	560	5:1 ^{a)}
12	ZnCl ₂	MeCN	0	480	4:1
12	ZnCl ₂	MeCN	23	480	4:3
12	ZnCl ₂	CH ₂ Cl ₂	–10	240	7:3 ^{a)}
12	ZnCl ₂	CH ₂ Cl ₂	–10	480	3:2 ^{a)}
12	BF ₃ · OEt ₂	CH ₂ Cl ₂	–78	30	2:3
13	BF ₃ · OEt ₂	CH ₂ Cl ₂	23	15	3:7
13	TiCl(O ⁱ Pr) ₃	CH ₂ Cl ₂	0	240	7:3
13	TiCl(O ⁱ Pr) ₃	MeCN	–10	530	7:3
13	TiCl(O ⁱ Pr) ₃	MeCN	0	240	7:3
13	TiCl(O ⁱ Pr) ₃	MeCN	23	240	3:5

^{a)} Incomplete reaction.Table 2. Equilibration of 8-Azidopyrrolopyridines with BF₃ · OEt₂ in the Presence of Trimethylsilyl Azide at 23°

Starting material	Solvent	gluco/manno
14 or 20	CD ₂ Cl ₂ or CH ₂ Cl ₂	1:7
23 or 29	CD ₂ Cl ₂ or CH ₂ Cl ₂	1:10
23 or 29	MeCN	1:9
23 or 29	toluene	1:11
30 or 36	CD ₂ Cl ₂ or CH ₂ Cl ₂	3:7
30 or 36	MeCN	1:3
30 or 36	toluene	2:5

Scheme 2



amine **15**. The same method was applied to the azides **23**, **30**, and **36** and led to the corresponding amines **24**, **31**, and **37** in yields between 93 and 99%. Acetylation of the amines **15**, **24**, **31**, and **37** gave the protected acetamido derivatives **16**, **25**, **32**, and **38** in over 95% yield. Similarly, treatment of the amines **15**, **24**, **31**, and **37** with trifluoroacetic anhydride in pyridine at 0° [48] led to the protected trifluoroacetamido-analogues **17**, **26**, **33**, and **39** in yields between 89 and 98%. Hydrogenolytic debenzoylation of the acetamides **16**, **21**, **25**, **32**, and **38** and trifluoroacetamides **17**, **26**, **33**, and **39** gave the crystalline target compounds **18**, **19**, **22**, **27**, **28**, **34**, **35**, **40**, and **41** in yields between 70 and 93%.

The azides **14**, **20**, **23**, **29**, **30**, and **36** are characterized by a strong IR band at 2103–2105 cm⁻¹. The CD spectra allow to distinguish two sets of diastereoisomers: the *gluco*-configured azides **14**, **23**, and **30**, showing negative molar ellipticities at 262, 264, and 261 nm, respectively, and the corresponding *manno*-azides **20**, **29**, and **36**, showing positive ellipticities. The assignment of the configuration of the azides and their protected derivatives is based on a NOE experiment (NOE for the H–C(6) signal of **30** – but not of **36** – upon irradiation of H–C(8)) and a comparison of the ¹H-NMR data of the deprotected acetamido-tetrahydroindolizines with those of the known acetamido-tetrahydrotetrazolopyridines [49]. In D₂O solution, the piperidine ring of the deprotected acetamides **18**, **19**, **22**, **27**, **28**, **34**, **35**, **40**, and **41** adopts predominantly a ⁷H₆ conformation, as evidenced by rather large *J*(5,6) and *J*(6,7) values. The assignment of the *gluco*-configuration to **18**, **19**, **27**, **28**, **34**, and **35** is based on the *J*(7,8) values (6.2–10.0 Hz), as is the assignment of the *manno*-configuration to **22**, **40**, and **41** (*J*(7,8) = 3.2–4.1 Hz). The *J*(5,6), *J*(6,7), and *J*(7,8) values decrease from ca. 9.3–10 Hz for the acetamido/trifluoroacetamido pair **34/35** via 8.5–9.0 Hz for **18/19** to 6.2–8.0 Hz for **27/28**, indicating the increasing population of the ⁶H₇ conformation⁷). This is rationalized by a destabilizing 1,5-interaction between the acetamido group and the COOMe group at C(1) in **18/19** and **27/28**, weaker in the former pair, presumably because the additional COOMe group prevents coplanarity of the π system of the ester moiety at C(1) with the π system of the pyrrole moiety, as suggested by force-field calculations. The *J* values of the *manno*-amide **40** agree well with an approximate ⁷E conformation. The conformation of **22** and **41** could not be determined due to signal overlapping. The 1,5-interaction between the N₃ and the COOMe group strongly influences the conformational equilibrium of the protected azides in apolar solvents. Whereas the *manno*-azides **20** and **29** and the C(1)-unsubstituted *gluco*-azide **30** possess a ⁷H₆ conformation, as indicated by the rather large values for *J*(5,6), *J*(6,7), and *J*(7,8) (7.0–9.4 Hz), the medium values for *J*(5,6), *J*(6,7), and *J*(7,8) of the C(1)-carboxylated *gluco*-azides **14** and **23** indicate an equilibrium between the ⁶H₇- and ^{5,8}B-conformers⁷). Again, the C(1)-substituted monocarboxylate **23** (*J* values of 2.5–4.1 Hz) shows a stronger preference for the ⁶H₇-conformation than the dicarboxylate **20** (*J* values of 3.8–5.9 Hz). The equilibrium ratios, in CD₂Cl₂ at 23°, of **14/20** (1:7) and **23/29** (1:10), respectively (cf. Table 2), agree well with the presumed weaker 1,5-interaction in **14** than in **23**. The ^{5,8}B-conformation of the *manno*-azide **36**, not disfavoured by an 1,5-interaction, contributes to the conformational equilibrium as indicated by the values for *J*(5,6) and *J*(6,7) of 8.3 and 6.6 Hz, respectively. In apolar solvents, the conformation of the amines **15**, **24**, **31**, and **37**, and of the protected amides **16**, **17**, **25**, **26**, **32**, and **33** may additionally be influenced by an intramolecular H-bond. The difference between the chemical shifts for H–C(5), H–C(6), and H–C(7) of **15** and **24**, and those of the corresponding azides **14** and **23** suggests a conformational change; an intramolecular H-bond between the amino group and the C(1)-carbonyl group may now favour the ⁷H₆-conformer. Unfortunately, signal overlapping prevents the determination of the conformation of the amines **15** and **24**. The C(1)-unsubstituted amines **31** and **37** adopt a similar conformation as the corresponding azides **30** and **36**, reflecting the absence of such a H-bond. In apolar solvents, the small values for *J*(5,6), *J*(6,7), and *J*(7,8) indicate a ⁶H₇-conformation for the protected *gluco*-configured acetamides **16**, **17**, **26**, **32**, and **33**. This conformation is stabilized by an intramolecular H-bond between the N–H and O–C(6), as it has already been observed for the corresponding *gluco*-configured tetrahydrotetrazolopyridine [10][49]. The conformation of the *gluco*-acetamide **25** could not be determined, due to the isochronicity of the H–N and H–C(8) signals, on the one hand, and of the H–C(6) and H–C(7) signals, on the other hand (cf. *Exper. Part*). The *J* values indicate that the C(1)-unsubstituted *manno*-configured acetamides **38** and **39** adopt a B_{5,8} conformation. Force-field calculations suggest that this conformer is stabilized by an intramolecular H-bond between the N–H and O–CH₂–C(5). Similarly as its deprotected derivative, the protected 1,2-disubstituted acetamide **21** adopts a ⁷E-conformation, as reflected by the somewhat larger values of

⁷) Force-field calculations (Macromodel V.4.5, MM3* force field, gas phase [50]) suggest *J*(5,6), *J*(6,7), and *J*(7,8) values of 10.1, 9.7, and 10.0 Hz for the ⁷H₆, of 1.2, 4.2, and 1.9 Hz for the ⁶H₇, and of 10.5, 4.8, and 0.9 Hz for the ^{5,8}B-conformation.

J(5,6) and *J*(6,7). As a rule, the H–C(8) signal of the *manno*-tetrahydroindolizines is shifted to lower field by 0.17 to 0.58 ppm as compared to the one of the corresponding *gluco*-tetrahydroindolizines.

Enzymatic Tests. – The trihydroxy compounds **18**, **19**, **27**, **28**, **34**, and **35** were tested against the *N*-acetyl- β -D-glucosaminidase from bovine kidney, and **19**, **34**, and **35** also against the *N*-acetyl- β -D-glucosaminidase from jack beans (Table 3). The large K_i values of these pyrroles, as compared to the K_i value of the tetrazole **8** [10], and the IC_{50} values of the imidazoles **9** [8] and **10** [11] (*cf.* Fig. 2) indicate clearly that a heteroatom, corresponding to the glycosidic O-atom, is required for strong inhibition. Comparison of the K_i value of the tetrazole **8** with the IC_{50} value of the imidazole **9**⁸⁾ suggests that a higher basicity favours a stronger binding, similarly to what has been observed for β -glycosidases⁹⁾.

Table 3. K_i Values of Pyrroles Determined at pH 4.2 and 37°

Hexosaminidase	Inhibitor	K_i [μ M]
Bovine kidney	18	75
Bovine kidney	19	35
Bovine kidney	27	20
Bovine kidney	28	13
Bovine kidney	4	19
Bovine kidney	5	10
Jack beans	19	140
Jack beans	4	160
Jack beans	5	100

The tested enzymes are inhibited about twice as strongly by the trifluoroacetamido analogues than by the acetamides. The slightly stronger inhibition observed may well be the result of the compensating influences of H-donation, H-acceptance, and hydrophobic interactions.

We thank T. Mäder for the HPLC separation of **23** and **24**, Dr. B. Bernet for his contribution to the conformation analyses and the Swiss National Science Foundation and F. Hoffmann-La Roche AG, Basel, Oxford Glycosciences Ltd., Abingdon (UK) for generous support.

Experimental Part

General. Solvents were distilled before use. Normal workup implies distribution of the crude product between CH_2Cl_2 and sat. aq. NH_4Cl soln. and ice, unless indicated otherwise, drying of the org. layer (MgSO_4), filtration, and evaporation of the filtrate. TLC: Merck silica gel 60F-254 plates; detection by heating with 'mostain' (400 ml of 10% H_2SO_4 soln., 20 g of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 6 \text{H}_2\text{O}$, 0.4 g of $\text{Ce}(\text{SO}_4)_3$). M.p.: uncorrected. Flash chromatography (FC): silica gel Merck 60 (0.04–0.063 mm). HPLC: Spherisorb SW 5 μm . Optical rotations: 1-dm cell. UV spectra (λ_{max} in nm (log ϵ)): 1-cm quartz cell. CD Spectra (λ_{max} in nm (molar ellipticity $[\theta]$ in $\text{deg} \cdot \text{cm}^2 \cdot \text{dmol}^{-1}$)) were recorded with a JASCO-J-710 spectropolarimeter. IR Spectra: KBr or 3% CHCl_3 soln. NMR Spectra: ^1H at 300 MHz, if not indicated otherwise; ^{19}F at 282 MHz; ^{13}C at 75 MHz, if not indicated otherwise; chemical shifts δ in ppm and coupling constants *J* in Hz. FAB- and CI-MS: 3-nitrobenzyl alcohol and NH_3 as matrix, resp., unless indicated otherwise.

⁸⁾ The K_i value of **8** has been measured at 37° and pH 4.1. Although the IC_{50} have been determined at 37° pH 5.0 [8], the difference between the inhibitor potency of **8**, on the one hand, and of **9** and **10**, on the other hand, is significant.

⁹⁾ To confirm this hypothesis, the GlcNAc analogue of the triazole **2** should be prepared and tested.

Dimethyl (5R,6R,7S,8S)- and (5R,6R,7S,8R)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (14 and 20, resp.). a) At -70° , a soln. of **11** (1.309 g, 1.94 mmol) in CH_2Cl_2 (30 ml) was treated with trimethylsilyl azide (0.9 ml, 6.8 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (0.5 ml, 4.0 mmol) and kept for 210 min at -7° . The mixture was cooled to -78° and poured into a sat. aq. NH_4Cl soln. Normal workup ($\rightarrow$ **14/15** 3:1, $^1\text{H-NMR}$) and FC (hexane/ Et_2O 3:1 $\rightarrow$ 2:1) gave **14** (922 mg, 78%) and **14/20** 2:1 (50 mg, 4%).

b) A soln. of **11** (454.4 mg, 0.67 mmol) in toluene (20 ml) was treated with trimethylsilyl azide (0.5 ml, 3.8 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (0.25 ml, 2.0 mmol), kept for 4 h at 23° , heated to 90° for 15 min, cooled to 23° , and poured into a sat. aq. NH_4Cl soln. Normal workup ($\rightarrow$ **14/15** 1:4, $^1\text{H-NMR}$) and FC (hexane/ Et_2O 3:1 $\rightarrow$ 2:1) gave **14** (52.3 mg, 13%), **14/20** 1:1 (27.8 mg, 7%) and **20** (266.4 mg, 65%).

Data of 14: R_f (hexane/ Et_2O 3:1) 0.15. UV (CHCl_3): 259 (3.8). CD (CHCl_3): 262 (-27110), 306 (627). IR (CHCl_3): 3090w, 3008m, 2985m, 2963m, 2929w, 2871m, 2106s, 1730s, 1571w, 1528m, 1497m, 1454m, 1374m, 1265s, 1158m, 1098s, 1070s, 1046m. $^1\text{H-NMR}$ (CDCl_3): 3.72 (dd, $J = 6.0, 10.3$, HC-C(5)); 3.81 (dd, $J = 3.8, 10.6$, HC-C(5)); 3.83 (s, MeO); 3.88 (t, $J = 5.9$, irrad. at $4.24 \rightarrow d, J \approx 6.0$, H-C(6)); 3.90 (s, MeO); 3.95 (dd, $J = 5.4, 3.8$, H-C(7)); 4.24 (dt, $J = 6.0, 3.8$, H-C(5)); 4.42 (d, $J = 12.0$, PhCH); 4.48 (d, $J = 12.1$, PhCH); 4.49 (d, $J = 11.7$, PhCH); 4.62 (d, $J = 11.4$, PhCH); 4.72 (d, $J = 11.6$, PhCH); 4.73 (d, $J = 11.7$, PhCH); 5.15 (d, $J = 3.8$, H-C(8)); 7.19–7.38 (m, 15 arom. H, H-C(3)). $^{13}\text{C-NMR}$ (CDCl_3): 51.58 (q, MeO); 51.94 (q, MeO); 55.74 (d, C(8)); 58.93 (d, C(5)); 68.86 (t, CH_2 -C(5)); 73.10 (t, PhCH_2); 73.21 (t, PhCH_2); 73.36 (t, PhCH_2); 74.72, 78.20 (2d, C(6), C(7)); 115.08, 116.07 (2s, C(1), C(2)); 126.17 (d, C(3)); 127.00–128.82 (several d); 129.31 (s, C(8a)); 136.94 (s); 137.05 (s); 137.12 (s); 163.85 (s, CO_2); 164.55 (s, CO_2).

Data of 20: R_f (hexane/ Et_2O 1:1) 0.11. UV (CHCl_3): 259 (3.8). CD (CHCl_3): 265 (10580), 307 (-674). IR (CHCl_3): 3089w, 3008m, 2985m, 2963m, 2939w, 2871m, 2106s, 1728s, 1571w, 1527m, 1497m, 1454m, 1374m, 1265s, 1158m, 1098s, 1070s, 1046m. $^1\text{H-NMR}$ (CDCl_3): 3.62 (dd, $J = 10.3, 5.8$, HC-C(5)); 3.74 (dd, $J = 10.2, 2.9$, HC-C(5)); 3.82 (s, MeO); 3.85 (dd, $J = 9.4, 3.7$, irrad. at $5.45 \rightarrow d, J \approx 9.4$, H-C(7)); 3.87 (s, MeO); 4.03 (ddd, $J = 8.0, 5.9, 2.8$, H-C(5)); 4.12 (dd, $J = 9.2, 7.8$, H-C(6)); 4.45 (s, PhCH_2); 4.57 (d, $J = 11.1$, PhCH); 4.77 (d, $J = 11.8$, PhCH); 4.84 (d, $J = 11.7$, PhCH); 4.96 (d, $J = 11.0$, PhCH); 5.45 (d, $J = 3.7$, H-C(8)); 7.21–7.44 (m, 15 arom. H, H-C(3)). $^{13}\text{C-NMR}$ (CDCl_3): 51.66 (q, MeO); 51.75 (q, MeO); 54.21 (d, C(8)); 61.30 (d, C(5)); 69.61 (t, CH_2 -C(5)); 72.63 (t, PhCH_2); 73.24 (t, PhCH_2); 75.23 (t, PhCH_2); 73.30, 79.15 (2d, C(6), C(7)); 113.43, 117.05 (2s, C(1), C(2)); 126.31 (d, C(3)); 127.87–128.64 (several d); 131.57 (s, C(8a)); 137.17 (s); 137.27 (s); 137.62 (s); 163.85 (s, CO_2); 164.07 (s, CO_2).

Dimethyl (5R,6R,7S,8S)-8-Amino-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (15). A soln. of **14** (150 mg, 0.246 mmol) in MeOH (8 ml) was treated with Et_3N (0.8 ml) and propane-1,3-dithiol (0.8 ml) and stirred for 38 h at 23° . After addition of CH_2Cl_2 and ice, the mixture was poured into 0.1M NaOH. Separation of the org. layer, extraction of the aq. layer with CH_2Cl_2 , drying (MgSO_4) of the combined org. layers, filtration, evaporation, and FC (AcOEt/hexane 2:1 $\rightarrow$ 10:1) gave **15** (142 mg, 99%). R_f (AcOEt) 0.40. IR (CHCl_3): 3380w, 3090w, 3008m, 2950m, 2868m, 1724s, 1685s, 1577w, 1523m, 1497w, 1454m, 1443m, 1399w, 1365w, 1286m, 1176w, 1097s, 1073s, 1028w, 909s, 651m. $^1\text{H-NMR}$ (CDCl_3): 2.20 (br. s, NH_2); 3.68 (dd, $J = 9.8, 7.0$, HC-C(5)); 3.73 (dd, $J = 9.8, 5.4$, HC-C(5)); 3.82 (s, MeO); 3.86 (s, MeO); 4.06–4.11 (m, H-C(6), H-C(7)); 4.39 (d, $J = 11.8$, PhCH); 4.39–4.46 (m, H-C(5), H-C(8)); 4.46 (d, $J = 11.8$, PhCH); 4.52 (d, $J = 11.8$, PhCH); 4.56 (d, $J = 11.8$, PhCH); 4.56 (d, $J = 12.1$, PhCH); 4.65 (d, $J = 11.8$, PhCH); 7.20–7.39 (m, 15 arom. H, H-C(3)). $^{13}\text{C-NMR}$ (CDCl_3): 47.07 (d, C(8)); 51.61 (q, MeO); 59.23 (d, C(5)); 72.19 (t, CH_2 -C(5)); 72.38 (t, PhCH_2); 72.59 (t, PhCH_2); 73.82, 76.42 (2d, C(6), C(7)); 111.74, 116.43 (2s, C(1), C(2)); 126.13 (d, C(3)); 127.75–128.85 (several d); 137.19 (s); 137.74 (s); 137.80 (s); 139.58 (s); 164.84 (s, CO_2); 165.60 (s, CO_2).

Dimethyl (5R,6R,7S,8S)-8-Acetamido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (16). a) A soln. of **14** (65 mg, 0.106 mmol) in AcOEt/MeOH 6:1 (3.5 ml) was treated with 10% Pd/C (4.5 mg), hydrogenated at 1 bar for 24 h at 23° , and filtered through *Celite*. After evaporation, the residue was dried i.v., dissolved in pyridine (2 ml), treated with Ac_2O (2 ml) and 4-(dimethylamino)pyridine (DMAP; 5.5 mg, 0.045 mmol) and stirred for 4 h at 23° . Evaporation and FC (AcOEt/hexane 1:1) gave **16** (46.4 mg, 70%) as an oil.

b) A soln. of **15** (10 mg, 0.0017 mmol) in pyridine (0.25 ml) and Ac_2O (0.1 ml) was stirred at 23° for 2 h. Evaporation and FC (AcOEt/hexane 1:1) gave **16** (12 mg, 97%). Colourless solid. R_f (AcOEt/hexane 1:1) 0.15. UV (CHCl_3): 259 (3.8). CD (CHCl_3): 265 (-4777). IR (CHCl_3): 3441m, 3068w, 3008w, 2951m, 2869m, 1728s, 1670s, 1524m, 1449m, 1445m, 1440m, 1400w, 1368w, 1340w, 1290m, 1248m, 1097s, 1074s. $^1\text{H-NMR}$ (C_6D_6): 1.53 (s, AcN); 3.47 (dd, $J = 9.7, 7.4$, irrad. at $4.34 \rightarrow d, J \approx 9.8$, HC-C(5)); 3.55 (dd, $J = 5.3, 9.7$, irrad. at $4.34 \rightarrow d, J \approx 10.0$, HC-C(5)); 3.59 (s, MeO); 3.67 (s, MeO); 3.79 (dd, $J = 2.3, 3.6$, irrad. at $4.06 \rightarrow d, J \approx 2.0$, irrad. at $4.34 \rightarrow d, J \approx 4.1$, H-C(6)); 4.04 (d, $J = 11.8$, PhCH); 4.05–4.07 (m, irrad. at $6.07 \rightarrow d, J \approx 3.7$,

H–C(7)); 4.12 (*d*, *J* = 11.7, PhCH); 4.13 (*d*, *J* = 12.1, PhCH); 4.17 (*d*, *J* = 11.8, PhCH); 4.34 (*ddd*, *J* = 2.4, 5.2, 7.2, H–C(5)); 4.65 (*d*, *J* = 12.1, PhCH); 4.76 (*d*, *J* = 12.0, PhCH); 5.76 (*d*, *J* = 8.1, *irrad.* at 6.07 → *s*, NH); 6.07 (*dd*, *J* = 1.7, 8.0, *irrad.* at 4.06 → *d*, *J* ≈ 8.1, H–C(8)); 6.99–7.21 (*m*, 15 arom. H); 7.44 (*s*, H–C(3)). ¹³C-NMR (CDCl₃): 22.97 (*q*, COMe); 43.55 (*d*, C(8)); 51.60 (*q*, MeO); 51.82 (*q*, MeO); 59.19 (*d*, C(5)); 71.90 (*t*, CH₂–C(5)); 72.16 (*t*, PhCH₂); 72.28 (*t*, PhCH₂); 73.52 (*t*, PhCH₂); 73.81, 74.06 (*2d*, C(6), C(7)); 114.16, 116.43 (*2s*, C(1), C(2)); 126.69 (*d*, C(3)); 127.57–128.71 (*several d*); 130.28 (*s*, C(8a)); 136.75 (*s*); 137.43 (*s*); 137.50 (*s*); 164.20 (*s*, CO₂); 164.27 (*s*, CO₂); 168.23 (*s*, NHCOMe).

Dimethyl (5R,6R,7S,8R)-8-Acetamido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (21). A soln. of **20** (266 mg, 0.44 mmol) in AcOEt/MeOH 5:1 (12 ml) was treated with 10% Pd/C (9.3 mg), hydrogenated at 1 bar for 31 h, and filtered through *Celite*. After evaporation, the residue was dried *i.v.*, dissolved in pyridine (2 ml), treated with Ac₂O (2 ml) and DMAP (10 mg, 0.082 mmol), stirred for 6 h at 25°, and evaporated. FC (AcOEt/hexane 1:1) gave **21** (191 mg, 70%). *R_f* (AcOEt/hexane 1:1) 0.15. UV (CHCl₃): 258 (3.9). IR (CHCl₃): 3392m, 3090w, 3067w, 3008m, 2952m, 2870m, 1716s, 1676s, 1530w, 1498m, 1454m, 1440m, 1400w, 1370m, 1297m, 1248m, 1174m, 1155w, 1075s, 1028w, 913w. ¹H-NMR (CDCl₃): 1.54 (*s*, Ac); 3.59 (*dd*, *J* = 3.2, 9.8, *irrad.* at 4.21 → *d*, *J* ≈ 10.0, HC–C(5)); 3.70 (*dd*, *J* = 3.1, 10.2, *irrad.* at 4.21 → *d*, *J* ≈ 10.0, HC–C(5)); 3.82 (*s*, MeO); 3.84 (*s*, MeO); 3.85–3.87 (*m*, H–C(7)); 4.09 (*dd*, *J* = 4.8, 8.4, *irrad.* at 4.21 → *d*, *J* ≈ 8.6, *irrad.* at 3.86 → *d*, *J* ≈ 4.3, H–C(6)); 4.19–4.23 (*m*, H–C(5)); 4.30 (*s*, PhCH₂); 4.53 (*d*, *J* = 11.2, PhCH); 4.62 (*d*, *J* = 11.8, PhCH); 4.86 (*d*, *J* = 11.1, PhCH); 4.88 (*d*, *J* = 11.8, PhCH); 5.99 (*br. s*, NH, H–C(8)); 7.11–7.41 (*m*, 15 arom. H, H–C(3)). ¹H-NMR (CDCl₃ + 5% CD₃OD): 1.56 (*s*, Ac); 3.59 (*dd*, *J* = 3.3, 10.0, HC–C(5)); 3.70 (*dd*, *J* = 3.2, 9.8, HC–C(5)); 3.79 (*s*, MeO); 3.81 (*s*, MeO); 3.83 (*dd*, *J* = 4.1, 5.2, H–C(7)); 4.04 (*dd*, *J* = 5.2, 8.7, H–C(6)); 4.13–4.17 (*m*, H–C(5)); 4.29 (*s*, PhCH₂); 4.52 (*d*, *J* = 11.1, PhCH); 4.58 (*d*, *J* = 11.7, PhCH); 4.83 (*d*, *J* = 11.1, PhCH); 4.85 (*d*, *J* = 11.6, PhCH); 5.96 (*dd*, *J* = 4.1, 9.2, *addn.* of CD₃OD → *d*, *J* ≈ 4.0, H–C(8)); 6.34 (*d*, *J* = 9.3, *slow exchange* with CD₃OD, NH); 7.11–7.41 (*m*, 15 arom. H, H–C(3)). ¹H-NMR (C₆D₆): 1.44 (*s*, Ac); 3.27–3.39 (*br. s*, CH₂–C(5)); 3.59 (*s*, MeO); 3.66 (*dd*, *J* = 4.1, 8.7, *irrad.* at 6.32 → *d*, *J* ≈ 8.7, H–C(7)); 3.75 (*s*, MeO); 3.79–3.86 (*br. s*, H–C(5)); 3.90 (*d*, *J* = 12.0, PhCH); 3.94 (*d*, *J* = 11.5, PhCH); 4.02 (*dd*, *J* = 5.7, 8.6 *irrad.* at 3.66 → *d*, *J* ≈ 5.3, *irrad.* at 3.83 → *d*, *J* ≈ 8.4, H–C(6)); 4.35 (*d*, *J* = 11.0, PhCH); 4.46 (*d*, *J* = 11.9, PhCH); 4.80 (*d*, *J* = 11.8, PhCH); 4.98 (*d*, *J* = 10.9, PhCH); 6.10–6.12 (*br. s*, NH); 6.32 (*dd*, *J* = 4.1, 9.0, *irrad.* at 3.66 → *d*, *J* ≈ 9.0, H–C(8)); 6.95–7.38 (*m*, 15 arom. H, H–C(3)). ¹³C-NMR (CDCl₃): 22.86 (*q*, COMe); 41.96 (*d*, C(8)); 51.61 (*q*, MeO); 52.01 (*q*, MeO); 60.91 (*d*, C(5)); 71.64 (*t*, CH₂–C(5)); 72.19 (*t*, PhCH₂); 73.91 (*t*, PhCH₂); 74.09 (*t*, PhCH₂); 73.14, 77.70 (*2d*, C(6), C(7)); 113.20, 116.92 (*2s*, C(1), C(2)); 124.35 (*d*, C(3)); 127.57–128.79 (*several d*); 132.40 (*s*, C(8a)); 136.53 (*s*); 137.63 (*s*); 137.83 (*s*, CO₂); 164.63 (*s*, CO₂); 164.09 (*s*, CO₂); 169.09 (*s*, NHCO).

Dimethyl (5R,6R,7S,8S)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-8-(trifluoroacetamido)indolizine-1,2-dicarboxylate (17). At 5°, a soln. of **15** (120 mg, 0.217 mmol) in pyridine (7 ml) was treated with (CF₃CO₂)₂O (0.1 ml), kept for 2 h at 5° and treated with sat. aq. NH₄Cl soln. Normal workup and FC (hexane/AcOEt 3:1) of the crude gave **17** (108 mg, 95%). White solid. *R_f* (hexane/AcOEt 3:1) 0.21. UV (CHCl₃): 277 (4.1). IR (CHCl₃): 3423m, 3007m, 2952m, 2870m, 1724s, 1526s, 1455m, 1442m, 1397w, 1364w, 1290s, 1172s, 1073s, 1028w, 909w. ¹H-NMR (CDCl₃): 3.71–3.75 (*m*, H₂C–C(5)); 3.78 (*s*, MeO); 3.84 (*s*, MeO); 3.89 (*dd*, *J* = 4.1, 1.9, *irrad.* at 4.48 → *d*, *J* ≈ 4.0, H–C(6)); 4.05 (*d*, *J* = 4.4, H–C(7)); 4.42 (*d*, *J* = 11.8, PhCH); 4.47 (*d*, *J* = 11.5, PhCH); 4.49 (*d*, *J* = 11.8, PhCH); 4.46–4.50 (*m*, H–C(5)); 4.54 (*d*, *J* = 11.2, PhCH); 4.59 (*d*, *J* = 11.8, PhCH); 4.79 (*d*, *J* = 11.8, PhCH); 5.76 (*br. d*, *J* = 8.4, 1.0, *addn.* of CD₃OD → *br. s*, H–C(8)); 6.83 (*d*, *J* = 8.7, *exchange* with CD₃OD, H–N); 7.13–7.41 (*m*, 15 arom. H, H–C(3)). ¹³C-NMR (CDCl₃): 43.73 (*d*, C(8)); 51.82 (*q*, MeO); 51.93 (*q*, MeO); 58.90 (*d*, C(5)); 71.88 (*t*, CH₂–C(5)); 72.66 (*t*, PhCH₂); 73.69 (*br. t*, 2 PhCH₂); 73.33, 74.11 (*2d*, C(6), C(7)); 114.99, 117.19 (*2s*, C(1), C(2)); 126.79 (*d*, C(3)); 127.42–129.00 (*several d* and 1 *s* for C(8a)); 136.33 (*s*); 137.09 (*s*); 137.56 (*s*); 155.80 (*q*, *J* = 37.6, COCF₃); 163.96 (*s*, CO₂); 164.38 (*s*, CO₂). ¹⁹F-NMR (CDCl₃): –75.84. EI-MS: 680 (0.1, *M*⁺), 649 (1, [*M* – MeO]⁺), 572 (3, [*M* – BnOH]⁺), 313 (13, 91 (100, C₇H₇⁺)).

Dimethyl (5R,6R,7S,8S)-8-Acetamido-5,6,7,8-tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)indolizine-1,2-dicarboxylate (18). A soln. of **16** (251 mg, 0.40 mmol) in AcOEt/MeOH/H₂O 4:4:1 (4.5 ml) was treated with AcOH (0.1 ml) and 10% Pd/C (170 mg) and hydrogenated for 31 h at 7 bar. Filtration through *Celite*, evaporation, and crystallization from MeOH/CH₂Cl₂ gave **18** (62 mg, 43%). White crystals. FC (AcOEt → AcOEt/MeOH 10:1) of the mother liquor gave additional **18** (37 mg, 26%). *R_f* (AcOEt/MeOH 10:1) 0.2. ¹H-NMR (D₂O): 1.98 (*s*, AcN); 3.77 (*s*, MeO); 3.78 (*s*, MeO); 3.78 (*t*, *J* ≈ 9.0, H–C(7)); 3.96 (*t*, *J* = 8.6, *irrad.* at 3.78 → *d*, *J* ≈ 8.0, H–C(6)); 4.01–4.07 (*m*, H–C(5)); 4.05 (*dd*, *J* ≈ 3.0, 13.0, HC–C(5)); 4.20 (*dd*, *J* = 2.8, 13.5, HC–C(5)); 5.01 (*d*, *J* = 8.5, *irrad.* at 3.78 → *change*, H–C(8)); 7.62 (*s*, H–C(3)). ¹³C-NMR (D₂O): 24.57 (*q*, COMe); 51.80 (*d*, C(8)); 54.75 (*q*, MeO); 55.70 (*q*, MeO); 61.68 (*t*, CH₂–C(5)); 64.42 (*d*, C(5)); 70.13, 75.12 (*2d*, C(6), C(7)); 115.44, 117.14 (*2s*, C(1), C(2)); 128.08 (*d*, C(3)); 134.04 (*s*, C(8a)); 168.54 (*s*, CO₂); 170.69 (*s*, CO₂); 176.09

(s, NHCO). FAB-MS: 375 (24, $[M + 1]^+$), 325 (69), 306 (100), 233 (35). Anal. calc. for $C_{15}H_{22}N_2O_9$ (374.4): C 48.13, H 5.92, N 7.48; found: C 47.87, H 5.81, N 7.41.

Dimethyl (5R,6R,7S,8R)-8-Acetamido-5,6,7,8-tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)indolizine-1,2-dicarboxylate (22). As described for **18**, with **21** (179 mg, 0.29 mmol), AcOEt/MeOH/H₂O 4:4:1 (4.5 ml), AcOH (0.1 ml), and 10% Pd/C (37 mg; 64 h). FC (AcOEt → AcOEt/MeOH 10:1) gave **35** (73 mg, 72%). R_f (AcOEt/MeOH 10:1) 0.2. ¹H-NMR (D₂O): 1.95 (s, AcN); 3.61 (s, MeO); 3.76 (s, MeO); 3.89–3.94 (m, H–C(5)); 3.94–3.98 (m, irradi. at 5.59 → change, H–C(6), H–C(7)); 4.06 (dd, $J = 2.5, 12.8$, irradi. at 3.92 → $d, J \approx 12.8$, HC–C(5)); 4.21 (dd, $J = 2.4, 12.8$, irradi. at 3.92 → $d, J \approx 12.8$, HC–C(5)); 5.59 (dd, $J = 3.2, 1.1$ irradi. at 3.92 → change, irradi. at 3.96 → br. s, H–C(8)); 7.56 (s, H–C(3)). ¹³C-NMR (D₂O): 24.57 (q, COMe); 48.08 (d, C(8)); 54.87 (q, MeO); 55.10 (q, MeO); 61.86 (t, CH₂–C(5)); 65.05 (d, C(5)); 67.83 (d), 72.49 (d, C(6), C(7)); 114.82 (s), 118.44 (s, C(1), C(2)); 128.73 (d, C(3)); 136.44 (s, C(8a)); 168.55 (s, CO₂); 168.69 (s, CO₂); 176.06 (s, NHCO). CI-MS (NH₃): 357 (43, $[M + 1]^+$), 339 (11), 338 (19), 307 (28), 306 (100), 298 (17), 295 (16), 281 (18), 233 (33), 232 (14).

Dimethyl (5R,6R,7S,8S)-5,6,7,8-Tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)-8-(trifluoroacetamido)indolizine-1,2-dicarboxylate (19). As described for **18**, with **17** (110 mg, 0.16 mmol), AcOEt/MeOH/H₂O 5:5:1 (4 ml), and 10% Pd/C (80 mg, 32 h at 6 bar). Crystallization from EtOH/CHCl₃ (63 mg) gave **19** (45 mg, 68%). White crystals. FC (AcOEt → AcOEt/MeOH 10:1) of the mother liquor gave additional **19** (10 mg, 15%). R_f (AcOEt/MeOH 10:1) 0.64. UV (MeOH): 283 (3.1). IR (KBr): 3500s (br.), 3300s, 3138m, 1728s, 1705s, 1570m, 1528m, 1450m, 1399m, 1321m, 1165m, 1095m, 1075m, 1058m, 1021w, 965w, 914w, 891w, 862w, 828w, 619w, 521w. ¹H-NMR (D₂O): 3.80 (s, MeO); 3.82 (s, MeO); 3.90 (dd, $J = 9.0, 8.4$, H–C(7)); 4.03 (dd, $J = 9.0, 8.4$, H–C(6)); 4.07–4.15 (m, H–C(5), HC–C(5)); 4.27 (dd, $J = 10.6, 2.0$, HC–C(5)); 5.21 (d, $J = 8.4$, H–C(8)); 7.69 (s, H–C(3)). ¹³C-NMR (CD₃OD): 50.70 (d, C(8)); 52.16 (q, MeO); 52.63 (q, MeO); 62.63 (t, CH₂–C(5)); 64.42 (d, C(5)); 69.48, 73.42 (2d, C(6), C(7)); 115.53, 117.08 (2s, C(1), C(2)); 127.21 (d, C(3)); 131.98 (s, C(8a)); 166.28 (s, CO₂); 167.36 (s, CO₂). ¹⁹F-NMR (D₂O): –75.34. CI-MS: 411 (100, $[M + 1]^+$), 353 (31), 345 (64), 313 (23). Anal. calc. for $C_{15}H_{17}F_3N_2O_9$ (410.3): C 43.91, H 4.18, N 6.83; found: C 44.19, H 4.27, N 6.78.

Methyl (5R,6R,7S,8S)- and (5R,6R,7S,8R)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-1-carboxylate (23 and 29, resp.). a) At –20°, a soln. of **12** (200 mg, 0.324 mmol) in MeCN (8 ml), was treated with trimethylsilyl azide (200 μ l, 1.52 mmol) and a soln. of TiCl₄(OⁱPr)₃ (416 mg, 1.6 mmol) in MeCN (0.8 ml) and stirred for 560 min at 0°. The mixture was cooled to –50° and poured into a sat. aq. NH₄Cl soln. Normal workup (→ 160 mg, **23/29** 4:1, ¹H-NMR) and HPLC (hexane/Et₂O 2:1) gave **23** (124 mg, 69%) and **29** (34 mg, 12%).

b) As described in a), but stirring for 720 min at –10°. Normal workup gave **23/29/12** 4:1:4 (155 mg, ¹H-NMR, 80%).

c) As described in a), but addition of a suspension of ZnCl₂ (224 mg, 0.84 mmol) in MeCN instead of TiCl₄(OⁱPr)₃ and stirring for 8 h at 0°. Normal workup (→ 168 mg, **23/29** 4:1, ¹H-NMR) and HPLC (hexane/Et₂O 2:1) gave **23** (124 mg, 69%) and **29** (34 mg, 12%).

d) At –25°, a soln. of **12** (25 mg, 0.040 mmol) in MeCN (1 ml) was treated with trimethylsilyl azide (25 μ l, 0.19 mmol) and a suspension of ZnCl₂ (28 mg, 0.21 mmol) in MeCN (0.5 ml), stirred for 560 min at –10°, cooled to –78° and poured into a sat. aq. NH₄Cl soln. Normal workup gave **23/29/12** 10:2:1 (18 mg, ¹H-NMR, 80%).

e) As described in d), but stirring for 480 min at 23°. Normal workup gave **23/29** 4:3 (18 mg, ¹H-NMR, 80%).

f) At –78°, a soln. of **12** (50 mg, 0.081 mmol) in CH₂Cl₂ (2 ml) was treated with trimethylsilyl azide (50 μ l, 0.38 mmol) and BF₃ · OEt₂ (25 μ l, 0.28 mmol), kept for 15 min at –78° and poured into a sat. aq. NH₄Cl soln. Normal workup (→ 36 mg, **23/29** 2:3, ¹H-NMR) and HPLC (hexane/Et₂O 2:1) gave **23** (13 mg, 29%) and **29** (21 mg, 47%).

g) As described in f), but stirring for 15 min at 0°. Normal workup gave **23/29** 1:7 (19 mg, ¹H-NMR, 85%).

h) As described in g), but stirring for 15 min at 23°. Normal workup gave **23/29** 1:10 (19 mg, ¹H-NMR, 85%).

Data of 23: R_f (hexane/Et₂O 1:1) 0.38. UV (CHCl₃): 241 (3.9), 259 (3.8). CD (CHCl₃): 264 (–36560). IR (CHCl₃): 3067w, 2926s, 2868m, 2104s, 1953w, 1875w, 1810w, 1699s, 1555m, 1496m, 1454m, 1364m, 1305m, 1155m, 1097s, 1028w, 912w. ¹H-NMR (200 MHz, CDCl₃): 3.75 (dd, $J = 10.2, 6.7$, HC–C(5)); 3.84 (dd, $J = 10.2, 4.6$, HC–C(5)); 3.87 (s, MeO); 3.97 (td, $J = 4.6, 0.8$, H–C(6)); 4.04 (dd, $J = 4.6, 2.5$, H–C(7)); 4.38 (dt, $J = 6.7, 4.6$, H–C(5)); 4.41 (d, $J = 12.8$, PhCH); 4.51 (d, $J = 12.8$, PhCH); 4.54 (d, $J = 12.0$, PhCH); 4.58 (d, $J = 11.6$, PhCH); 4.72 (d, $J = 11.6$, PhCH); 4.74 (d, $J = 11.6$, PhCH); 5.37 (dd, $J = 2.5, 0.8$, H–C(8)); 6.69 (d, $J = 3.3$, H–C(2)); 6.83 (d, $J = 3.3$, H–C(3)); 7.24–7.41 (m, 15 arom. H). ¹³C-NMR (50 MHz, CDCl₃): 51.19 (q, MeO); 54.88 (d, C(8)); 58.59 (d, C(5)); 70.34 (t, CH₂–C(5)); 72.53 (t, PhCH₂); 72.62 (t, PhCH₂); 73.35 (t, PhCH₂); 74.11, 76.97 (2d, C(6), C(7)); 110.81 (d, C(2)); 114.72 (s, C(1)); 121.10 (d, C(3)); 127.83–128.62 (several d and 1s for C(8a)); 137.19 (s); 137.35 (s); 137.51 (s); 165.00 (s, CO₂). CI-MS: 525 (23, $[M + 1 - N_2]^+$), 510

(100, $[M - N_3]^+$), 493 (3, $[M - COOMe]^+$), 433 (7, $[M - N_2 - Bn]^+$), 420 (85, $[M^+ - N_3 - Bn]$), 106 (25), 91 (89, $C_7H_7^+$).

Data of 29: R_f (hexane/Et₂O 1:1) 0.38. UV (CHCl₃): 242 (3.9), 258 (3.8). CD (CHCl₃): 265 (16210). IR (CHCl₃): 3067w, 3008m, 2926m, 2869s, 2103s, 1699s, 1561m, 1497m, 1454m, 1364m, 1318m, 1159m, 1130s, 1128m, 989w, 914w, 872w, 841w, 610w. ¹H-NMR (200 MHz, CDCl₃): 3.69 (dd, $J = 10.4, 5.4$, HC–C(5)); 3.81 (dd, $J = 10.4, 2.5$, HC–C(5)); 3.86 (s, MeO); 3.91 (dd, $J = 9.1, 3.7$, H–C(7)); 4.08 (ddd, $J = 7.9, 5.2, 2.5$, H–C(5)); 4.18 (dd, $J = 9.1, 8.3$, H–C(6)); 4.47 (s, PhCH); 4.61 (d, $J = 11.2$, PhCH); 4.78 (d, $J = 11.6$, PhCH); 4.90 (d, $J = 11.6$, PhCH); 5.02 (d, $J = 11.2$, PhCH); 5.72 (d, $J = 3.7$, H–C(8)); 6.65 (d, $J = 3.3$, H–C(2)); 6.87 (d, $J = 2.9$, H–C(3)); 7.25–7.49 (m, 15 arom. H). ¹³C-NMR (50 MHz, CDCl₃): 51.19 (q, MeO); 54.18 (d, C(8)); 61.13 (d, C(5)); 69.99 (t, CH₂–C(5)); 72.40 (t, PhCH₂); 73.26 (t, PhCH₂); 75.29 (t, PhCH₂); 73.67, 79.38 (d, C(6), C(7)); 111.57 (d, C(2)); 113.35 (s, C(1)); 120.59 (d, C(3)); 127.83–128.69 (several d); 130.34 (s, C(8a)); 137.54 (s); 137.96 (s); 164.97 (s). CI-MS: 552 (0.4, M^+), 525 (62, $[M + 1 - N_2]^+$), 510 (100, $[M - N_3]^+$), 493 (2, $[M - COOMe]^+$), 433 (11, $[M - N_2 - Bn]^+$), 420 (18, $[M + H - N_3 - Bn]^+$), 177 (41), 106 (13), 91 (50, $C_7H_7^+$).

Methyl (5R,6R,7S,8S)-8-Amino-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-1-carboxylate (24). As described for 15, with 23 (150 mg, 0.271 mmol), MeOH (9 ml), Et₃N (0.9 ml), and propane-1,3-dithiol (0.9 ml): 24 (136 mg, 97%). R_f (AcOEt) 0.52. IR (CHCl₃): 3378w, 3067w, 3008m, 2950m, 2868m, 1952w, 1872w, 1811w, 1688s, 1575w, 1547m, 1496s, 1454m, 1366w, 1334w, 1305w, 1165m, 1098s, 1047m, 1028m, 930w, 632w, 606w, 514w. ¹H-NMR (CDCl₃): 2.79 (br. s, NH₂); 3.73 (dd, $J = 9.8, 7.0$, HC–C(5)); 3.79 (dd, $J = 10.0, 5.8$, HC–C(5)); 3.84 (s, MeO); 4.13 (br. dd, $J \approx 5.0, 1.0$), 4.19 (br. dd, $J \approx 5.0, 1.6$, H–C(6), H–C(7)); 4.41 (d, $J = 11.8$, PhCH); 4.48 (d, $J = 11.8$, PhCH); 4.48 (m, H–C(5)); 4.56 (d, $J = 10.3$, PhCH); 4.38–4.58 (m, H–C(8)); 4.60 (d, $J = 10.6$, PhCH); 4.69 (d, $J = 11.8$, PhCH); 4.70 (d, $J = 11.8$, PhCH); 6.63 (d, $J = 2.8$, H–C(2)); 6.71 (d, $J = 3.1$, H–C(3)); 7.20–7.39 (m, 15 arom. H). ¹³C-NMR (CDCl₃): 47.01 (d, C(8)); 51.09 (q, MeO); 58.79 (d, C(5)); 72.33 (br. t, CH₂–C(5), PhCH₂); 72.46 (t, PhCH₂); 73.50 (t, PhCH₂); 73.90, 76.72 (2d, C(6), C(7)); 110.79 (d, C(2)); 111.61 (s, C(1)); 120.19 (d, C(3)); 127.42–129.00 (several d); 137.46 (s); 138.00 (s); 138.06 (s); 138.39 (s); 166.05 (s, CO₂).

Methyl (5R,6R,7S,8S)-8-Acetamido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-1-carboxylate (25). A soln. of 24 (50 mg, 0.095 mmol) in pyridine (1 ml) and Ac₂O (0.5 ml) was stirred at 23° for 2 h. Evaporation and FC (AcOEt/hexane 1:1) gave 25 (53 mg, 98%). Colourless solid. R_f (hexane/AcOEt 1:1) 0.33. UV (CHCl₃): 273 (3.4). IR (CHCl₃): 3446m, 3067w, 3007s, 2951w, 2870w, 1700s, 1670s, 1554w, 1497s, 1454s, 1369m, 1340m, 1309w, 1158m, 1097s, 1045w, 1028w, 987w, 910w. ¹H-NMR (200 MHz, CDCl₃): 3.73 (dd, $J = 9.5, 7.1$, HC–C(5)); 3.77 (s, MeO); 3.83 (dd, $J = 9.5, 5.8$, HC–C(5)); 4.07 (br. s, H–C(6), H–C(7)); 4.40–4.61 (m, 2 PhCH, H–C(5)); 4.67 (d, $J = 12.0$, PhCH); 4.89 (d, $J = 12.0$, PhCH); 5.84 (s, H–C(8), H–N); 6.69 (d, $J = 3.3$, H–C(2)); 6.79 (d, $J = 3.3$, H–C(3)); 7.17–7.37 (m, 15 arom. H). ¹³C-NMR (50 MHz, CDCl₃): 23.00 (q, COMe); 43.89 (d, C(8)); 51.07 (q, MeO); 58.91 (d, C(5)); 72.02 (t, CH₂–C(5)); 72.19 (t, PhCH₂); 72.43 (t, PhCH₂); 73.45 (t, PhCH₂); 73.92, 74.08 (2d, C(6), C(7)); 111.16 (d, C(2)); 113.54 (s, C(1)); 121.23 (d, C(3)); 127.35–128.75 (several d); 130.05 (s, C(8a)); 137.10 (s); 137.70 (s); 137.83 (s); 164.78 (s, CO₂); 168.30 (s, NHCO). EI-MS: 569 (3, $[M + 1]^+$), 537 (2, $[M - MeO]^+$), 460 (12, $[M - BnOH]^+$), 417 (9), 354 (19), 311 (78), 233 (70), 205 (86), 91 (100, $C_7H_7^+$).

Methyl (5R,6R,7S,8S)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-8-(trifluoroacetamido)-indolizine-1-carboxylate (26). As described for 17, with 24 (50 mg, 0.095 mmol), pyridine (1 ml), and (COCF₃)₂O (0.1 ml): 26 (56 mg, 98%). Colourless solid. R_f (hexane/AcOEt 3:1): 0.32. UV (CHCl₃): 272 (3.5). IR (CHCl₃): 3226m, 3007w, 2870w, 1721s, 1528m, 1496s, 1454m, 1365w, 1304w, 1168s, 1099s. ¹H-NMR (CDCl₃): 3.76 (dd, $J = 10.0, 7.2$, HC–C(5)); 3.77 (s, MeO); 3.81 (dd, $J = 10.0, 5.7$, HC–C(5)); 3.96 (dd, $J = 3.9, 1.7$, irr. at 4.58 → d, $J \approx 3.5$, H–C(6)); 4.12 (br. dd, $J = 4.1, 1.5$, H–C(7)); 4.45 (d, $J = 11.8$, PhCH); 4.51 (d, $J = 10.0$, PhCH); 4.54 (d, $J = 10.6$, PhCH); 4.55–4.61 (m, H–C(5)); 4.58 (d, $J = 11.5$, PhCH); 4.64 (d, $J = 11.8$, PhCH); 4.83 (d, $J = 12.1$, PhCH); 5.88 (br. dd, $J \approx 8.7, 1.5$, addn. of CD₃OD → br. s, H–C(8)); 6.75 (d, $J = 2.8$, H–C(2)); 6.77 (d, $J = 8.7$, exchange with CD₃OD, H–N); 6.86 (d, $J = 2.8$, H–C(3)); 7.16–7.41 (m, 15 arom. H). ¹³C-NMR (CDCl₃): 43.86 (d, C(8)); 51.23 (q, MeO); 58.43 (d, C(5)); 72.27 (t, CH₂–C(5)); 72.40 (t, PhCH₂); 73.51 (br. t, 2 PhCH₂); 73.29, 74.18 (2d, C(6), C(7)); 111.57 (d, C(2)); 114.53 (s, C(1)); 121.92 (d, C(3)); 127.35 (s, C(8a)); 127.35–128.75 (several d); 136.43 (s); 137.16 (s); 137.57 (s); 155.53 (q, $J = 36.7$, COCF₃); 164.49 (s, CO₂). ¹⁹F-NMR (CDCl₃): –75.76. EI-MS: 622 (0.1, M^+), 591 (0.3, $[M - MeO]^+$), 317 (15), 287 (15), 270 (7), 255 (10), 91 (100, $C_7H_7^+$).

Methyl (5R,6R,7S,8S)-8-Acetamido-5,6,7,8-tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)indolizine-1-carboxylate (27). A soln. of 25 (50 mg, 0.088 mmol) in AcOEt/MeOH/H₂O 5:5:1 (2 ml), was treated with 10% Pd/C (40 mg), hydrogenated for 33 h at 6 bar, and filtered through Celite. Evaporation and crystallization from EtOH gave 27 (17 mg, 65%). White crystals. FC (AcOEt/MeOH 10:1) of the mother liquor gave additional 27 (6 mg,

23%). R_f (AcOEt/MeOH 10:1) 0.20. UV (MeOH): 283 (3.3). IR (KBr): 3463s (br.), 3341s (br.), 2992m, 2947m, 2912m, 1691s, 1636s, 1575s, 1543m, 1498m, 1437m, 1384m, 1319s, 1291m, 1169m, 1134m, 1121m, 1083m, 1062s, 1030m, 1008m, 966m, 834m, 636m, 590m, 544w. $^1\text{H-NMR}$ (D_2O): 1.99 (s, AcN); 3.76 (s, MeO); 3.92 (dd, $J = 7.6$, 6.3, irradi. at 5.19 $\rightarrow$ d , $J \approx 7.0$, H-C(7)); 4.03 (dd, $J = 13.2$, 4.4, HC-C(5)); 4.08 (dd, $J = 7.7$, 6.2, H-C(6)); 4.12–4.19 (m, H-C(5), HC-C(5)); 5.19 (d , $J = 6.2$, H-C(8)); 6.71 (d , $J = 3.4$, H-C(2)); 6.97 (d , $J = 3.1$, H-C(3)). $^{13}\text{C-NMR}$ (D_2O): 24.56 (q , COMe); 52.09 (d , C(8)); 54.65 (q , MeO); 62.85 (t , CH_2 -C(5)); 64.26 (d , C(5)); 70.33, 75.18 ($2d$, C(6), C(7)); 114.56 (d , C(2)); 114.98 (s, C(1)); 122.97 (d , C(3)); 135.03 (s, C(8a)); 170.30 (s, CO_2); 176.00 (s, NHCO). CI-MS: 299 (46, $[M + 1]^+$), 281 (23, $[M - \text{OH}]$), 240 (100, $[M - \text{NHAc}]^+$). Anal. calc. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_6$ (298.3): C 52.35, H 6.08, N 9.39; found: C 52.24, H 6.06, N 9.33.

Methyl (5*R*,6*R*,7*S*,8*S*)-5,6,7,8-Tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)-8-(trifluoroacetamido)indolizine-1-carboxylate (28). As described for **27**, with **26** (55 mg, 0.088 mmol), AcOEt/MeOH/ H_2O 5:5:1 (2 ml), and 10% Pd/C (40 mg; 32 h). Crystallization from EtOH/ CHCl_3 gave **28** (19 mg, 61%). White crystals. FC (AcOEt/MeOH 20:1) of the mother liquor gave additional **28** (7 mg, 23%). R_f (AcOEt/MeOH 20:1) 0.42. UV (MeOH): 283 (3.6). IR (KBr): 3434s (br.), 3322s (br.), 2956m, 2503w, 2433w, 1711s, 1688s, 1564m, 1497w, 1441w, 1358w, 1289m, 1168s, 1103m, 1056w, 906w, 614w. $^1\text{H-NMR}$ (D_2O): 3.75 (s, MeO); 3.92 (dd, $J = 8.0$, 6.9, H-C(7)); 4.07 (dd, $J = 7.5$, 6.5, irradi. at 3.92 $\rightarrow$ d , $J \approx 6.5$, H-C(6)); 4.09 (dd, $J = 12.0$, 4.1, HC-C(5)); 4.11–4.17 (m, H-C(5)); 4.22 (dd, 12.0, 2.3, HC-C(5)); 5.31 (d , $J = 6.8$, irradi. at 3.92 $\rightarrow$ s, H-C(8)); 6.73 (d , $J = 3.4$, H-C(2)); 7.01 (d , $J = 3.1$, H-C(3)). $^{13}\text{C-NMR}$ (D_2O): 52.92 (d , C(8)); 54.68 (q , MeO); 62.19 (t , CH_2 -C(5)); 64.21 (d , C(5)); 70.08, 75.34 ($2d$, C(6), C(7)); 114.77 (d , C(2)); 115.40 (s, C(1)); 119.14 (q , $J = 252.7$, CF_3); 122.98 (d , C(3)); 133.58 (s, C(8a)); 161.37 (q , $J = 37.0$, CF_3CO); 170.03 (s, NHCOCF_3). $^{19}\text{F-NMR}$ (D_2O): -74.68. Anal. calc. for $\text{C}_{13}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_6$ (352.27): C 43.33, H 4.29, N 7.95; found: C 43.62, H 4.27, N 7.69.

Methyl (5*R*,6*R*,7*S*,8*S*)- and (5*R*,6*R*,7*S*,8*R*)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-2-carboxylate (30 and 36, resp.). a) At -10° , a soln. of **13** (100 mg, 0.162 mmol) in MeCN (4 ml) was treated with trimethylsilyl azide (100 μl , 0.76 mmol) and a soln. of $\text{TiCl}_4(\text{O}^i\text{Pr})_3$ (208 mg, 0.40 mmol) in CH_2Cl_2 (0.4 ml), kept for 4 h at 0° , cooled to -50° and poured into a sat. aq. NH_4Cl soln. Normal workup ($\rightarrow$ 82 mg, **30/36** 7:3, $^1\text{H-NMR}$) and HPLC (hexane/ Et_2O 2:1) gave **30** (52 mg, 58%), and **36** (21 mg, 23%).

b) As described in a), but with CH_2Cl_2 instead of MeCN and cooling to -78° before pouring into the aq. NH_4Cl soln. Normal workup ($\rightarrow$ 84 mg, **30/36** 7:3, $^1\text{H-NMR}$). HPLC (hexane/ Et_2O 2:1) gave **30** (55 mg, 61%) and **36** (22 mg, 25%).

c) As described in a), but stirring at 0° for 240 min. Normal workup gave **30/36** 7:3 (19 mg, $^1\text{H-NMR}$, (85%).

d) As described in a), but stirring at 23° for 240 min. Normal workup gave **30/36** 3:5 (19 mg, $^1\text{H-NMR}$, 85%).

e) At -78° , a soln. of **13** (25 mg, 0.04 mmol) in CH_2Cl_2 (1 ml) was treated with trimethylsilyl azide (25 μl , 0.19 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (13 μl , 0.15 mmol) and stirred for 30 min. The mixture was poured into a sat. aq. NH_4Cl soln. Normal workup gave **30/36** 2:3 (19 mg, $^1\text{H-NMR}$, 85%).

f) As described in e), but stirring at 23° for 15 min. Normal workup gave **30/36** 3:7 (19 mg, $^1\text{H-NMR}$, 85%).

Data of 30: R_f (hexane/ Et_2O 1:1) 0.34. UV (CHCl_3): 244 (4.0). CD (CHCl_3): 236 (–34980), 261 (6417). IR (CHCl_3): 3068w, 3008m, 2925s, 2864m, 2105s, 1706s, 1563w, 1517m, 1497m, 1455m, 1363w, 1337w, 1284w, 1146m, 1100s, 1028w, 1005m, 909m, 834w. $^1\text{H-NMR}$ (CDCl_3): 3.72 (dd, $J = 10.4$, 4.7, HC-C(5)); 3.81 (s, MeO); 3.82 (dd, $J = 10.4$, 2.5, HC-C(5)); 3.82 (t , $J = 7.4$, irradi. at 3.96 $\rightarrow$ d , $J \approx 7.0$, H-C(7)); 3.96 (t , $J = 7.5$, H-C(6)); 4.13 (ddd, $J = 7.4$, 4.4, 3.0, irradi. at 3.96 $\rightarrow$ dd, $J \approx 4.0$, 3.0, H-C(5)); 4.44 (s, PhCH_2); 4.53 (d , $J = 11.4$, PhCH); 4.60 (dd, $J = 7.0$, 1.1, H-C(8)); 4.79 (d , $J = 11.0$, PhCH); 4.84 (d , $J = 10.9$, 2 PhCH); 6.04 (t , $J \approx 1.6$, H-C(1)); 7.19–7.37 (m, 15 arom. H); 7.41 (d , $J \approx 1.7$, H-C(3)). $^{13}\text{C-NMR}$ (CDCl_3): 51.20 (q , MeO); 55.71 (d , C(8)); 60.31 (d , C(5)); 70.37 (t , CH_2 -C(5)); 72.85 (t , PhCH_2); 73.39 (t , PhCH_2); 74.50 (t , PhCH_2); 73.76, 78.72 ($2d$, C(6), C(7)); 109.38 (d , C(1)); 116.94 (s, C(2)); 125.73 (s, C(8a)); 126.08 (d , C(3)); 128.01–128.78 (several d); 137.44 (s); 137.63 (s); 137.79 (s); 165.09 (s, CO_2). CI-MS: 553 (10, $[M + 1]^+$), 525 (13, $[M + 1 - \text{N}_2]^+$), 510 (21, $[M - \text{N}_3]^+$), 493 (3, $[M - \text{COOMe}]^+$), 433 (13, $[M - \text{N}_2 - \text{Bn}]^+$), 420 (59, $[M + 1 - \text{N}_3 - \text{Bn}]^+$), 325 (23), 106 (44), 91 (100, C_7H_7^+).

Data of 36: R_f (hexane/ Et_2O 1:1) 0.34. UV (CHCl_3): 243 (4.2). CD (CHCl_3): 236 (36210), 261 (–2797), 278 (4065). IR (CHCl_3): 3073w, 3008m, 2951m, 2924m, 2868m, 2105s, 1953w, 1876w, 1810w, 1707s, 1564m, 1516m, 1497m, 1454m, 1392w, 1363w, 1312w, 1098s, 1028w, 1004m, 913m, 838w, 610w. $^1\text{H-NMR}$ (CDCl_3): 3.68 (dd, $J = 9.8$, 5.1, HC-C(5)); 3.77 (dd, $J = 9.7$, 2.8, HC-C(5)); 3.80 (s, MeO); 3.94 (dd, $J = 7.8$, 3.7, irradi. at 4.80 $\rightarrow$ d , $J \approx 7.5$, H-C(7)); 4.13–4.18 (m, irradi. at 3.94 $\rightarrow$ change, H-C(5), H-C(6)); 4.44 (d , $J = 11.8$, PhCH); 4.48 (d , $J = 12.1$, PhCH); 4.57 (d , $J = 11.4$, PhCH); 4.70 (d , $J = 11.8$, PhCH); 4.77 (d , $J = 11.5$, PhCH); 4.80 (d , $J = 3.7$, irradi. at 3.94 $\rightarrow$ s, H-C(8)); 4.85 (d , $J = 11.2$, PhCH); 6.60 (d , $J = 1.7$, H-C(1)); 7.21–7.38 (m, 15 arom. H); 7.50 (d , $J = 1.7$, H-C(3)). $^1\text{H-NMR}$ (200 MHz, C_6D_6): 3.23 (dd, $J = 10.2$, 6.2, HC-C(5)); 3.36 (dd, $J = 10.0$, 4.2, HC-C(5)); 3.45 (dd, $J = 8.3$, 3.7, H-C(7)); 3.53 (s, MeO); 3.74 (d , $J = 6.2$, 4.2, H-C(5)); 3.92

(*d*, *J* = 12.5, PhCH); 4.01 (*d*, *J* = 12.5, PhCH); 4.03 (*dd*, *J* = 8.3, 6.6, H–C(6)); 4.17 (*d*, *J* = 11.6, PhCH); 4.25 (*d*, *J* = 11.6, PhCH); 4.33 (*d*, *J* = 11.0, PhCH); 4.44 (*d*, *J* = 3.7, H–C(8)); 4.59 (*d*, *J* = 11.6, PhCH); 6.79 (*d*, *J* = 1.7, H–C(1)); 6.99–7.22 (*m*, 15 arom. H); 7.55 (*d*, *J* = 1.7, H–C(3)). ¹³C-NMR (CDCl₃): 51.24 (*q*, MeO); 59.23, 59.71 (*d*, C(5), C(8)); 68.50 (*t*, CH₂–C(5)); 73.45 (*t*, PhCH₂); 74.47 (*t*, PhCH₂); 74.71 (*t*, PhCH₂); 76.12, 81.25 (*2d*, C(6), C(7)); 108.88 (*d*, C(1)); 117.08 (*s*, C(2)); 124.81 (*d*, C(3)); 126.92 (*s*, C(8a)); 128.18–128.79 (several *d*); 137.56 (*br. s*, 3 C); 165.26 (*s*, CO₂). DCI-MS: 553 (23, [*M* + 1]⁺), 525 (35, [*M* + H – N₂]⁺), 510 (35, [*M* – N₃]⁺), 493 (3, [*M* – COOMe]⁺), 433 (7, [*M* – N₂ – Bn]⁺), 420 (85, [*M* + H – N₃ – Bn]⁺), 325 (24), 106 (37), 91 (100, C₇H₇⁺).

Methyl (5R,6R,7S,8S)-8-Amino-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-2-carboxylate (31). As described for **15**, with **30** (120 mg, 0.217 mmol), MeOH (7 ml), Et₃N (0.7 ml), and propane-1,3-dithiol (0.7 ml; 24 h): **22** (108 mg, 95%). *R_f* (AcOEt) 0.51. IR (CHCl₃): 3675w, 3378w, 3067w, 3008s, 2951m, 2868m, 1951w, 1877w, 1811w, 1703s, 1602w, 1562m, 1519m, 1454m, 1363m, 1312w, 1098s, 1028w, 1004w, 914w, 834w, 610w. ¹H-NMR (200 MHz, CDCl₃): 1.81 (*br. s*, NH₂); 3.57 (*t*, *J* = 7.9, H–C(7)); 3.71 (*dd*, *J* = 10.3, 5.0, HC–C(5)); 3.80 (*s*, MeO); 3.82 (*dd*, *J* = 10.0, 3.4, HC–C(5)); 3.96 (*dd*, *J* = 7.9, 1.1, H–C(8)); 3.98 (*dd*, *J* = 8.0, 6.9, H–C(6)); 4.18 (*ddd*, *J* = 6.9, 5.0, 3.4, H–C(5)); 4.45 (*s*, PhCH₂); 4.58 (*d*, *J* = 11.5, PhCH); 4.75 (*d*, *J* = 11.5, PhCH); 4.85 (*d*, *J* = 11.2, PhCH); 4.91 (*d*, *J* = 11.5, PhCH); 6.56 (*dd*, *J* = 1.9, 1.2, H–C(1)); 7.22–7.37 (*m*, 15 arom. H); 7.41 (*d*, *J* = 1.9, H–C(3)). ¹³C-NMR (CDCl₃): 45.83 (*d*, C(8)); 51.04 (*q*, MeO); 59.48 (*d*, C(5)); 71.48 (*t*, CH₂–C(5)); 72.69 (*t*, PhCH₂); 73.16 (*t*, PhCH₂); 73.35 (*t*, PhCH₂); 73.26, 79.13 (*2d*, C(6), C(7)); 106.12 (*d*, C(1)); 116.08 (*s*, C(2)); 124.91 (*d*, C(3)); 127.76–128.86 (several *d*); 133.19 (*s*, C(8a)); 137.64 (*s*); 137.83 (*s*); 165.35 (*s*, CO₂).

Methyl (5R,6R,7S,8R)-8-Amino-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-2-carboxylate (37). As described for **15**, with **36** (140 mg, 0.253 mmol), MeOH (8 ml), Et₃N (0.8 ml), propane-1,3-dithiol (0.8 ml; 38 h): **37** (124 mg, 93%). *R_f* (AcOEt) 0.52. ¹H-NMR (CDCl₃): 1.80 (*br. s*, NH₂); 3.72–3.78 (*m*, H₂C–C(5)); 3.82 (*s*, MeO); 3.86 (*dd*, *J* = 6.2, 3.7, H–C(7)); 4.23–4.31 (*m*, H–C(5), H–C(6)); 4.35 (*d*, *J* = 3.7, H–C(8)); 4.44 (*d*, *J* = 11.8, PhCH); 4.51 (*d*, *J* = 11.8, PhCH); 4.63 (*d*, *J* = 11.5, PhCH); 4.64 (*s*, PhCH₂); 4.76 (*d*, *J* = 11.5, PhCH); 6.55 (*t*, *J* = 0.9, H–C(1)); 7.26–7.41 (*m*, 15 arom. H); 7.46 (*d*, *J* = 1.8, H–C(3)). ¹³C-NMR (50 MHz, CDCl₃): 51.04 (*q*, MeO); 53.43 (*d*, C(8)); 60.15 (*d*, C(5)); 69.29 (*t*, CH₂–C(5)); 73.32 (*t*, PhCH₂); 74.27 (*t*, PhCH₂); 74.65 (*t*, PhCH₂); 77.07, 83.89 (*2d*, C(6), C(7)); 106.21 (*d*, C(1)); 116.59 (*s*, C(2)); 124.08 (*d*, C(3)); 127.92–128.59 (several *d*); 133.48 (*s*, C(8a)); 137.45 (*s*); 137.54 (*s*); 138.02 (*s*); 165.26 (*s*, CO₂).

Methyl (5R,6R,7S,8S)-8-Acetamido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-2-carboxylate (32). A soln. of **31** (50 mg, 0.095 mmol) in pyridine (1 ml) and Ac₂O (0.5 ml) was stirred for 3 h at 23°. Evaporation and FC (AcOEt/hexane 1:1) gave **32** (52 mg, 97%). Colourless solid. *R_f* (hexane/AcOEt 1:1) 0.38. UV (CHCl₃): 269 (3.6). IR (CHCl₃): 3436w, 3067w, 3007s, 2869w, 1704s, 1667s, 1563w, 1509s, 1454m, 1393w, 1360w, 1096s, 1028w, 1003w, 909w. ¹H-NMR (200 MHz, CDCl₃): 1.83 (*s*, AcN); 3.70 (*dd*, *J* = 10.0, 7.1, HC–C(5)); 3.78 (*dd*, *J* = 10.0, 6.2, HC–C(5)); 3.79 (*s*, MeO); 3.87 (*dd*, *J* = 5.0, 3.1, irradi. at 5.46 → *d*, *J* ≈ 2.5, H–C(7)); 4.09 (*dd*, *J* = 5.0, 2.3, irradi. at 4.45 → *d*, *J* ≈ 3.0, H–C(6)); 4.41 (*d*, *J* = 12.0, PhCH); 4.41–4.48 (*m*, H–C(5)); 4.49 (*d*, *J* = 12.0, PhCH); 4.55 (*d*, *J* = 12.4, PhCH); 4.62 (*d*, *J* = 12.0, PhCH); 4.63 (*d*, *J* = 12.0, PhCH); 4.78 (*d*, *J* = 12.0, PhCH); 5.46 (*dd*, *J* = 8.9, 3.1, irradi. at 3.87 → *d*, *J* ≈ 8.0, H–C(8)); 6.01 (*d*, *J* = 8.7, NH); 6.55 (*dd*, *J* = 1.6, 0.9, H–C(1)); 7.17–7.39 (*m*, 15 arom. H); 7.42 (*d*, *J* = 1.7, H–C(3)). ¹³C-NMR (50 MHz, CDCl₃): 23.35 (*q*, COMe); 44.52 (*d*, C(8)); 51.17 (*q*, MeO); 58.81 (*d*, C(5)); 71.62 (*t*, CH₂–C(5)); 72.59 (*t*, PhCH₂); 72.78 (*t*, PhCH₂); 73.59 (*t*, PhCH₂); 74.82, 75.99 (*2d*, C(6), C(7)); 108.88 (*d*, C(1)); 116.55 (*s*, C(2)); 125.61 (*d*, C(3)); 127.81 (*s*, C(8a)); 127.81–128.92 (several *d*); 137.27 (*s*); 137.82 (*s*); 165.44 (*s*, CO₂); 169.04 (*s*, NHCO). EI-MS: 569 (2, [*M* + 1]⁺), 537 (1, [*M* – MeO]⁺), 460 (15, [*M* – BnOH]⁺), 417 (6, 354 (22), 311 (71), 233 (55), 205 (69), 91 (100, C₇H₇⁺).

Methyl (5R,6R,7S,8R)-8-Acetamido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroindolizine-2-carboxylate (38). Similarly as for **32**, **37** (50 mg, 0.095 mmol) gave **38** (53 mg, 98%). Colourless solid. *R_f* (hexane/AcOEt 1:1) 0.38. UV (CHCl₃): 270 (3.7). ¹H-NMR (CDCl₃): 1.74 (*s*, AcN); 3.66 (*dd*, *J* = 9.7, 5.3, HC–C(5)); 3.71 (*dd*, *J* = 9.7, 5.3, HC–C(5)); 3.78 (*s*, MeO); 3.92 (*dd*, *J* = 6.2, 4.1, H–C(7)); 4.14 (*dd*, *J* = 6.2, 2.8, H–C(6)); 4.33 (*td*, *J* = 5.3, 2.8, H–C(5)); 4.35 (*d*, *J* = 11.5, PhCH); 4.43 (*d*, *J* = 11.5, PhCH); 4.46 (*d*, *J* = 11.5, PhCH); 4.51 (*d*, *J* = 11.5, PhCH); 4.63 (*d*, *J* = 12.1, PhCH); 4.73 (*d*, *J* = 11.8, PhCH); 5.59 (*br. ddd*, *J* = 9.4, 4.1, 1.2, H–C(8)); 5.95 (*d*, *J* = 9.3, H–N); 6.44 (*dd*, *J* = 2.8, 1.2, H–C(1)); 7.19–7.40 (*m*, 15 arom. H, H–C(3)). ¹³C-NMR (CDCl₃): 23.15 (*q*, COMe); 43.36 (*d*, C(8)); 51.19 (*q*, MeO); 59.22 (*d*, C(5)); 72.22 (*t*, CH₂–C(5)); 72.58 (*t*, PhCH₂); 72.93 (*t*, PhCH₂); 73.78 (*t*, PhCH₂); 72.58, 76.09 (*2d*, C(6), C(7)); 107.04 (*d*, C(1)); 116.70 (*s*, C(2)); 124.87 (*d*, C(3)); 128.29–129.18 (several *d*); 129.27 (*s*, C(8a)); 137.39 (*s*); 137.55 (*s*); 137.78 (*s*); 165.42 (*s*, CO₂); 169.84 (*s*, NHCO).

Methyl (5R,6R,7S,8S)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-8-(trifluoroacetamido)indolizine-2-carboxylate (33). As described for **17**, with **31** (50 mg, 0.095 mmol), pyridine (1 ml), and $(\text{CF}_3\text{CO})_2\text{O}$ (0.1 ml). FC (hexane/AcOEt 1:2) gave **33** (55 mg, 93%). Colourless solid. R_f (hexane/AcOEt 3:1) 0.42. UV (CHCl_3): 271 (3.7). IR (CHCl_3): 3417m, 3090w, 3008m, 2952m, 2870m, 1719s, 1603m, 1564m, 1512m, 1455m, 1394w, 1364w, 1170s, 1098m, 1003w, 910w, 838w. $^1\text{H-NMR}$ (CDCl_3): 3.70 (dd, $J = 9.8, 7.0$, $\text{HC-C}(5)$); 3.76 (dd, $J = 9.8, 6.1$, $\text{HC-C}(5)$); 3.80 (s, MeO); 3.86 (dd, $J = 4.4, 2.8$, irradi. at 4.16 $\rightarrow d, J \approx 2.8$, $\text{H-C}(7)$); 4.16 (dd, $J = 4.2, 1.6$, irradi. at 3.86 $\rightarrow d, J \approx 1.0$, $\text{H-C}(6)$); 4.42 (d, $J = 11.8$, PhCH); 4.49 (d, $J = 11.5$, PhCH); 4.51 (td, $J = 6.5, 2.0$, $\text{H-C}(5)$); 4.53 (d, $J = 11.5$, PhCH); 4.57 (d, $J = 11.8$, PhCH); 4.62 (d, $J = 11.5$, PhCH); 4.72 (d, $J = 11.8$, PhCH); 5.46 (br. ddd, $J = 9.0, 2.5, 0.9$, irradi. at 3.86 $\rightarrow$ br. d, $J \approx 9.0$, irradi. at 7.20 $\rightarrow d, J \approx 2.0$, $\text{H-C}(8)$); 6.63 (dd, $J = 1.7, 0.8$, $\text{H-C}(1)$); 7.17–7.39 (m, 15 arom. H, H-N); 7.45 (d, $J = 1.9$, $\text{H-C}(3)$). $^{13}\text{C-NMR}$ (CDCl_3): 44.41 (d, C(8)); 51.25 (q, MeO); 58.21 (d, C(5)); 71.73 (t, $\text{CH}_2\text{-C}(5)$); 72.62 (t, PhCH_2); 72.88 (t, PhCH_2); 73.66 (t, PhCH_2); 74.06, 74.97 (2d, C(6), C(7)); 109.99 (d, C(1)); 116.92 (s, C(2)); 125.31 (s, C(8a)); 126.19 (d, C(3)); 127.94–129.03 (several d); 136.53 (s); 137.09 (s); 137.69 (s); 165.21 (s, NHCOMe). $^{19}\text{F-NMR}$ (CDCl_3): –75.85. EI-MS: 622 (0.4, M^+), 591 (2, $[M - \text{MeO}]^+$), 514 (4, $[M - \text{BnOH}]^+$), 317 (6), 287 (29), 270 (7), 91 (100, C_7H_7^+).

Methyl (5R,6R,7S,8R)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-8-(trifluoroacetamido)indolizine-2-carboxylate (39). Similarly as for **33**, **37** (50 mg, 0.095 mmol) gave **39** (53 mg, 89%). Colourless solid. R_f (hexane/AcOEt 3:1) 0.42. UV (CHCl_3): 270 (3.6). $^1\text{H-NMR}$ (200 MHz, CDCl_3): 3.59 (dd, $J = 9.8, 4.8$, $\text{HC-C}(5)$); 3.65 (dd, $J = 9.5, 5.0$, $\text{HC-C}(5)$); 3.80 (s, MeO); 3.92 (dd, $J = 6.4, 3.7$, $\text{H-C}(7)$); 4.18 (dd, $J = 6.7, 2.9$, $\text{H-C}(6)$); 4.34 (td, $J = 4.8, 2.9$, $\text{H-C}(5)$); 4.39 (d, $J = 12.5$, PhCH); 4.48 (d, $J = 11.6$, PhCH); 4.50 (dd, $J = 12.0$, PhCH); 4.56 (d, $J = 11.6$, PhCH); 4.61 (d, $J = 11.6$, PhCH); 4.71 (d, $J = 12.0$, PhCH); 5.63 (dd, $J = 9.1, 3.7$, $\text{H-C}(8)$); 6.50 (dd, $J = 1.6, 0.9$, $\text{H-C}(1)$); 7.14–7.40 (m, 15 arom. H, $\text{H-C}(3)$, H-N). $^{13}\text{C-NMR}$ (CDCl_3): 43.94 (d, C(8)); 51.27 (q, MeO); 59.47 (d, C(5)); 71.68 (t, $\text{CH}_2\text{-C}(5)$); 72.48 (t, PhCH_2); 73.30 (t, PhCH_2); 73.61 (t, PhCH_2); 72.48, 75.89 (2d, C(6), C(7)); 107.86 (d, C(1)); 117.16 (s, C(2)); 125.19 (s, C(8a)); 126.88 (d, C(3)); 128.13–128.92 (several d); 136.91 (s); 136.95 (s); 137.53 (s); 157.05 (q, $J = 37.8$, COCF_3); 165.13 (s, NHCO). $^{19}\text{F-NMR}$ (CDCl_3): –75.60. EI-MS: 622 (0.3, M^+), 591 (0.8, $[M - \text{MeO}]^+$), 514 (3, $[M - \text{BnOH}]^+$), 317 (15), 287 (16), 270 (7), 255 (12), 91 (100, C_7H_7^+).

Methyl (5R,6R,7S,8S)-8-Acetamido-5,6,7,8-tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)indolizine-2-carboxylate (34). As described for **27**, with **32** (50 mg, 0.088 mmol), $\text{AcOEt}/\text{MeOH}/\text{H}_2\text{O}$ 5:5:1 (2 ml), 10% Pd/C (40 mg; 32 h). Crystallization from EtOH gave **34** (16 mg, 61%). White crystals. FC (AcOEt/MeOH 10:1) of the mother liquor gave additional **34** (8 mg, 31%). Off-white residue. R_f (AcOEt/MeOH 2:1) 0.42. UV (MeOH): 273 (3.6). IR (KBr): 3330s (br.), 3137s, 2991m, 2949m, 2897s, 1717s, 1680s, 1644s, 1558s, 1524s, 1445s, 1385s, 1334w, 1299m, 1113m, 1071m, 1042w, 1005m, 934w, 882m, 657w, 587w. $^1\text{H-NMR}$ (D_2O): 2.17 (s, AcN); 3.73 (m, virtual coupling, $J = 10.0$, $\text{H-C}(7)$); 3.79 (s, MeO); 3.93–4.01 (m, $\text{H-C}(5)$, $\text{H-C}(6)$); 4.06 (dd, $J = 12.5, 1.7$, $\text{HC-C}(5)$); 4.24 (dd, $J = 12.7, 1.6$, $\text{HC-C}(5)$); 4.88 (dd, $J = 10.0, 1.2$, $\text{H-C}(8)$); 6.56 (dd, $J = 1.6, 1.2$, $\text{H-C}(1)$); 7.60 (d, $J = 1.9$, $\text{H-C}(3)$). $^1\text{H-NMR}$ (CD_3OD): 2.06 (s, AcN); 3.60 (m, virtual coupling $J = 9.6$, irradi. at 4.93 $\rightarrow$ m, virtual coupling, $J \approx 9.5$, $\text{H-C}(7)$); 3.75 (s, MeO); 3.79–3.85 (m, $\text{H-C}(5)$, $\text{H-C}(6)$); 3.92 (dd, $J = 11.4, 4.0$, $\text{CH-C}(5)$); 4.21 (br. dd, $J = 11.5, 2.0$, $\text{CH-C}(5)$); 4.93 (dd, $J = 9.6, 1.0$, $\text{H-C}(8)$); 6.29 (dd, $J = 1.6, 1.2$, $\text{H-C}(1)$); 7.60 (d, $J = 1.6$, $\text{H-C}(3)$). $^{13}\text{C-NMR}$ (CD_3OD): 22.96 (q, COMe); 51.06 (d, C(8)); 51.72 (q, MeO); 62.16 (t, $\text{CH}_2\text{-C}(5)$); 64.02 (d, C(5)); 70.81, 74.84 (2d, C(6), C(7)); 107.62 (d, C(1)); 117.42 (s, C(2)); 125.88 (d, C(3)); 132.00 (s, C(8a)); 167.80 (s, CO_2); 174.09 (s, NHCO). CI-MS: 299 (16, $[M + 1]^+$), 280 (39, $[M + 1 - \text{H}_2\text{O}]^+$), 240 (100, $[M - \text{NHAc}]^+$). Anal. calc. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_6$ (298.30): C 52.35, H 6.08, N 9.39; found: C 51.91, H 6.10, N 9.18.

Methyl (5R,6R,7S,8R)-8-Acetamido-5,6,7,8-tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)indolizine-2-carboxylate (40). As described for **27**, with **38** (50 mg, 0.088 mmol), $\text{AcOEt}/\text{MeOH}/\text{H}_2\text{O}$ 5:5:1 (2 ml), and 10% Pd/C (40 mg, 36 h). Crystallization from EtOH gave **40** (17 mg, 65%). White crystals. FC (AcOEt/MeOH 10:1) of the mother liquor gave additional **40** (9 mg, 23%). Off-white residue. R_f (AcOEt/MeOH 2:1) 0.42. UV (MeOH): 272 (3.4). IR (KBr): 3330s (br.), 3137s, 2991m, 2949m, 2897s, 1717s, 1680s, 1644s, 1558s, 1524s, 1445s, 1385s, 1334w, 1299m, 1113m, 1071m, 1042w, 1005m, 934w, 882m, 657w, 587w. $^1\text{H-NMR}$ (D_2O): 2.06 (s, AcN); 3.80 (s, MeO); 4.03 (dd, $J = 11.7, 3.4$, $\text{HC-C}(5)$); 4.03–4.09 (m, $\text{H-C}(5)$); 4.09 (dd, $J = 7.8, 4.7$, $\text{H-C}(7)$); 4.16 (dd, $J = 11.7, 3.1$, $\text{HC-C}(5)$); 4.20 (dd, $J = 7.8, 5.3$, $\text{H-C}(6)$); 5.36 (br. d, $J = 4.4$, $\text{H-C}(8)$); 6.56 (dd, $J = 1.9, 0.6$, $\text{H-C}(1)$); 7.61 (d, $J = 1.9$, $\text{H-C}(3)$). $^{13}\text{C-NMR}$ (D_2O): 24.77 (q, COMe); 48.31 (d, C(8)); 54.58 (q, MeO); 63.77 (t, $\text{CH}_2\text{-C}(5)$); 64.79 (d, C(5)); 69.81, 71.88 (2d, C(6), C(7)); 110.58 (d, C(1)); 118.29 (s, C(2)); 128.39 (d, C(3)); 132.00 (s, C(8a)); 170.68 (s, CO_2); 177.13 (s, NHCO).

Methyl (5R,6R,7S,8S)-5,6,7,8-Tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)-8-(trifluoroacetamido)indolizine-2-carboxylate (35). As described for **27**, with **33** (51 mg, 0.082 mmol), $\text{AcOEt}/\text{MeOH}/\text{H}_2\text{O}$ 5:5:1 (2 ml), and

10% Pd/C (40 mg; 32 h). Crystallization from EtOH/CHCl₃ gave **35** (15 mg, 52%). White crystals. FC (AcOEt/EtOH 20:1) of the mother liquor gave additional **35** (8 mg, 28%). R_f (AcOEt/MeOH 20:1) 0.35. UV (MeOH): 272 (3.6). IR (KBr): 3460s (br.), 3254s, 3155m, 3100m, 2939m, 1718s, 1669s, 1564s, 1518s, 1448s, 1380s, 1322w, 1260m, 1154s, 1121w, 1094w, 1003m, 918w, 843w, 644w, 614w. ¹H-NMR (D₂O): 3.80 (s, MeO); 3.87 (m, virtual coupling, $J = 9.7, 9.3$, H–C(7)); 3.97–4.04 (m, H–C(5), H–C(6)); 4.10 (br. dd, $J = 12.5, 1.5$, HC–C(5)); 4.27 (br. dd, $J = 12.5, 1.5$, HC–C(5)); 5.02 (d, $J = 10.0$, H–C(8)); 6.44 (br. d, $J = 0.6$, H–C(1)); 7.64 (br. d, $J = 0.5$, H–C(3)). ¹³C-NMR (D₂O): 53.05 (d, C(8)); 54.60 (q, MeO); 61.88 (t, CH₂–C(5)); 64.40 (d, C(5)); 71.21, 75.00 (2d, C(6), C(7)); 109.20 (d, C(1)); 118.68 (s, C(2)); 118.88 (q, $J = 280.6$, COCF₃); 127.89 (d, C(3)); 131.98 (s, C(8a)); 162.42 (q, $J = 37.5$, CF₃CO); 170.58 (s, NHCOCF₃). ¹⁹F-NMR (D₂O): –74.60. CI-MS: 370 (100, $[M + NH_4]^+$), 353 (52, $[M + 1]^+$), 334 (11, $[M - H_2O]^+$), 240 (66, $[M - NHCOCF_3]^+$). Anal. calc. for C₁₃H₁₅F₃N₂O₆ (352.27): C 44.33, H 4.29, N 7.95; found: C 44.37, H 4.43, N 7.73.

Methyl (5R,6R,7S,8R)5,6,7,8-Tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)-8-(trifluoroacetamido)indoline-2-carboxylate (41). As described for **27**, with **39** (52 mg, 0.084 mmol), AcOEt/MeOH/H₂O 5:5:1 (2 ml), and 10% Pd/C (40 mg; 36 h). Crystallization from EtOH/CHCl₃ gave **41** (18 mg, 60%). White crystals. Evaporation of the mother liquor gave additional **41** (10 mg, 33%). Off-white residue. R_f (AcOEt/MeOH 20:1) 0.35. UV (MeOH): 271 (3.5). IR (KBr): 3444s (br.), 3275s (br.), 3130s, 2964s, 2932s, 2892m, 1682s (br.), 1556s, 1520s, 1482m, 1444m, 1373m, 1051m, 1007s, 962m, 934m, 907m, 859w, 842m, 647m, 632m, 516w. ¹H-NMR (D₂O): 3.80 (s, MeO); 4.07–4.25 (m, H–C(5), H–C(6), H–C(7), H₂C–C(5)); 5.48 (br. d, $J \approx 3.5$, H–C(8)); 6.56 (dd, $J = 1.9, 0.9$, H–C(1)); 7.63 (d, $J = 1.9$, H–C(3)). ¹³C-NMR (D₂O): 49.49 (d, C(8)); 52.92 (q, MeO); 63.82 (t, CH₂–C(5)); 64.82 (d, C(5)); 69.21, 72.19 (2d, C(6), C(7)); 111.64 (d, C(1)); 118.66 (s, C(2)); 128.32 (d, C(3)); 130.33 (s, C(8a)); 170.51 (s, CO₂). ¹⁹F-NMR (D₂O): –75.07. CI-MS: 370 (6, $[M + NH_4]^+$), 353 (34, $[M + 1]^+$), 334 (100, $[M - H_2O]^+$), 303 (88), 240 (73, $[M - NHCOCF_3]^+$).

Equilibration Studies. a) A soln. of the pure azide (5 mg of **14**, **23**, or **30**), trimethylsilyl azide (15 μ l), and BF₃ · OEt₂ (7.5 μ l) in CD₂Cl₂ (0.7 ml) was kept at 23° and monitored by ¹H-NMR spectroscopy until the ratio of **14/20**, **23/29**, and **30/36** (as determined by integration of the H–C(8) or H–C(1) signals) showed no change (**14/20** 1:7 after 64 h, **23/29** 1:10 after 5 min, **30/36** 3:7 after 5 min).

b) A soln. of the pure azide (5 mg of **23**, **29**, **30**, or **36**), trimethylsilyl azide (10 μ l), and BF₃ · OEt₂ (5 μ l) in either CH₂Cl₂, MeCN, or toluene (0.5 ml) was stirred at 23° for 24 h. After normal workup, the ratio of *gluco*- and *manno*-configured azide was determined by integration of the H–C(8) or H–C(1) signal in the ¹H-NMR spectrum.

Enzyme-Inhibition Studies. Determinations of the inhibition constants (K_i) were performed in the presence of 4 inhibitor concentrations which bracket the K_i value. 4-Nitrophenyl 2-acetamido-2-deoxy- β -D-glucopyranoside (GlcNAc-Np) from Sigma (No. N-9376), β -N-acetylglucosaminidase (EC 3.2.1.30) from bovine kidney and jack beans from Sigma (No. A-2415 and A-2264, resp.) were used. The suspensions of the enzymes in 3.2M (NH₄)₂SO₄ (0.1 ml, 5 U), and 2.5M (NH₄)₂SO₄ (0.1 ml, 5 U), resp., were centrifuged, and the pellets were dissolved in H₂O. Citrate buffer (0.5M, pH 4.2, 100 μ l), inhibitor soln., or H₂O (300 μ l), resp., and enzyme soln. (52 mU in H₂O, 100 μ l) were incubated at 37° for 5 min. After addition of GlcNAc-Np (5.0, 2.5, 1.6, 1.0, 0.5 mM in H₂O, 500 μ l), incubation was continued for 3, 6, 9, or 12 min. The reaction was stopped by addition of borate buffer (0.2M, pH 9.2, 1000 μ l). The amount of 4-nitrophenolate liberated was determined by measurement of the UV/VIS absorption at 400 nm and the increase of absorption per min taken, as velocity for the hydrolysis of the substrate. The K_i were determined by taking the slopes from the *Lineweaver-Burk* plots [51] and plotting them against the inhibitor concentrations [52]. After fitting the data to a straight line, the negative [I]-intercept of this plot gave the appropriate K_i values.

REFERENCES

- [1] D. E. Koshland, *Biol. Rev.* **1953**, 28, 1953.
- [2] T. D. Heightman, Personal Communication.
- [3] N. C. J. Strynadka, M. N. G. James, *J. Mol. Biol.* **1991**, 220, 401.
- [4] T. D. Heightman, M. Locatelli, A. Vasella, *Helv. Chim. Acta* **1996**, 79, 2190.
- [5] J. Sakon, W. S. Adney, M. E. Himmel, S. R. Thomas, P. A. Karplus, *Biochemistry* **1996**, 35, 10648.
- [6] P. Ermert, A. Vasella, *Helv. Chim. Acta* **1991**, 74, 2043.
- [7] T. Granier, N. Panday, A. Vasella, *Helv. Chim. Acta* **1997**, 80, 979.
- [8] K. Tatsuta, S. Miura, S. Ohta, H. Gunji, *J. Antibiot.* **1995**, 48, 286.
- [9] T. Granier, F. Gaiser, L. Hintermann, A. Vasella, *Helv. Chim. Acta* **1997**, 80, 1443.
- [10] T. D. Heightman, P. Ermert, D. Klein, A. Vasella, *Helv. Chim. Acta* **1995**, 78, 514.

- [11] T. Aoyagi, H. Suda, K. Uotani, F. Kojima, T. Aoyama, K. Hiroguchi, M. Hamada, *J. Antibiot.* **1992**, *45*, 1404.
- [12] B. Henrissat, *Biochem. J.* **1991**, *280*, 309.
- [13] B. Henrissat, A. Bairoch, *Biochem. J.* **1996**, *293*, 695.
- [14] A. C. Terwisscha van Scheltinga, K. H. Kalk, J. J. Beintema, B. W. Dijkstra, *Biochemistry* **1994**, *34*, 15619.
- [15] I. Tews, A. Perrakis, A. Oppenheim, Z. Dauter, K. S. Wilson, C. E. Vorgias, *Nature Struct. Biol.* **1996**, *3*, 638.
- [16] R. Hoos, A. B. Naughton, A. Vasella, *Helv. Chim. Acta* **1993**, *76*, 1802.
- [17] H. S. Overkleeft, J. van Wiltenburg, U. K. Pandit, *Tetrahedron* **1994**, *50*, 4215.
- [18] K. Tatsuta, S. Miura, H. Gunji, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 427.
- [19] E. C. K. Lai, S. G. Withers, *Biochemistry* **1994**, *33*, 14743.
- [20] L. D. Hall, C. W. M. Grant, *Carbohydr. Res.* **1972**, *24*, 218.
- [21] P. Meindl, G. Bodo, P. Palese, J. Schulmann, H. Tuppy, *Virology* **1974**, *58*, 457.
- [22] Y. Nishimura, T. Kudo, S. Kondo, T. Takeuchi, *J. Antibiot.* **1994**, *47*, 101.
- [23] H. R. Synder, E. L. Eliel, *J. Am. Chem. Soc.* **1948**, *70*, 1703.
- [24] B. C. Ennis, G. Holan, E. L. Samuel, *J. Chem. Soc. (C)* **1967**, 30.
- [25] G. Holan, E. L. Samuel, *J. Chem. Soc., Perkin Trans. 1* **1967**, 25.
- [26] J. G. Buchanan, S. J. Moorhouse, R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2258.
- [27] L. H. Foley, G. Büchi, *J. Am. Chem. Soc.* **1982**, *104*, 1776.
- [28] R. Breslow, J. T. Hunt, R. Smiley, T. Tarnowski, *J. Am. Chem. Soc.* **1983**, *105*, 5337.
- [29] J. G. Buchanan, A. Millar, R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1* **1985**, 1425.
- [30] M. P. Sammes, 'Physical and theoretical aspects synthesis and chemical reactivity of 2H- and 3H-Pyrroles', Wiley, New York, 1990, p. 549.
- [31] S. A. Patil, B. A. Otter, R. S. Klein, *Nucleosides Nucleotides* **1990**, *9*, 937.
- [32] A. D. Abell, J. C. Litten, *Tetrahedron Lett.* **1992**, *33*, 3005.
- [33] R. A. Barcock, N. A. Moorcroft, R. C. Storr, J. W. Young, L. S. Fuller, *Tetrahedron Lett.* **1993**, *34*, 1187.
- [34] C.-A. Harrison, R. Leineweber, C. J. Moody, J. M. J. Williams, *Tetrahedron Lett.* **1993**, *34*, 8527.
- [35] C.-A. Harrison, R. Leineweber, C. J. Moody, J. M. J. Williams, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1127.
- [36] T. J. Bond, J. R. P. C. Taylor, *Tetrahedron Lett.* **1994**, *35*, 9263.
- [37] S. Harusawa, Y. Murai, H. Moriyama, H. Ohishi, R. Yoneda, T. Kurihara, *Tetrahedron Lett.* **1995**, *36*, 3165.
- [38] C.-Y. Chen, D. R. Liebermann, L. J. Street, A. R. Guiblin, R. D. Larsen, T. R. Verhoeven, *Synth. Commun.* **1996**, *26*, 1977.
- [39] Y. Xu, K. Yakushijin, D. A. Horne, *J. Org. Chem.* **1996**, *61*, 9569.
- [40] S. Harusawa, Y. Murai, H. Moriyama, T. Imazu, H. Ohishi, R. Yoneda, T. Kurihara, *J. Org. Chem.* **1996**, *61*, 4405.
- [41] L. F. Tietze, G. Kettschau, K. Heitmann, *Synthesis* **1996**, 851.
- [42] V. Lee, M.-K. Cheung, W.-T. Wong, K.-F. Cheng, *Tetrahedron* **1996**, *52*, 9455.
- [43] J. Moyroud, J. Gelin, A. Chêne, J. Mortier, *Tetrahedron* **1996**, *52*, 8525.
- [44] S. D. Lindell, C. G. Earnshaw, B. J. Wright, D. S. Carver, M. J. O'Mahony, E. A. Saville-Stones, *Bioorg. Medicinal Chem. Lett.* **1996**, *6*, 547.
- [45] S. Harusawa, H. Moriyama, Y. Murai, T. Imazu, H. Moriyama, H. Ohishi, R. Yoneda, T. Kurihara, H. Hata, Y. Sakamoto, *Chem. Pharm. Bull.* **1997**, *45*, 53.
- [46] M. D. Cliff, S. G. Pyne, *J. Org. Chem.* **1997**, *62*, 1023.
- [47] H. Bayley, D. N. Standring, J. R. Knowles, *Tetrahedron Lett.* **1978**, *39*, 3633.
- [48] V. A. Timoshuk, L. N. Kulinkovich, *J. Gen. Chem. USSR (Engl. Transl.)* **1988**, *58*, 1019.
- [49] P. Ermert, Synthese und Evaluation übergangszustandsanaloger β -Glycosidasehemmer, Ph.D. Thesis ETH-Zürich No. 11407, 1996.
- [50] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, 400.
- [51] H. Lineweaver, D. Burk, *J. Am. Chem. Soc.* **1934**, *56*, 658.
- [52] I. H. Segel, 'Enzyme Kinetics', Wiley, New York, 1975.