Probing the Interaction of the Hydroxy Group at C(4) of Lactone-Type Inhibitors with β-Glucosidases and β-Galactosidases

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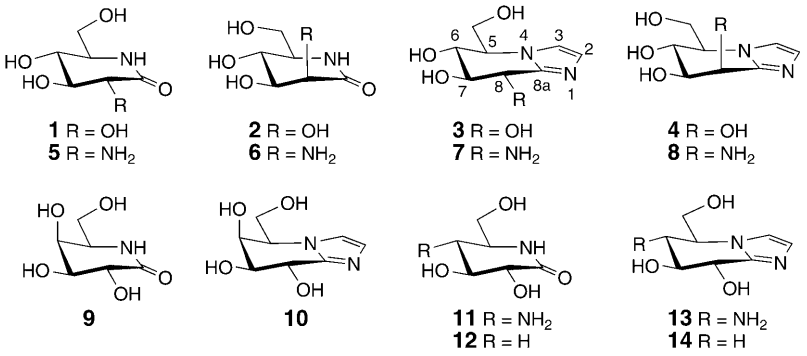
The inhibition of the β-glucosidases from sweet almonds and from *Caldocellum saccharolyticum* by the 4-amino-4-deoxy lactam **11**, the 4-deoxy lactam **12**, and the corresponding imidazoles **13** and **14** was compared to the inhibition by the hydroxy analogues **1** and **3**. Substitution of the OH group at C(4) by an amino group or by hydrogen weakened the inhibition by $\Delta\Delta G_{diss} = +1.9$ to $+3.1$ kcal/mol. Similarly, the inhibition of the β-galactosidase from bovine liver and from *E. coli* by the 4-deoxy lactam **12** and the imidazole **14**, as compared to the one by the *galacto*-configured lactam **9** and imidazole **10**, is weakened by deoxygenation at C(4) ($\Delta\Delta G_{diss} = +2.6$ and 4.5 kcal/mol, resp.). The effect of these substitutions on the inhibition of the *C. saccharolyticum* β-glucosidase is slightly stronger than the one on the sweet almonds β-glucosidases. The effect is also stronger on the inhibition by the imidazoles than by the lactams, and depends on the flexibility of the inhibitors. The amino and deoxy lactams **11** and **12** were prepared from the galactonolactam-derived triflate **17** by substitution with azide and hydride, respectively, followed by hydrogenation. Azidation of the *galacto*-configured imidazopyridine-derived triflate **24** and hydrogenation gave the amino-imidazole **13**. The deoxy lactam **20** was transformed to the *manno*- and *gluco*-configured deoxy-imidazoles **29** and **30** *via* the thionolactam **28**. Hydrogenolytic deprotection of **30** gave the deoxy-imidazole **14**.

Introduction. – Replacement of one or several OH groups of carbohydrates by other substituents, particularly by H and F, has been extensively used to analyze the interaction of carbohydrates with lectins and carbohydrate-transforming enzymes [1]. *Roeser* and *Legler* [2], and *Withers* and co-workers [3][4] estimated the contribution of individual OH groups to the binding of the transition state during enzymatic hydrolysis by comparing the hydrolysis rate of the parent and modified glycosides. A similar, albeit restricted substitution of OH by NH_2 groups of glycosidase inhibitors, such as for the lactams **1** and **2**, and the imidazoles **3** and **4**, leading to **5**–**8**, contributed to analyzing the interaction with the catalytic residues of β-glycosidases [5][6]. Although such substitutions in glycosidase inhibitors have not been systematically explored, they contribute to analyze the topology of functional groups of the binding site, and can greatly affect the strength of an inhibitor, as illustrated by the introduction of a basic substituent leading to the very strong inhibition of viral neuraminidases [7] by *Zanamivir* [8] and *Oseltamivir* [9].



We wished to explore the effect on the inhibition of the family 1[1]) β-glucosidases from sweet almonds and from *Caldocellum saccharolyticum* of substituting the OH[2]) group at C(4) of the gluconolactam **1** and the corresponding OH group at C(6) of the more rigid imidazole **3** by an NH_2 group or by H, as in **11**–**14**. We also wondered if the amino lactam **11** and perhaps even the amino-imidazole **13**, possessing a basic substituent at the C-atom corresponding to C(4) of β-glucosides, may occupy the $+1$ rather than the -1 subsite of β-glucosidases, and be protonated by the catalytic acid. It was also of interest to compare the inhibiton of β-galactosidases by the 4-deoxylactam **12** and the corresponding 6-deoxy-imidazole **14** to the inhibition by the known OH analogues **9** [11] and **10** [12][13]. For this, we planned to prepare the *gluco*-configured NH_2-substituted lactam and imidazole **11** and **13**, and the deoxy lactam and deoxy-imidazole **12** and **14** from the *galacto*-configured lactam triflate **17** and the imidazole triflate **24**.

Results and Discussion. – Regioselective opening of the 1,3-dioxane ring of the benzylidene acetal **15** (prepared from D-galactose in eight steps and an overall yield of 13% [14]) with TfOH and Et_3SiH [15] gave the secondary alcohol **16** (86%; *Scheme*). The alcohol **16** was triflated to **17** (61%) that was purified by chromatography on silica gel. The triflate **17** reacted with NaN_3 in DMF to yield 64% of the azide **18** besides 28% of the elimination[3]) product **19**. Similarly, deoxygenation of **17** with $NaBH_4$ in MeCN gave the 4-deoxy-D-*xylo*-hexonolactam **20** (58%), the alkene **19** (32%), and a mixture of unidentified products. Hydrogenolysis of the *O*-benzylated azide **18**, followed by ion-exchange chromatography, afforded the deprotected amino lactam **11** (68%). Hydrogenolytic debenzylation of **20** was followed by reverse-phase chromatography to afford the deoxygluconolactam **12** (98%).

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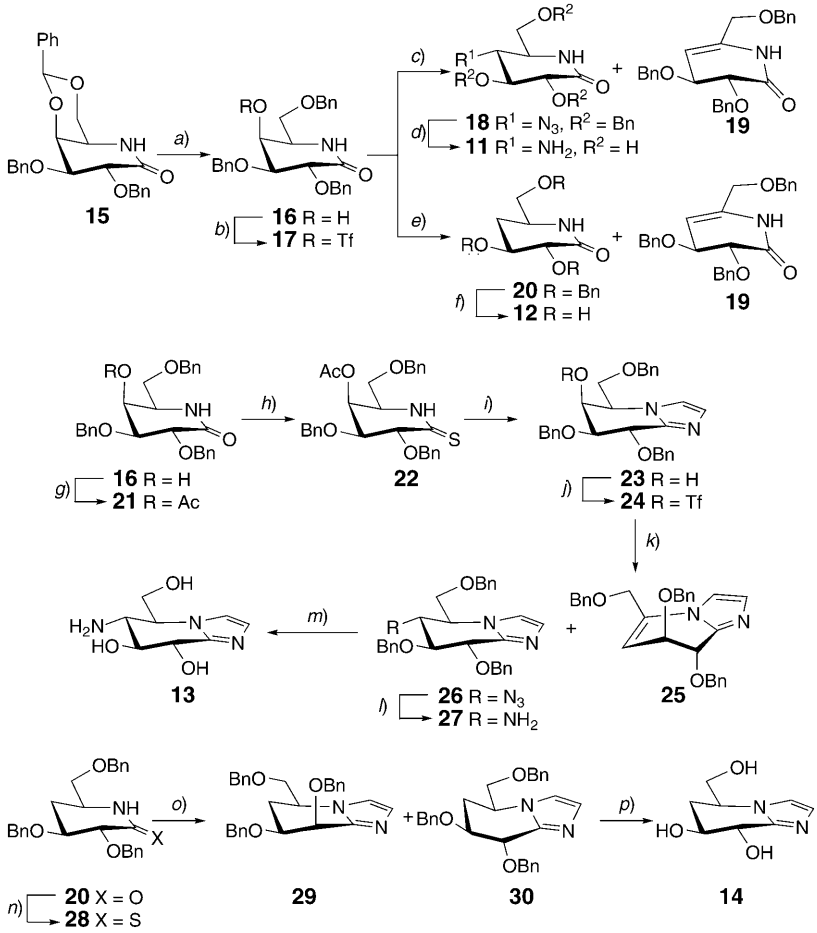
[1]) Glycosidases are classified into families based on their sequence similarities [10]. A regularly updated database is available on the internet (http://afmb.cnrs-mrs.fr/CAZY/index.html).

[2]) The OH group at C(4) of aryl β-glucopyranosides stabilises the glycosyl–enzyme intermediate more strongly than the transition state (hydrolysis by *Agrobacterium faecalis* β-glucosidase) [3][4].

[3]) Treatment of the triflate **17** with sulfur nucleophiles such as thioacetate and thiocyanate led exclusively to elimination.

Scheme



a) TfOH, Et_3SiH, molecular sieves (4 Å), CH_2Cl_2, −78°; 86%. *b*) Tf_2O, pyridine, CH_2Cl_2, −15°; 61%. *c*) NaN_3, DMF; 64% of **18** and 28% of **19**. *d*) 1. 10% Pd/C, H_2 (6 bar), MeOH/AcOH 2:1; 2. Chromatography on *Amberlite CG-120* (H^+); 68%. *e*) $NaBH_4$, MeCN; 58% of **20** and 32% of **19**. *f*) 10% Pd/C, H_2 (6 bar), MeOH/H_2O 2:1; 98%. *g*) Ac_2O, pyridine; 99%. *h*) *Lawesson*'s reagent, toluene, 80°; 90%. *i*) 1. $NH_2CH_2CH(OMe)_2$, $Hg(OAc)_2$, THF; 2. $TsOH \cdot H_2O$, toluene/H_2O 10:1, 75°; 78%. *j*) Tf_2O, pyridine, CH_2Cl_2, 0°. *k*) NaN_3, DMF. *l*) 10% Pd/$CaCO_3$, H_2 (1 bar), THF; 39% of **25** and 42% of **27** (from **23**). *m*) 1. 10% Pd/C, H_2 (6 bar), MeOH/AcOH 2:1; 2. Chromatography on *Amberlite CG-120* (H^+); 96%. *n*) *Lawesson*'s reagent, toluene, 80°; 96%. *o*) 1. $NH_2CH_2CH(OMe)_2$, $Hg(OAc)_2$, THF; 2. $TsOH \cdot H_2O$, toluene/H_2O 30:1, 75°; 64% of **30** and 20% of **29**. *p*) 10% Pd/C, H_2 (6 bar), MeOH/AcOH 2:1; 98%.

The tri-*O*-benzyl *galacto*-imidazole **23** (*Scheme*) was prepared from **16** similarly as the tetra-*O*-benzyl *gluco*- and *galacto*-analogues [12][16]. Thionation of the acetylated lactam **21** with *Lawesson*'s reagent provided the thionolactam **22** (90%). Condensation of **22** with aminoacetaldehyde dimethyl acetal in the presence of $Hg(OAc)_2$, followed by acid-promoted cyclisation in wet toluene, was accompanied by deacetylation and

yielded 78% of the *galacto*-configured imidazopyridine **23**. Triflation of **23** to **24** was followed by treatment of **24** with NaN_3 in DMF to give an inseparable *ca.* 1:1 mixture of the alkene **25** and azide **26** that was hydrogenated (1 bar) in the presence of 10% Pd/$CaCO_3$ in THF to afford, after chromatography, the alkene **25** (39%) and the amine **27** (42%). Hydrogenolytic debenzylation of the amine **27** required harsher conditions (6 bar H_2). Ion-exchange chromatography afforded the deprotected amino lactam **13** (96%).

Deoxygenation with $NaBH_4$ of the triflated imidazole **24** proceeded in lower yields than the corresponding transformation of the lactam **17**, and gave only 20% of the deoxygenated product **30**. We, therefore, prepared **30** from the deoxy lactam **20** (*Scheme*). Thionation of **20** to **28** (96%), followed by condensation of **28** with aminoacetaldehyde dimethyl acetal and acid-promoted cyclisation, yielded the desired 4-deoxy-D-*xylo*-configured imidazole **30** (64%) besides the 4-deoxy D-*lyxo*-configured imidazole **29** (20%). Hydrogenolysis of **30** was followed by chromatography on a *RP-18* column to afford the deoxygluconolactam **14** (98%).

The *gluco*-configuration and the $^4H_3$ conformation of the 4-azido lactam **18** is confirmed by the large J(H,H) values of 8.4–10.2 Hz (*Table 4* in *Exper. Part*). Formation of the 4-deoxy-D-*xylo*-hexonolactam **20** is evidenced by ^{1}H signals at 1.52 and 2.16 ppm, corresponding to $H_2C(4)$ with a large geminal coupling of 13.4 Hz and by a corresponding ^{13}C *t* at 29.54 ppm. The deoxy lactam **20** adopts the $^4H_3$ conformation, as evidenced by $J(2,3)=8.1$, $J(3,4_{ax})=10.3$, and $J(4_{ax},5)=10.6$ (*Exper. Part*), while the 4-deoxy thionolactam **28** exists in $CDCl_3$ as a *ca.* 2:3 mixture of $^4H_3$ and $^3H_4$ conformers (modeling with MM3* and J(H,H), *cf. Exper. Part*). The *galacto*-imidazole **23** exists in $CDCl_3$ as a *ca.* 3:2 mixture of the $^6H_7$ and $^7H_6$ conformers (*Table 5* in *Exper. Part*). Similar to their tetrabenzyl ether analogues [16], the *gluco*-configured 6-amino-imidazopyridine **27** and the *manno*-configured deoxy-imidazopyridine **29** adopt predominantly the $^6H_7$ conformation in $CDCl_3$. The $B_{2,5}$ conformation of the deoxyimidazole **30** is evidenced by $J(7,8)=3.7$, $J(6_{ax},7)=5.6$, and $J(5,6_{ax})=3.4$ Hz. The deprotected lactams **11** and **12** adopt predominantly the $^4H_3$, and the imidazoles **13** and **14** the $^6H_7$ conformation in D_2O (for J(H,H), see *Exper. Part*).

Enzymatic Tests and Discussion. – The lactams and imidazoles **11**–**14** were tested as inhibitors of the β-glucosidases from sweet almonds (phosphate buffer, pH 6.8, 37°) and *C. saccharolyticum* (phosphate buffer, pH 6.8, 55°) with 4-nitrophenyl β-D-glucopyranoside as substrate. The deoxy lactam **12** and deoxy-imidazole **14** were also tested as inhibitors of the β-galactosidase from bovine liver and from *E. coli* (both phosphate buffer, pH 7.0, 37°) acting on 2-nitrophenyl β-D-galactopyranoside as substrate. The data for the inhibition of the β-glucosidases are summarised in *Table 1* and compared to those for the inhibition by the known OH analogues **1** and **3**. The data for the inhibition of the β-galactosidases by the deoxy lactam **12**, the deoxy-imidazole **14**, and the OH analogues **9** and **10** are shown in *Table 2*. The $\Delta\Delta G_{diss}$ values for the inhibition of the β-glucosidases by the amino lactam **11** and the deoxy-lactam **12** relative to the gluconolactam **1**, and similarly by the imidazoles **13** and **14** relative to the *gluco*-imidazole **3**, and of the β-galactosidases by the deoxy lactam **12** relative to galactonolactam **9** and by the imidazole **14** relative to the *galacto*-imidazole **10** are summarized in *Table 3*.

Table 1. *Inhibition of the β-Glucosidases from Sweet Almonds* (37°) *and* Caldocellum saccharolyticum (55°) *by the Lactams* **1**, **11**, *and* **12** (IC_{50}/2 [μM]), *and the Imidazoles* **3**, **13**, *and* **14** (K_i [μM])

Compound (pK_{HA})	β-Glucosidase (Sweet almonds)		β-Glucosidase (*C. saccharolyticum*)	
	pH 6.8	pH 5.0	pH 6.8	pH 5.0
1[a])	69	38.5	5	3.5
11 (6.6)	1795	3300	475	340
12	3855		545	
3[a]) (6.1)	0.1[b])	0.21[c])	0.02[b])	0.175[c])
13 (5.8)	18.9 (α = 1.2)	84[c])	4.2[b])	19.5[c])
14 (6.1)	10.6 (α = 1.7)		4.0[b])	

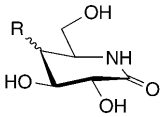
[a]) Data taken from [5]. [b]) Competitive inhibition. [c]) IC_{50}/2 [μM].

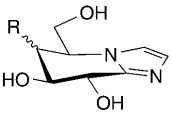
Table 2. *Inhibition of the β-Galactosidases* (pH 7.0 and 37°) *from Bovine Liver and* E. coli *by the Lactams* **9** *and* **12** (IC_{50}/2 [μM]), *and the Imidazoles* **10** *and* **14** (K_i [μM])

Compound (pK_{HA})	β-Galactosidase (Bovine liver)	β-Galactosidase (*E. coli*)
9[a])	n.d.[b])	35[c])
12	1125[c])	[d])
10[e])	0.02[f])[g])	0.004[f])[g])
14 (6.1)	1.7[f]) (α = 1.5)	8.4[f]) (α = 5.8)

[a]) Data taken from [11]. [b]) n.d.: not determined. [c]) IC_{50}/2 [μM]. [d]) 10% Inhibition at 2.25 mM. [e]) Data taken from [12][13]. [f]) K_i [μM]. [g]) Competitive inhibition.

Table 3. *Comparison* ($\Delta\Delta G_{diss}$ values [kcal/mol]) *of the Inhibition of β-Glucosidases from Sweet Almonds and* Caldocellum saccharolyticum *by* C(4)-*Substituted Lactams* **1**, **11**, *and* **12**, *and* C(6)-*Substituted Imidazoles* **3**, **13**, *and* **14**, *and of the Inhibition of the β-Galactosidases from Bovine Liver and* E. coli *by C(4) Substituted Lactams* **9** *and* **12**, *and* C(6)-*Substituted Imidazoles* **10** *and* **14** (R = OH *vs.* R = NH_2, R = OH *vs.* R = H, and R = NH_2 *vs.* R = H)





	OH → NH_2	OH → H	OH → NH_2	OH → H
gluco				
β-Glucosidase (Sweet almonds)	+1.9	+2.4	+3.1	+2.7
β-Glucosidase (*C. saccharolyticum*)	+2.7	+2.8	+3.1	+3.1
galacto				
β-Galactosidase (Bovine liver)	–	[a])	–	+2.6
β-Galactosidase (*E. coli*)	–	≥ +3.0	–	+4.5

[a]) Data not available.

Inspection of *Tables 1* and *3* shows that substitution of the OH group at C(4) of the lactam **1** and of the corresponding OH group at C(6) of the imidazole **3** by an NH_2 group or by H weakens the inhibition of the β-glucosidases from sweet almonds and *C. saccharolyticum* ($\Delta\Delta G = +1.9$ to $+3.1$ kcal/mol). The effect on the inhibition of the *C. saccharolyticum* β-glucosidase is stronger than the one on the inhibition of the β-glucosidase from sweet almonds. Remarkably, inhibition by the imidazoles is more strongly affected by the substitution than the one by lactams. Thus, substitution of the OH group at C(4) of the lactam **1** by NH_2, as in **11**, weakens the inhibition against the β-glucosidases from sweet almonds (26 times) and *C. saccharolyticum* (95 times). Substitution of the OH group at C(6) of the imidazole **3** by NH_2, as in **13**, weakens the inhibition of the β-glucosidases from sweet almonds and *C. saccharolyticum ca.* 200 times. Lowering the pH from 6.8 to 5 barely weakens the inhibition of the sweet almond glucosidases by the amino lactam **11** (1.8 times), while the inhibition by **1** is very slightly improved (1.8 times). The amino-imidazole **13** is a weaker inhibitor at pH 5.0 (4.6 times), similarly to **3** (2 times weaker). A similar effect of lowering the pH on the inhibition of the *C. saccharolyticum* glucosidase is observed for **3** (8.7 times weaker) and **13** (4.6 times weaker). The inhibition of this glucosidase by **11** and by **1** is hardly improved at pH 5 (1.4 times). The effect of the pH difference is thus weak, and the similar basicity of the NH_2 group at C(6) and of the imidazole moiety, meaning that both monocations of **13** exist at pH 5, cautions against an interpretation. The data do not suggest that the aminodeoxy analogues bind in a different subsite than the parent inhibitors.

Considering the contribution of the OH group at C(4) of β-glucopyranosides to the binding of the transition state of the *Agrobacterium faecalis* β-glucosidase (family 1) ($\Delta\Delta G^{\circ\ddagger} = 0.59$ kcal/mol [4]), one expects that the removal of the OH group at C(4), as in the lactam **12**, and of the OH group at C(6), as in the imidazole **14**, will lead to a *ca.* 2.7-fold increase of the inhibition constant, as compared to that of **1** and **3**. The increase of K_i values for the inhibition of the β-glucosidases from sweet almonds and *C. saccharolyticum* is, however, *ca.* 56- and 109-fold for the 4-deoxy lactam **12**, and 106- and 200-fold for the 6-deoxyimidazole **14** (*Table 1*), showing a stronger interaction of the OH group at C(4) of the inhibitor, and suggesting a stronger interaction (1–3 kcal/mol) with these glycosidases of the OH group at C(4) also of the substrates in or near the transition state. Remarkably, the effect of the deoxygenation on the inhibition is again stronger for the imidazoles than for the lactams.

Deoxygenation at C(4) of the *galacto*-lactam **9**, as in **12**, and at C(6) of the *galacto*-imidazole **10**, as in **14**, also weakens the inhibition of the β-galactosidases from bovine liver (**14** *vs.* **10**) and *E. coli* (*Table 2*). The inhibition data mean that the interaction of the OH group at C(6) of the imidazole **10** contributes to the inhibition of the β-galactosidases from bovine liver and *E. coli* by a $\Delta\Delta G_{diss}$ value of $+2.6$ and $+4.5$ kcal/mol, respectively (*Table 3*).

The different effect of replacing the OH group at C(4) of the lactams and of the corresponding OH group of the imidazoles is remarkable, as it shows that the same functional group may exert a different effect on the inhibition by even closely related com-

pounds. The difference suggests that the more flexible monocyclic lactam[4]) adapts better to the constraints of the active site than the more rigid bicyclic imidazole. Conformational flexibility of glycosidase inhibitors may indeed decrease selectivity, particularly when the inhibitor possesses a substitutent which interacts strongly with the enzyme, as exemplified by monocyclic, rather flexible lactone-type inhibitors, where analogues that interact more strongly with the catalytic acid are less selective inhibitors of α- *vs.* β-glycosidases[5]) [21]. Similarly, *galacto*- and *gluco*-configured glycarolactams inhibit bovine liver β-glucuronidase to about the same extent ($K_i \approx 30$ nM), while the corresponding *galacto*- and *gluco*-configured imidazoles inhibit this enzyme to a very different extent ($K_i = 6$ μM *vs.* 12 nM), similarly to the analogous tetrazoles ($K_i = 6$ μM *vs.* 25 nM) [14][22]. That the imidazoles and tetrazoles behave similarly is in agreement with the assumption that the selectivity differences are correlated with the flexibility rather than with the basicity of the inhibitors. A systematic study of the effect of the nature of substituents on the inhibition of glycosidases by a range of inhibitor types appears in order.

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Experimental Part

General. See [14]. The pK_{HA} values were determined in H_2O by potentiometric titration with 0.1N HCl at 25°. β-Glucosidases from sweet almonds (3.2.1.21, as lyophilised powder), β-glucosidase from *C. saccharolyticum* (3.2.1.21, as lyophilised powder), β-galactosidase from bovine liver (3.2.1.23, as lyophilised powder), β-galactosidase from *E. coli* (3.2.1.23, as lyophilised powder), and all nitrophenyl glycopyranosides were purchased from *Sigma* and used without any further purification.

5-Amino-2,3,6-tri-O-*benzyl-5-deoxy*-D-*galactono-1,5-lactam* (**16**). A soln. of **15** (2.9 g, 6.51 mmol) in CH_2Cl_2 (40 ml) was treated with molecular sieves (MS, 4 Å; 5 g), stirred for 1 h, cooled to −78°, treated with Et_3SiH (5.2 ml, 32.5 mmol) and TfOH (2.9 ml, 32.5 mmol), stirred for 1 h, treated with Et_3N (5 ml) and MeOH (5 ml), warmed to 23° over 1 h, and filtered. The filtrate was washed with sat. $NaHCO_3$ soln., and the aq. layer was extracted with CH_2Cl_2 (2×50 ml). The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:2) gave **16** (2.5 g, 86%). Colourless solid. R_f (AcOEt/cyclohexane 1:1) 0.33. $[\alpha]_D^{25} = +83.2$ ($c = 1.17$, $CHCl_3$). M.p. 94–95°. IR ($CHCl_3$): 3572*w*, 3385*m*, 2871*m*, 1950*w*, 1870*w*, 1810*w*, 1672*s*, 1496*m*, 1454*m*, 1362*m*, 1341*m*, 1312*m*, 1208*m*, 1176*m*, 1104*s*, 1061*m*, 937*w*, 912*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.46–7.26 (*m*, 15 arom. H); 5.86 (br. *s*, exchange with D_2O, NH); 5.26 (*d*, $J = 11.2$, PhC*H*); 4.81 (*d*, $J = 11.2$, PhC*H*); 4.76 (*d*, $J = 11.5$, PhC*H*); 4.67 (*d*, $J = 11.5$, PhC*H*); 4.57 (*d*, $J = 12.1$, PhC*H*); 4.51(*d*, $J = 11.8$, PhC*H*); 4.12 (addition of $D_2O \rightarrow t$, $J = 2.5$); 2.40 (br. *s*, exchange with CD_3OD, HO–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 138.15, 137.56, 137.29 (3*s*); 128.59–127.75 (several *d*); 75.50, 73.64, 72.86 (3*t*, 3 Ph*C*H$_2$). HR-MALDI-MS: 470.1927 (100, $[M + Na]^+$, $C_{27}H_{29}NNaO_5^+$; calc. 470.1943). Anal. calc. for $C_{27}H_{29}NO_5$ (447.20): C 72.46, H 6.53, N 3.13; found: C 72.42, H 6.71, N 3.12.

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[4]) While the preferred conformation of glyconolactams has been determined [17], their flexibility was not determined to the best of our knowledge. The conformation of the glucono-1,5-lactone and the corresponding hydroximo lactone, however, depends strongly on temperature and solvent [18]. A higher rigidity of the imidazoles is expected due to the larger energy barrier for a rotation about the endocyclic C=C bond and to the $A_{1,3}$-interaction of the $HOCH_2$ group [19].

[5]) Conversely, the rigidity of isoquinuclidines may contribute to their selectivity [20].

Table 4. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz], *and ^{13}C-NMR Chemical Shifts* [ppm] *of the Protected Lactams* **16**–**19**, **21**, *and* **22** *in $CDCl_3$, and of the Deprotected Lactam* **11** *in D_2O*

	16	**17**	**18**	**19**	**21**	**22**	**11**
H–C(2)	4.22	4.14	4.01	4.20	4.15	4.29	3.96
H–C(3)	3.78	3.90	3.79	4.36	3.87	3.83	3.57
H–C(4)	4.12	5.37	3.51	5.12	5.67	5.62	2.92
H–C(5)	3.66–3.61	3.80	3.29	–	3.76	3.29	3.26
H–C(6)	3.66–3.61	3.59	3.71	4.02	3.53	3.54	3.77
H′–C(6)	3.66–3.61	3.53	3.40	4.02	3.37	3.46	3.69
J(2,3)	9.0	9.3	8.4	7.5	9.0	8.4	9.9
J(3,4)	2.5	2.2	9.2	3.4	2.2	2.5	10.0
J(4,5)	2.5	2.2	10.2	–	2.8	2.5	10.3
J(5,6)	[a])	5.6	2.8	–	4.7	4.0	3.0
J(5,6′)	[a])	8.6	8.6	–	8.7	9.5	4.4
J(6,6′)	[a])	8.7	9.3	–	9.0	9.5	12.1
C(1)	170.73	169.76	170.01	169.79	170.07[b])	201.87	173.35
C(2)	76.97	76.07[c])	79.06[c])	74.99	76.89	77.25	71.00
C(3)	79.79	76.74[c])	80.81[c])	77.97	78.04	80.77	73.37
C(4)	66.72	81.26	60.72	133.74	65.96	65.99	57.05
C(5)	52.72	51.99	52.86	103.71	52.14	55.89	49.85
C(6)	70.23	68.52	70.44	68.20	69.24	68.65	60.80

[a]) Not assigned. [b]) Can be interchanged with that of AcO at 171.33. [c]) Assignments may be interchanged.

5-Amino-2,3,6-tri-O-*benzyl-5-deoxy-4*-O-*[(trifluoromethyl)sulfonyl]*-D-*galactono-1,5-lactam* (**17**). A soln. of **16** (715 mg, 1.16 mmol)) in CH_2Cl_2 (15 ml) was cooled to −15°, treated with pyridine (0.47 ml, 5.8 mmol) and Tf_2O (0.21 ml, 1.28 mmol), and stirred for 1 h. The mixture was washed with ice-cold 1M HCl and sat. aq. $NaHCO_3$ soln. The org. layer was dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:4) afforded **17** (569 mg, 61%). R_f (AcOEt/cyclohexane 1:1) 0.41. $[\alpha]_D^{25} = +88.5$ ($c = 1.15$, $CHCl_3$). IR ($CHCl_3$): 3338*w*, 3090*w*, 3068*w*, 3030*w*, 3015*m*, 2873*w*, 1952*w*, 1878*w*, 1810*w*, 1687*m*, 1602*w*, 1497*w*, 1455*m*, 1414*s*, 1364*w*, 1316*w*, 1240*m*, 1140*s*, 1106*s*, 1028*w*, 1001*w*, 914*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.40–7.26 (*m*, 15 arom. H); 6.25 (br. *s*, NH); 5.18 (*d*, $J = 10.9$, PhC*H*); 4.79 (*d*, $J = 10.9$, PhC*H*); 4.78 (*d*, $J = 12.1$, PhC*H*); 4.62 (*d*, $J = 12.1$, PhC*H*); 4.57 (*d*, $J = 11.5$, PhC*H*); 4.50 (*d*, $J = 11.5$, PhC*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 137.38 (*s*); 136.51 (2*s*); 128.57–127.86 (several *d*); 75.98, 73.83, 72.81 (3*t*, 3 Ph*C*H$_2$). HR-MALDI-MS: 602.1439 (8, $[M+Na]^+$, $C_{28}H_{28}F_3NNaO_7S^+$; calc. 602.1431); 448.2115 (100, $[M-131]^+$).

Azidation of **17**. A soln. of **17** (870 mg, 1.50 mmol) in DMF (8 ml) was treated with NaN_3 (341 mg, 5.25 mmol) and stirred for 30 min. Normal workup (AcOEt/H_2O) and FC (AcOEt/cyclohexane 1:4) gave **19** (180 mg, 28%) and **18** (710 mg, 64%).

Data of 5-Amino-2,3,6-tri-O-*benzyl-4,5-dideoxy*-L-threo-*hex-4-enono-1,5-lactam* (**19**). R_f (AcOEt/cyclohexane 1:1) 0.60. M.p. 101–103°. $[\alpha]_D^{25} = +74.6$ ($c = 1.14$, $CHCl_3$). IR (ATR): 3272*w*, 3184*w*, 3148*w*, 3062*w*, 3031*w*, 2900*w*, 2855*w*, 2800*w*, 1958*w*, 1878*w*, 1819*w*, 1711*s*, 1691*s*, 1495*w*, 1485*w*, 1452*m*, 1404*w*, 1389*w*, 1339*m*, 1277*m*, 1217*w*, 1174*w*, 1117*s*, 1090*s*, 1078*s*, 1045*w*, 1025*s*, 1013*m*, 1005*m*, 913*w*, 820*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.44–7.26 (*m*, 10 arom. H, NH); 5.03 (*d*, $J = 11.5$, PhC*H*); 4.75 (*d*, $J = 11.8$, PhC*H*); 4.68 (*d*, $J = 11.5$, PhC*H*); 4.60 (*d*, $J = 11.5$, PhC*H*); 4.49 (*s*, PhCH_2); 4.36 (irrad. at 5.12 → *d*, $J = 7.8$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 137.89, 137.49, 136.97 (3*s*); 128.49–127.68 (several *d*); 73.53, 72.06, 71.57 (3*t*, 3 Ph*C*H$_2$). HR-MALDI-MS: 452.1824 (100, $[M+Na]^+$, $C_{27}H_{27}NNaO_4^+$; calc. 452.1832). Anal. calc. for $C_{27}H_{27}NO_4$ (429.19): C 75.50, H 6.34, N 3.26; found: C 75.32, H 6.44, N 3.37.

*Data of 5-Amino-4-azido-2,3,6-tri-*O*-benzyl-4,5-dideoxy-*D*-glucono-1,5-lactam* (**18**). Fluffy solid. R_f (AcOEt/cyclohexane 1:1) 0.56. $[\alpha]_D^{25} = +172.5$ ($c = 1.75$, $CHCl_3$). M.p. 103–105°. IR (KBr): 3387*w*, 3067*w*, 3030*w*, 3013*w*, 2926*w*, 2869*w*, 2114*s*, 1683*s*, 1603*w*, 1497*w*, 1454*m*, 1362*w*, 1315*w*, 1280*w*, 1117*m*, 1028*w*, 910*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.43–7.29 (*m*, 15 arom. H); 5.95 (br. *s*, NH); 5.24 (*d*, $J = 10.9$, PhC*H*); 4.89 (*d*, $J = 10.6$, PhC*H*); 4.78 (*d*, $J = 11.2$, PhC*H*); 4.77 (*d*, $J = 10.6$, PhC*H*); 4.57 (*d*, $J = 11.5$, PhC*H*); 4.52 (*d*, $J = 11.8$, PhC*H*); 4.01 (irrad. at 3.79 → *d*, $J = 3.1$); 3.79 (irrad. at 4.01 → *dd*, $J = 10.0$, 1.9); 3.51 (irrad. at 3.79 → *dd*, $J = 10.0$, 3.1). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 137.43, 137.13, 136.88 (3*s*); 128.52–127.74 (several *d*); 75.10 (*t*, 2 Ph*C*H$_2$); 73.54 (*t*, Ph*C*H$_2$). HR-MALDI-MS: 495.1990 (52, $[M+Na]^+$, $C_{27}H_{28}N_4NaO_4^+$; calc. 495.2003), 473.2176 (100, $[M+H]^+$, $C_{27}H_{29}N_4NaO_4^+$; calc. 473.2183). Anal. calc. for $C_{27}H_{28}N_4O_4$ (472.54): C 68.63, H 5.97, N 11.86; found: C 68.84, H 6.07, N 11.76.

*4,5-Diamino-4,5-dideoxy-*D*-glucono-1,5-lactam* (**11**). A suspension of **18** (150 mg, 0.32 mmol) and 10% Pd/C (45 mg) in MeOH/AcOH 2:1 (6 ml) was hydrogenated (6 bar) for 24 h. The suspension was filtered through *Celite*, and the residue was washed with MeOH (30 ml). Evaporation of the combined filtrate and washings, ion-exchange chromatography (*Amberlite CG-120,* H^+ form, elution with 0.1M aq. NH_3), and lyophilisation afforded **11** (38 mg, 68%). R_f (AcOEt/MeOH/H_2O 3:1:1) 0.07. $[\alpha]_D^{25} = +37.6$ ($c = 1.10$, H_2O). M.p. 209–211° (dec.). IR (KBr): 3376*s*, 3310*s*, 3178*m*, 3074*m*, 2925*m*, 2712*w*, 1670*s*, 1615*m*, 1582*m*, 1486*w*, 1451*m*, 1385*w*, 1314*w*, 1283*m*, 1232*w*, 1182*w*, 1123*m*, 1103*m*, 1071*m*, 1056*m*, 1028*m*, 989*w*, 909*w*, 835*w*. ^{1}H-NMR (300 MHz, D_2O): see *Table 4*; additionally, 3.77 (irrad. at 3.26 → *d*, $J = 12.1$); 3.69 (irrad. at 3.26 → *d*, $J = 12.4$); 3.57 (irrad. at 3.96 → *d*, $J = 10.6$); 2.92 (irrad. at 3.26 → *d*, $J = 10.0$). ^{13}C-NMR (75 MHz, D_2O): see *Table 4*. ESI-MS: 375.25 (100, $[2M+Na]^+$), 353.15 (24, $[2M+H]^+$), 199.17 (20, $[M+Na]^+$), 177.18 (37, $[M+H]^+$).

Reduction of **17** *with* $NaBH_4$. A soln. of **17** (460 mg, 0.79 mmol) in MeCN (6 ml) was treated with $NaBH_4$ (90 mg, 2.37 mmol) and stirred for 30 min. Normal workup (AcOEt/1M HCl) and FC (AcOEt/cyclohexane 1:4) gave **19** (110 mg, 32%) and **20** (198 mg, 58%).

*Data of 5-Amino-2,3,6-tri-*O*-benzyl-4,5-dideoxy-*D*-xylo-hexono-1,5-lactam* (**20**). R_f (AcOEt/cyclohexane 1:1) 0.50. $[\alpha]_D^{25} = +73.6$ ($c = 1.05$, $CHCl_3$). IR (KBr): 3204*w*, 3062*w*, 3029*w*, 2865*w*, 1955*w*, 1878*w*, 1815*w*, 1673*s*, 1603*w*, 1495*w*, 1452*m*, 1417*w*, 1392*w*, 1351*w*, 1305*w*, 1207*w*, 1098*s*, 1027*m,* 988*w*, 909*w*, 805*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46–7.26 (*m*, 15 arom. H); 6.18 (br. *s*, NH); 5.19 (*d*, $J = 11.2$, PhC*H*); 4.82 (*d*, $J = 11.2$, PhC*H*); 4.71 (*d*, $J = 11.8$, PhC*H*); 4.63 (*d*, $J = 11.8$, PhC*H*); 4.54 (*d*, $J = 12.1$, PhC*H*); 4.49 (*d*, $J = 11.8$, PhC*H*); 3.95 (*d*, $J = 8.1$, irrad. at 3.85 → *s*, H–C(2)); 3.85 (*ddd*, $J = 10.6$, 8.1, 3.7, H–C(3)); 3.61 (br. *tt*, $J \approx 9.7$, 3.7, H–C(5)); 3.47 (*dd*, $J = 9.0$, 3.4, H–C(6)); 3.32 (*t*, $J = 9.2$, H′–C(6)); 2.16 (*dtd*, $J = 13.4$, 4.0, 1.2, irrad. at 3.85 → *dd*, $J = 13.7$, 4.7, H_{eq}–C(4)); 1.52 (*dt*, $J = 13.4$, 10.6, irrad. at 3.85 → *dd*, $J = 13.4$, 10.3, H_{ax}–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.70 (*s*, C=O); 138.04, 138.02, 137.23 (3*s*); 128.50–127.42 (several *d*); 79.83 (*d*, C(3)); 76.13 (*d*, C(2)); 74.84, 73.65, 73.44 (3*t*, 3 Ph*C*H$_2$); 72.39 (*t*, C(6)); 41.18 (*d*, C(5)); 29.54 (*t*, C(4)). HR-MALDI-MS: 454.1982 (100, $[M+Na]^+$, $C_{27}H_{29}NNaO_4^+$; calc. 454.1989). Anal. calc. for $C_{27}H_{29}NO_4$ (431.52): C 75.15, H 6.77, N 3.25; found: C 74.98, H 6.90, N 3.26.

*5-Amino-4,5-dideoxy-*D*-xylo-hexono-1,5-lactam* (**12**). A suspension of **20** (60 mg, 0.11 mmol) and 10% Pd/C (15 mg) in MeOH/H_2O 2:1 (3 ml) was hydrogenated (6 bar) for 24 h. The suspension was filtered through *Celite*, and the residue was washed with MeOH (10 ml). Evaporation of the combined filtrate and washings, and FC (*RP-18,* elution with MeOH) afforded **12** (22 mg, 98%). R_f (AcOEt/MeOH/H_2O 3:2:1) 0.39. M.p. 150–152°. $[\alpha]_D^{25} = +65.0$ ($c = 0.65$, $CHCl_3$). IR (KBr): 3360*s* (br.), 2921*m*, 2879*w*, 1661*s*, 1471*w*, 1449*m*, 1406*m*, 1296*m*, 1248*w*, 1178*w*, 1125*m*, 1106*m*, 1064*m*, 1050*m*, 930*w*, 884*w*, 824*w*. ^{1}H-NMR (300 MHz, D_2O): 3.94–3.91 (*m*, H–C(2), H–C(3)); 3.64 (*dd*, $J \approx 11.0$, 3.6, H–C(6)); 3.62–3.55 (*m*, H–C(5)); 3.48 (*dd*, $J = 11.0$, 4.9, H′–C(6)); 2.15 (*dt*, $J = 13.2$, 3.6, irrad. at 3.93 → *dd*, $J = 13.2$, 4.7, H_{eq}–C(4)); 1.68 (*dt*, $J \approx 13.2$, 11.0, irrad. at 3.93 → *dd*, $J = 13.2$, 11.0, H_{ax}–C(4)). ^{13}C-NMR (75 MHz, D_2O): 173.87 (*s*, C=O); 72.77 (*d*, C(3)); 68.69 (*d*, C(2)); 63.59 (*t*, C(6)); 50.67 (*d*, C(5)); 30.54 (*t*, C(4)). ESI-MS: 345.15 (71, $[2M+Na]^+$), 184.17 (100, $[M+Na]^+$). Anal. calc. for $C_6H_{11}NO_4 \cdot 0.3\ H_2O$ (166.56): C 43.27, H 7.02, N 8.41; found: C 42.89, H 7.04, N 8.69.

*5-Amino-4-*O*-acetyl-2,3,6-tri-*O*-benzyl-5-deoxy-*D*-galactono-1,5-lactam* (**21**). A soln. of **16** (2.0 g, 4.46 mmol) in pyridine (15 ml) was cooled to 0°, treated with Ac_2O (4.2 ml, 44.6 mmol), kept for 2 h, and evaporated to afford **21** (2.2 g, 99%). Colourless oil. A small sample was purified by FC (AcOEt/cyclo-

hexane 1:4). R_f (AcOEt/cyclohexane 1:1) 0.48. $[\alpha]_D^{25} = +110.4$ ($c = 1.14$, $CHCl_3$). IR (ATR): 3214*w* (br.), 3087*w*, 3063*w*, 3031*w*, 2869*w*, 1957*w*, 1880*w*, 1813*w*, 1774*m*, 1679*s*, 1605*w*, 1496*w*, 1453*m*, 1416*w*, 1369*m*, 1307*w*, 1222*s*, 1174*w*, 1150*m*, 1104*s*, 1018*m*, 955*w*, 915*w*, 830*w*, 735*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 7.43–7.26 (*m*, 15 arom. H); 6.76 (br. *s*, NH); 5.19 (*d*, $J = 10.9$, PhC*H*); 4.79 (*d*, $J = 11.2$, PhC*H*); 4.73 (*d*, $J = 11.5$, PhC*H*); 4.55 (*d*, $J \approx 12.5$, 2 PhC*H*); 4.47 (*d*, $J = 11.5$, PhC*H*); 2.07 (*s*, AcO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 171.33 (*s*, C=O); 138.11, 137.39, 137.08 (3*s*); 128.60–127.74 (several *d*); 75.78, 73.67, 71.96 (3*t*, 3 Ph*C*H$_2$); 20.75 (*q*, Me). HR-MALDI-MS: 512.2042 (100, $[M+Na]^+$, $C_{29}H_{31}NNaO_6^+$; calc. 512.2044). Anal. calc. for $C_{29}H_{31}NO_6$ (489.21): C 71.15, H 6.38, N 2.86; found: C 70.94, H 6.38, N 2.86.

*5-Amino-4-*O*-acetyl-2,3,6-tri-*O*-benzyl-5-deoxy-*D*-galactono-1,5-thiolactam* (**22**). A soln. of **21** (547 mg, 1.11 mmol) in toluene (10 ml) was treated with *Lawesson*'s reagent (449 mg, 1.11 mmol), heated to 80° for 30 min, cooled to 25°, treated with $NaHCO_3$ (93 mg, 1.11 mmol), and stirred for 10 min. FC (AcOEt/cyclohexane 1:4) afforded **22** (508 mg, 90%). R_f (AcOEt/cyclohexane 1:2) 0.51. $[\alpha]_D^{25} = +123.3$ ($c = 0.92$, $CHCl_3$). IR (ATR): 3364*w*, 3170*w*, 3030*w*, 2924*w*, 2867*w*, 1955*w*, 1881*w*, 1810*w*, 1746*s*, 1555*m*, 1496*m*, 1453*m*, 1407*w*, 1370*m*, 1320*m*, 1295*w*, 1221*s*, 1178*w*, 1096*s*, 1017*m*, 947*m*, 915*m*, 859*w*, 826*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 8.18 (br. *s*, NH); 7.48–7.26 (*m*, 15 arom. H); 5.35 (*d*, $J = 10.3$, PhC*H*); 4.82 (*d*, $J = 10.3$, PhC*H*); 4.65 (*d*, $J = 11.5$, PhC*H*); 4.57 (*d*, $J = 11.8$, PhC*H*); 4.55 (*d*, $J = 11.5$, PhC*H*); 4.47 (*d*, $J = 11.8$, PhC*H*); 2.09 (*s*, AcO). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 4*; additionally, 169.84 (*s*, C=O); 137.77, 137.13, 136.69 (3*s*); 128.57–127.77 (several *d*); 76.31, 73.72, 72.13 (3*t*, 3 Ph*C*H$_2$); 20.90 (*q*, Me). HR-MALDI-MS: 506.1988 (100, $[M+H]^+$, $C_{29}H_{32}NO_5S^+$; calc. 506.1996). Anal. calc. for $C_{29}H_{31}NO_5S$ (505.62): C 68.89, H 6.18, N 2.77; found: C 68.61, H 6.33, N 2.77.

*(5*R*,6*S*,7*S*,8*S*)-7,8-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-6-ol* (**23**). A soln. of **22** (740 mg, 1.46 mmol) in THF (25 ml) was cooled to 0°, treated with $Hg(OAc)_2$ (513 mg, 1.61 mmol) and $H_2NCH_2CH(OMe)_2$ (0.23 ml, 7.30 mmol), stirred for 2 h, diluted with Et_2O (50 ml), filtered through *Celite*, and evaporated. A soln. of the residue in toluene/H_2O 10:1 (22 ml) was treated with $TsOH \cdot H_2O$ (1.1 g, 5.84 mmol) and stirred at 75° for 24 h. The mixture was diluted with AcOEt (50 ml) and washed with sat. K_2CO_3 soln. The aq. layer was extracted with AcOEt (2×50 ml). The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:3) afforded **23** (540 mg, 78%). R_f (AcOEt/cyclohexane 1:1) 0.31. $[\alpha]_D^{25} = +71.1$ ($c = 1.05$, $CHCl_3$). IR (CH_2Cl_2): 3575*w* (br.), 3089*m*, 3051*w*, 3033*w*, 2918*w*, 2873*w*, 1955*w*, 1879*w*, 1812*w*, 1732*w*, 1605*w*, 1496*w*, 1481*w*, 1421*w*, 1364*w*, 1316*w*, 1210*w*, 1128*m*, 1091*s*, 1028*m*, 896*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.43–7.25 (*m*, 15 arom. H); 7.16, 7.10 (2*d*, $J = 1.4$, H–C(2), H–C(3)); 5.13 (*d*, $J = 11.5$, PhC*H*); 4.85 (*d*, $J = 11.5$, PhC*H*); 4.71 (*d*, $J = 11.5$, PhC*H*); 4.64 (*d*, $J = 11.8$, PhC*H*); 4.55 (*d*, $J = 12.1$, PhC*H*); 4.51 (*d*, $J = 11.8$, PhC*H*); 4.55–4.51 (addition of $CD_3OD \rightarrow$ *dd*, $J = 4.1, 1.9$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*; additionally, 138.51, 137.96, 137.76 (3*s*); 129.40 (*d*, C(2)); 128.80–127.85 (several *d*); 118.52 (*d*, C(3)); 73.73, 73.08, 72.79 (3*t*, 3 Ph*C*H$_2$). HR-MALDI-MS: 471.2270 (100, $[M+H]^+$, $C_{29}H_{31}N_2O_4^+$; calc. 471.2278). Anal. calc. for $C_{29}H_{30}N_2O_4$ (470.56): C 74.02, H 6.43, N 5.95; found: C 73.75, H 6.45, N 5.90.

Preparation of **25** *and* **27**. A soln. of **23** (140 mg, 0.30 mmol) in CH_2Cl_2 (8 ml) was cooled to 0°, treated with pyridine (0.12 ml, 1.49 mmol) and Tf_2O (56 µl, 0.33 mmol), and stirred for 1 h. The mixture was washed with ice-cold 1M HCl and ice-cold $NaHCO_3$ soln. The org. layer was dried (Na_2SO_4), filtered, and evaporated. A soln. of the residue (**24**) in DMF (6 ml) was treated with NaN_3 (98 mg, 1.50 mmol) and stirred for 30 min. Normal workup (AcOEt/H_2O) gave a 1:1 mixture of **25** and **26** (130 mg). The crude was dissolved in THF (6 ml), treated with 10% Pd/$CaCO_3$ (15 mg), and hydrogenated (1 bar) for 20 h. Filtration through *Celite*, evaporation, and FC (AcOEt/cyclohexane 1:2 → AcOEt) gave **25** (53 mg, 39%) and **27** (59 mg, 42%).

*Data of (7*S*,8*S*)-7,8-Bis(benzyloxy)-5-[(benzyloxy)methyl]-7,8-dihydroimidazo[1,2-*a*]pyridine* (**25**). R_f (AcOEt/cyclohexane 1:1) 0.36. IR (ATR): 3058*w*, 3030*w*, 2908*w*, 2862*w*, 1953*w*, 1876*w*, 1809*w*, 1673*w*, 1603*w*, 1585*w*, 1484*m*, 1453*m*, 1434*m*, 1389*w*, 1362*w*, 1327*w*, 1226*m*, 1207*w*, 1137*m*, 1084*s*, 1066*s*, 1027*m*, 909*w*, 862*w*, 817*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.38–7.24 (*m*, 15 arom. H, H–C(2)); 7.10 (*d*, $J = 1.2$, H–C(3)); 4.73 (*d*, $J = 11.8$, PhC*H*); 4.67 (*d*, $J = 11.8$, PhC*H*); 4.59 (*d*, $J = 11.8$, PhC*H*); 4.53 (*s*, PhC*H*$_2$); 4.51 (*d*, $J = 10.3$, PhC*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table*

Table 5. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz], *and ^{13}C-NMR Chemical Shifts* [ppm] *of the Protected Imidazoles* **23**, **25**, *and* **27** *in $CDCl_3$, and of the Deprotected Imidazole* **13** *in D_2O*

	23	**25**	**27**	**13**
H–C(5)	4.32	–	4.00	3.84
HC–C(5)	4.04	4.40	3.93	4.13
H′C–C(5)	3.86	4.34	3.781	3.97
H–C(6)	4.55–4.51	5.63	3.25	3.12
H–C(7)	3.97	4.28	3.776	3.54
H–C(8)	4.84	4.78	4.73	4.46
J(5,CH)	3.8	–	3.1	3.1
J(5,CH″)	7.7	–	6.2	3.7
J(CH,CH′)	10.2	13.1	10.3	12.1
J(5,6)	4.1	–	9.7	9.0
J(6,7)	2.2	5.3	7.8	10.0
J(7,8)	5.8	3.1	5.9	8.1
C(5)	57.53	133.78	51.19	49.74
CH_2–C(5)	71.52	68.23	70.65	59.18
C(6)	67.56	111.87	60.97	60.31
C(7)	80.60	73.05	81.63	74.47
C(8)	73.03	70.88	74.94	68.35
C(8a)	143.55	142.88	144.02	146.32

5; additionally, 138.02, 137.86, 137.35 (3*s*); 128.77–127.92 (several *d*, including C(2)); 116.00 (*d*, C(3)); 71.96, 71.25, 70.93 (3*t*, 3 Ph*C*H$_2$). HR-MALDI-MS: 453.2167 (100, $[M+H]^+$, $C_{29}H_{29}N_2O_3^+$; calc. 453.2173).

*Data of (5*R,*6*R,*7*S,*8*S*)-6-Amino-7,8-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**27**). R_f (AcOEt) 0.33. $[\alpha]_D^{25} = +51.9$ ($c = 0.69$, $CHCl_3$). IR ($CHCl_3$): 3387*w*, 3089*w*, 3068*w*, 3034*w*, 2907*w*, 2870*m*, 1955*w*, 1877*w*, 1812*w*, 1669*w*, 1605*w*, 1496*m*, 1483*w*, 1454*m*, 1361*w*, 1313*w*, 1282*m*, 1208*w*, 1088*s*, 1028*m*, 927*w*, 911*w*, 851*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 5*; additionally, 7.46–7.25 (*m*, 15 arom. H); 7.34, 7.11 (2*d*, $J = 1.2$, H–C(2), H–C(3)); 5.28 (*d*, $J = 11.5$, PhC*H*); 4.92 (*d*, $J = 11.8$, PhC*H*); 4.88 (*d*, $J = 11.5$, PhC*H*); 4.62 (*d*, $J = 11.5$, PhC*H*); 4.53 (*s*, PhCH_2); 1.64 (br. *s*, exchange with CD_3OD, NH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 5*; additionally, 138.26, 137.97, 137.60 (3*s*); 129.41 (*d*, C(2)); 128.73–127.88 (several *d*); 117.94 (*d*, C(3)); 74.04, 73.56, 73.04 (3*t*, 3 Ph*C*H$_2$). HR-MALDI-MS: 470.2430 (100, $[M+H]^+$, $C_{29}H_{32}N_3O_3^+$; calc. 470.2438). Anal. calc. for $C_{29}H_{31}N_3O_3$ (469.57): C 74.18, H 6.65, N 8.95; found: C 74.40, H 6.77, N 9.01.

*(5*R,*6*R,*7*S,*8*S*)-6-Amino-5-(hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-7,8-diol* (**13**). A suspension of **27** (46 mg, 0.098 mmol) and 10% Pd/C (20 mg) in MeOH/AcOH 2:1 (3 ml) was hydrogenated (6 bar) for 24 h. The suspension was filtered through *Celite*, and the residue was washed with MeOH (10 ml). Evaporation of the filtrate, ion-exchange chromatography (*Amberlite CG-120*, H^+ form, elution with 0.1M aq. NH_3), and lyophilisation afforded **13** (18.8 mg, 96%). R_f (AcOEt/MeOH/H_2O 3:1:1) 0.06. pK_{HA} = 5.80. M.p. 178–180° (dec.). $[\alpha]_D^{25} = -43.9$ ($c = 0.60$, H_2O). IR (KBr): 3401*s* (br.), 2921*m*, 2851*m*, 1606*m*, 1528*w*, 1490*m*, 1456*w*, 1384*w*, 1313*w*, 1282*w*, 1239*w*, 1163*w*, 1092*m*, 1068*m*, 1035*w*, 937*w*, 894*w*, 844*w*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 5*; additionally, 7.26, 7.01 (2*d*, $J = 1.6$, H–C(2), H–C(3)); 3.54 (irrad. at 4.46 → *d*, $J = 10.0$). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 5*; additionally, 128.23 (*d*, C(2)); 117.53 (*d*, C(3)). ESI-MS: 421.15 (64, $[2M+Na]^+$), 222.17 (96, $[M+Na]^+$), 200.17 (100, $[M+H]^+$).

5-Amino-2,3,6-tri-O-*benzyl-4,5-dideoxy*-D-xylo-*hexono-1,5-thiolactam* (**28**). A soln. of **20** (125 mg, 0.29 mmol) in toluene (6 ml) was treated with *Lawesson*'s reagent (118 mg, 0.29 mmol), heated at 80° for 30 min, cooled to 25°, treated with $NaHCO_3$ (25 mg, 0.29 mmol), and stirred for 10 min. FC (AcOEt/cyclohexane 1:5) afforded **28** (125 mg, 96%). R_f (AcOEt/cyclohexane 1:4) 0.33.

$[\alpha]_D^{25} = +135.2$ ($c = 0.85$, $CHCl_3$). IR (ATR): 3363*w*, 3172*w* (br.), 3058*w*, 3029*w*, 2863*w*, 1951*w*, 1876*w*, 1811*w*, 1656*w*, 1526*m*, 1495*m*, 1453*m*, 1392*w*, 1360*m*, 1326*m*, 1250*w*, 1205*m*, 1087*s*, 1067*s*, 909*m*, 847*w*, 820*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.42 (br. *s*, NH); 7.42–7.23 (*m*, 15 arom. H); 5.14 (*d*, $J = 11.2$, PhC*H*); 4.81 (*d*, $J = 11.5$, PhC*H*); 4.62 (*d*, $J = 11.8$, PhC*H*); 4.58 (*d*, $J = 11.5$, PhC*H*); 4.49 (*d*, $J = 11.8$, PhC*H*); 4.47 (*d*, $J = 11.8$, PhC*H*); 4.36 (*d*, $J = 5.0$, irrad. at 3.83 → *s*, H–C(2)); 3.83 (*dt*, $J = 6.0$, 4.7, irrad. at 4.36 → *dd*, $J = 5.9$, 4.4, H–C(3)); 3.79–3.71 (*m*, H–C(5)); 3.51 (*t*, $J = 9.3$, H–C(6)); 3.45 (*dd*, $J = 9.0$, 4.4, H′–C(6)); 2.26 (*ddd*, $J = 14.0$, 6.5, 4.4, irrad. at 3.83 → *dd*, $J = 14.0$, 6.2, H_{eq}–C(4)); 1.59 (*td*, $J = 14.0$, 6.3, irrad. at 3.83 → *dd*, $J = 14.9$, 5.8, H_{ax}–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): 199.64 (*s*, C=S); 137.66, 137.59, 137.06 (3*s*); 128.48–127.53 (several *d*); 81.00 (*d*, C(3)); 73.93 (*d*, C(2)); 73.73, 73.41, 72.69 (3*t*, 3 Ph*C*H$_2$); 71.58 (*t*, C(6)); 52.41 (*d*, C(5)); 26.57 (*t*, C(4)). HR-MALDI-MS: 470.1753 (100, $[M+Na]^+$, $C_{27}H_{29}NNaO_3S^+$; calc. 470.1760). Anal. calc. for $C_{27}H_{29}NO_3S$ (447.59): C 72.45, H 6.53, N 3.13, S 7.16; found: C 72.34, H 6.42, N 3.05, S 7.27.

Preparation of **29** *and* **30**. A soln. of **28** (58 mg, 0.13 mmol) in THF (4 ml) was cooled to 0°, treated with $Hg(OAc)_2$ (46 mg, 0.14 mmol) and $H_2NCH_2CH(OMe)_2$ (71 µl, 0.64 mmol), stirred for 2 h, diluted with Et_2O (10 ml), filtered through *Celite*, and evaporated. A soln. of the residue in toluene/H_2O 30:1 (3.1 ml) was treated with $TsOH \cdot H_2O$ (100 mg, 0.52 mmol) and stirred at 75° for 24 h. The mixture was diluted with AcOEt (50 ml) and washed with sat. K_2CO_3 soln. The aq. layer was extracted with AcOEt (2 × 50 ml). The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. FC (AcOEt/cyclohexane 1:4) afforded **30** (38 mg, 64%) and **29** (12 mg, 20%).

*Data of (5*R*,7*S*,8*S*)-7,8-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**30**). R_f (AcOEt/cyclohexane 1:1) 0.34. $[\alpha]_D^{25} = +122.6$ ($c = 0.66$, $CHCl_3$). IR (ATR): 3062*w*, 3029*w*, 2920*w*, 2863*w*, 1953*w*, 1876*w*, 1811*w*, 1724*w*, 1676*w*, 1604*w*, 1585*w*, 1495*m*, 1481*w*, 1453*m*, 1360*m*, 1327*w*, 1305*w*, 1254*w*, 1207*w*, 1175*w*, 1086*s*, 1063*s*, 1027*s*, 909*m*, 822*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39–7.21 (*m*, 15 arom. H); 7.20, 7.11 (2*d*, $J = 1.2$, H–C(2), H–C(3)); 4.95 (*d*, $J = 11.8$, PhC*H*); 4.80 (*d*, $J = 12.1$, PhC*H*); 4.69 (*d*, $J = 3.7$, irrad. at 4.02 → *s*, H–C(8)); 4.61 (*d*, $J = 11.8$, PhC*H*); 4.54 (*d*, $J = 11.8$, PhC*H*); 4.51 (*d*, $J = 11.8$, PhC*H*); 4.48 (*d*, $J = 11.8$, PhC*H*); 4.39 (*dddd*, $J \approx 7.8$, 6.5, 4.7, 3.7, H–C(5)); 4.02 (*ddd*, $J = 5.6$, 3.7, 2.8, irrad. at 4.69 → *dd*, $J = 5.6$, 2.8, H–C(7)); 3.80 (*dd*, $J = 9.6$, 7.5, HC–C(5)); 3.69 (*dd*, $J = 9.6$, 4.7, H′C–C(5)); 2.49 (*ddd*, $J = 14.6$, 6.8, 2.8, irrad. at 4.02 → *dd*, $J = 14.3$, 6.8, H_{eq}–C(6)); 2.12 (*ddd*, $J = 14.6$, 5.3, 3.7, irrad. at 4.02 → *dd*, $J = 14.9$, 3.4, H_{ax}–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 142.39 (*s*, C=N); 138.18, 137.74, 137.58 (3*s*); 128.44–127.36 (several *d*, including C(2)); 119.09 (*d*, C(3)); 75.00 (*d*, C(7)); 74.73, 73.43, 71.56 (2 C) (3*t*, 3 Ph*C*H$_2$, *C*H$_2$–C(5)); 71.00 (*d*, C(8)); 53.28 (*d*, C(5)); 26.73 (*t*, C(6)). HR-MALDI-MS: 477.2147 (100, $[M+Na]^+$, $C_{29}H_{30}N_2NaO_3^+$; calc. 477.2149), 455.2329 (76, $[M+H]^+$, $C_{29}H_{31}N_2O_3^+$; calc. 455.2329). Anal. calc. for $C_{29}H_{30}N_2O_3$ (454.56): C 76.63, H 6.65, N 6.16; found: C 76.46, H 6.95, N 6.06.

*Data of (5*R*,7*S*,8*R*)-7,8-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine* (**29**). R_f (AcOEt/cyclohexane 1:1) 0.30. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.44–7.27 (*m*, 15 arom. H, H–C(2)); 7.07 (*d*, $J = 1.2$, H–C(3)); 4.83 (br. *d*, $J = 2.2$, H–C(8)); 4.82 (*d*, $J \approx 12.7$, PhC*H*); 4.77 (*d*, $J = 12.1$, PhC*H*); 4.59 (*d*, $J = 12.1$, PhC*H*); 4.54 (*d*, $J = 14.3$, PhC*H*); 4.53 (*d*, $J = 14.9$, PhC*H*); 4.46 (*d*, $J = 12.1$, PhC*H*); 4.29–4.19 (*m*, H–C(5)); 3.78 (*dt*, $J \approx 12.1$, 3.4, irrad. at 4.83 → *dd*, $J = 12.1$, 3.7, H–C(7)); 3.68 (*dd*, $J = 12.8$, 10.0, HC–C(5)); 3.68–3.65 (hidden signal, H′C–C(5)); 2.41 (*q*, $J \approx 12.1$, H_{ax}–C(6)); 2.15 (*dddd*, $J = 13.1$, 5.9, 3.7, 1.2, irrad. at 4.83 → *ddd*, $J = 12.9$, 6.0, 3.8, H_{eq}–C(6)).

*(5*R*,7*S*,8*S*)-5-(Hydroxymethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine-7,8-diol* (**14**). A suspension of **30** (18 mg, 0.04 mmol) and 10% Pd/C (10 mg) in MeOH/AcOH 2:1 (3 ml) was hydrogenated (6 bar) for 24 h. The suspension was filtered through *Celite*, and the residue was washed with MeOH (10 ml). Evaporation of the filtrate and FC (*RP-18*, elution with MeOH) afforded **14** (7.2 mg, 98%). R_f (AcOEt/MeOH/H_2O 3:1:1) 0.26. IR (KBr): 3390*s* (br.), 2925*s*, 2855*m*, 1575*s*, 1528*m*, 1489*m*, 1446*s*, 1413*s*, 1321*m*, 1257*m*, 1171*m*, 1119*m*, 1090*s*, 1070*s*, 1044*s*, 1013*m*, 938*w*, 882*w*, 835*w*. ^{1}H-NMR (300 MHz, D_2O): 7.32, 7.05 (2 br. *s*, H–C(2), H–C(3)); 4.51 (*d*, $J = 6.2$, H–C(8)); 4.30–4.23 (*m*, H–C(5)); 3.97–3.90 (hidden signal, H–C(7)); 3.93 (*dd*, $J = 11.8$, 4.0, HC–C(5)); 3.79 (*dd*, $J = 11.8$, 5.3, H′C–C(5)); 2.36 (*ddd*, $J = 13.9$, 5.6, 3.1, H_{eq}–C(6)); 1.99 (*dt*, $J = 14.3$, 8.4, H_{ax}–C(6)). ^{13}C-NMR (75 MHz, CD_3OD): 146.22 (*s*, C=N); 125.81 (*d*, C(2)); 118.37 (*d*, C(3)); 69.22, 69.00 (2*d*, C(7), C(8)); 62.41 (*t*, *C*H$_2$–C(5)); 54.86 (*d*, C(5)); 30.36 (*d*, C(6)).

Inhibition Studies. Determination of the inhibition constants (K_i) was performed with a range of inhibitor concentrations (typically 5–7 concentrations) which bracket the K_i value, and substrate concentrations which bracket the K_M of each enzyme (typically 3–6 concentrations).

a) *Inhibition of* Caldocellum saccharolyticum *β-Glucosidase.* $K_M = 0.68–0.77$ mM ([23]: $K_M = 0.51$ mM; [24]: $K_M = 0.51–0.78$ mM). Inhibition studies were carried out at 55° at an enzyme concentration of 0.009 units/ml, with a 0.1M NaH_2PO_4/Na_2HPO_4 buffer (pH 6.8) and 4-nitrophenyl β-D-glucopyranoside (*Fluka 73676*) as the substrate. The enzymatic reaction was started, after incubation of the enzyme (120 µl) in the presence of the inhibitor (40 µl) for 30 min at 55°, by addition of the substrate (40 µl). The enzymatic reaction was quenched by addition of 0.2M borate buffer (pH 9.0, 100 µl) after 30 min, and the absorption at 405 nm was taken as rate of hydrolysis of the substrate after subtraction of the absorption of a blank probe (H_2O, buffer, substrate). IC_{50} Values were determined by plotting the reciprocal value of the rate of substrate hydrolysis *vs.* the inhibitor concentration. After fitting a straight line to the data by linear regression, the negative [*I*] intercept of this plot provided the appropriate IC_{50} value. K_i Values were determined by taking the slopes from the *Lineweaver–Burk* plots [25] and plotting them *vs.* the inhibitor concentrations [26]. After fitting a straight line to the data by linear regression, the negative [*I*] intercept of this plot provided the appropriate K_i value. α Values were determined by plotting the $1/v$ axis intercepts from the *Lineweaver–Burk* plots *vs.* the inhibitor concentrations [26].

b) *Inhibition of Sweet Almond β-Glucosidase.* $K_M = 3.2–3.3$ mM ([24]: $K_M = 2.9–3.1$ mM). Inhibition studies were carried out at 37° at an enzyme concentration of 0.09 units/ml, with a 0.1M NaH_2PO_4/Na_2HPO_4 buffer (pH 6.8) and 4-nitrophenyl β-D-glucopyranoside (*Fluka 73676*) as the substrate. The enzymatic reaction was started, after incubation of the enzyme (120 µl) in the presence of the inhibitor (40 µl) for 30 min at 37°, by addition of the substrate (40 µl). The increase of absorption per min at 405 nm was taken as the rate for the hydrolysis of the substrate. The increase was linear during 10 min. IC_{50}, K_i, and α values were determined by plots as described in *a*.

c) *Inhibition of Bovine Liver β-Galactosidase.* $K_M = 0.8–1.1$ mM ([24]: $K_M = 0.77–1.05$ mM). Inhibition studies were carried out as described in *a* at 37° at an enzyme concentration of 0.030 units/ml, with a 0.05M NaH_2PO_4/Na_2HPO_4 buffer containing 1 mM of $MgCl_2$ (pH 7.0) and 2-nitrophenyl β-D-galactopyranoside as the substrate. IC_{50}, K_i, and α values were determined by plots as described in *a*. The increase in absorption was linear during 7 min.

d) *Inhibition of* E. coli *β-Galactosidase.* $K_M = 0.9–1.6$ mM ([27]: $K_M = 0.18$ mM; [24]: $K_M = 0.11–0.20$ mM). Inhibition studies were carried as described in *a* out at 37° at an enzyme concentration of 0.15 units/ml, with a 0.2M NaH_2PO_4/Na_2HPO_4 buffer containing 1 mM of $MgCl_2$ (pH 7.0) and 2-nitrophenyl β-D-galactopyranoside as the substrate. IC_{50}, K_i, and α values were determined by plots as described in *a*. The increase in absorption was linear during 7 min.

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