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

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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 Et_3N, followed by acetylation or trifluoroacetylation and hydrogenolytic debenzylation, 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 μM), indicating the necessity of a heteroatom at the glycosidic position. K_i Values between 100 and 160 μM 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 → 4)-2-acetamido-2-deoxy-D-glucose-β-(1 → 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 sp^2-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 enzyme[1]) 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].

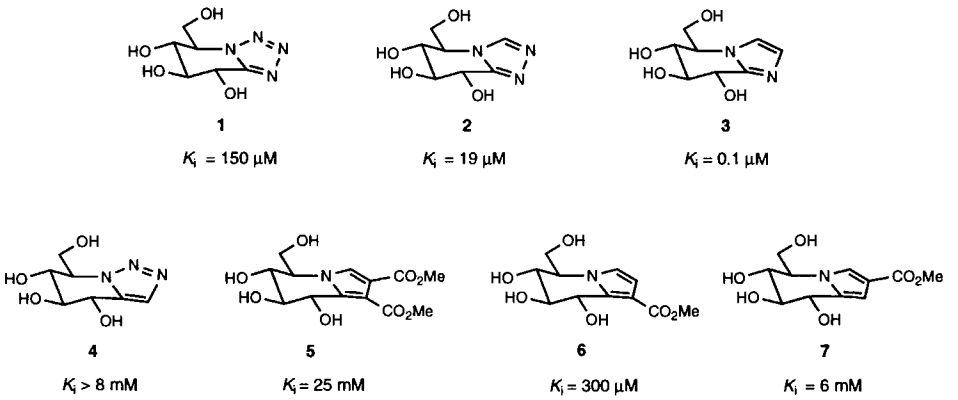

Fig. 1. K_i *Values of* gluco-*configurated tetrahydropyridoazoles against sweet-almonds β-glucosidases*

been tested. As the pyrroles (tetrahydroindolizines) **11**–**13** are readily available[2]), 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.

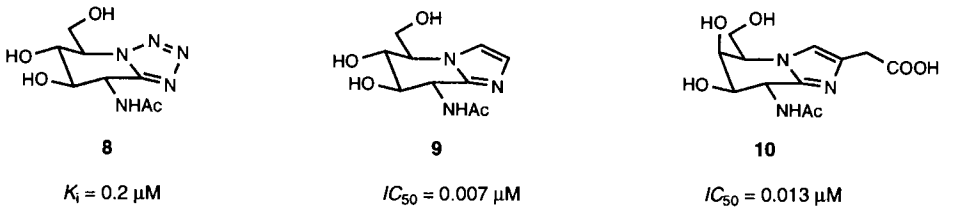

Fig. 2. K_i *and* IC_{50} *Values of three strong tetrahydropyridazole-type hexosaminidase inhibitors against* N-*acetyl-β*-D-*glucosaminidase from bovine kidney*

The acetamido group is expected to contribute significantly to the binding of inhibitors to *N*-acetyl-β-D-glucosaminidases[3]). 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 $BF_3 \cdot OEt_2$ in CH_2Cl_2 at $-7°$[4]) gave a *ca.* 3:1 mixture[5]) of the azides **14**/**20** (82%), from which the *gluco*-configurated 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*-configurated azide **20** was isolated in 65% yield.

Treatment of the more reactive monoester **12** with trimethylsilyl azide and $BF_3 \cdot OEt_2$ 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 $TiCl(O^iPr)_3$ 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 $TiCl(O^iPr)_3$ 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*-configurated azides **20**, **29**, and **36**, while shorter reaction times and lower temperatures gave mainly the *gluco*-configurated 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 $BF_3 \cdot OEt_2$ in the presence of trimethylsilyl azide at 23°. Under these conditions, as shown by monitoring the reaction in CD_2Cl_2 by ^{1}H-NMR spectroscopy, the equilibrium for **23**/**29** and **30**/**36** was reached whithin 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 azoniafulvene[6]) **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*-configurated 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

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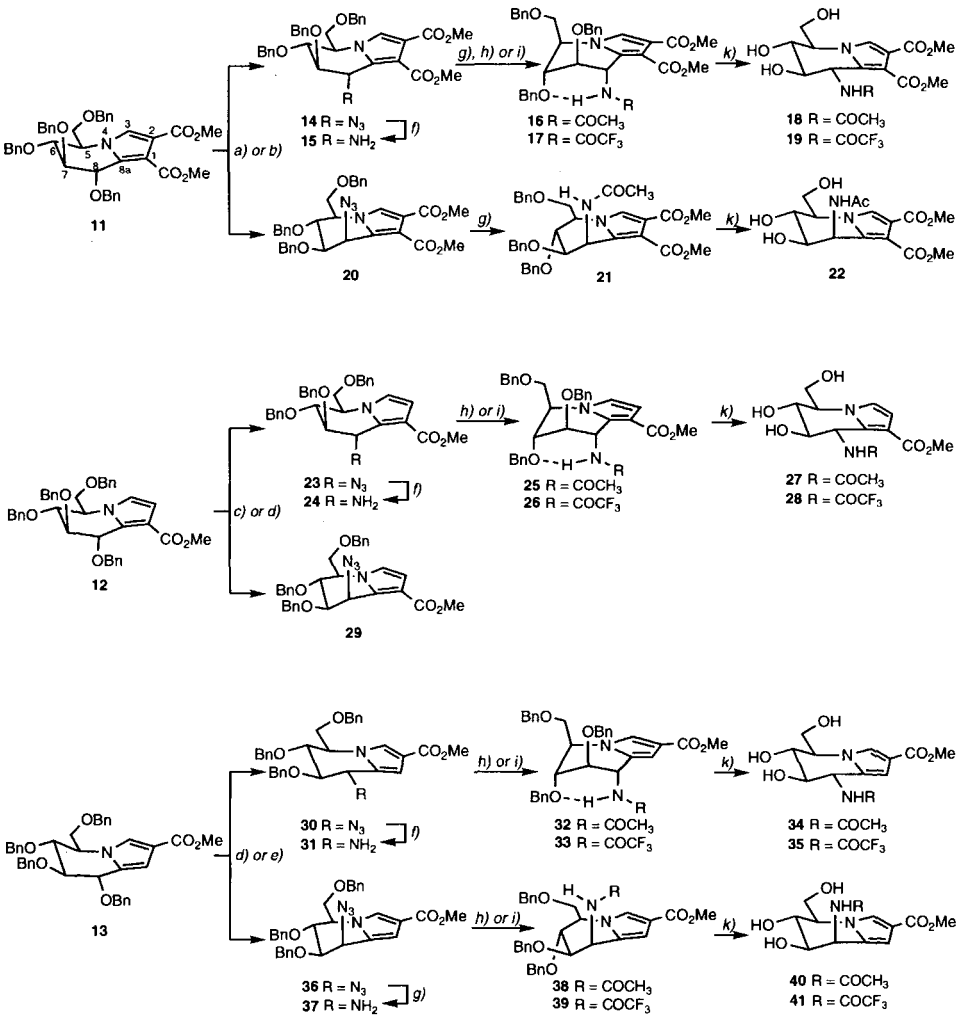
[4]) Running the reaction at lower temperatures considerably protracted the reaction without modifying the ratio **14**/**20**.

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

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

Scheme 1



a) Trimethylsilyl azide, $BF_3 \cdot OEt_2$, CH_2Cl_2, $-7°$; **14**/**20** 3:1, 82%. *b*) Trimethylsilyl azide, $BF_3 \cdot OEt_2$, toluene, 90°; **14**/**20** 1:4, 85%. *c*) Trimethylsilyl azide, $TiCl(O^iPr)_3$ or $ZnCl_2$, MeCN, 0°; **23**/**29** 4:1, 81%. *d*) Trimethylsilyl azide, $BF_3 \cdot OEt_2$, CH_2Cl_2, $-78°$; **23**/**29** 2:3, 76%; **30**/**36** 1:2, 85%. *e*) Trimethylsilyl azide, $TiCl(O^iPr)_3$, MeCN or CH_2Cl_2, 0°; **30**/**36** 7:3, 81–86%. *f*) $HS(CH_2)_3SH$, Et_3N, MeOH, 23°; **15**, 99%; **24**, 97%; **31**, 95%; **37**, 93%. *g*) 1. H_2, Pd/C, AcOEt, MeOH. 2. Ac_2O, pyridine; **16**, 70% from **14**; **21**, 70%. *h*) Ac_2O, pyridine; **16**, 97%; **25**, 98%; **32**, 97%; **38**, 97%. *i*) $(CF_3O)_2O$, pyridine; **17**, 95%; **26**, 98%; **33**, 95%; **39**, 89%. *k*) H_2, 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 N_3 group and acetylation (70%). To improve the yields, we reduced **14** with propane-1,3-dithiol and Et_3N [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*

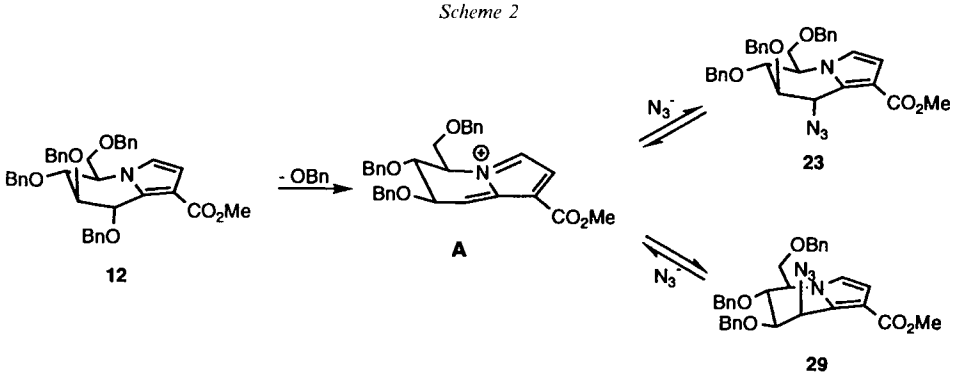
Starting material	*Lewis* acid	Solvent	Temperature [°]	Reaction time [min]	*gluco/manno*
11	$BF_3 \cdot OEt_2$	CH_2Cl_2	−7	210	3:1
11	$BF_3 \cdot OEt_2$	toluene	90	15	1:4
12	$BF_3 \cdot OEt_2$	CH_2Cl_2	−78	15	2:3
12	$BF_3 \cdot OEt_2$	CH_2Cl_2	0	15	1:7
12	$BF_3 \cdot OEt_2$	CH_2Cl_2	23	15	1:10
12	$TiCl(O^iPr)_3$	MeCN	0	560	4:1
12	$TiCl(O^iPr)_3$	MeCN	−10	720	4:1[a])
12	$TiCl(O^iPr)_3$	CH_2Cl_2	0	480	7:3
12	$TiCl(O^iPr)_3$	CH_2Cl_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_2Cl_2	−10	240	7:3[a])
12	$ZnCl_2$	CH_2Cl_2	−10	480	3:2[a])
12	$BF_3 \cdot OEt_2$	CH_2Cl_2	−78	30	2:3
13	$BF_3 \cdot OEt_2$	CH_2Cl_2	23	15	3:7
13	$TiCl(O^iPr)_3$	CH_2Cl_2	0	240	7:3
13	$TiCl(O^iPr)_3$	MeCN	−10	530	7:3
13	$TiCl(O^iPr)_3$	MeCN	0	240	7:3
13	$TiCl(O^iPr)_3$	MeCN	23	240	3:5

[a]) Incomplete reaction.

Table 2. *Equilibration of 8-Azidopyrrolopyridines with $BF_3 \cdot OEt_2$ in the Presence of Trimethylsilyl Azide at 23°*

Starting material	Solvent	*gluco/manno*
14 or **20**	CD_2Cl_2 or CH_2Cl_2	1:7
23 or **29**	CD_2Cl_2 or CH_2Cl_2	1:10
23 or **29**	MeCN	1:9
23 or **29**	toluene	1:11
30 or **36**	CD_2Cl_2 or CH_2Cl_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 debenzylation 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*-configurated 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 ^{1}H-NMR data of the deprotected acetamido-tetrahydroindolizines with those of the known acetamido-tetrahydrotetrazolopyridines [49]. In D_2O solution, the piperidine ring of the deprotected acetamides **18**, **19**, **22**, **27**, **28**, **34**, **35**, **40**, and **41** adopts predominantly a $^7H_6$ 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 $^6H_7$ conformation [7]. 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 N_3 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 $^7H_6$ 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 $^6H_7$- and $^{5,8}B$-conformers [7]. Again, the C(1)-substituted monocarboxylate **23** (J values of 2.5–4.1 Hz) shows a stronger preference for the $^6H_7$-conformation than the dicarboxylate **20** (J values of 3.8–5.9 Hz). The equilibrium ratios, in CD_2Cl_2 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 $^7H_6$-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 $^6H_7$-conformation for the protected *gluco*-configurated 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*-configurated 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*-configurated 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–CH_2–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 $^7H_6$, of 1.2, 4.2, and 1.9 Hz for the $^6H_7$, 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-glycosidases[9]).

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

Hexosaminidase	Inhibitor	K_i [μM]
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 Ldt.*, 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 $(NH_4)_6Mo_7O_{24} \cdot 6\,H_2O$, 0.4 g of $Ce(SO_4)_2$). 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 [θ] in deg · cm^2 · 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.

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[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 $BF_3 \cdot OEt_2$ (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 (→ **14**/**15** 3:1, ^{1}H-NMR) and FC (hexane/Et_2O 3:1 → 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 $BF_3 \cdot OEt_2$ (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 (→ **14**/**15** 1:4, ^{1}H-NMR) and FC (hexane/Et_2O 3:1 → 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 ($CHCl_3$): 3090*w*, 3008*m*, 2985*m*, 2963*m*, 2929*w*, 2871*m*, 2106*s*, 1730*s*, 1571*w*, 1528*m*, 1497*m*, 1454*m*, 1374*m*, 1265*s*, 1158*m*, 1098*s*, 1070*s*, 1046*m*. ^{1}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 → *d*, *J* ≈ 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, PhC*H*); 4.48 (*d*, *J* = 12.1, PhC*H*); 4.49 (*d*, *J* = 11.7, PhC*H*); 4.62 (*d*, *J* = 11.4, PhC*H*); 4.72 (*d*, *J* = 11.6, PhC*H*); 4.73 (*d*, *J* = 11.7, PhC*H*); 5.15 (*d*, *J* = 3.8, H−C(8)); 7.19–7.38 (*m*, 15 arom. H, H−C(3)). ^{13}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 (2*d*, C(6), C(7)); 115.08, 116.07 (2*s*, 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 ($CHCl_3$): 3089*w*, 3008*m*, 2985*m*, 2963*m*, 2939*w*, 2871*m*, 2106*s*, 1728*s*, 1571*w*, 1527*m*, 1497*m*, 1454*m*, 1374*m*, 1265*s*, 1158*m*, 1098*s*, 1070*s*, 1046*m*. ^{1}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 → *d*, *J* ≈ 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, PhC*H*); 4.77 (*d*, *J* = 11.8, PhC*H*); 4.84 (*d*, *J* = 11.7, PhC*H*); 4.96 (*d*, *J* = 11.0, PhC*H*); 5.45 (*d*, *J* = 3.7, H−C(8)); 7.21–7.44 (*m*, 15 arom. H, H−C(3)). ^{13}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 (2*d*, C(6), C(7)); 113.43, 117.05 (2*s*, 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 → 10:1) gave **15** (142 mg, 99%). R_f (AcOEt) 0.40. IR ($CHCl_3$): 3380*w*, 3090*w*, 3008*m*, 2950*m*, 2868*m*, 1724*s*, 1685*s*, 1577*w*, 1523*m*, 1497*w*, 1454*m*, 1443*m*, 1399*w*, 1365*w*, 1286*m*, 1176*w*, 1097*s*, 1073*s*, 1028*w*, 909*s*, 651*m*. ^{1}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, PhC*H*); 4.39–4.46 (*m*, H−C(5), H−C(8)); 4.46 (*d*, *J* = 11.8, PhC*H*); 4.52 (*d*, *J* = 11.8, PhC*H*); 4.56 (*d*, *J* = 11.8, PhC*H*); 4.56 (*d*, *J* = 12.1, PhC*H*); 4.65 (*d*, *J* = 11.8, PhC*H*); 7.20–7.39 (*m*, 15 arom. H, H−C(3)). ^{13}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 (2*d*, C(6), C(7)); 111.74, 116.43 (2*s*, 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 ($CHCl_3$): 3441*m*, 3068*w*, 3008*w*, 2951*m*, 2869*m*, 1728*s*, 1670*s*, 1524*m*, 1449*m*, 1445*m*, 1440*m*, 1400*w*, 1368*w*, 1340*w*, 1290*m*, 1248*m*, 1097*s*, 1074*s*. ^{1}H-NMR (C_6D_6): 1.53 (*s*, AcN); 3.47 (*dd*, *J* = 9.7, 7.4, irrad. at 4.34 → *d*, *J* ≈ 9.8, HC−C(5)); 3.55 (*dd*, *J* = 5.3, 9.7, irrad. at 4.34 → *d*, *J* ≈ 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 → *d*, *J* ≈ 2.0, irrad. at 4.34 → *d*, *J* ≈ 4.1, H−C(6)); 4.04 (*d*, *J* = 11.8, PhC*H*); 4.05–4.07 (*m*, irrad. at 6.07 → *d*, *J* ≈ 3.7,

H–C(7)); 4.12 (*d*, *J* = 11.7, PhC*H*); 4.13 (*d*, *J* = 12.1, PhC*H*); 4.17 (*d*, *J* = 11.8, PhC*H*); 4.34 (*ddd*, *J* = 2.4, 5.2, 7.2, H–C(5)); 4.65 (*d*, *J* = 12.1, PhC*H*); 4.76 (*d*, *J* = 12.0, PhC*H*); 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)). ^{13}C-NMR ($CDCl_3$): 22.97 (*q*, CO*Me*); 43.55 (*d*, C(8)); 51.60 (*q*, MeO); 51.82 (*q*, MeO); 59.19 (*d*, C(5)); 71.90 (*t*, CH_2–C(5)); 72.16 (*t*, PhCH_2); 72.28 (*t*, PhCH_2); 73.52 (*t*, PhCH_2); 73.81, 74.06 (2*d*, C(6), C(7)); 114.16, 116.43 (2*s*, 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*, CO_2); 164.27 (*s*, CO_2); 168.23 (*s*, NHCOMe).

*Dimethyl (5*R*,6*R*,7*S*,8*R*)-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 Ac_2O (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 ($CHCl_3$): 258 (3.9). IR ($CHCl_3$): 3392*m*, 3090*w*, 3067*w*, 3008*m*, 2952*m*, 2870*m*, 1716*s*, 1676*s*, 1530*w*, 1498*m*, 1454*m*, 1440*m*, 1400*w*, 1370*m*, 1297*m*, 1248*m*, 1174*m*, 1155*w*, 1075*s*, 1028*w*, 913*w*. ^{1}H-NMR ($CDCl_3$): 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*, PhCH_2); 4.53 (*d*, *J* = 11.2, PhC*H*); 4.62 (*d*, *J* = 11.8, PhC*H*); 4.86 (*d*, *J* = 11.1, PhC*H*); 4.88 (*d*, *J* = 11.8, PhC*H*); 5.99 (br. *s*, NH, H–C(8)); 7.11–7.41 (*m*, 15 arom. H, H–C(3)). ^{1}H-NMR ($CDCl_3$ + 5% CD_3OD): 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*, PhCH_2); 4.52 (*d*, *J* = 11.1, PhC*H*); 4.58 (*d*, *J* = 11.7, PhC*H*); 4.83 (*d*, *J* = 11.1, PhC*H*); 4.85 (*d*, *J* = 11.6, PhC*H*); 5.96 (*dd*, *J* = 4.1, 9.2, addn. of CD_3OD → *d*, *J* ≈ 4.0, H–C(8)); 6.34 (*d*, *J* = 9.3, slow exchange with CD_3OD, NH); 7.11–7.41 (*m*, 15 arom. H, H–C(3)). ^{1}H-NMR (C_6D_6): 1.44 (*s*, Ac); 3.27–3.39 (br. *s*, CH_2–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, PhC*H*); 3.94 (*d*, *J* = 11.5, PhC*H*); 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, PhC*H*); 4.46 (*d*, *J* = 11.9, PhC*H*); 4.80 (*d*, *J* = 11.8, PhC*H*); 4.98 (*d*, *J* = 10.9, PhC*H*); 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)). ^{13}C-NMR ($CDCl_3$): 22.86 (*q*, CO*Me*); 41.96 (*d*, C(8)); 51.61 (*q*, MeO); 52.01 (*q*, MeO); 60.91 (*d*, C(5)); 71.64 (*t*, CH_2–C(5)); 72.19 (*t*, PhCH_2); 73.91 (*t*, PhCH_2); 74.09 (*t*, PhCH_2); 73.14, 77.70 (2*d*, C(6), C(7)); 113.20, 116.92 (2*s*, C(1), C(2)); 124.35 (*d*, C(3)); 127.57–128.79 (several *d*); 132.40 (*s*, C(8a)); 136.53 (*s*); 137.56 (*s*); 137.83 (*s*); 164.63 (*s*, CO_2); 164.09 (*s*, CO_2); 169.09 (*s*, NHCO).

*Dimethyl (5*R*,6*R*,7*S*,8*S*)-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 $(CF_3CO)_2O$ (0.1 ml), kept for 2 h at 5° and treated with sat. aq. NH_4Cl 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 ($CHCl_3$): 277 (4.1). IR ($CHCl_3$): 3423*m*, 3007*m*, 2952*m*, 2870*m*, 1724*s*, 1526*s*, 1455*m*, 1442*m*, 1397*w*, 1364*w*, 1290*s*, 1172*s*, 1073*s*, 1028*w*, 909*w*. ^{1}H-NMR ($CDCl_3$): 3.71–3.75 (*m*, H_2C–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, PhC*H*); 4.47 (*d*, *J* = 11.5, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.46–4.50 (*m*, H–C(5)); 4.54 (*d*, *J* = 11.2, PhC*H*); 4.59 (*d*, *J* = 11.8, PhC*H*); 4.79 (*d*, *J* = 11.8, PhC*H*); 5.76 (br. *d*, *J* = 8.4, 1.0, addn. of CD_3OD → br. *s*, H–C(8)); 6.83 (*d*, *J* = 8.7, exchange with CD_3OD, H–N); 7.13–7.41 (*m*, 15 arom. H, H–C(3)). ^{13}C-NMR ($CDCl_3$): 43.73 (*d*, C(8)); 51.82 (*q*, MeO); 51.93 (*q*, MeO); 58.90 (*d*, C(5)); 71.88 (*t*, CH_2–C(5)); 72.66 (*t*, PhCH_2); 73.69 (br. *t*, 2 PhCH_2); 73.33, 74.11 (2*d*, C(6), C(7)); 114.99, 117.19 (2*s*, 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, $COCF_3$); 163.96 (*s*, CO_2); 164.38 (*s*, CO_2). ^{19}F-NMR ($CDCl_3$): –75.84. EI-MS: 680 (0.1, M^+), 649 (1, $[M - MeO]^+$), 572 (3, $[M - BnOH]^+$), 313 (13), 91 (100, $C_7H_7^+$).

*Dimethyl (5*R*,6*R*,7*S*,8*S*)-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/H_2O 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/CH_2Cl_2 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. ^{1}H-NMR (D_2O): 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)). ^{13}C-NMR (D_2O): 24.57 (*q*, CO*Me*); 51.80 (*d*, C(8)); 54.75 (*q*, MeO); 55.70 (*q*, MeO); 61.68 (*t*, CH_2–C(5)); 64.42 (*d*, C(5)); 70.13, 75.12 (2*d*, C(6), C(7)); 115.44, 117.14 (2*s*, C(1), C(2)); 128.08 (*d*, C(3)); 134.04 (*s*, C(8a)); 168.54 (*s*, CO_2); 170.69 (*s*, CO_2); 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/H_2O 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. ^{1}H-NMR (D_2O): 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*, irrad. at 5.59 → change, H–C(6), H–C(7)); 4.06 (*dd*, J = 2.5, 12.8, irrad. at 3.92 → *d*, $J \approx 12.8$, HC–C(5)); 4.21 (*dd*, J = 2.4, 12.8, irrad. at 3.92 → *d*, $J \approx 12.8$, HC–C(5)); 5.59 (*dd*, J = 3.2, 1.1 irrad. at 3.92 → change, irrad. at 3.96 → br. *s*, H–C(8)); 7.56 (*s*, H–C(3)). ^{13}C-NMR (D_2O): 24.57 (*q*, *CO*Me); 48.08 (*d*, C(8)); 54.87 (*q*, MeO); 55.10 (*q*, MeO); 61.86 (*t*, CH_2–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*, CO_2); 168.69 (*s*, CO_2); 176.06 (*s*, NHCO). CI-MS (NH_3): 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/H_2O 5:5:1 (4 ml), and 10% Pd/C (80 mg, 32 h at 6 bar). Crystallization from EtOH/$CHCl_3$ (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): 3500*s* (br.), 3300*s*, 3138*m*, 1728*s*, 1705*s*, 1570*m*, 1528*m*, 1450*m*, 1399*m*, 1321*m*, 1165*m*, 1095*m*, 1075*m*, 1058*m*, 1021*w*, 965*w*, 914*w*, 891*w*, 862*w*, 828*w*, 619*w*, 521*w*. ^{1}H-NMR (D_2O): 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)). ^{13}C-NMR (CD_3OD): 50.70 (*d*, C(8)); 52.16 (*q*, MeO); 52.63 (*q*, MeO); 62.63 (*t*, CH_2–C(5)); 64.42 (*d*, C(5)); 69.48, 73.42 (2*d*, C(6), C(7)); 115.53, 117.08 (2*s*, C(1), C(2)); 127.21 (*d*, C(3)); 131.98 (*s*, C(8a)); 166.28 (*s*, CO_2); 167.36 (*s*, CO_2). ^{19}F-NMR (D_2O): –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 µl, 1.52 mmol) and a soln. of $TiCl(O^iPr)_3$ (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. NH_4Cl soln. Normal workup (→ 160 mg, **23**/**29** 4:1, ^{1}H-NMR) and HPLC (hexane/Et_2O 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, ^{1}H-NMR, 80%).

c) As described in *a*), but addition of a suspension of $ZnCl_2$ (224 mg, 0.84 mmol) in MeCN instead of $TiCl(O^iPr)_3$ and stirring for 8 h at 0°. Normal workup (→ 168 mg, **23**/**29** 4:1, ^{1}H-NMR) and HPLC (hexane/Et_2O 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 µl, 0.19 mmol) and a suspension of $ZnCl_2$ (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. NH_4Cl soln. Normal workup gave **23**/**29**/**12** 10:2:1 (18 mg, ^{1}H-NMR, 80%).

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

f) At –78°, a soln. of **12** (50 mg, 0.081 mmol) in CH_2Cl_2 (2 ml) was treated with trimethylsilyl azide (50 µl, 0.38 mmol) and $BF_3 \cdot OEt_2$ (25 µl, 0.28 mmol), kept for 15 min at –78° and poured into a sat. aq. NH_4Cl soln. Normal workup (→ 36 mg, **23**/**29** 2:3, ^{1}H-NMR) and HPLC (hexane/Et_2O 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, ^{1}H-NMR, 85%).

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

Data of **23**: R_f (hexane/Et_2O 1:1) 0.38. UV ($CHCl_3$): 241 (3.9), 259 (3.8). CD ($CHCl_3$): 264 (–36560). IR ($CHCl_3$): 3067*w*, 2926*s*, 2868*m*, 2104*s*, 1953*w*, 1875*w*, 1810*w*, 1699*s*, 1555*m*, 1496*m*, 1454*m*, 1364*m*, 1305*m*, 1155*m*, 1097*s*, 1028*w*, 912*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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, PhC*H*); 4.51 (*d*, J = 12.8, PhC*H*); 4.54 (*d*, J = 12.0, PhC*H*); 4.58 (*d*, J = 11.6, PhC*H*); 4.72 (*d*, J = 11.6, PhC*H*); 4.74 (*d*, J = 11.6, PhC*H*); 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 51.19 (*q*, MeO); 54.88 (*d*, C(8)); 58.59 (*d*, C(5)); 70.34 (*t*, CH_2–C(5)); 72.53 (*t*, PhCH_2); 72.62 (*t*, PhCH_2); 73.35 (*t*, PhCH_2); 74.11, 76.97 (2*d*, 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 1*s* for C(8a)); 137.19 (*s*); 137.35 (*s*); 137.51 (*s*); 165.00 (*s*, CO_2). 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/Et_2O 1:1) 0.38. UV ($CHCl_3$): 242 (3.9), 258 (3.8). CD ($CHCl_3$): 265 (16210). IR ($CHCl_3$): 3067*w*, 3008*m*, 2926*m*, 2869*s*, 2103*s*, 1699*s*, 1561*m*, 1497*m*, 1454*m*, 1364*m*, 1318*m*, 1159*m*, 1130*s*, 1128*m*, 989*w*, 914*w*, 872*w*, 841*w*, 610*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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*, PhC*H*); 4.61 (*d*, J = 11.2, PhC*H*); 4.78 (*d*, J = 11.6, PhC*H*); 4.90 (*d*, J = 11.6, PhC*H*); 5.02 (*d*, J = 11.2, PhC*H*); 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 51.19 (*q*, MeO); 54.18 (*d*, C(8)); 61.13 (*d*, C(5)); 69.99 (*t*, CH_2–C(5)); 72.40 (*t*, PhCH_2); 73.26 (*t*, PhCH_2); 75.29 (*t*, PhCH_2); 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 (5*R*,6*R*,7*S*,8*S*)-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), Et_3N (0.9 ml), and propane-1,3-dithiol (0.9 ml): **24** (136 mg, 97%). R_f (AcOEt) 0.52. IR ($CHCl_3$): 3378*w*, 3067*w*, 3008*m*, 2950*m*, 2868*m*, 1952*w*, 1872*w*, 1811*w*, 1688*s*, 1575*w*, 1547*m*, 1496*s*, 1454*m*, 1366*w*, 1334*w*, 1305*w*, 1165*m*, 1098*s*, 1047*m*, 1028*m*, 930*w*, 632*w*, 606*w*, 514*w*. ^{1}H-NMR ($CDCl_3$): 2.79 (br. *s*, NH_2): 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, PhC*H*); 4.48 (*d*, J = 11.8, PhC*H*); 4.48 (*m*, H–C(5)); 4.56 (*d*, J = 10.3, PhC*H*); 4.38–4.58 (*m*, H–C(8)); 4.60 (*d*, J = 10.6, PhC*H*); 4.69 (*d*, J = 11.8, PhC*H*); 4.70 (*d*, J = 11.8, PhC*H*); 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). ^{13}C-NMR ($CDCl_3$): 47.01 (*d*, C(8)); 51.09 (*q*, MeO); 58.79 (*d*, C(5)); 72.33 (br. *t*, CH_2–C(5), PhCH_2); 72.46 (*t*, PhCH_2); 73.50 (*t* PhCH_2); 73.90, 76.72 (2*d*, 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*, CO_2).

*Methyl (5*R*,6*R*,7*S*,8*S*)-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 Ac_2O (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 ($CHCl_3$): 273 (3.4). IR ($CHCl_3$): 3446*m*, 3067*w*, 3007*s*, 2951*w*, 2870*w*, 1700*s*, 1670*s*, 1554*w*, 1497*s*, 1454*s*, 1369*m*, 1340*m*, 1309*w*, 1158*m*, 1097*s*, 1045*w*, 1028*w*, 987*w*, 910*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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 PhC*H*, H–C(5)); 4.67 (*d*, J = 12.0, PhC*H*); 4.89 (*d*, J = 12.0, PhC*H*); 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 23.00 (*q*, CO*Me*); 43.89 (*d*, C(8)); 51.07 (*q*, MeO); 58.91 (*d*, C(5)); 72.02 (*t*, CH_2–C(5)); 72.19 (*t*, PhCH_2); 72.43 (*t*, PhCH_2); 73.45 (*t*, PhCH_2); 73.92, 74.08 (2*d*, 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*, CO_2); 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 (5*R*,6*R*,7*S*,8*S*)-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 $(COCF_3)_2O$ (0.1 ml): **30** (56 mg, 98%). Colourless solid. R_f (hexane/AcOEt 3:1): 0.32. UV ($CHCl_3$): 272 (3.5). IR ($CHCl_3$): 3226*m*, 3007*w*, 2870*w*, 1721*s*, 1528*m*, 1496*s*, 1454*m*, 1365*w*, 1304*w*, 1168*s*, 1099*s*. ^{1}H-NMR ($CDCl_3$): 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, irrad. 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, PhC*H*); 4.51 (*d*, J = 10.0, PhC*H*); 4.54 (*d*, J = 10.6, PhC*H*); 4.55–4.61 (*m*, H–C(5)); 4.58 (*d*, J = 11.5, PhC*H*); 4.64 (*d*, J = 11.8, PhC*H*); 4.83 (*d*, J = 12.1, PhC*H*); 5.88 (br. *dd*, $J \approx$ 8.7, 1.5, addn. of CD_3OD → br. *s*, H–C(8)); 6.75 (*d*, J = 2.8, H–C(2)); 6.77 (*d*, J = 8.7, exchange with CD_3OD, H–N); 6.86 (*d*, J = 2.8, H–C(3)); 7.16–7.41 (*m*, 15 arom. H). ^{13}C-NMR ($CDCl_3$): 43.86 (*d*, C(8)); 51.23 (*q*, MeO); 58.43 (*d*, C(5)); 72.27 (*t*, CH_2–C(5)); 72.40 (*t*, PhCH_2); 73.51 (br. *t*, 2 PhCH_2); 73.29, 74.18 (2*d*, 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, $COCF_3$); 164.49 (*s*, CO_2). ^{19}F-NMR ($CDCl_3$): –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 (5*R*,6*R*,7*S*,8*S*)-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/H_2O 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): 3463*s* (br.), 3341*s* (br.), 2992*m*, 2947*m*, 2912*m*, 1691*s*, 1636*s*, 1575*s*, 1543*m*, 1498*m*, 1437*m*, 1384*m*, 1319*s*, 1291*m*, 1169*m*, 1134*m*, 1121*m*, 1083*m*, 1062*s*, 1030*m*, 1008*m*, 966*m*, 834*m*, 636*m*, 590*m*, 544*w*. ^{1}H-NMR (D_2O): 1.99 (*s*, AcN); 3.76 (*s*, MeO); 3.92 (*dd*, J = 7.6, 6.3, irrad. at 5.19 → *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}C-NMR (D_2O): 24.56 (*q*, CO*Me*); 52.09 (*d*, C(8)); 54.65 (*q*, MeO); 62.85 (*t*, *C*H_2–C(5)); 64.26 (*d*, C(5)); 70.33, 75.18 (2*d*, 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, $[M - OH]$), 240 (100, $[M - NHAc]^+$). Anal. calc. for $C_{13}H_{18}N_2O_6$ (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): 3434*s* (br.), 3322*s* (br.), 2956*m*, 2503*w*, 2433*w*, 1711*s*, 1688*s*, 1564*m*, 1497*w*, 1441*w*, 1358*w*, 1289*m*, 1168*s*, 1103*m*, 1056*w*, 906*w*, 614*w*. ^{1}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, irrad. at 3.92 → *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, irrad. at 3.92 → *s*, H–C(8)); 6.73 (*d*, J = 3.4, H–C(2)); 7.01 (*d*, J = 3.1, H–C(3)). ^{13}C-NMR (D_2O): 52.92 (*d*, C(8)); 54.68 (*q*, MeO); 62.19 (*t*, *C*H_2–C(5)); 64.21 (*d*, C(5)); 70.08, 75.34 (2*d*, 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_3*C*O); 170.03 (*s*, NH*C*OCF_3). ^{19}F-NMR (D_2O): –74.68. Anal. calc. for $C_{13}H_{15}F_3N_2O_6$ (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 $TiCl(O^iPr)_3$ (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 (→ 82 mg, **30**/**36** 7:3, ^{1}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 (→ 84 mg, **30**/**36** 7:3, ^{1}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}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}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 $BF_3 \cdot OEt_2$ (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}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}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 ($CHCl_3$): 3068*w*, 3008*m*, 2925*s*, 2864*m*, 2105*s*, 1706*s*, 1563*w*, 1517*m*, 1497*m*, 1455*m*, 1363*w*, 1337*w*, 1284*w*, 1146*m*, 1100*s*, 1028*w*, 1005*m*, 909*m*, 834*w*. ^{1}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, irrad. at 3.96 → *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, irrad. at 3.96 → *dd*, $J \approx 4.0$, 3.0, H–C(5)); 4.44 (*s*, PhCH_2); 4.53 (*d*, J = 11.4, PhC*H*); 4.60 (*dd*, J = 7.0, 1.1, H–C(8)); 4.79 (*d*, J = 11.0, PhC*H*); 4.84 (*d*, J = 10.9, 2 PhC*H*); 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}C-NMR ($CDCl_3$): 51.20 (*q*, MeO); 55.71 (*d*, C(8)); 60.31 (*d*, C(5)); 70.37 (*t*, *C*H_2–C(5)); 72.85 (*t*, PhCH_2); 73.39 (*t*, PhCH_2); 74.50 (*t*, PhCH_2); 73.76, 78.72 (2*d*, 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, $[M + 1 - N_2]^+$), 510 (21, $[M - N_3]^+$), 493, (3, $[M - COOMe]^+$), 433 (13, $[M - N_2 - Bn]^+$), 420 (59, $[M + 1 - N_3 - Bn]^+$), 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 ($CHCl_3$): 3073*w*, 3008*m*, 2951*m*, 2924*m*, 2868*m*, 2105*s*, 1953*w*, 1876*w*, 1810*w*, 1707*s*, 1564*m*, 1516*m*, 1497*m*, 1454*m*, 1392*w*, 1363*w*, 1312*w*, 1098*s*, 1028*w*, 1004*m*, 913*m*, 838*w*, 610*w*. ^{1}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, irrad. at 4.80 → *d*, $J \approx 7.5$, H–C(7)); 4.13–4.18 (*m*, irrad. at 3.94 → change, H–C(5), H–C(6)); 4.44 (*d*, J = 11.8, PhC*H*); 4.48 (*d*, J = 12.1, PhC*H*); 4.57 (*d*, J = 11.4, PhC*H*); 4.70 (*d*, J = 11.8, PhC*H*); 4.77 (*d*, J = 11.5, PhC*H*); 4.80 (*d*, J = 3.7, irrad. at 3.94 → *s*, H–C(8)); 4.85 (*d*, J = 11.2, PhC*H*); 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}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 (*td*, J = 6.2, 4.2, H–C(5)); 3.92

(*d*, *J* = 12.5, PhC*H*); 4.01 (*d*, *J* = 12.5, PhC*H*); 4.03 (*dd*, *J* = 8.3, 6.6, H–C(6)); 4.17 (*d*, *J* = 11.6, PhC*H*); 4.25 (*d*, *J* = 11.6, PhC*H*); 4.33 (*d*, *J* = 11.0, PhC*H*); 4.44 (*d*, *J* = 3.7, H–C(8)); 4.59 (*d*, *J* = 11.6, PhC*H*); 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)). ^{13}C-NMR ($CDCl_3$): 51.24 (*q*, MeO); 59.23, 59.71 (*d*, C(5), C(8)); 68.50 (*t*, CH_2–C(5)); 73.45 (*t*, PhCH_2); 74.47 (*t*, PhCH_2), 74.71 (*t*, PhCH_2); 76.12, 81.25 (2*d*, 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*, CO_2). DCI-MS: 553 (23, $[M + 1]^+$), 525 (35, $[M + H - N_2]^+$), 510 (35, $[M - N_3]^+$), 493 (3, $[M - COOMe]^+$), 433 (7, $[M - N_2 - Bn]^+$), 420 (85, $[M + H - N_3 - Bn]^+$), 325 (24), 106 (37), 91 (100, $C_7H_7^+$).

*Methyl (5*R,*6*R,*7*S,*8*S*)-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), Et_3N (0.7 ml), and propane-1,3-dithiol (0.7 ml; 24 h): **22** (108 mg, 95%). R_f (AcOEt) 0.51. IR ($CHCl_3$): 3675*w*, 3378*w*, 3067*w*, 3008*s*, 2951*m*, 2868*m*, 1951*w*, 1877*w*, 1811*w*, 1703*s*, 1602*w*, 1562*m*, 1519*m*, 1454*m*, 1363*m*, 1312*w*, 1098*s*, 1028*w*, 1004*w*, 914*w*, 834*w*, 610*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.81 (br. *s*, NH_2); 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*, PhCH_2); 4.58 (*d*, *J* = 11.5, PhC*H*); 4.75 (*d*, *J* = 11.5, PhC*H*); 4.85 (*d*, *J* = 11.2, PhC*H*); 4.91 (*d*, *J* = 11.5, PhC*H*); 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)). ^{13}C-NMR ($CDCl_3$): 45.83 (*d*, C(8)); 51.04 (*q*, MeO); 59.48 (*d*, C(5)); 71.48 (*t*, CH_2–C(5)); 72.69 (*t*, PhCH_2); 73.16 (*t*, PhCH_2); 73.35 (*t*, PhCH_2); 73.26, 79.13 (2*d*, 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*, CO_2).

*Methyl (5*R,*6*R,*7*S,*8*R*)-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), Et_3N (0.8 ml), propane-1,3-dithiol (0.8 ml; 38 h): **37** (124 mg, 93%). R_f (AcOEt) 0.52. ^{1}H-NMR ($CDCl_3$): 1.80 (br. *s*, NH_2); 3.72–3.78 (*m*, H_2C–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, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 4.63 (*d*, *J* = 11.5, PhC*H*); 4.64 (*s*, PhCH_2); 4.76 (*d*, *J* = 11.5, PhC*H*); 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)). ^{13}C-NMR (50 MHz, $CDCl_3$): 51.04 (*q*, MeO); 53.43 (*d*, C(8)); 60.15 (*d*, C(5)); 69.29 (*t*, CH_2–C(5)); 73.32 (*t*, PhCH_2); 74.27 (*t*, PhCH_2); 74.65 (*t*, PhCH_2); 77.07, 83.89 (2*d*, 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*, CO_2).

*Methyl (5*R,*6*R,*7*S,*8*S*)-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 Ac_2O (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 ($CHCl_3$): 269 (3.6). IR ($CHCl_3$): 3436*w*, 3067*w*, 3007*s*, 2869*w*, 1704*s*, 1667*s*, 1563*w*, 1509*s*, 1454*m*, 1393*w*, 1360*w*, 1096*s*, 1028*w*, 1003*w*, 909*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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, irrad. at 5.46 → *d*, *J* ≈ 2.5, H–C(7)); 4.09 (*dd*, *J* = 5.0, 2.3, irrad. at 4.45 → *d*, *J* ≈ 3.0, H–C(6)); 4.41 (*d*, *J* = 12.0, PhC*H*); 4.41–4.48 (*m*, H–C(5)); 4.49 (*d*, *J* = 12.0, PhC*H*); 4.55 (*d*, *J* = 12.4, PhC*H*); 4.62 (*d*, *J* = 12.0, PhC*H*); 4.63 (*d*, *J* = 12.0, PhC*H*); 4.78 (*d*, *J* = 12.0, PhC*H*); 5.46 (*dd*, *J* = 8.9, 3.1, irrad. 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)). ^{13}C-NMR (50 MHz, $CDCl_3$): 23.35 (*q*, CO*Me*); 44.52 (*d*, C(8)); 51.17 (*q*, MeO); 58.81 (*d*, C(5)); 71.62 (*t*, CH_2–C(5)); 72.59 (*t*, PhCH_2); 72.78 (*t*, PhCH_2); 73.59 (*t*, PhCH_2); 74.82, 75.99 (2*d*, 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*, CO_2); 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, $C_7H_7^+$).

*Methyl (5*R,*6*R,*7*S,*8*R*)-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 ($CHCl_3$): 270 (3.7). ^{1}H-NMR ($CDCl_3$): 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, PhC*H*); 4.43 (*d*, *J* = 11.5, PhC*H*); 4.46 (*d*, *J* = 11.5, PhC*H*); 4.51 (*d*, *J* = 11.5, PhC*H*); 4.63 (*d*, *J* = 12.1, PhC*H*); 4.73 (*d*, *J* = 11.8, PhC*H*); 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)). ^{13}C-NMR ($CDCl_3$): 23.15 (*q*, CO*Me*); 43.36 (*d*, C(8)); 51.19 (*q*, MeO); 59.22 (*d*, C(5)); 72.22 (*t*, CH_2–C(5)); 72.58 (*t*, PhCH_2); 72.93 (*t*, PhCH_2); 73.78 (*t*, PhCH_2); 72.58, 76.09 (2*d*, 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*, CO_2); 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 $(CF_3CO)_2O$ (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 ($CHCl_3$): 3417*m*, 3090*w*, 3008*m*, 2952*m*, 2870*m*, 1719*s*, 1603*m*, 1564*m*, 1512*m*, 1455*m*, 1394*w*, 1364*w*, 1170*s*, 1098*m*, 1003*w*, 910*w*, 838*w*. ^{1}H-NMR ($CDCl_3$): 3.70 (*dd*, J = 9.8, 7.0, HC–C(5)); 3.76 (*dd*, J = 9.8, 6.1, HC–C(5)); 3.80 (*s*, MeO); 3.86 (*dd*, J = 4.4, 2.8, irrad. at 4.16 → *d*, $J \approx 2.8$, H–C(7)); 4.16 (*dd*, J = 4.2, 1.6, irrad. at 3.86 → *d*, $J \approx 1.0$, H–C(6)); 4.42 (*d*, J = 11.8, PhC*H*); 4.49 (*d*, J = 11.5, PhC*H*); 4.51 (*td*, J = 6.5, 2.0, H–C(5)); 4.53 (*d*, J = 11.5, PhC*H*); 4.57 (*d*, J = 11.8, PhC*H*); 4.62 (*d*, J = 11.5, PhC*H*); 4.72 (*d*, J = 11.8, PhC*H*); 5.46 (br. *ddd*, J = 9.0, 2.5, 0.9, irrad. at 3.86 → br. *d*, $J \approx 9.0$, irrad. at 7.20 → *d*, $J \approx 2.0$, H–C(8)); 6.63 (*dd*, J = 1.7, 0.8, H–C(1)); 7.17–7.39 (*m*, 15 arom. H, H–N); 7.45 (*d*, J = 1.9, H–C(3)). ^{13}C-NMR ($CDCl_3$): 44.41 (*d*, C(8)); 51.25 (*q*, MeO); 58.21 (*d*, C(5)); 71.73 (*t*, CH_2–C(5)); 72.62 (*t*, PhCH_2); 72.88 (*t*, PhCH_2); 73.66 (*t*, PhCH_2); 74.06, 74.97 (2*d*, 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}F-NMR ($CDCl_3$): −75.85. EI-MS: 622 (0.4, M^+), 591 (2, $[M - MeO]^+$), 514 (4, $[M - BnOH]^+$), 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}H-NMR (200 MHz, $CDCl_3$): 3.59 (*dd*, J = 9.8, 4.8, HC–C(5)); 3.65 (*dd*, J = 9.5, 5.0, HC–C(5)); 3.80 (*s*, MeO); 3.92 (*dd*, J = 6.4, 3.7, H–C(7)); 4.18 (*dd*, J = 6.7, 2.9, H–C(6)); 4.34 (*td*, J = 4.8, 2.9, H–C(5)); 4.39 (*d*, J = 12.5, PhC*H*); 4.48 (*d*, J = 11.6, PhC*H*); 4.50 (*d*, J = 12.0, PhC*H*); 4.56 (*d*, J = 11.6, PhC*H*); 4.61 (*d*, J = 11.6, PhC*H*); 4.71 (*d*, J = 12.0, PhC*H*); 5.63 (*dd*, J = 9.1, 3.7, H–C(8)); 6.50 (*dd*, J = 1.6, 0.9, H–C(1)); 7.14–7.40 (*m*, 15 arom. H, H–C(3), H–N). ^{13}C-NMR ($CDCl_3$): 43.94 (*d*, C(8)); 51.27 (*q*, MeO); 59.47 (*d*, C(5)); 71.68 (*t*, CH_2–C(5)); 72.48 (*t*, PhCH_2); 73.30 (*t*, PhCH_2); 73.61 (*t*, PhCH_2); 72.48, 75.89 (2*d*, 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}F-NMR ($CDCl_3$): −75.60. EI-MS: 622 (0.3, M^+), 591 (0.8, $[M - MeO]^+$), 514 (3, $[M - BnOH]^+$), 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), AcOEt/MeOH/H_2O 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): 3330*s* (br.), 3137*s*, 2991*m*, 2949*m*, 2897*s*, 1717*s*, 1680*s*, 1644*s*, 1558*s*, 1524*s*, 1445*s*, 1385*s*, 1334*w*, 1299*m*, 1113*m*, 1071*m*, 1042*w*, 1005*m*, 934*w*, 882*m*, 657*w*, 587*w*. ^{1}H-NMR (D_2O): 2.17 (*s*, AcN); 3.73 (*m*, virtual coupling, J = 10.0, H–C(7)); 3.79 (*s*, MeO); 3.93–4.01 (*m*, H–C(5), H–C(6)); 4.06 (*dd*, J = 12.5, 1.7, HC–C(5)); 4.24 (*dd*, J = 12.7, 1.6, HC–C(5)); 4.88 (*dd*, J = 10.0, 1.2, H–C(8)); 6.56 (*dd*, J = 1.6, 1.2, H–C(1)); 7.60 (*d*, J = 1.9, H–C(3)). ^{1}H-NMR (CD_3OD); 2.06 (*s*, AcN); 3.60 (*m*, virtual coupling J = 9.6, irrad. at 4.93 → *m*, virtual coupling, $J \approx 9.5$, H–C(7)); 3.75 (*s*, MeO); 3.79–3.85 (*m*, H–C(5), H–C(6)); 3.92 (*dd*, J = 11.4, 4.0, CH–C(5)); 4.21 (br. *dd*, J = 11.5, 2.0, CH–C(5)); 4.93 (*dd*, J = 9.6, 1.0, H–C(8)); 6.29 (*dd*, J = 1.6, 1.2, H–C(1)); 7.60 (*d*, J = 1.6, H–C(3)). ^{13}C-NMR (CD_3OD): 22.96 (*q*, *COMe*); 51.06 (*d*, C(8)); 51.72 (*q*, MeO); 62.16 (*t*, CH_2–C(5)); 64.02 (*d*, C(5)); 70.81, 74.84 (2*d*, 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, $[M + 1 - H_2O]^+$), 240 (100, $[M - NHAc]^+$). Anal. calc. for $C_{13}H_{18}N_2O_6$ (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), AcOEt/MeOH/H_2O 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): 3330*s* (br.), 3137*s*, 2991*m*, 2949*m*, 2897*s*, 1717*s*, 1680*s*, 1644*s*, 1558*s*, 1524*s*, 1445*s*, 1385*s*, 1334*w*, 1299*m*, 1113*m*, 1071*m*, 1042*w*, 1005*m*, 934*w*, 882*m*, 657*w*, 587*w*. ^{1}H-NMR (D_2O): 2.06 (*s*, AcN); 3.80 (*s*, MeO); 4.03 (*dd*, J = 11.7, 3.4, HC–C(5)); 4.03–4.09 (*m*, H–C(5)); 4.09 (*dd*, J = 7.8 4.7, H–C(7)); 4.16 (*dd*, J = 11.7, 3.1, HC–C(5)); 4.20 (*dd*, J = 7.8, 5.3, H–C(6)); 5.36 (br. *d*, J = 4.4, H–C(8)); 6.56 (*dd*, J = 1.9, 0.6, H–C(1)); 7.61 (*d*, J = 1.9, H–C(3)). ^{13}C-NMR (D_2O): 24.77 (*q*, *COMe*); 48.31 (*d*, C(8)); 54.58 (*q*, MeO); 63.77 (*t*, CH_2–C(5)); 64.79 (*d*, C(5)); 69.81, 71.88 (2*d*, 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), AcOEt/MeOH/H_2O 5:5:1 (2 ml), and

10% Pd/C (40 mg; 32 h). Crystallization from EtOH/$CHCl_3$ 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): 3460*s* (br.), 3254*s*, 3155*m*, 3100*m*, 2939*m*, 1718*s*, 1669*s*, 1564*s*, 1518*s*, 1448*s*, 1380*s*, 1322*w*, 1260*m*, 1154*s*, 1121*w*, 1094*w*, 1003*m*, 918*w*, 843*w*, 644*w*, 614*w*. ^{1}H-NMR (D_2O): 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)). ^{13}C-NMR (D_2O): 53.05 (*d*, C(8)); 54.60 (*q*, MeO); 61.88 (*t*, CH_2–C(5)); 64.40 (*d*, C(5)); 71.21, 75.00 (2*d*, C(6), C(7)); 109.20 (*d*, C(1)); 118.68 (*s*, C(2)); 118.88 (*q*, J = 280.6, $COCF_3$); 127.89 (*d*, C(3)); 131.98 (*s*, C(8a)); 162.42 (*q*, J = 37.5, CF_3CO); 170.58 (*s*, $NHCOCF_3$). ^{19}F-NMR (D_2O): –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 $C_{13}H_{15}F_3N_2O_6$ (352.27): C 44.33, H 4.29, N 7.95; found: C 44.37, H 4.43, N 7.73.

*Methyl (5*R*,6*R*,7*S*,8*R*)-5,6,7,8-Tetrahydro-6,7-dihydroxy-5-(hydroxymethyl)-8-(trifluoroacetamido)indolizine-2-carboxylate* (**41**). As described for **27**, with **39** (52 mg, 0.084 mmol), AcOEt/MeOH/H_2O 5:5:1 (2 ml), and 10% Pd/C (40 mg; 36 h). Crystallization from EtOH/$CHCl_3$ 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): 3444*s* (br.), 3275*s* (br.), 3130*s*, 2964*s*, 2932*s*, 2892*m*, 1682*s* (br.), 1556*s*, 1520*s*, 1482*m*, 1444*m*, 1373*m*, 1051*m*, 1007*s*, 962*m*, 934*m*, 907*m*, 859*w*, 842*m*, 647*m*, 632*m*, 516*w*. ^{1}H-NMR (D_2O): 3.80 (*s*, MeO); 4.07–4.25 (*m*, H–C(5), H–C(6), H–C(7), H_2C–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)). ^{13}C-NMR (D_2O); 49.49 (*d*, C(8)); 52.92 (*q*, MeO); 63.82 (*t*, CH_2–C(5)); 64.82 (*d*, C(5)); 69.21, 72.19 (2*d*, 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*, CO_2). ^{19}F-NMR (D_2O): –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 µl), and $BF_3 \cdot OEt_2$ (7.5 µl) in CD_2Cl_2 (0.7 ml) was kept at 23° and monitored by ^{1}H-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 µl), and $BF_3 \cdot OEt_2$ (5 µl) in either CH_2Cl_2, MeCN, or toluene (0.5 ml) was stirred at 23° for 24 h. After normal workup, the ratio of *gluco*- and *manno*-configurated azide was determined by integration of the H–C(8) or H–C(1) signal in the ^{1}H-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 $(NH_4)SO_4$ (0.1 ml, 5 U), and 2.5M $(NH_4)SO_4$ (0.1 ml, 5 U), resp., were centrifuged, and the pellets were dissolved in H_2O. Citrate buffer (0.5M, pH 4.2, 100 µl), inhibitor soln., or H_2O (300 µl), resp., and enzyme soln. (52 mU in H_2O, 100 µl) were incubated at 37° for 5 min. After addition of GlcNAc-Np (5.0, 2.5, 1.6, 1.0, 0.5 mM in H_2O, 500 µl), 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 µl). 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.

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