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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 449–469

Synthesis and evaluation of two mannosamine-derived lactone-type inhibitors of snail β-mannosidase

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Received 8 November 2004; accepted 25 November 2004

Abstract—The inhibition of snail β-mannosidase by the *manno*-configured amino- and hydroxy-lactams and -imidazoles **7**–**10** was compared to the inhibition of the β-glucosidases from *Caldocellum saccharolyticum* and from sweet almonds by the *gluco*-configured amino- and hydroxy-lactams and -imidazoles **1**, **2**, **5** and **6** [$\Delta\Delta G_{diss.}(OH \rightarrow NH_3^+)$]. Substitution in the *gluco*-configured **1**, **3** and **5**, of C(2)–OH by an ammonium group strengthens the interaction of the inhibitor with the catalytic nucleophile of retaining β-glucosidases, and weakens the interaction with the catalytic acid. The analogous substitution in the *manno*-configured inhibitors **7** and **9**, leading to **8** and **10**, respectively, was expected to only reflect the impaired interaction of the inhibitor with the catalytic acid, as the catalytic nucleophile and the C(2) substituent are located on opposite sides of the average ring plane.

The mannonolactam **10** was synthesized from the known hydroxy-lactam **11** by *O*-mesylation followed by azidation and hydrogenation. Sultone **13** was formed as side product upon mesylation of **11**. The imidazole **8** was obtained from **11**, similarly to the synthesis of the known *gluco*-isomer **2**, via the hydroxy-imidazoles **22** and **23**; best results were obtained by protecting **11** as the triisopropylsilyl ether **29**.

The resulting inhibition by the imidazoles **7** and **8** was interpreted as reflecting an improved binding of the catalytic nucleophile of snail β-mannosidase with the protonated imidazole ring of **8** and an impaired interaction with the catalytic acid, while a comparison of the inhibition by the lactams **9** and **10** is in keeping with the results that are expected if there is no significant interaction between the catalytic nucleophile of snail β-mannosidase and the C(2)–OH group of β-mannosides. The amino-imidazole **8** is a surprisingly strong inhibitor of the α-mannosidase from *Jack* beans [K_i = 1.22 μM; mixed-type (α = 2.3)].

1. Introduction

Substitution of the C(8)–OH group of the *gluco*-configured tetrahydropyridoimidazole **1** (Fig. 1) by an amino group, as in **2**, leads to a significantly weaker inhibition of the β-glucosidases from *Caldocellum saccharolyticum* ($\Delta\Delta G_{diss.}$ = +4.7 kcal/mol) and from sweet almonds ($\Delta\Delta G_{diss.}$ = +4.4 kcal/mol). The analogous substitution of the tetrahydropyrrolopyridine **3** into **4**, leads, however, to a stronger inhibition ($\Delta\Delta G_{diss.}$ = −2.8 to −2.9 kcal/mol).[1] These observations were interpreted as the result of opposite influences. While the ammonium group forms a stronger hydrogen bond to the catalytic nucleophile of the β-glucosidases than the hydroxy group, this effect is overcompensated by the lowered basicity of the imidazole ring of **2** and the impairment of the hydrogen bond from the catalytic acid to the imidazole. The effect on the hydrogen bond from the catalytic acid is not relevant for the inhibition by the 8-hydroxypyrrole **3** and the corresponding amine **4**, and the stronger hydrogen bond from the ammonium group to the catalytic nucleophile leads to an stronger inhibition by **4**. In agreement with this interpretation, substitution of the C(2)–OH group of the gluconolactam **5** by an amino group led to an slightly increased inhibition by **6** of the β-glucosidases from *C. saccharolyticum* ($\Delta\Delta G_{diss.}$ = −1.1 kcal/mol) and from sweet almonds ($\Delta\Delta G_{diss.}$ = −1.1 kcal/mol) evidencing that the carbonyl group of **6** is a relatively weak H-bond acceptor for the catalytic acid since the overall effect on the inhibition is dominated by the interaction of the ammonium group with the catalytic nucleophile.

We wished to explore the effect on the inhibition of snail β-mannosidase of the analogous substitution of C(8)–OH of the *manno*-configured tetrahydroimidazole **7** and of the corresponding lactam **9** by an amino group. As the catalytic nucleophile of this mannosidase and

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doi:10.1016/j.tetasy.2004.11.068

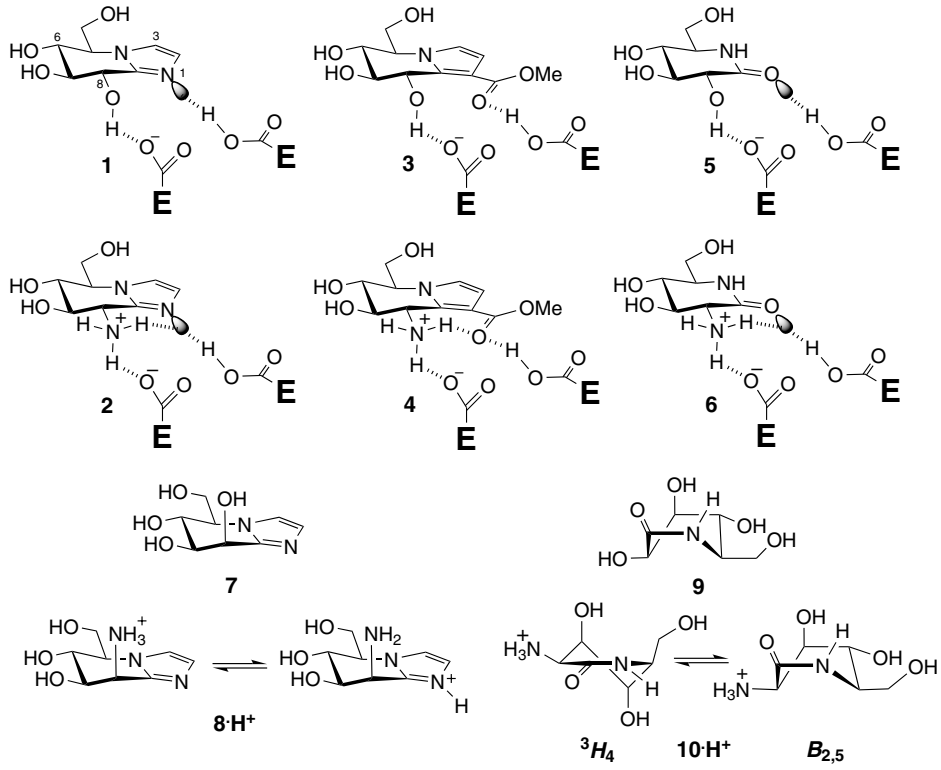


Figure 1.

the C(8) substituent of **7** and the corresponding amine **8** (and similarly the C(2) substituents of the lactams **9** and **10**) are located on opposite sites of the average plane of the tetrahydropyridine ring,[†] one does not expect an interaction of the C(8) substituent with the catalytic nucleophile. As snail β-mannosidase has a lower pH-optimum (pH 4.0–4.5[3]) than the *C. saccharolyticum* and sweet almond β-glucosidases (pH 6.2 and 5.6, resp.[4,5]) **7** and **8** will be extensively protonated at the low pH of the assay. Protonation of **8** should lead to an equilibrating mixture of ammonium and imidazolium salts **8**·H^+; the interaction of both species with the catalytic acid will be impaired.[‡] Since protonation may result in a compensating binding interaction of the catalytic nucleophile with the imidazolium (and imidazole) ring[7,8] we also wished to test the essentially neutral hydroxy-lactam **9** and the corresponding aminomannono-lactam **10**. A $B_{2,5}$ conformation for the (protonated) amine **10** is expected by analogy to the mannono-1,5-lactam **9** where the $B_{2,5}$-conformer is found in the solid state and dominates in solution.[9]

2. Synthesis

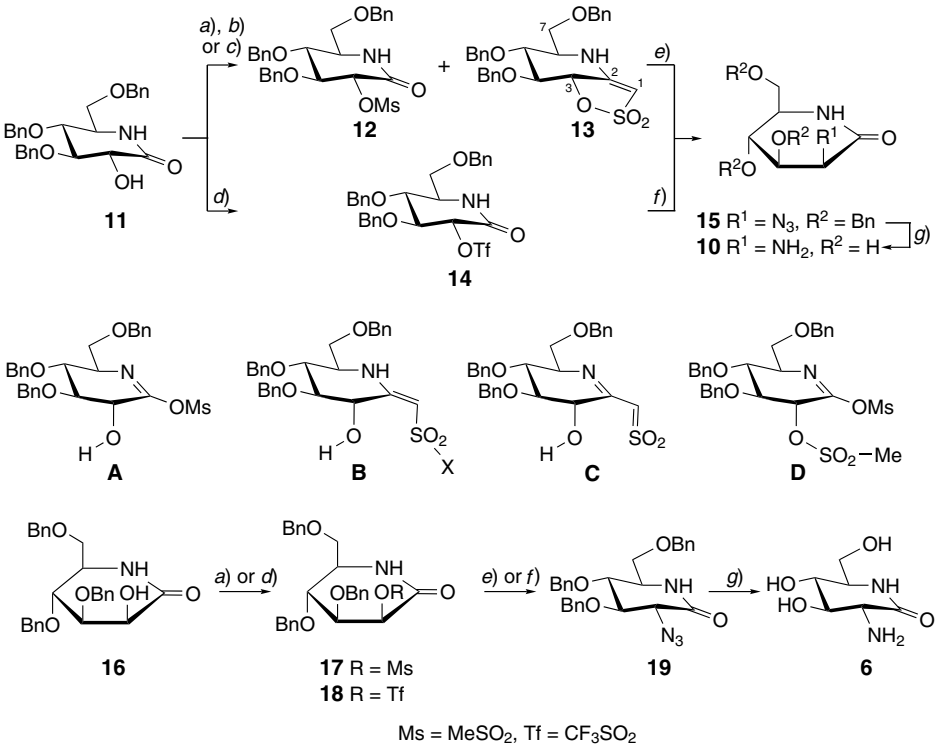
The *manno*-configured C(2)-amino lactam **10** was prepared in three steps from the known *gluco*-hydroxy-lactam **11**[1] (Scheme 1). Treatment of **11** with MsCl and Et_3N in CH_2Cl_2 at 0 °C gave a 18:1 mixture of the mesylate **12** and the sultone **13**.[§] which were isolated by chromatography in 91% and 5% yield, respectively. These results were hardly affected by varying the reaction temperature (−78 to 23 °C) and/or the amount of MsCl (1.2–2.4 equiv) and Et_3N (2–6 equiv). Replacing Et_3N/CH_2Cl_2 by pyridine did not lead to complete conversion, and **11** was invariably recovered (18%) besides a 15:1 mixture of **12** (73%) and **13** (5%). The yield of the sultone **13** increased to 35–50% upon treating **11** with MsCl and *i*-Pr_2NH. The sultone was always obtained together with the mesylate **12** (48–60%). Mesylation in the presence of 2,6-lutidine, NaH or DBU led to poor conversion of the lactam **11** to **12**; TLC indicated that sultone **13** was not formed under these conditions. Treating the mesylate **12** with excess Et_3N, *i*-Pr_2NH or DBU did not lead to **13**.

The formation of **13** may be rationalized by assuming that the iminomesylate **A** is generated first. Condensation of **A** with the carbanion derived from the reaction

[†] The location of the C(2) substituent and the catalytic nucleophile on opposite sites of the mannopyranoside ring was shown by the crystal structure of the complex between 2,4-dinitrophenyl 2-deoxy-2-fluoro-β-mannotrioside and the E212A mutant of the Man2A mannosidase.[2]

[‡] If pseudoequatorially oriented, the ammonium group of **8**·H^+ could also form a hydrogen bond to the imidazole ring, but the geometry of this hydrogen bond does not appear favourable (modelling by Macromodel MM3*[6]).

[§] There are only a few examples of the transformation, under standard mesylation conditions, of an α-hydroxy ketone to a dehydro-γ-sultone[10–13] and/or a δ-hydroxy-γ-sultone.[11–16] One sugar-derived sultone was prepared in this way.[17] For a recent review on carbanion-mediated intermolecular coupling reactions of sulfonates (or sulfonamides), see Ref. 18.



Scheme 1. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C; 91% of **12** and 5% of **13**; 91% of **17**. (b) MsCl, pyridine, 0 → 23 °C; 73% of **12**, 5% of **13**, and 18% of **11**. (c) MsCl, *i*-Pr_2NH, CH_2Cl_2, 0 °C; 48% of **12** and 50% of **13**. (d) Tf_2O, pyridine, CH_2Cl_2, −78 → −10 °C; 73% of **14**; 60% of **18**. (e) NaN_3, DMF, 70 °C; 77% of **15** from **12**; 62% of **19** from **17**. (f) As (e), but 23 °C; 52% of **15** from **14**; 26% of **19** from **18**. (g) H_2, Pd/C, MeOH/AcOH; 92% of **10**; 96% of **6**.

of the sulfene resulting from the elimination of HCl from MsCl[19,20] and the amine may form **B**. Elimination transforms **B** to **C**, and further to **13**. Alternatively, the imino ether **A** may be mesylated to **D**. Deprotonation of **D** followed by cyclization also provides **13**.

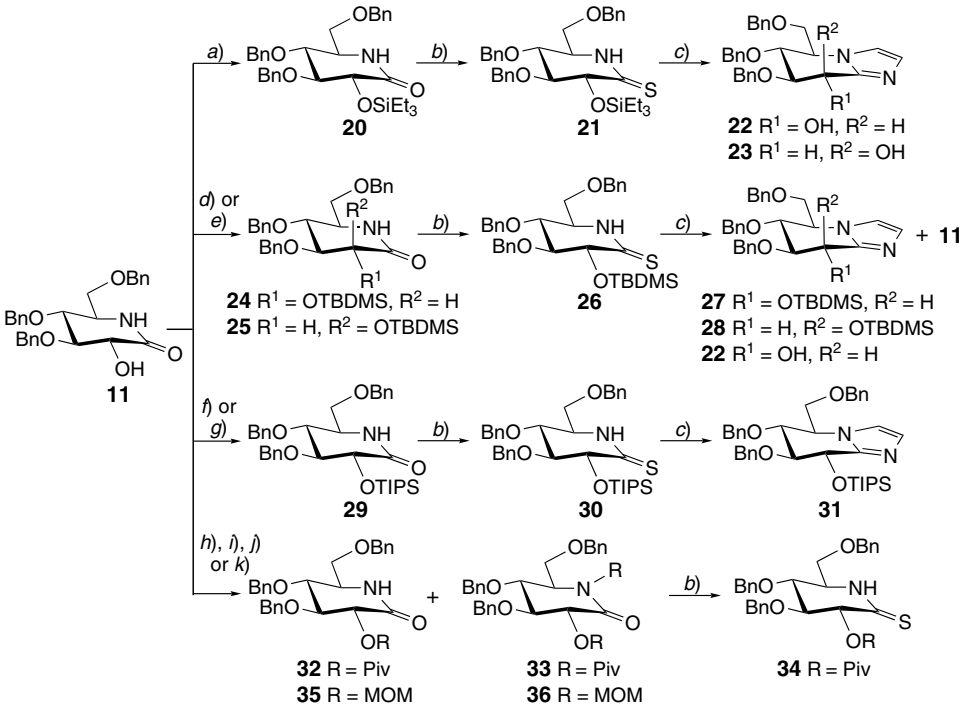
The mesylate **12** reacted with NaN_3 at 70 °C to provide the *manno*-configured azido-lactam **15** in 77% yield. Hydrogenation of **15** in the presence of 10% Pd/C yielded 92% of a nonseparable 90:10 mixture of the *manno*-amino-lactam **10** and its *gluco*-isomer **6** (64% from **11**). The azide **15** was obtained in lower yields (38%) by triflation of **11** to **14** (73%) and its reaction with NaN_3 at 23 °C to afford 52% of **15**.

In parallel to the synthesis of the 2-amino-2-deoxy-mannonolactam **10** from the gluconolactam **11**, we examined the preparation of the known 2-amino-2-deoxy-gluconolactam **6** from the known mannonolactam **16**,[1] hoping to find an advantageous alternative to the known synthesis.[¶] Mesylation of **16** cleanly afforded 91% of **17**. Treatment of **17** with NaN_3 led to the *gluco*-azide **19** (62%), which was hydrogenated to **6** (96%; 54% from **16**). Proceeding via the labile triflate **18** led to lower yields. There is no significant advantage of this new synthesis of **6** over the known synthesis, as judged by yields, number of steps and price of starting materials.

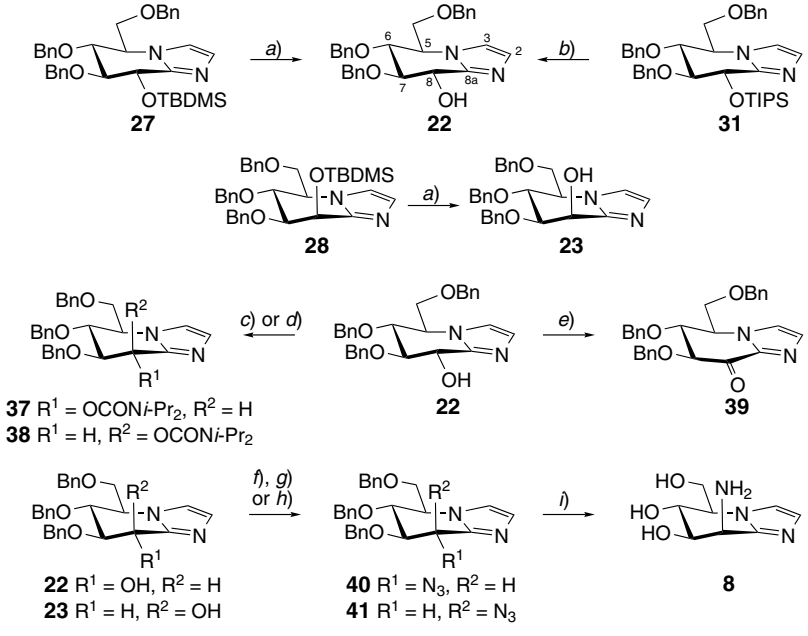
We planned to prepare the *manno*-configured amino-imidazole **8** by a similar strategy as described for the synthesis of the *gluco* analogue **2**.[1] In the course of this synthesis, the lactam **11** was transformed in four steps (O-acetylation, thionation, Hg(OAc)-promoted condensation with aminoacetaldehyde dimethyl acetal and treatment with *p*-TsOH·H_2O) and in an overall yield of 44% to a 1:1 mixture of the known *gluco*- and *manno*-alcohols **22** and **23**[1,24,25] (Scheme 2). Depending on the concentration of HN_3, *Mitsunobu* substitution[26–28] of the hydroxy-imidazoles **22** and **23** led either exclusively to the pure *gluco*-azide **40** or to a ca. 1:1 mixture of **40** and its *manno*-isomer **41** (Scheme 3).[1,29] We examined the influence of the nature of the protecting group at O–C(2) on the yield and ratio of the alcohols **22** and **23** intending to find a more readily reproducible alternative for their transformation into the *manno*-configured azido-imidazole **41** (Schemes 2 and 3).

The silyl ethers **20** (86%), **24** (91%) and **29** (92%) were readily obtained by treating the hydroxy-gluconolactam **11** with the corresponding silyl triflates (pyridine, CH_2Cl_2, 0 °C). Under these conditions, the (*tert*-butyl)dimethylsilyl ether **24** was accompanied by 3% of the *manno*-isomer **25**. The silyl ethers **24** and **29** were obtained in slightly improved yields by silylating **11** with the corresponding chlorosilanes; no C(2)-epimerized by-products were then observed. Thionation of the

[¶] The lactam **6** was obtained in 92% by hydrogenation of tri-*O*-benzyl-glucosamino-1,5-lactam,[1] which was prepared in five steps from tri-*O*-benzyl-*N*-acetyl-glucosamine[21,22] and its *N*-benzyloxycarbonyl analogue[23] in overall yields of 54% and 35%, respectively.



Scheme 2. Reagents and conditions: (a) Et_3SiOTf, pyridine, CH_2Cl_2, 0 °C; 86%. (b) Lawesson's reagent, toluene, 23 °C; 73% of **21**; 91% of **26**; 96% of **30**; 58% of **34**. (c) 1. Aminoacetaldehyde dimethyl acetal, $Hg(OAc)_2$, THF, 0 °C; 2. *p*-TsOH·H_2O, toluene/H_2O, 70 °C; 40% of **22**/**23** 60:40 from **21**; 8% of **27**, 1% of **28**, 7% of **11**, and 83% of **22** from **26**; 88% of **31** from **30**. (d) TBDMSCl, imidazole, DMF, 23 °C; 97% of **24**. (e) TBDMSOTf, pyridine, CH_2Cl_2, 0 °C; 91% of **24** and 3% of **25**. (f) TIPSCl, imidazole, DMF, 23 °C; 97%. (g) TIPSOTf, pyridine, CH_2Cl_2, 0 °C; 92%. (h) Pivaloyl chloride, pyridine, 5 → 50 °C; 68% of **32** and 7% of **33**. (i) As (h), but 50 °C; 17% of **32** and 76% of **33**. (j) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$, 23 °C; 62% of **35** and 9% of **36**. (k) P_2O_5, $CH_2(OMe)_2$, 23 °C; 46% of **35** and 23% of **36**.



Scheme 3. Reagents and conditions: (a) *n*-Bu_4NF, THF, 23 °C; 91% of **22**; 77% of **23**. (b) As (a), but 0 °C; 94%. (c) *i*-Pr_2NCOCl, DMAP, pyridine, 120 °C; 41% of **37** and 36% of **38**. (d) *i*-Pr_2NCOCl, NaH, THF, 0 → 23 °C; 96% of **37**. (e) Dess–Martin periodinane, CH_2Cl_2, 0 °C; 72%. (f) Diphenyl phosphorazidate (DPPA), DBU, toluene, 23 °C; 65% of **40** and 15% of **41** from **22**; 62% of **40** and 11% of **41** from **22**/**23** 55:45; 66% of **40**/**41** 85:15 from **23**. (g) Di-*p*-nitrophenyl phosphorazidate, DBU, toluene, 23 °C; 53% of **40** and 11% of **41** from **22**. (h) DPPA, NaH, THF, 0 → 23 °C; 38% of **40**/**41** 85:15 from **22**. (i) H_2, Pd/C, AcOH; 65% from **41**.

gluconolactams **20**, **24** and **29** with Lawesson's reagent[30] at 23 °C provided the thionolactams **21** (73%), **26** (91%) and **30** (96%). According to TLC analysis, thionation at 70–90 °C led to epimerization at C(2), in contrast to what was observed by Panday et al.[1] Condensation of the triethylsilylated thionolactam **21** with aminoacetaldehyde dimethyl acetal followed by acid-promoted cyclization in the presence of small amounts of H_2O[1,31] was accompanied by desilylation and yielded 40% of a 60:40 mixture of the *gluco*- and *manno*-hydroxy-imidazoles **22** and **23**.[‖] Under the same conditions, the (*tert*-butyl)dimethylsilyloxy-thionolactam **26** provided 83% of the desilylated *gluco*-imidazole **22** besides a mixture of the silylated *gluco*- and *manno*-imidazoles **27** and **28** (8% and 1%, respectively) and the hydroxy-lactam **11** (7%). Lowering the temperature of the cyclization to 55 °C increased the yield of the protected imidazole **27** to 45% and that of **28** to 2%. However, the cyclization did not go to completion, and an intricate mixture of the hydroxy-imidazole **22** and the intermediary amidine was also isolated (ca. 37%; 9:1). No epimerization or deprotection was observed during the condensation of the triisopropylsilylated thionolactam **30**. The same conditions as those used for the condensation of **21** transformed **30** cleanly into the *gluco*-imidazole **31** (88%).

Protection of **11** by a pivaloyl or (methoxy)methyl group proved less attractive. Treatment of **11** with pivaloyl chloride in pyridine led consistently to a mixture of the pivaloate **32** and the imide **33**. Yields depended on the reaction temperature; higher temperatures favouring **33** (**32**: 17–68% and **33**: 7–76%). The pivaloate **32** reacted slowly with Lawesson's reagent to provide, after 168 h, the thionolactam **34** (58%); 37% of **32** were recovered. Methoxymethylation of **11** (dimethoxymethane/P_2O_5) provided a mixture of the *O*- and *N*,*O*-protected lactams **35** (46–62%) and **36** (9–23%), respectively. Thionation of **35** gave only traces of the corresponding thionolactam and was accompanied by extensive epimerization at C(2) as indicated by TLC analysis. We did not pursue these routes to **22** and **23**.

The synthesis of **8** was continued (Scheme 3) by standard desilylation[32,33] of the *gluco*-imidazopyridines **27** and **31**, to provide **22** in 91% and 94%, respectively. Similarly, desilylation of the analogue **28** gave the *manno*-configured hydroxy-imidazole **23** (77%). The triisopropylsilyl group proved most advantageous for the synthesis of the *gluco*-alcohol **22** or its *manno*-isomer **23**. It allowed a clean transformation of the gluconolactam **11** into **22** in five steps and 77% overall yield.

We originally intended to prepare the *gluco*- and *manno*-azido-imidazoles **40** and **41** via the carbamates **37** and **38**. The formation of azides by heating similar α-imidazolyl-*N*,*N*-diisopropylcarbamates with NaN_3 in the presence of $BF_3{\cdot}OEt_2$ and trifluoroacetic acid has recently been reported.[34] Carbamoylation of the *gluco*-imidazole **22** with *N*,*N*-diisopropylcarbamoyl chloride (DMAP, pyridine, 120 °C[35]) provided a 55:45 mixture of carbamates, which were separated by chromatography to yield 41% of **37** and 36% of the *manno*-isomer **38**. Replacing DMAP/pyridine by NaH/THF[36] and lowering the temperature from 120 to 0–23 °C led exclusively to the *gluco*-isomer **37** (96%). Unfortunately, neither of the carbamates **37** and **38** reacted with NaN_3 under the reported (or under slightly harsher) conditions, and starting material was recovered.

Attempts to introduce the C(8) amino group by reductive amination of the ketone **39** failed. The ketone was obtained in 72% yield by oxidation of **22** with Dess–Martin's periodinane,[37–40] but did not react with $BnNH_2$ in the presence of $MgSO_4$ at 23 °C and decomposed at 70 °C. Decomposition was also observed upon attempted oximation of **39** ($NH_2OH{\cdot}HCl$, pyridine, MeOH). Reduction of **39** with $NaBH_4$ or L-Selectride[41,42] led to the *gluco*- and *manno*-configured hydroxy-imidazoles **22** and **23** in ratios between 3:1 and 5:1 (according to ^1H NMR spectra of the crude) as the result of a preferred pseudoaxial hydride addition. Finally, a 80:20 mixture of the *gluco*- and *manno*-azido-imidazoles **40** and **41** was obtained by treating the *gluco*-alcohol **22** with diphenyl phosphorazidate (DPPA) and DBU in toluene.[43] Chromatographic separation afforded 65% of **40** and 15% of **41**. Similar yields and ratios of **40/41** resulted from the DPPA azidation of the *manno*-alcohol **23** and of a mixture **22/23** (55:45).[**] The azides **40** (53%) and **41** (11%) were also obtained by replacing DPPA with di-*p*-nitrophenyl phosphorazidate,[45] which was prepared in 62% yield[46] (see Experimental). A considerably lower yield of **40/41** (38%; 85:15) resulted from treating **22** with DPPA and NaH. Hydrogenation of the *manno*-azido-imidazole **41** resulted in 65% of the desired amine **8**.

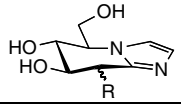
The amino-mannonolactam **10** in D_2O adopts the $^3H_4$-conformation, as evidenced by *J*(2,3), *J*(3,4) and *J*(4,5) of 3.7, 3.7 and 4.0 Hz, respectively (Table 9). A downfield shift of ca. 0.7 ppm for H–C(2) of **10** was observed upon protonation by CF_3CO_2H. Unfortunately, signal overlap prevented an unambiguous assignment of the conformation of $\mathbf{10}{\cdot}H^+$. The coupling constants of the amino-imidazole **8** agree best with a ca. 1:1 mixture of the $^7H_6$- and E_7-conformers[††] (modelling with MM3*[6]). Protonation of **8** led to a downfield shift for H–C(8) ($\Delta\delta$ = 0.96 ppm) and to slightly increased vicinal constants, indicating a slightly larger contribution of the $^7H_6$ conformer, excluding a H-bond between the ammonium group and the imidazole ring. Lowering the pH value further did not significantly affect the chemical shift and *J*(H,H) values.

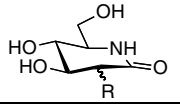
[‖] Under otherwise identical conditions, the tetrabenzylated analogue of **21** led exclusively to the corresponding analogue of the *gluco*-imidazopyridine **22**.[31]

[**] In agreement with earlier reports[5,29,44] these results suggest that the formal substitution of C(8)–OH proceeds via an azafulvenium intermediate.

[††] The direction of numbering of imidazopyridines (cf. **22** in Scheme 3) is opposite to that of pyranosides. Thus, the sides above and below the plane of the imidazoles, as defined by the clockwise and counterclockwise numbering, are interchanged relative to those defined by carbohydrate nomenclature.

Table 1. Mannose- and mannosamine-derived lactams and imidazoles **7**–**10**: pK_{HA} values and comparison of their inhibition of snail β-mannosidase and of the α-mannosidase from *Jack* beans to the inhibition of the β-glucosidases from *Caldocellum saccharolyticum* and from sweet almonds by the glucose- and glucosamine-derived analogues **1**, **2**, **5** and **6** (K_i values in [μM])





manno (R)	pH	**7** (OH)	**8** (NH_2)	$\Delta\Delta G_{diss.}$ [kcal/mol]	**9** (OH)	**10** (NH_2)	$\Delta\Delta G_{diss.}$ [kcal/mol]
pK_{HA}		5.7[a]	7.02[b]		—	7.46	
β-Mannosidase (snail)	4.5	0.115[c]	138	+4.2	3.01[d,e]	2000[f]	+3.8
	5.5	0.045	28	+3.8	5.12	350[f]	+2.6
α-Mannosidase (*Jack* beans)	4.5	0.75[c]	1.22[g]	+0.3	43[h]	4850[f]	+2.9
gluco (R)	pH	**1**[i] (OH)	**2**[i] (NH_2)	$\Delta\Delta G_{diss.}$ [kcal/mol]	**5**[i] (OH)	**6**[i] (NH_2)	$\Delta\Delta G_{diss.}$ [kcal/mol]
pK_{HA}		6.12[a]	6.33		—	7.04	
β-Glucosidase (*C. saccharolyticum*)	4.6	0.41	241	+4.1	7	21	+0.7
	5.4	[j]	77	—	7.5	8	+0.04
	6.8	0.05	85	+4.8	10	1.4	−1.3
β-Glucosidase (sweet almonds)	4.6	0.71	593	+4.1	79	129	+0.3
	5.4	0.31	200	+4.0	80	[j]	—
	6.8	0.15	213	+4.5	138	8	−1.8

[a] Data taken from Ref. 47.
[b] No additional pK_{HA} value was observed in the pH range 2.9–10.3.
[c] Data taken from Ref. 48.
[d] Mixed-type inhibition (α = 8.4).
[e] K_i = 9.0 μM (at 37 °C and pH 4.0).[9]
[f] IC_{50}/2.
[g] Mixed-type inhibition (α = 2.3).
[h] K_i = 68 μM (at 37 °C and pH 4.5).[9]
[i] Data taken from Ref. 1 (IC_{50} values in [μM]).
[j] Not determined.

Similarly to the *gluco*- and *manno*-configured lactams **11** and **16**,[1] the protected *gluco*-lactams **12**, **14**, **19**, **32** and **35** and *gluco*-thiolactam **34** (in solution) adopt the $^4C_1$-conformation, while the protected *manno*-lactams **15**, **17**, **18** and **25** form 2:1 mixtures of the $^1C_4$- and $^4C_1$-conformers (see Experimental, Tables 2, 3 and 5). A sterically demanding C(2) substituent leads to an increased population of the $B_{2,5}$-conformation of the *gluco*-lactams **20**, **24** and **29**. This conformation is dominating in the *gluco*-thiolactams **21**, **26** and **30**, as evidenced by their *J*(H,H) values. The large *J*(2,3) (7.2–9.0 Hz) and rather small *J*(3,4) and *J*(4,5) (3.1–5.0 Hz) evidence the $^{2,5}B$-conformation of the *N*-substituted *gluco*-lactams **33** and **36**. The ^{13}C(2)–C(6) signals of the protected *gluco*-lactams **19** and **24** and of their *manno*-isomers **15** and **25** were assigned on the basis of HSQC-GRASP spectra; those of the other lactams were assigned by analogy (see Table 4 in Experimental). Similarly to their tetra-*O*-benzylated analogues,[31,47] the *gluco*- and *manno*-configured imidazopyridines **22**, **23**, **27**, **28**, **38**, **40** and **41** exist in $CDCl_3$ as 2:1 mixtures of $^7H_6$- and $^6H_7$-conformers, while the *gluco*-imidazoles **31** and **37** adopt a conformation close to $^{5,8}B$ and $^6H_7$, respectively (see Tables 6 and 8 in Experimental). The ^{13}C signals of C(5)–C(8) of all imidazoles were assigned in analogy to Refs. 48–50 (see Table 7 in Experimental).

The structure of the sultone **13** was deduced on the basis of a ^{13}C(1) d at 92.35 ppm, a ^{13}C(2) s at 151.94 ppm, a ^{1}H–C(1) d at 5.60 ppm with *J*(1,3) = 1.9 Hz (see numbering of **13** in Scheme 1), a strong IR OSO_2 band at 1335 cm^{-1} and the $[M+Na]^+$ peak at *m*/*z* 530.1631. Formation of the ketone **39** is confirmed by the disappearance of the ^{1}H–C(8) signal for **39**, the replacement of the ^{13}C(8) d at 67.87 ppm for **22** by a ^{13}C s at 181.93 ppm, and by a strong IR C=O band at 1696 cm^{-1}.

3. Enzymatic tests and discussion

The *manno*-configured hydroxy- and amino-imidazoles **7** and **8** and the corresponding lactams **9** and **10** were tested as inhibitors of snail β-mannosidase (pH optimum 4.0–4.5[3]) at 25 °C and pH 4.5 and 5.5 and of the α-mannosidase from *Jack* beans (pH optimum 4.0–5.0[51,52]) at 37 °C and pH 4.5, using the corresponding 4-nitrophenyl mannopyranosides as substrates. The inhibition data are summarized in Table 1 and compared to the inhibition of the β-glucosidases from *C. saccharolyticum* and from almonds by the *gluco*-configured hydroxy- and amino-imidazoles **1** and **2** and the corresponding lactams **5** and **6**.[1]

Inspection of Table 1 shows a clear difference between the effect of substitution of the hydroxy by the amino group for the *manno*-imidazoles **7** and **8** as compared to the effect on the *gluco*-imidazoles **1** and **2** versus the

effect of the analogous substitution of the *manno*-lactams **9** and **10** as compared to the *gluco*-lactams **5** and **6**.[‡‡] The amino-imidazole **8** (K_i = 138 μM at pH 4.5; competitive) is a 1200 times weaker inhibitor of snail β-mannosidase than the hydroxy-imidazole **7**. A similar, slightly stronger influence of the C(8) substituent is observed for the inhibition of the two β-glucosidases by the *gluco*-configured imidazoles **1** and **2**. The difference for **7** and **8** is slightly smaller at higher pH. The pK_{HA} values of **8** and the pH of the enzymatic assay mean that the inhibitor is bound to the enzyme as imidazolium/ammonium salt **8**·H^+. The effect of the amino group on the inhibition appears to be dominated, for both *gluco* and *manno* compounds, by the (partial or complete) disruption of the interaction with the catalytic acid. However, one expects this effect to manifest itself significantly more strongly in the *manno* series, as there should be no compensating effect from an improved interaction of the ammonium group with the catalytic nucleophile. That this is not observed points to a stronger compensation, in the *manno* than in the *gluco* series, from the interaction of the cat. nucleophile with the imidazolium (and/or the imidazole) ring. This implies a different positioning of the catalytic nucleophile, depending on whether the C(8) ammonium group is on the opposite or same face of the tetrahydropyridine ring. One has to assume that the interaction of the catalytic nucleophile of the β-glucosidases with the C(8) ammonium group of the inhibitor entails a position of the catalytic nucleophile that is not favourable to a simultaneous interaction with the imidazolium ring; no such detraction of the cat. nucleophile form its optimal position for such an interaction is expected for the β-mannosidase.[§§]

The situation for the lactams is quite different. A comparison of the β-mannosidase inhibition by the hydroxy- and amino-mannonolactams **9** and **10** to the inhibition of the β-glucosidases by the hydroxy- and amino-gluconolactams **5** and **6**, respectively, shows that the introduction of the C(2) amino group weakens the inhibition of the β-mannosidase (at pH 4.5 and 5.5) 68–664 times, while the inhibition of the β-glucosidases (at similar pH values) is only weakened 1.1–3.0 times (it is increased at pH 6.8). The hydroxy-imidazole **7** is a much stronger inhibitor than the hydroxy-lactam **9**. Similarly as observed for the amino-imidazole **8**, the amino-lactam **10** is a six times better inhibitor of the β-mannosidase at pH 5.5 (IC_{50} = 700 μM) than at pH 4.5 (IC_{50} = 4000 μM). The hydroxy-lactam **9** is a slightly weaker inhibitor at pH 5.5 (K_i = 5.12 μM) than at pH 4.5 (K_i = 3.01 μM; compare Ref. 9) while the hydroxy-imidazole **7** is a slightly better inhibitor at pH 5.5. That a more extensive protonation of **10** reduces its inhibitory activity is in keeping with the weakening effect of the ammonium group (a strong σ-acceptor) on the interaction of the lactam moiety with the catalytic acid; this effect is not (partially) compensated by a stronger interaction with the catalytic nucleophile, requiring a significant proton transfer to the lactam moiety of **10**, a much weaker proton acceptor than the imidazole ring of **8**. While the catalytic nucleophile can strongly interact with the imidazolium ring of **8**,[7,8] partially compensating for the impaired interaction with the catalytic acid, it cannot likewise interact significantly more strongly with the essentially neutral lactam moiety of **10** than of **9**. These results are thus in keeping with the assumption that the catalytic nucleophile of the retaining snail β-mannosidase does not interact with the C(2) hydroxy group.

The lactams **9** and **10** and the amino-imidazopyridine **8** were also tested as inhibitors of the retaining α-mannosidase from *Jack* beans (family 38;[53,54] Table 1). Substitution of the C(2)–OH group of **9** (K_i = 43 μM; compare Ref. 9) by the amino group, as in **10**, led to a 110 times weaker inhibition of the α-mannosidase. The imidazole **8** is, however, only a 1.6 times weaker (mixed-type) inhibitor (K_i = 1.22 μM; α = 2.3) of this enzyme than the hydroxy analogue **7** (K_i = 0.75 μM; competitive). That **8** is a better inhibitor of the α- than of the β-mannosidase may be due to the conformational change of the inhibitor at the pH of the assay and/or to a particularly favourable interaction of the cat. nucleophile with the imidazolium ring, or with the ammonium group. A stronger interaction with the catalytic nucleophile is, however, not in agreement with the observation that **10** is a weaker inhibitor of the α-mannosidase than **9**.

4. Experimental

4.1. General

Solvents were distilled: THF and toluene from Na and benzophenone, CH_2Cl_2 from P_2O_5, DMF from CaH_2. Reactions were carried out under Ar, unless stated otherwise. Qual. TLC: precoated silica-gel plates (Merck silica-gel 60 F_{254}); detection by heating with 'mostain' (400 mL of 10% H_2SO_4 soln, 20 g of $(NH_4)_6Mo_7O_{24}\cdot 6H_2O$, 0.4 g of $Ce(SO_4)_2$. Flash chromatography (FC): silica-gel Fluka 60 (0.04–0.063 mm). Mp's uncorrected. Optical rotations: 1-dm cell at 25 °C, 589 nm. UV spectra (ca. 0.2 mM solutions) were taken in 1-cm cell at 25 °C in the range of 190–500 nm (log ε values in parenthesis). FT-IR spectra: KBr or ca. 2% solution in $CHCl_3$, absorption in cm^{-1}. ^1H and ^{13}C NMR spectra: chemical shifts δ in ppm rel. to TMS as external standard, and coupling constants *J* in hertz. FAB-MS: in 3-nitrobenzyl alcohol (NOBA) matrix. MALDI-MS and HR-MALDI-MS: in gentisic acid (= 2,5-dihydroxybenzoic acid, DHB) matrix. The pK_{HA} values were determined in H_2O by potentiometric titration with HCl at 25 °C. The β-mannosidase from snail acetone powder (EC 3.2.1.25, as a suspension in 3.0 M $(NH_4)_2SO_4$ containing 10 mM AcONa, pH ≈ 4.0, Sigma M-9400), α-mannosidase from *Jack* beans (EC 3.2.1.24,

[‡‡] The different pH optima of the enzymes and the different pH of the assay mean that only differences of differences can be interpreted, that is, the relative inhibition by **7** and **8**, as compared to the one by **1** and **2** can be compared to the relative inhibition by **9** and **10**, as compared to the one by **5** and **6**.

[§§] An alternative rationalization postulates that the interaction with the catalytic acid of a β-mannosidase at a late stage of the reaction is less important for a *manno*-configured inhibitor mimicking the putative reactive intermediate than it is for the analogous interaction of the two β-glucosidases with an analogous *gluco*-configured inhibitor.

as a suspension in 3.0 M $(NH_4)_2SO_4$ and 0.1 mM zinc acetate, pH 7.5, Sigma M-7257), *p*-nitrophenyl β-D-mannopyranoside (Sigma N-1268) and *p*-nitrophenyl α-D-mannopyranoside (Sigma N-2127) were used without further purification.

4.2. Di-(*p*-nitrophenyl) phosphorazidate[46]

R_f (AcOEt) 0.62. Mp 108–110 °C (lit.:[46] 108–110 °C). IR ($CHCl_3$): 3437w, 3117w, 3087w, 3027w, 2867w, 2458w, 2179s, 1915w, 1775w, 1671w, 1617m, 1591s, 1530s, 1490s, 1349s, 1305s, 1271m, 1189m, 1160s, 1111w, 1014w, 965s, 859s, 829w. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.43–7.48 (m, H–C(2), H–C(6)); 8.28–8.34 (m, H–C(3), H–C(5)). ^{13}C NMR ($CDCl_3$, 75 MHz): 120.87 (dd, ^3J(C,P) = 5.5, C(2), C(6)); 125.93 (d, C(3), C(5)); 145.56 (s, C(4)); 153.62 (d, ^2J(C,P) = 7.3, C(1)). ^{31}P NMR ($CDCl_3$, 121 MHz): −10.39. HR-ESI-MS: 388.0055 (100, $[M+Na]^+$, $C_{12}H_8N_5NaO_7P^+$; calcd 388.0059), 377.0148 (56), 369.2002 (28), 281.0055 (51). Anal. Calcd for $C_{12}H_8N_5O_7P$ (365.20): C, 39.47; H, 2.21; N, 19.18. Found: C, 39.51; H, 2.33; N, 19.07.

4.3. 5-Amino-5-deoxy-D-mannono-1,5-lactam 9[55]

FC (AcOEt/MeOH/H_2O 5:2:1) gave **9** (171 mg, 86%) as an amorphous solid, which was recrystallized from a mixture of EtOH and H_2O. Colourless crystals. R_f (AcOEt/MeOH/H_2O 5:2:1) 0.29. Mp 174–175 °C (lit.:[56] 164–167 °C, lit.:[9] 169–171 °C, lit.:[57] 169–170 °C, lit.:[58] 165–169 °C, lit.:[59] 170–172 °C). $[\alpha]_D^{25} = +0.2$ (*c* 1.07, H_2O) [lit.:[56] +1.2 (H_2O), lit.:[9] +1.0 (H_2O), lit.:[59] +2.0 (H_2O), lit.:[55] +1.6 (H_2O), lit.:[58] +0.9 (H_2O), lit.:[57] +1.6 (H_2O)]. IR (0.5% in KBr): 3600–3000s (br), 3324s, 3201s, 2949m, 2938m, 2888m, 2830m, 2747w, 2663w, 1655s, 1461w, 1418m, 1385m, 1357m, 1335s, 1306w, 1267m, 1240m, 1215w, 1159w, 1131s, 1111m, 1089m, 1056s, 1030s, 1004m, 962w, 928w, 847m, 746m. ^{1}H NMR (D_2O, 300 MHz): 3.22 (dt, *J* = 3.6, 6.0, H–C(5)); 3.55 (dd, *J* = 6.0, 11.8, irrad. at 3.22 → d, *J* = 12.4, H–C(6)); 3.67 (dd, *J* = 3.6, 11.8, irrad. at 3.22 → d, *J* = 12.4, H′–C(6)); 3.72 (t, *J* = 6.0, irrad. at 3.22 → d, *J* = 6.0, irrad. at 3.89 → d, *J* = 6.0, H–C(4)); 3.89 (dd, *J* = 3.8, 6.0, irrad. at 4.19 → d, *J* = 6.0, H–C(3)); 4.19 (d, *J* = 3.8, irrad. at 3.89 → s, H–C(2)). ^{1}H NMR (DMSO-d_6, 300 MHz): 3.11 (q, *J* = 5.0, H–C(5)); 3.40 (td, *J* = 5.6, 10.6, H–C(6)); 3.57 (td, *J* = 5.3, 10.9, H′–C(6)); 3.61 (br q, *J* ≈ 5.3, H–C(4)); 3.79 (dt, *J* = 3.7, 5.0, H–C(3)); 4.03 (br t, *J* ≈ 3.7, H–C(2)); 4.67 (d, *J* = 4.7, irrad. at 4.03 → s, HO–C(2)); 4.78 (t, *J* = 5.6, irrad. at 3.40 → change, HO–C(6)); 4.98 (d, *J* = 3.7, irrad. at 3.79 → s, HO–C(3)); 5.24 (d, *J* = 4.7, irrad. at 3.61 → s, HO–C(4)); 7.18 (br s, NH). ^{13}C NMR (D_2O, 75 MHz, assignment based on HSQC-GRASP spectrum): 57.63 (d, C(5)); 61.37 (t, C(6)); 67.40 (d, C(4)); 68.48 (d, C(2)); 72.22 (d, C(3)); 173.53 (s, C(1)). ^{13}C NMR (DMSO-d_6, 75 MHz): 59.07 (d, C(5)); 62.24 (t, C(6)); 67.98 (d, C(4)); 68.47 (d, C(2)); 73.16 (d, C(3)); 171.37 (s, C(1)). HR-ESI-MS: 554.1720 (15, $[3M+Na]^+$, $C_{18}H_{33}N_3NaO_{15}^+$; calcd 554.1809), 377.1134 (100, $[2M+Na]^+$, $C_{12}H_{22}N_2NaO_{10}^+$; calcd 377.1172), 200.0533 (8, $[M+Na]^+$, $C_6H_{11}NNaO_5^+$; calcd 200.0535). Anal. Calcd for $C_6H_{11}NO_5$ (177.16): C, 40.68; H, 6.26; N, 7.91. Found: C, 40.42; H, 6.08; N, 7.81.

4.4. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-glucono-1,5-lactam 12 and 1[1],3-anhydro-4,5,7-tri-*O*-benzyl-1,2,6-trideoxy-2,6-imino-D-*gluco*-hept-1-enitol-1-sulfonic acid 13

(a) At 0 °C, a soln of **11** (250 mg, 0.559 mmol) in CH_2Cl_2 (5 mL) was successively treated with Et_3N (0.15 mL, 1.08 mmol) and MsCl (55 μL, 0.708 mmol), stirred at 0 °C for 30 min and treated with satd NH_4Cl soln (1 mL). The mixture was diluted with Et_2O (15 mL) and washed with satd NH_4Cl soln (3 × 15 mL). The combined aq layers were extracted with Et_2O (2 × 15 mL). The combined org. layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 2:1 → 1:1) gave **13** (15 mg, 5%) and **12** (266 mg, 91%).

(b) At 0 °C, a soln of **11** (50 mg, 0.112 mmol) in pyridine (5 mL) was treated with MsCl (17 μL, 0.219 mmol), stirred at 0 °C for 1 h and at 23 °C for 19 h and treated with satd NH_4Cl soln (1 mL). Workup and FC as described in (a) gave **13** (3 mg, 5%), **12** (43 mg, 73%) and **11** (9 mg, 18%).

(c) At 0 °C, a soln of **11** (25 mg, 55.9 μmol) in CH_2Cl_2 (1 mL) was successively treated with (*i*-Pr)$_2$NH (32 μL, 0.226 mmol) and MsCl (10 μL, 0.129 mmol), stirred at 0 °C for 30 min and treated with satd NH_4Cl soln (1 mL). Workup and FC as described in (a) gave **13** (14 mg, 50%) and **12** (14 mg, 48%).

4.4.1. Data of 12. Colourless oil. R_f (hexane/AcOEt 1:1) 0.32. $[\alpha]_D^{25} = +73.3$ (*c* 1.12, $CHCl_3$). IR ($CHCl_3$): 3387w, 3089w, 3067w, 3032w, 3013w, 2914w, 2869w, 1953w, 1877w, 1810w, 1695s, 1603w, 1497w, 1454m, 1366s, 1331m, 1174m, 1109s, 1052m, 1026m, 971m, 910w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 2; additionally, 3.31 (s, MsO); 3.48–3.58 (irrad. at 3.24 → change); 3.64 (irrad. at 4.00 → d, *J* ≈ 9.0); 4.00 (irrad. at 3.64 → d, *J* = 9.3, irrad. at 5.10 → d, *J* = 9.3); 4.42 (d, *J* = 12.5, PhC*H*); 4.46 (d, *J* = 12.5, PhC*H*); 4.52 (d, *J* = 11.2, PhC*H*); 4.79 (d, *J* = 10.3, PhC*H*); 4.90 (d, *J* = 11.2, PhC*H*); 5.00 (d, *J* = 10.6, PhC*H*); 5.10 (irrad. at 4.00 → s); 6.38 (exchange with CD_3OD); 7.19–7.23 (m, 2 arom. H); 7.26–7.45 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 39.79 (q, MsO); 73.24, 75.01, 75.38 (3t, 3Ph*C*H$_2$); 127.80–128.61 (several d); 136.99 (s); 137.13 (2s). HR-MALDI-MS: 564.1447 (18, $[M+K]^+$, $C_{28}H_{31}KNO_7S^+$; calcd 564.1458), 548.1706 (100, $[M+Na]^+$, $C_{28}H_{31}NNaO_7S^+$; calcd 548.1719), 526.1882 (11, $[M+H]^+$, $C_{28}H_{32}NO_7S^+$; calcd 526.1899), 452.1828 (8, $[M+Na-MsOH]^+$, $C_{27}H_{27}NNaO_4^+$; calcd 452.1838), 362.1363 (82, $[M+Na-MsO-Bn]^+$, $C_{20}H_{21}NNaO_4^+$; calcd 362.1368), 346.0953 (11). Anal. Calcd for $C_{28}H_{31}NO_7S$ (525.62): C, 63.98; H, 5.94; N, 2.66; S, 6.10. Found: C, 63.83; H, 6.11; N, 2.48; S, 5.92.

4.4.2. Data of 13. Colourless oil. R_f (hexane/AcOEt 1:1) 0.56. IR ($CHCl_3$): 3391w, 3034w, 2927m, 2866m,

Table 2. Selected ^{1}H NMR chemical shifts [ppm] and coupling constants [Hz] of the protected *gluco*-lactams **12**, **14**, **19**, **20** and **24** and the *gluco*-thiolactams **21** and **26** in $CDCl_3$

	12	14	19	20	21	24	26
NH	6.38	7.03	6.11	6.04	8.01[a]	6.02	7.99[b]
H–C(2)	5.10	5.15	4.06	4.18	4.70[c]	4.15	4.719[d]
H–C(3)	4.00	4.03	3.70	3.82	3.80	3.81	3.78
H–C(4)	3.64	3.80	3.55	3.54	3.54[c]	3.58	3.53[d]
H–C(5)	3.48–3.58	3.50–3.58	3.45–3.53	3.57–3.65	4.02[a]	3.52–3.64	3.99[b]
H–C(6)	3.24	3.35	3.22	3.29	3.41	3.28	3.41
H′–C(6)	3.48–3.58	3.53	3.57	3.61	3.66	3.52–3.64	3.67
J(2,3)	9.3	10.0	9.3	7.8	2.5	8.1	2.5
J(3,4)	9.3	9.3	9.0	7.8	2.8	7.8	2.8
J(4,5)	9.3	8.1	9.0	8.1	9.3	7.8	9.3
J(5,6)	7.5	6.5	7.5	8.1	7.5	7.8	7.5
J(5,6′)	[e]	2.8	2.8	2.8	3.4	[e]	3.4
J(6,6′)	9.3	10.3	9.0	10.0	10.0	10.0	10.0

[a] *J*(5,NH) = 2.2 Hz.
[b] *J*(5,NH) = 1.9 Hz.
[c] *J*(2,4) = 1.2 Hz.
[d] *J*(2,4) = 0.9 Hz.
[e] Not determined.

Table 3. Selected ^{1}H NMR chemical shifts [ppm] and coupling constants [Hz] of the protected *gluco*-lactams **29**, **32**, **33**, **35** and **36** and the *gluco*-thiolactams **30** and **34** in $CDCl_3$

	29	30	32	33	34	35	36
NH	5.87	8.06[a]	6.05	—	8.11	6.01	—
H–C(2)	4.34	4.91[b]	5.28	5.56	5.60	4.19	4.35
H–C(3)	3.85	3.91	4.07	3.95[c]	3.96	3.90	3.86
H–C(4)	3.53	3.55[b]	3.56–3.68	3.98	3.56–3.70	3.50–3.62	3.96
H–C(5)	3.80–3.92	4.14[a]	3.56–3.68	4.69[c]	3.56–3.70	3.50–3.62	3.79–3.83
H–C(6)	3.34	3.45	3.22–3.33	3.57	3.29	3.20–3.30	3.52
H′–C(6)	3.63	3.69	3.56–3.68	3.63	3.56–3.70	3.50–3.62	3.63
J(2,3)	5.3	2.8	9.3	7.2	8.1	8.7	9.0
J(3,4)	5.0	1.6	9.0	4.1	8.1	8.7	5.0
J(4,5)	9.0	9.3	[d]	4.1	[d]	[d]	3.1
J(5,6)	8.1	7.5	[d]	5.3	7.5	[d]	4.7
J(5,6′)	3.1	3.1	[d]	5.9	[d]	[d]	5.9
J(6,6′)	9.7	10.0	[d]	10.0	9.3	[d]	9.7

[a] *J*(5,NH) = 2.2 Hz.
[b] *J*(2,4) = 1.3 Hz.
[c] *J*(3,5) = 1.3 Hz.
[d] Not determined.

1951w, 1886w, 1806w, 1733w, 1648s, 1497w, 1455m, 1367m, 1335s, 1262m, 1159m, 1133s, 1098s, 1054m, 1015m, 911w. ^{1}H NMR ($CDCl_3$, 300 MHz): 3.24 (t, *J* = 9.0, irrad. at 3.63 → d, *J* ≈ 7.8, H–C(7)); 3.38–3.46 (m, irrad. at 3.63 → br t, *J* ≈ 9.0, H–C(6)); 3.50 (t, *J* = 8.4, irrad. at 3.89 → d, *J* = 8.7, H–C(5)); 3.63 (dd, *J* = 2.8, 9.0, irrad. at 3.24 → d, *J* ≈ 2.5, H′–C(7)); 3.89 (dd, *J* = 8.4, 9.3, irrad. at 3.50 → d, *J* = 9.3, irrad. at 4.98 → d, *J* = 8.1, H–C(4)); 4.46 (br s, PhCH_2); 4.51 (d, *J* = 11.2, PhC*H*); 4.74 (d, *J* = 10.9, PhC*H*); 4.85 (br s, exchange with CD_3OD, NH); 4.89 (d, *J* = 11.2, PhC*H*); 4.97 (d, *J* = 11.2, PhC*H*); 4.98 (dd, *J* = 1.9, 9.3, irrad. at 3.89 → d, *J* ≈ 1.3, irrad. at 5.60 → d, *J* = 9.7, addition of CD_3OD → d, *J* = 9.7, H–C(3)); 5.60 (d, *J* = 1.9, irrad. at 4.98 → s, exchange with CD_3OD, H–C(1)); 7.17–7.20 (m, 2 arom. H); 7.28–7.41 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): 57.78 (d, C(6)); 70.46 (t, C(7)); 73.57, 74.51, 75.22 (3t, 3Ph*C*H_2); 76.35 (d, C(5)); 80.64, 81.35 (2d, C(3), C(4)); 92.35 (d, C(1)); 128.09–128.72 (several d); 137.21 (2s); 137.31 (s); 151.94 (s, C(2)). HR-MALDI-MS: 530.1631 (49, $[M+Na]^+$, $C_{28}H_{29}NNaO_6S^+$; calcd 530.1613), 450.2055 (100, $[M+Na-SO_3]^+$, $C_{28}H_{29}NNaO_3^+$; calcd 450.2045).

4.5. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(trifluoromethanesulfonyl)-D-glucono-1,5-lactam 14

At −78 °C, a soln of **11** (96 mg, 0.215 mmol) in CH_2Cl_2 (2 mL) was treated successively with pyridine (36 μL, 0.446 mmol) and Tf_2O (48 μL, 0.291 mmol), stirred for 3 h at −78 to −10 °C and treated with satd NH_4Cl soln (5 mL). The mixture was diluted with Et_2O (20 mL), washed with satd NH_4Cl soln (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. FC (hexane/AcOEt 2:1) gave **14** (91 mg, 73%). Colourless oil.

Table 4. Selected ^{13}C NMR chemical shifts [ppm] of the protected *gluco*-lactams and thiolactams **12**, **14**, **19**, **20**, **21**, **24**, **26**, **29**, **30** and **32**–**36** and of the protected *manno*-lactams **15**, **17**, **18** and **25** in $CDCl_3$

Compound	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
gluco						
12	166.18	79.10	80.26	75.89	54.27	69.44
14	164.19	79.28	82.15	76.44	54.89	68.90
19[a]	167.22	63.78	81.22	76.53	54.15	69.82
20	170.59	73.40	83.48	77.20	53.89	70.04
21	201.61	79.02	81.55	77.03	55.35	68.43
24[a]	170.58	73.14	83.22	77.43	53.97	70.04
26	201.44	79.06	81.25	77.05	55.40	68.50
29	170.60	72.93	82.57	78.64	53.15	69.54
30	201.18	79.31	80.67	77.05	55.11	68.31
32	166.63	72.39	80.72	76.77	54.08	69.98
33	168.58	72.90	81.11	74.43	57.52	68.36
34	197.72	75.94[b]	80.11	76.44[b]	58.08	68.87
35	169.89	74.63	81.90	77.11	54.14	70.13
36	170.25	74.20	82.44	76.86	57.85	68.61
manno						
15[a]	166.77	59.57	77.59	72.80	55.51	70.96
17	165.63	76.82[b]	76.20[b]	73.43	55.77	70.94
18	163.34	80.34	75.68	72.11	55.81	70.43
25[a]	170.00	70.60	79.11	74.63	55.35	71.40

[a] Assignments based on a HSQC-GRASP spectrum.
[b] Assignment may be interchanged.

Table 5. Selected ^{1}H NMR chemical shifts [ppm] and coupling constants [Hz] of the protected *manno*-lactams **15**, **17**, **18** and **25** in $CDCl_3$

	15	**17**	**18**	**25**
NH	6.12[a]	6.18	6.81	5.97
H–C(2)	4.12	5.39	5.44	4.450
H–C(3)	3.98	4.15	4.08	3.90
H–C(4)	3.59	3.57	3.68–3.78	3.68
H–C(5)	3.64[a]	3.62–3.70	3.68–3.78	3.53–3.62
H–C(6)	3.42	3.44–3.49	3.46–3.56	3.40
H′–C(6)	3.48	3.44–3.49	3.46–3.56	3.53
J(2,3)	3.4	3.3	3.1	2.8
J(3,4)	4.7	4.1	3.4	5.0
J(4,5)	4.4	4.1	[b]	5.0
J(5,6)	8.7	[b]	[b]	8.7
J(5,6′)	4.4	[b]	[b]	3.7
J(6,6′)	8.7	[b]	[b]	8.7

[a] $J(5,NH) \approx 1.3$ Hz.
[b] Not determined.

R_f (hexane/AcOEt 2:1) 0.21. $[\alpha]_D^{25} = +56.9$ (*c* 2.01, $CHCl_3$). IR ($CHCl_3$): 3385w, 3234w (br), 3089w, 3068w, 3033w, 3013w, 2914w, 2869w, 1951w, 1877w, 1810w, 1704s, 1603w, 1497w, 1454m, 1419s, 1363m, 1317w, 1285w, 1230m, 1170m, 1141s, 1111s, 1028m, 1004m, 935w, 910w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 2; additionally, 3.50–3.58 (irrad. at 3.80 → change); 3.80 (irrad. at 4.03 → d, $J = 8.1$); 4.03 (irrad. at 3.80 → d, $J \approx 10.0$, irrad. at 5.15 → d, $J = 9.3$); 4.43 (d, $J = 11.8$, PhC*H*); 4.51 (d, $J = 11.8$, PhC*H*); 4.53 (d, $J = 11.2$, PhC*H*); 4.84 (d, $J = 10.6$, PhC*H*); 4.873 (d, $J = 11.8$, PhC*H*); 4.875 (d, $J = 10.6$, PhC*H*); 5.15 (irrad. at 4.03 → s); 7.16–7.21 (m, 2 arom. H); 7.27–7.40 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 73.36, 75.09, 75.46 (3t, 3Ph*C*H_2); 118.38 (q, $^{1}J(C,F) = 319.2$, CF_3); 127.82–128.40 (several d); 136.65, 136.80, 136.98 (3s). ^{19}F NMR ($CDCl_3$, 282 MHz): −74.05. HR-MALDI-MS: 899.3843 (8, $[2M+Na-Tf_2O]^+$, $C_{54}H_{56}N_2NaO_9^+$; calcd 899.3884), 877.3989 (43, $[2M+H-Tf_2O]^+$, $C_{54}H_{57}N_2O_9^+$; calcd 877.4064), 859.3908 (28, $[2M-H-2TfO]^+$, $C_{54}H_{55}N_2O_8^+$; calcd 859.3958), 769.3438 (10), 620.2632 (11), 470.1936 (14, $[M+H+Na-Tf]^+$, $C_{27}H_{29}NNaO_5^+$; calcd 470.1943), 448.2110 (36, $[M+2H-Tf]^+$, $C_{27}H_{30}NO_5^+$; calcd 448.2124), 402.2056 (100).

4.6. 5-Amino-2-azido-3,4,6-tri-*O*-benzyl-2,5-dideoxy-D-mannono-1,5-lactam 15

(a) A suspension of **12** (135 mg, 0.257 mmol) and NaN_3 (165 mg, 2.54 mmol) in DMF (3.2 mL) was stirred for 2 h at 70 °C, cooled to 22 °C, diluted with Et_2O (40 mL) and washed with satd NH_4Cl soln (3 × 20 mL). The combined aq layers were extracted with Et_2O (2 × 20 mL). The combined org. layers were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated. FC (hexane/AcOEt 2:1) gave **19** (3 mg, 2%) and **15** (94 mg, 77%).

(b) A suspension of **14** (75 mg, 0.129 mmol) and NaN_3 (17 mg, 0.261 mmol) in DMF (1 mL) was stirred for 3 h at 23 °C. Workup as described in (a) and FC (hexane/AcOEt 2:1 → 1:1 → 1:3) gave **15** (32 mg, 52%) and **16**[1] (9 mg, 16%).

4.6.1. Data of 15. Colourless oil. R_f (hexane/AcOEt 2:1) 0.11. $[\alpha]_D^{25} = -16.5$ (*c* 1.00, $CHCl_3$). UV ($CHCl_3$): 259 (2.89). IR ($CHCl_3$): 3389m, 3089w, 3061w, 2920m, 2868m, 2116s, 1953w, 1877w, 1811w, 1681s, 1604w, 1496m, 1454m, 1393w, 1362m, 1311m, 1075s, 1028m, 911w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 5; additionally, 4.42 (d, $J = 12.1$, PhC*H*); 4.46 (d, $J = 12.5$, PhC*H*); 4.49 (d, $J = 11.8$, PhC*H*); 4.55 (d, $J = 11.5$, PhC*H*); 4.57 (d, $J = 11.8$, PhC*H*); 4.70 (d, $J = 11.8$, PhC*H*); 6.12 (exchange with CD_3OD); 7.19–7.22 (m, 2 arom. H); 7.25–7.39 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 72.40, 73.15, 73.33 (3t, 3Ph*C*H_2); 127.81–128.57 (several d); 136.94, 136.96, 137.25 (3s). HR-MALDI-MS: 495.1997 (100, $[M+Na]^+$, $C_{27}H_{28}N_4NaO_4^+$; calcd 495.2008), 469.2101 (16, $[M+2H+Na-N_2]^+$, $C_{27}H_{30}N_2NaO_4^+$; calcd 469.2103), 467.1938 (39, $[M+Na-N_2]^+$, $C_{27}H_{28}N_2NaO_4^+$; calcd 467.1947), 447.2283 (34, $[M+3H-N_2]^+$, $C_{27}H_{31}N_2O_4^+$; calcd 447.2284), 445.2121 (85, $[M+H-N_2]^+$, $C_{27}H_{29}N_2O_4^+$; calcd 445.2127). Anal. Calcd for $C_{27}H_{28}N_4O_4$ (472.54): C, 68.63; H, 5.97; N, 11.86. Found: C, 68.82; H, 6.08; N, 11.70.

4.7. 2,5-Diamino-2,5-dideoxy-D-mannono-1,5-lactam 10

A soln of **15** (100 mg, 0.212 mmol) in MeOH (4 mL) was treated with AcOH (0.8 mL) and 10% Pd/C (90 mg), hydrogenated at 6 bar for 22 h and filtered through Celite. Evaporation of the combined filtrate and washing

(25 mL of MeOH), co-evaporation with toluene (4 × 5 mL), ion-exchange chromatography (Amberlite CG-120, NH_4^+ form, elution with 0.05 M aq NH_3) and lyophilization gave **10/6** 9:1 (34.1 mg, 92%). R_f ($CHCl_3$/MeOH/NH_4OH 5:4:1) 0.19. $[\alpha]_D^{25} = +9.7$ (*c* 1.04, H_2O). pK_{HA} = 7.46. IR (0.5% in KBr): 3600–2600s (br), 2925m, 1659s, 1588s, 1459m, 1416m, 1374m, 1056m, 895w. ^{1}H NMR (D_2O, 300 MHz, only signals of **10** listed): see Table 9; additionally, 3.64 (irrad. at 3.44 → d, *J* = 12.5); 3.72 (irrad. at 3.44 → d, *J* = 12.1); 3.87 (irrad. at 3.44 → d, *J* = 4.4); 3.98 (irrad. at 3.58 → d, *J* = 4.0). ^{1}H NMR (D_2O, 300 MHz, 1 equiv of CF_3CO_2H, only signals of **10**·CF_3CO_2H listed): see Table 9. ^{13}C NMR (D_2O, 75 MHz, only signals of **10** listed): 51.49 (d, C(2)); 58.81 (d, C(5)); 61.73 (t, C(6)); 69.37 (d, C(4)); 71.66 (d, C(3)); 175.11 (s, C(1)). HR-ESI-MS: 511.1296 (17), 375.1507 (100, $[2M+Na]^+$, $C_{12}H_{24}N_4NaO_8^+$; calcd 375.1492), 353.1687 (23, $[2M+H]^+$, $C_{12}H_{25}N_4O_8^+$; calcd 353.1672), 273.1817 (41), 199.0694 (4, $[M+Na]^+$, $C_6H_{12}N_2NaO_4^+$; calcd 199.0695), 177.0869 (8, $[M+H]^+$, $C_6H_{13}N_2O_4^+$; calcd 177.0875).

4.8. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-mannono-1,5-lactam 17

At 0 °C, a soln of **16** (270 mg, 0.603 mmol) in CH_2Cl_2 (5 mL) was successively treated with Et_3N (0.17 mL, 1.22 mmol) and MsCl (60 μL, 0.772 mmol), stirred at 0 °C for 30 min and treated with satd NH_4Cl soln (1 mL). The mixture was diluted with Et_2O (25 mL) and washed with satd NH_4Cl soln (3 × 15 mL). The combined aq layers were extracted with Et_2O (2 × 15 mL). The combined org. layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 2:1 → 1:1) gave **17** (288 mg, 91%). Colourless oil. R_f (hexane/AcOEt 1:1) 0.24. $[\alpha]_D^{25} = -2.4$ (*c* 1.32, $CHCl_3$). IR ($CHCl_3$): 3392w, 3089w, 3067w, 3032m, 3013w, 2924w, 2868w, 1953w, 1877w, 1810w, 1693s, 1603w, 1496w, 1455m, 1361s, 1333m, 1268w, 1174m, 1087s, 1048m, 1028m, 971s, 927w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 5; additionally, 3.30 (s, MsO); 3.44–3.49 (irrad. at 3.66 → change); 3.57 (irrad. at 3.66 → d, *J* ≈ 2.9, irrad. at 4.15 → d, *J* = 3.3); 4.15 (irrad. at 3.57 → d, *J* = 3.3, irrad. at 5.39 → d, *J* = 4.4); 4.41 (d, *J* = 11.8, PhC*H*); 4.42 (d, *J* = 11.8, PhC*H*); 4.48 (d, *J* = 11.8, PhC*H*); 4.54 (d, *J* = 11.8, PhC*H*); 4.55 (d, *J* = 11.8, PhC*H*); 4.80 (d, *J* = 12.1, PhC*H*); 5.39 (irrad. at 4.15 → s); 6.18 (exchange with CD_3OD); 7.18–7.22 (m, 2 arom. H); 7.25–7.39 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 39.35 (q, MsO); 72.17, 73.29, 73.68 (3t, 3Ph*C*H_2); 127.78–128.56 (several d); 136.65, 137.11, 137.20 (3s). HR-MALDI-MS: 564.1446 (7, $[M+K]^+$, $C_{28}H_{31}KNO_7S^+$; calcd 564.1458), 548.1705 (100, $[M+Na]^+$, $C_{28}H_{31}NNaO_7S^+$; calcd 548.1719), 526.1879 (7, $[M+H]^+$, $C_{28}H_{32}NO_7S^+$; calcd 526.1899), 452.1828 (17, $[M+Na-MsOH]^+$, $C_{27}H_{27}NNaO_4^+$; calcd 452.1838), 362.1359 (4, $[M+Na-MsO-Bn]^+$, $C_{20}H_{21}NNaO_4^+$; calcd 362.1368), 346.0955 (11). Anal. Calcd for $C_{28}H_{31}NO_7S$ (525.62): C, 63.98; H, 5.94; N, 2.66; S, 6.10. Found: C, 63.90; H, 5.98; N, 2.55; S, 5.87.

4.9. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(trifluoromethanesulfonyl)-D-mannono-1,5-lactam 18

At −78 °C, a soln of **16** (105 mg, 0.235 mmol) in CH_2Cl_2 (2 mL) was treated successively with pyridine (36 μL, 0.446 mmol) and Tf_2O (48 μL, 0.291 mmol), stirred for 3 h at −78 to −10 °C and treated with satd NH_4Cl soln (5 mL). The mixture was diluted with Et_2O (20 mL), washed with satd NH_4Cl soln (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 3:2) gave **18** (81 mg, 60%). Colourless oil. R_f (hexane/AcOEt 3:2) 0.14. $[\alpha]_D^{25} = +6.4$ (*c* 2.02, $CHCl_3$). IR ($CHCl_3$): 3389w, 3241w (br), 3089w, 3067w, 3032m, 3013w, 2925w, 2870w, 1953w, 1877w, 1810w, 1702s, 1602w, 1496w, 1454m, 1420s, 1362m, 1287m, 1236s, 1169m, 1143s, 1089s, 1027s, 908w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 5; additionally, 4.43 (d, *J* = 11.8, PhC*H*); 4.48 (d, *J* = 12.1, PhC*H*); 4.51 (br s, PhCH_2); 4.52 (d, *J* = 11.2, PhC*H*); 4.62 (d, *J* = 12.1, PhC*H*); 7.19–7.24 (m, 4 arom. H); 7.27–7.40 (m, 11 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 72.19 (t, Ph*C*H_2); 73.30 (t, 2Ph*C*H_2); 118.37 (q, ^1J(C,F) = 318.6, CF_3); 127.73–128.51 (several d); 136.21, 136.40, 137.15 (3s). ^{19}F NMR ($CDCl_3$, 282 MHz): −74.64. HR-MALDI-MS: 899.3867 (2, $[2M+Na-Tf_2O]^+$, $C_{54}H_{56}N_2NaO_9^+$; calcd 899.3884), 877.4002 (31), 859.3915 (36, $[2M-H-2TfO]^+$, $C_{54}H_{55}N_2O_8^+$; calcd 859.3958), 751.3357 (100, $[2M-H-BnOH-2TfO]^+$, $C_{47}H_{47}N_2O_7^+$; calcd 751.3383), 620.2634 (15), 602.1423 (5, $[M+Na]^+$, $C_{28}H_{28}F_3NNaO_7S^+$; calcd 602.1436), 580.1610 (2, $[M+H]^+$, $C_{28}H_{29}F_3NO_7S^+$; calcd 580.1617), 470.1936 (13, $[M+H+Na-Tf]^+$, $C_{27}H_{29}NNaO_5^+$; calcd 470.1943), 448.2112 (20, $[M+2H-Tf]^+$, $C_{27}H_{30}NO_5^+$; calcd 448.2124), 402.2055 (57).

4.10. 5-Amino-2-azido-3,4,6-tri-*O*-benzyl-2,5-dideoxy-D-glucono-1,5-lactam 19

(a) A suspension of **17** (100 mg, 0.190 mmol) and NaN_3 (124 mg, 1.91 mmol) in DMF (2.4 mL) was stirred for 2 h at 70 °C, cooled to 23 °C, diluted with Et_2O (40 mL) and washed with satd NH_4Cl soln (3 × 20 mL). The combined aq layers were extracted with Et_2O (2 × 20 mL). The combined org. layers were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and filtered. Evaporation and FC (hexane/AcOEt 2:1) gave **19** (56 mg, 62%) and **15** (5 mg, 6%).

(b) A suspension of **18** (65 mg, 0.112 mmol) and NaN_3 (15 mg, 0.231 mmol) in DMF (1 mL) was stirred for 3 h at 23 °C. Workup (as described in a) and FC (hexane/AcOEt 2:1 → 1:1 → 1:3) gave **19** (14 mg, 26%) and **11**[1] (13 mg, 26%).

4.10.1. Data of 19. Colourless solid. R_f (hexane/AcOEt 2:1) 0.18. Mp 90–91 °C. $[\alpha]_D^{25} = +105.1$ (*c* 0.79, $CHCl_3$). UV ($CHCl_3$): 259 (2.94). IR ($CHCl_3$): 3385w, 3090w, 3061w, 2960w, 2869w, 2114s, 1952w, 1877w, 1810w, 1683s, 1605w, 1497w, 1454m, 1398w, 1362m, 1313m, 1148m, 1110s, 1051m, 1028m, 912w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 2; additionally, 3.70 (irrad. at 4.06 → d, *J* = 9.0); 4.06 (irrad. at 3.70 → s); 4.42 (d,

J = 12.5, PhC*H*); 4.46 (d, J = 12.1, PhC*H*); 4.53 (d, J = 11.2, PhC*H*); 4.83 (d, J = 10.9, PhC*H*); 4.89 (d, J = 10.9, PhC*H*); 4.90 (d, J = 10.6, PhC*H*); 6.11 (exchange with CD_3OD); 7.19–7.22 (m, 2 arom. H); 7.25–7.28 (m, 3 arom. H); 7.30–7.40 (m, 10 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 73.37, 75.08, 75.32 (3t, 3Ph*C*H_2); 127.77–128.46 (several d); 136.93, 137.09, 137.31 (3s). HR-MALDI-MS: 495.1996 (100, $[M+Na]^+$, $C_{27}H_{28}N_4NaO_4^+$; calcd 495.2008), 469.2100 (23, $[M+2H+Na-N_2]^+$, $C_{27}H_{30}N_2NaO_4^+$; calcd 469.2103), 467.1934 (64, $[M+Na-N_2]^+$, $C_{27}H_{28}N_2NaO_4^+$; calcd 467.1947), 447.2275 (51, $[M+3H-N_2]^+$, $C_{27}H_{31}N_2O_4^+$; calcd 447.2284), 445.2116 (55, $[M+H-N_2]^+$, $C_{27}H_{29}N_2O_4^+$; calcd 445.2127). Anal. Calcd for $C_{27}H_{28}N_4O_4$ (472.54): C, 68.63; H, 5.97; N, 11.86. Found: C, 68.55; H, 6.09; N, 11.71.

4.11. 2,5-Diamino-2,5-dideoxy-D-glucono-1,5-lactam 6

A soln of **19** (50 mg, 0.106 mmol) in MeOH (1 mL) was treated with AcOH (1 mL) and 10% Pd/C (50 mg), hydrogenated at 6 bar for 22 h and filtered through Celite. Evaporation of the combined filtrate and washing (20 mL of MeOH), co-evaporation with toluene (4 × 5 mL), ion-exchange chromatography (Amberlite CG-120, NH_4^+ form, elution with 0.05 M aq NH_3) and lyophilization gave **6**[1] (17.9 mg, 96%).

4.12. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(triethylsilyl)-D-glucono-1,5-lactam 20

At 0 °C, a soln of **11** (50 mg, 0.112 mmol) in CH_2Cl_2 (0.5 mL) was successively treated with pyridine (25 μL, 0.309 mmol) and Et_3SiOTf (34 μL, 0.149 mmol), stirred at 0 °C for 2 h and treated with satd NH_4Cl soln (5 mL). The mixture was diluted with Et_2O (30 mL) and washed with satd NH_4Cl soln (3 × 15 mL). The combined aq layers were extracted with Et_2O (2 × 15 mL). The combined org. layers were extracted with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 4:1 → 2:1) gave **20** (54 mg, 86%). Colourless oil. R_f (hexane/AcOEt 2:1) 0.40. $[\alpha]_D^{25} = +64.6$ (c 1.03, $CHCl_3$). IR ($CHCl_3$): 3390w, 3089w, 3067w, 3032w, 3010m, 2956m, 2912m, 2877m, 1952w, 1875w, 1810w, 1684s, 1603w, 1497w, 1454m, 1412w, 1363m, 1315m, 1258w, 1161m, 1099s, 1070s, 1028m, 1007m, 912w. ^1H NMR ($CDCl_3$, 300 MHz): see Table 2; additionally, 0.64–0.84 (m, (MeC*H*$_2$)$_3$Si); 0.95–1.04 (m, (*Me*CH$_2$)$_3$Si); 4.44 (d, J = 12.1, PhC*H*); 4.48 (d, J = 11.8, PhC*H*); 4.50 (d, J = 11.8, PhC*H*); 4.78 (d, J = 11.2, PhC*H*); 4.82 (d, J = 11.2, PhC*H*); 4.94 (d, J = 11.2, PhC*H*); 6.04 (exchange with CD_3OD); 7.16–7.21 (m, 2 arom. H); 7.26–7.40 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 5.16 (t, (Me*C*H$_2$)$_3$Si); 7.02 (q, (*Me*CH$_2$)$_3$Si); 73.25, 74.44, 74.61 (3t, 3Ph*C*H$_2$); 127.53–128.38 (several d); 137.19, 137.50, 138.06 (3s). HR-MALDI-MS: 584.2797 (100, $[M+Na]^+$, $C_{33}H_{43}NNaO_5Si^+$; calcd 584.2808), 562.2981 (4, $[M+H]^+$, $C_{33}H_{44}NO_5Si^+$; calcd 562.2989), 532.2514 (40, $[M-Et]^+$, $C_{31}H_{38}NO_5Si^+$; calcd 532.2519), 424.1936 (40, $[M-BnOH-Et]^+$, $C_{24}H_{30}NO_4Si^+$; calcd 424.1944), 286.1256 (25). Anal. Calcd for $C_{33}H_{43}NO_5Si$ (561.79): C, 70.55; H, 7.71; N, 2.49. Found: C, 70.38; H, 7.69; N, 2.59.

4.13. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(triethylsilyl)-D-glucono-1,5-thiolactam 21

A soln of **20** (40 mg, 71.2 μmol) in toluene (1.3 mL) was treated with Lawesson's reagent (22 mg, 54.4 μmol), stirred at 23 °C for 24 h, diluted with Et_2O (30 mL) and washed with satd $NaHCO_3$ soln (3 × 20 mL). The combined aq layers were extracted with Et_2O (2 × 20 mL). The combined org. layers were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 6:1) gave **21** (30 mg, 73%). Colourless oil. R_f (hexane/AcOEt 6:1) 0.39. $[\alpha]_D^{25} = +78.0$ (c 1.00, $CHCl_3$). IR ($CHCl_3$): 3376w, 3089w, 3068w, 3020s, 2957m, 2936m, 2914m, 2876m, 1953w, 1877w, 1810w, 1753w, 1682w, 1601w, 1513s, 1455m, 1412w, 1363w, 1313w, 1233w, 1159m, 1092s, 1028m, 1005m, 911w. ^1H NMR ($CDCl_3$, 300 MHz): see Table 2; additionally, 0.60–0.79 (m, (MeC*H*$_2$)$_3$Si); 0.88–1.00 (m, (*Me*CH$_2$)$_3$Si); 4.33 (d, J = 11.5, PhC*H*); 4.45 (d, J = 11.8, PhC*H*); 4.50 (d, J = 11.8, PhC*H*); 4.52 (d, J = 11.5, PhC*H*); 4.53 (d, J = 11.5, PhC*H*); 4.73 (d, J = 11.5, PhC*H*); 7.13–7.19 (m, 2 arom. H); 7.27–7.39 (m, 13 arom. H); 8.01 (exchange with CD_3OD). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 4.96 (t, (Me*C*H$_2$)$_3$Si); 6.91 (q, (*Me*CH$_2$)$_3$Si); 71.97, 71.98, 73.30 (3t, 3Ph*C*H$_2$); 127.77–128.43 (several d); 136.97, 137.28, 137.32 (3s). HR-MALDI-MS: 600.2577 (100, $[M+Na]^+$, $C_{33}H_{43}NNaO_4SSi^+$; calcd 600.2580), 578.2756 (21, $[M+H]^+$, $C_{33}H_{44}NO_4SSi^+$; calcd 578.2760), 440.1701 (32). Anal. Calcd for $C_{33}H_{43}NO_4SSi$ (577.86): C, 68.59; H, 7.50; N, 2.42. Found: C, 68.59; H, 7.63; N, 2.60.

4.13.1. Condensation of 21 with aminoacetaldehyde dimethyl acetal in the presence of $Hg(OAc)_2$. At 0 °C, a suspension of **21** (24 mg, 41.5 μmol) and $Hg(OAc)_2$ (24 mg, 75.3 μmol) in THF (1.3 mL) was treated with aminoacetaldehyde dimethyl acetal (70 μL, 0.649 mmol) and stirred at 0 °C for 8 h. The black mixture was diluted with AcOEt (5 mL), filtered over Celite (the solid was washed with 30 mL of AcOEt). The combined filtrates were washed with brine (20 mL), dried ($MgSO_4$), filtered and evaporated. A soln of the residue (25 mg) in toluene (2 mL) and H_2O (0.2 mL) was treated with p-TsOH·H_2O (26 mg, 0.137 mmol), stirred for 20 h at 70 °C, cooled to 22 °C, diluted with AcOEt (20 mL) and washed with satd $NaHCO_3$ soln (3 × 10 mL). The combined aq layers were extracted with AcOEt (2 × 10 mL). The combined org. layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. FC (AcOEt) gave **22/23** 60:40 (7.8 mg, 40%).

4.14. Data of (5*R*,6*R*,7*S*,8*S*)-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-8-ol 22[1,24,25]

Colourless oil. R_f (AcOEt/MeOH 20:1) 0.15. $[\alpha]_D^{25} = +12.5$ (c 1.02, $CHCl_3$). UV ($CHCl_3$): 259 (2.78),

Table 6. Selected ^{1}H NMR chemical shifts [ppm] and coupling constants [Hz] of the protected *gluco*-imidazoles **22**, **27**, **31**, **37** and **40** and of the *arabino*-imidazole **39** in $CDCl_3$

	22[1]	**27**	**31**	**37**	**39**	**40**[1]
H–C(2)	7.05[a]	7.02[a]	7.02[a]	7.06[a]	7.39	7.03[a]
H–C(3)	7.12[a]	7.08[a]	7.06[a]	7.14[a]	7.24	7.15[a]
H–C(5)	4.17	4.21	4.39	4.35–4.42	4.46–4.54	4.16
H–C(6)	3.95	3.85	3.76	3.93	4.13	3.98
H–C(7)	4.08	3.98	4.11	4.21	4.22	3.90
H–C(8)	4.99	4.93	5.12	6.11	—	4.75
CH–C(5)	3.75	3.76	3.83	3.71	3.81	3.70
CH′–C(5)	3.87	3.87	3.93	3.78	3.87	3.80
J(2,3)	1.3	1.3	1.2	1.3	1.2	1.2
J(5,6)	7.8	8.1	8.4	5.3	5.0	7.5
J(6,7)	8.7	6.9	3.4	5.3	6.2	8.1
J(7,8)	7.5	5.3	3.1	3.7	—	6.9
J(5,CH)	5.0	5.3	5.9	6.5	6.8	5.0
J(5,CH′)	2.8	3.1	2.8	4.4	3.7	3.1
J(CH,CH′)	10.3	10.3	10.6	10.0	10.3	10.3

[a] Assignment may be interchanged.

Table 7. Selected ^{13}C NMR chemical shifts [ppm] of the protected *gluco*-imidazoles **22**, **27**, **31**, **37** and **40**, of the protected *manno*-imidazoles **23**, **28**, **38** and **41**, and of the *arabino*-imidazole **39** in $CDCl_3$

Compound	C(2)	C(3)	C(5)	CH_2–C(5)	C(6)	C(7)	C(8)	C(8a)
gluco								
22[1]	128.72	116.65	58.48	68.35	75.26	82.92	67.87	147.29
27	128.95	116.93	57.86	68.37	76.81	83.49	68.26	145.22
31	[a]	117.11	56.58	68.04	78.50	82.77	66.38	145.36
37	129.33	118.32	58.50	70.46	74.55	77.79	66.54	140.90
39 (*arabino*)	133.17	122.31	59.62	69.87	75.68	79.84	181.93	140.24
40[1]	129.96	117.79	58.72[b]	68.56	75.23	80.76	59.10[b]	140.91
manno								
23[1]	128.83	118.20	59.26	70.84	73.59	79.19	62.46	144.93
28	128.86	118.68	59.65	71.00	73.60	81.26	63.75	144.74
38	129.94	118.03	59.15	69.33	73.18	78.60	63.15	141.74
41[1]	129.77	118.72	58.96	70.03	73.14	78.29	55.57	140.26

[a] Not assigned.
[b] Assignment may be interchanged.

240 (3.03). IR ($CHCl_3$): 3327w (br), 3163w, 3090w, 3067m, 3032m, 3012m, 2914m, 2869m, 1952w, 1879w, 1810w, 1751w, 1603w, 1525w, 1496m, 1454m, 1362m, 1310m, 1283w, 1167w, 1114s, 1085s, 1049s, 1028m, 912w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 6. ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7. HR-MALDI-MS: 493.2094 (19, $[M+Na]^+$, $C_{29}H_{30}N_2NaO_4^+$; calcd 493.2103), 471.2279 (100, $[M+H]^+$, $C_{29}H_{31}N_2O_4^+$; calcd 471.2284), 453.2163 (41, $[M-OH]^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178).

4.15. Data of (5*R*,6*R*,7*S*,8*R*)-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-8-ol 23[1,24,25]

Colourless solid. R_f (AcOEt/MeOH 20:1) 0.14. Mp 112–113 °C (lit.:[24,25] 116.5–117.5 °C). $[\alpha]_D^{25} = -0.3$ (*c* 0.98, $CHCl_3$) [lit.:[24,25] −4.0 ($CHCl_3$)]. UV ($CHCl_3$): 259 (2.71), 240 (3.03). IR ($CHCl_3$): 3325w (br), 3163w, 3090w, 3067w, 3032m, 3011m, 2926m, 2868m, 1952w, 1877w, 1810w, 1725w, 1603w, 1496m, 1454m, 1363m, 1312w, 1269w, 1170w, 1100s, 1028m, 1013m, 912w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 8. ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7. HR-MALDI-MS: 493.2094 (22, $[M+Na]^+$, $C_{29}H_{30}N_2NaO_4^+$; calcd 493.2103), 471.2277 (100, $[M+H]^+$, $C_{29}H_{31}N_2O_4^+$; calcd 471.2284), 453.2158 (34, $[M-OH]^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178).

4.16. 5-Amino-3,4,6-tri-*O*-benzyl-2-*O*-[(*tert*-butyl)dimethylsilyl]-5-deoxy-D-glucono-1,5-lactam 24 and 5-amino-3,4,6-tri-*O*-benzyl-2-*O*-[(*tert*-butyl)dimethylsilyl]-5-deoxy-D-mannono-1,5-lactam 25

(a) A mixture of **11** (150 mg, 0.335 mmol), imidazole (57 mg, 0.837 mmol) and *t*-BuMe$_2$SiCl (66 mg, 0.438 mmol) in DMF (1.2 mL) was stirred at 23 °C for 22 h, diluted with Et_2O (30 mL) and washed with satd NH_4Cl soln (3 × 15 mL). The combined aq layers were extracted with Et_2O (2 × 20 mL). The combined org. layers were extracted with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 4:1) gave **24** (182 mg, 97%).

(b) At 0 °C, a soln of **11** (150 mg, 0.335 mmol) in CH_2Cl_2 (1.2 mL) was successively treated with pyridine (60 μL, 0.742 mmol) and *t*-BuMe$_2$SiOTf (100 μL, 0.435 mmol) and stirred at 0 °C for 4 h. Workup and

Table 8. Selected ^{1}H NMR chemical shifts [ppm] and coupling constants [Hz] of the protected *manno*-imidazoles **23**, **28**, **38** and **41** in $CDCl_3$

	23[1]	**28**	**38**	**41**[1]
H–C(2)[a]	7.01	7.01	7.07	7.11
H–C(3)[a]	7.11	7.07	7.13	7.13
H–C(5)	4.16	4.10	4.07	4.11–4.17
H–C(6)	4.23	4.25	4.24	4.11–4.17
H–C(7)	3.97	3.79	4.05	4.02
H–C(8)	5.16	5.10	6.58	4.93
CH–C(5)	3.71	3.56	3.70	3.67
CH′–C(5)	3.81	3.69	3.80	3.77
J(2,3)	1.2	1.2	1.3	1.2
J(5,6)	6.5	6.9	7.8	[b]
J(6,7)	8.4	9.0	9.3	8.4
J(7,8)	3.4	2.8	3.7	3.7
J(5,CH)	6.5	6.9	5.3	5.9
J(5,CH′)	3.1	3.1	2.8	3.1
J(CH,CH′)	10.0	10.0	10.0	10.0

[a] Assignment may be interchanged.
[b] Not determined.

Table 9. Selected ^{1}H NMR chemical shifts [ppm] and coupling constants [Hz] of the unprotonated and protonated mannosamine-derived imidazole **8** and lactam **10** in D_2O (conventional carbohydrate numbering used)

	8	**8**·H$^+$	**8**·2H$^+$	**10**	**10**·H$^+$
H–C(2)	4.10	5.06	5.15	3.58	4.24–4.36
H–C(3)	4.009	4.32	4.32	3.98	4.24–4.36
H–C(4)	4.22	4.43	4.43	3.87	3.95–4.02
H–C(5)	4.14	4.32–4.39	4.38	3.44	3.48–3.58
H–C(6)	3.88	4.10	4.09	3.64	3.71
H′–C(6)	4.008	4.20	4.18	3.72	3.80
J(2,3)	4.0	5.3	5.0	3.7	[a]
J(3,4)	6.5	7.2	7.5	3.7	[a]
J(4,5)	4.0	5.0	5.0	4.0	[a]
J(5,6)	2.8	5.0	5.3	5.0	6.9
J(5,6′)	3.4	3.1	3.4	4.0	4.4
J(6,6′)	12.1	12.8	12.8	11.8	10.9

[a] Not determined.

FC (as described in a) gave **24** (172 mg, 91%) and **25** (6 mg, 3%).

4.16.1. Data of 24. Colourless oil. R_f (hexane/AcOEt 4:1) 0.11. $[\alpha]_D^{25} = +66.0$ (*c* 1.01, $CHCl_3$). IR ($CHCl_3$): 3391w, 3090w, 3067w, 3032w, 3012m, 2954m, 2930m, 2886m, 2858m, 1951w, 1875w, 1810w, 1686s, 1604w, 1497w, 1472w, 1454m, 1389w, 1362m, 1314m, 1259m, 1160m, 1100s, 1072s, 1028m, 1005w, 939w, 911w, 841m. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 2; additionally, 0.15, 0.22 (2s, Me_2Si); 0.94 (s, Me_3CSi); 4.43 (d, *J* = 12.1, PhC*H*); 4.47 (d, *J* = 11.8, PhC*H*); 4.49 (d, *J* = 12.1, PhC*H*); 4.79 (d, *J* = 11.5, PhC*H*); 4.80 (d, *J* = 11.2, PhC*H*); 4.92 (d, *J* = 11.5, PhC*H*); 6.02 (exchange with CD_3OD); 7.14–7.18 (m, 2 arom. H); 7.26–7.36 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, −5.01, −4.02 (2q, Me_2Si); 18.56 (s, Me_3CSi); 25.95 (q, Me_3CSi); 73.25, 74.47, 74.73 (3t, 3PhCH_2); 127.51–128.39 (several d); 137.18, 137.44, 137.92 (3s). HR-MALDI-MS: 584.2797 (100, $[M+Na]^+$, $C_{33}H_{43}NNaO_5Si^+$; calcd 584.2808), 562.2980 (11, $[M+H]^+$, $C_{33}H_{44}NO_5Si^+$; calcd 562.2989), 546.2662 (55), 528.2559 (15), 438.2088 (56), 300.1412 (35). Anal. Calcd for $C_{33}H_{43}NO_5Si$ (561.79): C, 70.55; H, 7.71; N, 2.49. Found: C, 70.34; H, 7.57; N, 2.54.

4.16.2. Data of 25. Colourless oil. R_f (hexane/AcOEt 2:1) 0.21. $[\alpha]_D^{25} = +0.9$ (*c* 2.01, $CHCl_3$). IR ($CHCl_3$): 3394w, 3089w, 3067w, 3031w, 3012m, 2954m, 2930m, 2885m, 2858m, 1951w, 1875w, 1810w, 1681s, 1604w, 1496w, 1471m, 1462m, 1454m, 1389w, 1362m, 1319w, 1260m, 1098s, 1072s, 1028m, 1006w, 939w, 907w, 838s. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 5; additionally, 0.17, 0.23 (2s, Me_2Si); 0.97 (s, Me_3CSi); 4.448 (d, *J* = 11.8, PhC*H*); 4.48 (d, *J* = 11.8, PhC*H*); 4.50 (d, *J* = 11.8, PhC*H*); 4.62 (d, *J* = 11.8, PhC*H*); 4.65 (d, *J* = 11.8, PhC*H*); 4.86 (d, *J* = 12.1, PhC*H*); 5.97 (exchange with CD_3OD); 7.21–7.24 (m, 2 arom. H); 7.28–7.40 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, −5.33, −4.39 (2q, Me_2Si); 18.51 (s, Me_3CSi); 25.91 (q, Me_3CSi); 72.60, 73.05, 73.18 (3t, 3PhCH_2); 127.51–128.31 (several d); 137.26, 137.30, 138.02 (3s). HR-MALDI-MS: 600.2540 (4, $[M+K]^+$, $C_{33}H_{43}KNO_5Si^+$; calcd 600.2548), 584.2797 (100, $[M+Na]^+$, $C_{33}H_{43}NNaO_5Si^+$; calcd 584.2808), 562.2964 (15, $[M+H]^+$, $C_{33}H_{44}NO_5Si^+$; calcd 562.2989), 546.2666 (97). Anal. Calcd for $C_{33}H_{43}NO_5Si$ (561.79): C, 70.55; H, 7.71; N, 2.49. Found: C, 70.56; H, 7.76; N, 2.64.

4.17. 5-Amino-3,4,6-tri-*O*-benzyl-2-*O*-[(*tert*-butyl)dimethylsilyl]-5-deoxy-D-glucono-1,5-thiolactam 26

A soln of **24** (301 mg, 0.536 mmol) in toluene (9 mL) was treated with Lawesson's reagent (160 mg, 0.396 mmol), stirred at 23 °C for 22 h, diluted with Et_2O (60 mL) and washed with satd $NaHCO_3$ soln (3 × 40 mL). The combined aq layers were extracted with Et_2O (2 × 40 mL). The combined org. layers were washed with H_2O (70 mL) and brine (70 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 6:1) gave **26** (283 mg, 91%). Colourless oil. R_f (hexane/AcOEt 6:1) 0.20. $[\alpha]_D^{25} = +84.8$ (*c* 0.86, $CHCl_3$). IR ($CHCl_3$): 3376w, 3090w, 3067w, 3020m, 2955m, 2931m, 2884m, 2859m, 1952w, 1875w, 1811w, 1602w, 1513s, 1471m, 1463m, 1454m, 1390w, 1363m, 1313w, 1258m, 1160m, 1093s, 1028m, 1006w, 911w, 841s. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 2; additionally, 0.16, 0.18 (2s, Me_2Si); 0.89 (s, Me_3CSi); 3.41 (irrad. at 3.67 → d, *J* = 7.2, irrad. at 3.99 → d, *J* = 10.3); 3.53 (irrad. at 3.78 → br d, *J* ≈ 7.5, irrad. at 3.99 → br s, irrad. at 4.72 → dd, *J* = 2.8, 9.0); 3.67 (irrad. at 3.41 → change, irrad. at 3.99 → d, *J* = 9.3); 3.78 (irrad. at 3.53 → d, *J* = 3.1, irrad. at 4.72 → d, *J* = 2.8); 3.99 (irrad. at 3.41 → change, irrad. at 3.53 → change, irrad. at 3.67 → change); 4.33 (d, *J* = 11.5, PhC*H*); 4.45 (d, *J* = 12.1, PhC*H*); 4.49 (br s, PhCH_2); 4.51 (d, *J* = 11.5, PhC*H*); 4.719 (irrad. at 3.53 → d, *J* = 3.1, irrad. at 3.78 → br s); 4.723 (d, *J* = 11.8, PhC*H*); 7.15–7.21 (m, 2 arom. H); 7.28–7.40 (m, 13 arom. H); 7.99 (exchange with CD_3OD). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, −4.91, −4.06 (2q, Me_2Si); 18.20 (s, Me_3CSi); 25.76 (q, Me_3CSi); 71.88, 71.91, 73.31 (3t, 3PhCH_2); 127.76–128.46 (several d); 136.98, 137.24, 137.36 (3s). HR-MALDI-MS: 616.2522 (21, $[M+K]^+$,

$C_{33}H_{43}KNO_4SSi^+$; calcd 616.2319), 600.2575 (100, $[M+Na]^+$, $C_{33}H_{43}NNaO_4SSi^+$; calcd 600.2580), 594.2687 (16), 584.2795 (12), 578.2757 (53, $[M+H]^+$, $C_{33}H_{44}NO_4SSi^+$; calcd 578.2760), 560.2652 (18), 470.2176 (13, $[M-BnO]^+$, $C_{26}H_{36}NO_3SSi^+$; calcd 470.2185), 422.1968 (18). Anal. Calcd for $C_{33}H_{43}NO_4SSi$ (577.86): C, 68.59; H, 7.50; N, 2.42. Found: C, 68.40; H, 7.52; N, 2.46.

4.17.1. Condensation of 26 with aminoacetaldehyde dimethyl acetal in the presence of $Hg(OAc)_2$. (a) At 0 °C, a suspension of **26** (258 mg, 0.446 mmol) and $Hg(OAc)_2$ (200 mg, 0.628 mmol) in THF (2.5 mL) was treated with aminoacetaldehyde dimethyl acetal (0.25 mL, 2.28 mmol) and stirred at 0 °C for 5 h. The black mixture was diluted with AcOEt (4 mL), filtered over Celite (the solid was washed with 50 mL of AcOEt). The combined filtrate and washing were washed with brine (40 mL), dried ($MgSO_4$), filtered and evaporated. A soln of the residue (340 mg) in toluene (12.5 mL) and H_2O (1.2 mL) was treated with *p*-TsOH·H_2O (225 mg, 1.18 mmol), stirred for 20 h at 70°, cooled to 22 °C, diluted with AcOEt (60 mL) and washed with satd $NaHCO_3$ soln (3 × 40 mL). The combined aq layers were extracted with AcOEt (2 × 40 mL). The combined org. layers were washed with H_2O (80 mL) and brine (80 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 1:0 → 4:1 → 2:1 → 1:1 → 0:1) gave **27** (21 mg, 8%), **28** (3 mg, 1%), **11**[1] (13 mg, 7%) and **22**[1,24,25] (174 mg, 83%).

(b) Similarly as described in a, but the mixture of the residue with *p*-TsOH·H_2O was stirred at 55 °C for 96 h. After workup and FC, such a transformation of **26** (4.47 g, 7.74 mmol) afforded **27** (2.02 g, 45%), **28** (0.11 g, 2%) and a mixture of **22**[1,24,25] and intermediate amidine 9:1 (1.34 g, ca. 37%).

4.18. Data of (5*R*,6*R*,7*S*,8*S*)-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-8-[(*tert*-butyl)dimethylsilyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine 27

Colourless oil. R_f (hexane/AcOEt 2:1) 0.63. $[\alpha]_D^{25} = +41.9$ (*c* 1.99, $CHCl_3$). UV ($CHCl_3$): 259 (2.77), 240 (3.03). IR ($CHCl_3$): 3089w, 3067w, 3032w, 3012w, 2954m, 2930m, 2884m, 2859m, 1951w, 1875w, 1810w, 1725w, 1603w, 1496w, 1472w, 1454m, 1389w, 1362m, 1308w, 1283w, 1261m, 1090s, 1028m, 1005w, 940w, 909w, 840s. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 6; additionally, 0.17, 0.23 (2s, Me_2Si); 0.94 (s, Me_3CSi); 4.46 (d, *J* = 12.1, PhC*H*); 4.49 (d, *J* = 11.2, PhC*H*); 4.51 (d, *J* = 12.1, PhC*H*); 4.77 (d, *J* = 11.5, PhC*H*); 4.80 (d, *J* = 11.2, PhC*H*); 4.87 (d, *J* = 11.5, PhC*H*); 7.16–7.19 (m, 2 arom. H); 7.27–7.39 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7; additionally, −4.80, −4.23 (2q, Me_2Si); 18.36 (s, Me_3CSi); 25.92 (q, Me_3CSi); 73.20, 73.80, 73.82 (3t, 3Ph*C*H_2); 127.53–128.35 (several d); 137.19, 137.48, 137.78 (3s). FAB-MS: 1170 (11, $[2M+H]^+$), 585 (100, $[M+H]^+$), 528 (81, $[M+H-t\text{-}Bu]^+$), 478 (6), 453 (19, $[M-TBDMSO]^+$), 154 (7), 91 (50, $C_7H_7^+$). HR-MALDI-MS: 607.2962 (7, $[M+Na]^+$, $C_{35}H_{44}N_2NaO4Si^+$; calcd 607.2968), 585.3149 (12, $[M+H]^+$, $C_{35}H_{45}N_2O_4Si^+$; calcd 585.3149), 453.2181 (100, $[M-TBDMSO]^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178). Anal. Calcd for $C_{35}H_{44}N_2O_4Si$ (584.83): C, 71.88; H, 7.58; N, 4.79. Found: C, 71.85; H, 7.53; N, 4.97.

4.19. Data of (5*R*,6*R*,7*S*,8*R*)-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-8-[(*tert*-butyl)dimethylsilyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine 28

Colourless oil. R_f (hexane/AcOEt 2:1) 0.43. $[\alpha]_D^{25} = -17.3$ (*c* 0.96, $CHCl_3$). UV ($CHCl_3$): 259 (2.80), 240 (3.01). IR ($CHCl_3$): 3089w, 3067w, 3032w, 3013m, 2955s, 2929s, 2892m, 2858m, 1951w, 1875w, 1810w, 1725w, 1603w, 1496m, 1471m, 1462m, 1454m, 1362m, 1313w, 1264w, 1170w, 1133s, 1100s, 1028w, 1006w, 954m, 912w, 838s. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 8; additionally, −0.04, 0.22 (2s, Me_2Si); 0.87 (s, Me_3CSi); 4.44 (br s, PhCH_2); 4.64 (d, *J* = 11.5, PhC*H*); 4.65 (d, *J* = 11.8, PhC*H*); 4.81 (d, *J* = 11.8, PhC*H*); 4.93 (d, *J* = 11.5, PhC*H*); 7.24–7.40 (m, 15 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7; additionally, −4.90, −4.60 (2q, Me_2Si); 18.24 (s, Me_3CSi); 25.79 (q, Me_3CSi); 71.59, 73.08, 74.58 (3t, 3Ph*C*H_2); 127.51–128.33 (several d); 137.45, 137.82, 137.92 (3s). FAB-MS: 585 (100, $[M+H]^+$), 528 (44, $[M+H-t\text{-}Bu]^+$), 478 (6), 453 (16, $[M-TBDMSO]^+$), 391 (57), 167 (9), 149 (42), 91 (44, $C_7H_7^+$). HR-MALDI-MS: 607.2947 (17, $[M+Na]^+$, $C_{35}H_{44}N_2NaO_4Si^+$; calcd 607.2968), 585.3135 (65, $[M+H]^+$, $C_{35}H_{45}N_2O_4Si^+$; calcd 585.3149), 453.2168 (100, $[M-TBDMSO]^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178). Anal. Calcd for $C_{35}H_{44}N_2O_4Si$ (584.83): C, 71.88; H, 7.58; N, 4.79. Found: C, 72.07; H, 7.76; N, 4.84.

4.20. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(triisopropylsilyl)-D-glucono-1,5-lactam 29

(a) A mixture of **11** (1.00 g, 2.23 mmol), imidazole (0.37 g, 5.43 mmol) and TIPSCl (0.63 mL, 2.94 mmol) in DMF (8 mL) was stirred at 23 °C for 16 h, diluted with Et_2O (250 mL) and washed with satd NH_4Cl soln (3 × 100 mL). The combined aq layers were extracted with Et_2O (2 × 60 mL). The combined org. layers were washed with H_2O (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 4:1) gave **29** (1.31 g, 97%).

(b) At 0 °C, a soln of **11** (125 mg, 0.279 mmol) and pyridine (50 μL, 0.618 mmol) in CH_2Cl_2 (1 mL) was treated with TIPSOTf (100 μL, 0.372 mmol) and stirred at 0 °C for 3.5 h. Workup and FC (as described in a) gave **29** (156 mg, 92%).

4.20.1. Data of 29. Colourless oil. R_f (hexane/AcOEt 4:1) 0.17. $[\alpha]_D^{25} = +62.0$ (*c* 0.61, $CHCl_3$). IR ($CHCl_3$): 3396w, 3090w, 3067w, 3033w, 3011m, 2946s, 2893s, 2868s, 1952w, 1877w, 1808w, 1688s, 1497w, 1455m, 1386w, 1363m, 1314w, 1261w, 1213m, 1100s, 1072s, 1028m, 913w, 883m. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 3; additionally, 1.00–1.32 (m, $(Me_2CH)_3Si$); 4.38 (d, *J* = 11.8, PhC*H*); 4.43 (d, *J* = 11.8, PhC*H*); 4.50 (d, *J* = 11.8, PhC*H*); 4.63 (d, *J* = 11.5, PhC*H*); 4.64 (d, *J* = 11.8, PhC*H*); 4.79 (d, *J* = 11.5, PhC*H*); 5.87 (exchange with CD_3OD); 7.16–7.19 (m, 2 arom. H);

7.27–7.39 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 12.61 (d, $(Me_2CH)_3$-Si); 18.05, 18.12 (2q, $(Me_2CH)_3Si$); 72.93, 73.00, 73.06 (3t, $3PhCH_2$); 127.62–128.29 (several d); 137.23, 137.49, 137.67 (3s). HR-MALDI-MS: 626.3278 (100, $[M+Na]^+$, $C_{36}H_{49}NNaO_5Si^+$; calcd 626.3278), 604.3456 (2, $[M+H]^+$, $C_{36}H_{50}NO_5Si^+$; calcd 604.3458), 560.2826 (64, $[M-i\text{-}Pr]^+$, $C_{33}H_{42}NO_5Si^+$; calcd 560.2832), 452.2245 (35, $[M-i\text{-}Pr-BnOH]^+$, $C_{26}H_{34}NO_4Si^+$; calcd 452.2257), 314.1565 (17). Anal. Calcd for $C_{36}H_{49}NO_5Si$ (603.87): C, 71.60; H, 8.18; N, 2.32. Found: C, 71.77; H, 8.01; N, 2.37.

4.21. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(triisopropylsilyl)-D-glucono-1,5-thiolactam 30

A soln of **29** (1.28 g, 2.12 mmol) in toluene (35 mL) was treated with Lawesson's reagent (630 mg, 1.56 mmol), stirred for 36 h at 23 °C, diluted with Et_2O (250 mL) and washed with satd $NaHCO_3$ soln (3 × 100 mL). The combined aq layers were extracted with Et_2O (2 × 80 mL). The combined org. layers were washed with H_2O (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 8:1) gave **30** (1.26 g, 96%). Colourless oil. R_f (hexane/AcOEt 8:1) 0.15. $[\alpha]_D^{25} = +73.1$ (*c* 0.67, $CHCl_3$). IR ($CHCl_3$): 3376w, 3090w, 3068w, 3020m, 2946s, 2892m, 2868s, 1952w, 1882w, 1813w, 1604w, 1513s, 1465m, 1455m, 1385w, 1365m, 1313w, 1252w, 1160m, 1098s, 1029m, 910w, 883m. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 3; additionally, 1.02–1.26 (m, $(Me_2CH)_3Si$); 4.32 (d, $J = 11.8$, PhC*H*); 4.46 (d, $J = 11.8$, PhC*H*); 4.49 (d, $J = 11.8$, PhC*H*); 4.50 (d, $J = 11.8$, PhC*H*); 4.54 (d, $J = 11.8$, PhC*H*); 4.72 (d, $J = 11.8$, PhC*H*); 7.18–7.21 (m, 2 arom. H); 7.29–7.40 (m, 13 arom. H); 8.06 (exchange with CD_3OD). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 12.33 (d, $(Me_2CH)_3Si$); 18.09, 18.13 (2q, $(Me_2CH)_3Si$); 71.53 (t, $2PhCH_2$); 73.11 (t, $PhCH_2$); 127.67–128.38 (several d); 137.00, 137.19, 137.29 (3s). HR-MALDI-MS: 658.3001 (24, $[M+K]^+$, $C_{36}H_{49}KNO_4SSi^+$; calcd 658.2789), 642.3038 (100, $[M+Na]^+$, $C_{36}H_{49}NNaO_4SSi^+$; calcd 642.3049), 636.3159 (23), 626.3273 (25), 620.3257 (18, $[M+H]^+$, $C_{36}H_{50}NO_4SSi^+$; calcd 620.3230), 576.2593 (32, $[M-i\text{-}Pr]^+$, $C_{33}H_{42}NO_4SSi^+$; calcd 576.2604), 468.2011 (73, $[M-i\text{-}Pr-BnOH]^+$, $C_{26}H_{34}NO_3SSi^+$; calcd 468.2029), 462.1731 (73, $[M-i\text{-}Pr_3Si]^+$, $C_{27}H_{28}NO_4S^+$; calcd 462.1739). Anal. Calcd for $C_{36}H_{49}NO_4SSi$ (619.94): C, 69.75; H, 7.97; N, 2.26. Found: C, 69.81; H, 7.73; N, 2.38.

4.21.1. Condensation of 30 with aminoacetaldehyde dimethyl acetal in the presence of $Hg(OAc)_2$.

At 0 °C, a suspension of **30** (500 mg, 0.807 mmol) and $Hg(OAc)_2$ (360 mg, 1.13 mmol) in THF (4.5 mL) was treated with aminoacetaldehyde dimethyl acetal (0.45 mL, 4.17 mmol) and stirred at 0 °C for 4 h. The black mixture was diluted with AcOEt (4 mL), filtered over Celite (the solid was washed with 50 mL of AcOEt). The combined filtrates were washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated. A soln of the residue (600 mg) was dissolved in toluene (22.5 mL) and H_2O (2.2 mL), treated with *p*-TsOH·H_2O (405 mg, 2.13 mmol), stirred for 20 h at 70 °C, cooled to 22 °C, diluted with AcOEt (70 mL) and washed with satd $NaHCO_3$ soln (3 × 40 mL). The combined aq layers were extracted with AcOEt (2 × 40 mL). The combined org. layers were washed with H_2O (80 mL) and brine (80 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 1:0 → 5:1 → 3:1) gave **31** (445 mg, 88%). Colourless oil.

4.22. Data of (5*R*,6*R*,7*S*,8*S*)-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydro-8-(triisopropylsilyl)-imidazo[1,2-*a*]pyridine 31

R_f (hexane/AcOEt 3:1) 0.22. $[\alpha]_D^{25} = +49.9$ (*c* 1.10, $CHCl_3$). UV ($CHCl_3$): 259 (2.77), 239 (3.09). IR ($CHCl_3$): 3089w, 3067w, 3033w, 3010w, 2945s, 2892m, 2867s, 1951w, 1877w, 1810w, 1731w, 1686w, 1602w, 1534w, 1496w, 1454m, 1384w, 1363w, 1337w, 1319w, 1289w, 1263w, 1092s, 1028w, 1015w, 909w, 883m, 843w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 6; additionally, 0.96–1.26 (m, $(Me_2CH)_3Si$); 4.45 (d, $J = 11.8$, PhC*H*); 4.53 (br s, $PhCH_2$); 4.60 (d, $J = 11.8$, PhC*H*); 4.63 (d, $J = 11.5$, PhC*H*); 4.73 (d, $J = 11.8$, PhC*H*); 7.20–7.40 (m, 15 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7; additionally, 12.34 (d, $(Me_2CH)_3$-Si); 17.87, 18.05 (2q, $(Me_2CH)_3Si$); 72.09, 72.38, 73.13 (3t, $3PhCH_2$); 127.73–128.45 (several d including C(2)); 137.37 (s); 137.65 (2s). HR-MALDI-MS: 649.3438 (6, $[M+Na]^+$, $C_{38}H_{50}N_2NaO_4Si^+$; calcd 649.3437), 627.3621 (7, $[M+H]^+$, $C_{38}H_{51}N_2O_4Si^+$; calcd 627.3618), 583.2990 (8, $[M-i\text{-}Pr]^+$, $C_{35}H_{43}N_2O_4Si^+$; calcd 583.2992), 453.2175 (100, $[M-TIPSO]^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178). Anal. Calcd for $C_{38}H_{50}N_2O_4Si$ (626.91): C, 72.80; H, 8.04; N, 4.47. Found: C, 72.69; H, 8.02; N, 4.45.

4.23. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-pivaloyl-D-glucono-1,5-lactam 32 and 3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-pivaloyl-5-(pivaloylamino)-D-glucono-1,5-lactam 33

(a) At 5 °C, a soln of **11** (83 mg, 0.185 mmol) in pyridine (2.5 mL) was treated with pivaloyl chloride (40 μL, 0.325 mmol), stirred for 1 h at 5 °C and for 22 h at 23 °C, treated with pivaloyl chloride (40 μL, 0.325 mmol), stirred for 8 h at 23 °C and for 6 h at 50 °C and evaporated. A soln of the residue in $CHCl_3$ (10 mL) was washed with satd $NaHCO_3$ soln (2 × 10 mL), H_2O (10 mL) and brine (15 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 6:1 → 4:1 → 2:1) gave **33** (8 mg, 7%) and **32** (67 mg, 68%).

(b) At 23 °C, a soln of **11** (75 mg, 0.168 mmol) in pyridine (2.4 mL) was treated with pivaloyl chloride (43 μL, 0.350 mmol), stirred for 3 h at 50 °C and evaporated. A soln of the residue in Et_2O (40 mL) was washed with satd NH_4Cl soln (3 × 15 mL). The combined aq extracts were extracted with Et_2O (2 × 15 mL). The combined org. extracts were washed with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and evaporated. FC (as described in a) gave **33** (78 mg, 76%, colourless oil crystallizing upon drying) and **32** (15 mg, 17%).

4.23.1. Data of 32. Colourless crystals. R_f (hexane/AcOEt 2:1) 0.20. Mp 105–107 °C. $[\alpha]_D^{25} = +176.8$ (*c* 0.69, $CHCl_3$). IR ($CHCl_3$): 3390m, 3090w, 3067w, 3031m, 3012m, 2973m, 2933m, 2909m, 2871m, 1952w, 1875w, 1810w, 1737s, 1689s, 1605w, 1497w, 1479m, 1454s, 1398m, 1363m, 1317m, 1278m, 1257m, 1139s, 1113s, 1061s, 1039m, 1028m, 941w, 912w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 3; additionally, 1.27 (s, Me_3C); 4.07 (with virtual coupling); 4.45 (d, J = 12.1, PhC*H*); 4.49 (d, J = 12.1, PhC*H*); 4.53 (d, J = 10.9, PhC*H*); 4.77 (br s, PhCH_2); 4.94 (d, J = 11.2, PhC*H*); 6.05 (exchange with CD_3OD); 7.17–7.22 (m, 2 arom. H); 7.27–7.40 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 27.27 (q, Me_3C); 38.83 (s, Me$_3$*C*); 73.27, 74.79, 74.92 (3t, 3Ph*C*H$_2$); 127.49–128.41 (several d); 137.06, 137.22, 137.58 (3s); 177.35 (s, OC=O). HR-MALDI-MS: 570.2234 (5, $[M+K]^+$, $C_{32}H_{37}KNO_6^+$; calcd 570.2258), 554.2506 (100, $[M+Na]^+$, $C_{32}H_{37}NNaO_6^+$; calcd 554.2519), 532.2690 (12, $[M+H]^+$, $C_{32}H_{38}NO_6^+$; calcd 532.2699), 430.2006 (6, $[M-PivO]^+$, $C_{27}H_{28}NO_4^+$; calcd 430.2018). Anal. Calcd for $C_{32}H_{37}NO_6$ (531.65): C, 72.29; H, 7.01; N, 2.63. Found: C, 72.09; H, 6.95; N, 2.66.

4.23.2. Data of 33. Colourless oil. R_f (hexane/AcOEt 2:1) 0.80. $[\alpha]_D^{25} = +54.2$ (*c* 1.04, $CHCl_3$). IR ($CHCl_3$): 3089w, 3067w, 3031w, 3013w, 2971m, 2932m, 2872m, 1953w, 1875w, 1810w, 1737s, 1723s, 1700s, 1603w, 1496w, 1481m, 1455m, 1397m, 1365m, 1281m, 1262m, 1139s, 1099s, 1074s, 1042m, 1028m, 942w, 909w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 3; additionally, 1.27, 1.29 (2s, 2Me_3C); 3.57 (irrad. at 4.69 → d, J = 10.3); 3.63 (irrad. at 4.69 → d, J = 9.7); 3.95 (irrad. at 4.69 → dd, J = 4.4, 7.2, irrad. at 5.56 → dd, J = 1.3, 4.1); 3.98 (irrad. at 4.69 → d, J = 4.4); 4.42 (d, J = 11.8, PhC*H*); 4.48 (d, J = 11.8, PhC*H*); 4.57 (d, $J \approx 12.1$, PhC*H*); 4.58 (d, J = 11.2, PhC*H*); 4.62 (d, J = 11.5, PhC*H*); 4.63 (d, J = 12.1, PhC*H*); 7.22–7.36 (m, 15 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 27.23, 27.78 (2q, 2Me_3C); 38.78 (s, Me$_3$*C*CO$_2$); 43.78 (s, Me$_3$*C*CON); 71.74, 72.90, 73.25 (3t, 3Ph*C*H$_2$); 127.49–128.34 (several d); 137.15 (2s); 137.18 (s); 177.19 (s, OC=O); 188.17 (s, NC=O). HR-MALDI-MS: 654.2817 (3, $[M+K]^+$, $C_{37}H_{45}KNO_7^+$; calcd 654.2833), 638.3080 (100, $[M+Na]^+$, $C_{37}H_{45}NNaO_7^+$; calcd 638.3094), 616.3252 (12, $[M+H]^+$, $C_{37}H_{46}NO_7^+$; calcd 616.3274), 532.2699 (8), 319.1518 (7). Anal. Calcd for $C_{37}H_{45}NO_7$ (615.77): C, 72.17; H, 7.37; N, 2.27. Found: C, 72.04; H, 7.21; N, 2.39.

4.24. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-pivaloyl-D-glucono-1,5-thiolactam 34

A soln of **32** (25 mg, 47.02 μmol) in toluene (0.9 mL) was treated with Lawesson's reagent (14 mg, 34.61 μmol), stirred for 168 h at 23 °C, diluted with Et_2O (30 mL) and washed with satd $NaHCO_3$ soln (3 × 15 mL). The combined aq layers were extracted with Et_2O (2 × 10 mL). The combined org. layers were washed with H_2O (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 5:1 → 3:1 → 2:1) gave **34** (15.0 mg, 58%) and **32** (9.3 mg, 37%).

4.24.1. Data of 34. Colourless oil. R_f (hexane/AcOEt 3:1) 0.32. $[\alpha]_D^{25} = +92.3$ (*c* 0.56, $CHCl_3$). IR ($CHCl_3$): 3360w, 3089w, 3067w, 3019m, 2974m, 2931m, 2870m, 1951w, 1875w, 1810w, 1736s, 1603w, 1514s, 1479m, 1455m, 1398w, 1364m, 1313m, 1276m, 1143s, 1122s, 1071s, 1028m, 944w, 911w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 3; additionally, 1.26 (s, Me_3C); 3.29 (with virtual coupling); 3.56–3.70 (irrad. at 3.29 → change, irrad. at 3.96 → change); 3.96 (with virtual coupling, irrad. at 5.60 d, J = 8.1, with virtual coupling); 4.443 (d, J = 12.5, PhC*H*); 4.444 (d, J = 11.8, PhC*H*); 4.48 (d, J = 12.5, PhC*H*); 4.71 (d, J = 11.2, PhC*H*); 4.73 (d, J = 11.2, PhC*H*); 4.79 (d, J = 11.2, PhC*H*); 5.60 (irrad. at 3.96 → s); 7.12–7.16 (m, 2 arom. H); 7.26–7.40 (m, 13 arom. H); 8.11 (exchange with CD_3OD). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 27.27 (q, Me_3C); 38.82 (s, Me$_3$*C*); 73.42, 74.40, 74.43 (3t, 3Ph*C*H$_2$); 127.54–128.48 (several d); 136.76, 136.97, 137.39 (3s); 176.90 (s, OC=O). HR-MALDI-MS: 570.2279 (98, $[M+Na]^+$, $C_{32}H_{37}NNaO_5S^+$; calcd 570.2290), 554.2512 (42), 548.2462 (5, $[M+H]^+$, $C_{32}H_{38}NO_5S^+$; calcd 548.2471), 448.1939 (69, $[M+2H-PivO]^+$, $C_{27}H_{30}NO_3S^+$; calcd 448.1946), 446.1787 (17, $[M-PivO]^+$, $C_{27}H_{28}NO_3S^+$; calcd 446.1790), 440.1888 (12, $[M-BnO]^+$, $C_{25}H_{30}NO_4S^+$; calcd 440.1896), 425.3598 (47), 397.3288 (100). Anal. Calcd for $C_{32}H_{37}NO_5S$ (547.71): C, 70.17; H, 6.81; N, 2.56. Found: C, 69.98; H, 6.74; N, 2.62.

4.25. 5-Amino-3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(methoxymethyl)-D-glucono-1,5-lactam 35 and 3,4,6-tri-*O*-benzyl-5-deoxy-2-*O*-(methoxymethyl)-5-[(methoxymethyl)-amino]-D-glucono-1,5-lactam 36

(a) A soln of **11** (22 mg, 49.2 μmol) in $CHCl_3$ (1 mL) was treated successively with $MeOCH_2OMe$ (0.3 mL, 3.38 mmol) and P_2O_5 (163 mg, 1.15 mmol), stirred for 30 min at 23 °C, cooled to 0 °C and treated with satd $NaHCO_3$ soln (2 mL). The mixture was diluted with Et_2O (20 mL) and washed with satd $NaHCO_3$ soln (3 × 15 mL). The combined aq layers were extracted with Et_2O (2 × 15 mL). The combined org. layers were washed with H_2O (25 mL) and brine (25 mL), dried over ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 4:1 → 2:1) gave **36** (2 mg, 9%) and **35** (15 mg, 62%).

(b) A suspension of **11** (50 mg, 0.112 mmol) and P_2O_5 (32 mg, 0.225 mmol) in $MeOCH_2OMe$ (0.5 mL) was stirred for 3 h at 23 °C. Workup and FC as described in (a) gave **36** (14 mg, 23%) and **35** (25 mg, 46%).

4.25.1. Data of 35. Colourless oil. R_f (hexane/AcOEt 2:1) 0.15. $[\alpha]_D^{25} = +158.5$ (*c* 0.80, $CHCl_3$). IR ($CHCl_3$): 3388w, 3090w, 3067w, 3031w, 3012m, 2903m, 2866w, 1952w, 1875w, 1810w, 1682s, 1603w, 1497w, 1454m, 1400w, 1363m, 1316m, 1282w, 1259w, 1150s, 1117s, 1102s, 1036s, 1029s, 915w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 3; additionally, 3.45 (s, MeO); 3.90 (with virtual coupling, irrad. at 4.19 → d, J = 8.7, with virtual coupling); 4.19 (irrad. at 3.90 → s); 4.43 (d, J = 12.1, PhC*H*); 4.48 (d, J = 12.1, PhC*H*); 4.51 (d, J = 11.2, PhC*H*); 4.83 (d, J = 11.2, PhC*H*); 4.85 (d, J = 11.2, PhC*H*); 4.86 (d, J = 6.5, OCHO); 4.92 (d,

J = 11.2, PhC*H*); 5.11 (d, J = 6.5, OCH′O); 6.01 (exchange with CD_3OD); 7.17–7.22 (m, 2 arom. H); 7.25–7.40 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 56.30 (q, MeO); 73.29, 74.68, 74.87 (3t, 3Ph*C*H_2); 97.34 (t, O*C*H_2O); 127.66–128.40 (several d); 137.09, 137.29, 137.80 (3s). HR-MALDI-MS: 514.2191 (100, $[M+Na]^+$, $C_{29}H_{33}NNaO_6^+$; calcd 514.2206), 460.2111 (32, $[M-MeO]^+$, $C_{28}H_{30}NO_5^+$; calcd 460.2124). Anal. Calcd for $C_{29}H_{33}NO_6$ (491.58): C, 70.86; H, 6.77; N, 2.85. Found: C, 70.69; H, 6.75; N, 2.91.

4.25.2. Data of 36. Colourless oil. R_f (hexane/AcOEt 2:1) 0.38. $[\alpha]_D^{25} = +34.1$ (c 0.58, $CHCl_3$). IR ($CHCl_3$): 3090w, 3067w, 3030m, 3012m, 2934m, 2900m, 2866m, 1952w, 1873w, 1810w, 1679s, 1603w, 1496w, 1454m, 1387w, 1363m, 1290w, 1261w, 1172m, 1149m, 1099s, 1071s, 1039s, 1028s, 914m. ^1H NMR ($CDCl_3$, 300 MHz): see Table 3; additionally, 3.27, 3.43 (2s, 2MeO); 4.44 (d, J = 12.1, PhC*H*); 4.48 (d, J = 12.1, PhC*H*); 4.57 (d, J = 11.8, PhC*H*); 4.61 (d, J = 10.6, NCHO); 4.62 (d, J = 11.8, PhC*H*); 4.67 (d, J = 11.2, PhC*H*); 4.80 (d, J = 11.5, PhC*H*); 4.86 (d, J = 6.8, OCHO); 5.00 (d, J = 6.5, OCH′O); 5.10 (d, J = 10.6, NCH′O); 7.24–7.37 (m, 15 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 4; additionally, 56.10, 56.27 (2q, 2MeO); 72.09, 73.31, 73.72 (3t, 3Ph*C*H_2); 75.74 (t, N*C*H_2O); 96.89 (t, O*C*H_2O); 127.53–128.34 (several d); 137.34, 137.48, 137.84 (3s). HR-MALDI-MS: 558.2459 (100, $[M+Na]^+$, $C_{31}H_{37}NNaO_7^+$; calcd 558.2468), 504.2383 (15, $[M-MeO]^+$, $C_{30}H_{34}NO_6^+$; calcd 504.2386), 382.1643 (8, $[M-MOM-BnOH]^+$, $C_{22}H_{24}NO_5^+$; calcd 382.1654). Anal. Calcd for $C_{31}H_{37}NO_7$ (535.64): C, 69.51; H, 6.96; N, 2.61. Found: C, 69.54; H, 6.96; N, 2.71.

4.25.3. Desilylation of 27. A soln of **27** (660 mg, 1.13 mmol) in THF (13 mL) was treated with 1 M Bu_4NF in THF (2.2 mL, 2.20 mmol) and stirred at 23 °C for 3.5 h. The mixture was diluted with Et_2O (30 mL) and washed with satd NH_4Cl soln (3 × 20 mL). The combined aq layers were extracted with Et_2O (2 × 20 mL). The combined org. layers were washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt/MeOH 1:3:0 → 0:1:0 → 0:20:1) gave **22**[1,24,25] (482 mg, 91%).

4.25.4. Desilylation of 31. At 0 °C, a soln of **31** (350 mg, 0.558 mmol) in THF (6 mL) was treated with 1 M Bu_4NF in THF (1.1 mL, 1.10 mmol), stirred at 0 °C for 1 h and treated with satd NH_4Cl soln (10 mL). Workup and FC as described for the desilylation of **27** afforded **22**[1,24,25] (248 mg, 94%).

4.25.5. Desilylation of 28. A soln of **28** (34 mg, 58.1 μmol) in THF (0.7 mL) was treated with 1 M Bu_4NF in THF (0.12 mL, 0.12 mmol) and stirred at 23 °C for 3.5 h. The mixture was diluted with Et_2O (30 mL) and washed with satd NH_4Cl soln (3 × 20 mL). The combined aq layers were extracted with Et_2O (2 × 20 mL). The combined org. layers were washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt/MeOH 1:3:0 → 0:1:0 → 0:20:1) gave **23**[1,24,25] (21 mg, 77%).

4.26. (5*R*,6*R*,7*S*,8*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-8-yl *N*,*N*-diisopropylcarbamate 37 and (5*R*,6*R*,7*S*,8*R*)-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-8-yl *N*,*N*-diisopropylcarbamate 38

(a) A soln of **22**[1,24,25] (25 mg, 53.1 μmol), *i*-Pr_2NCOCl (17.3 mg, 0.106 mmol) and DMAP (12.9 mg, 0.106 mmol) in pyridine (1 mL) was stirred at 120 °C for 7 h, treated with H_2O (1 mL) and evaporated. A soln of the brown residue in Et_2O (50 mL) was washed with 2M aq HCl (3 × 30 mL). The combined aq layers were extracted with Et_2O (2 × 30 mL). The combined org. layers were washed with water (60 mL) and brine (60 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 1:1 → 0:1) gave **37** (13.0 mg, 41%) and **38** (11.3 mg, 36%).

(b) A suspension of **22**[1,24,25] (25 mg, 53.1 μmol) and 55% NaH in oil (4.5 mg, 0.103 mmol) in THF (1 mL) was stirred at 23 °C for 1 h, cooled to 0 °C and treated with *i*-Pr_2NCOCl (13.8 mg, 84.3 μmol). The mixture was stirred at 0 °C for 15 min and at 23 °C for 6 h, treated with satd NH_4Cl soln (3 mL) at 0 °C, diluted with Et_2O (20 mL) and washed with satd NH_4Cl soln (3 × 15 mL). The combined aq layers were extracted with Et_2O (2 × 15 mL). The combined org. layers were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 1:1) gave **37** (30.4 mg, 96%).

4.26.1. Data of 37. R_f (AcOEt) 0.40. $[\alpha]_D^{25} = +25.5$ (c 0.70, $CHCl_3$). UV ($CHCl_3$): 259 (2.78), 240 (3.24). IR ($CHCl_3$): 3089w, 3067w, 3032w, 3008m, 2970m, 2935m, 2873m, 1951w, 1873w, 1810w, 1684s, 1604w, 1495m, 1478m, 1454s, 1441m, 1369m, 1342m, 1289s, 1135s, 1086s, 1029m, 910w. ^1H NMR ($CDCl_3$, 300 MHz): see Table 6; additionally, 1.02–1.36 (m, (*Me*$_2$CH)$_2$N); 3.64–3.84 (m, Me$_2$C*H*); 3.71 (irrad. at 3.78 → change, irrad. at 4.39 → d, J = 10.0); 3.78 (irrad. at 3.71 → change, irrad. at 4.39 → d, J = 10.0); 3.93 (irrad. at 4.21 → d, $J \approx 4.0$, irrad. at 4.39 → d, $J \approx 5.6$); 3.96–4.12 (br s, Me$_2$C*H*); 4.21 (irrad. at 3.93 → d, J = 3.7, irrad. at 6.11 → d, J = 5.3); 4.35–4.42 (irrad. at 3.71 → change, irrad. at 3.78 → t, J = 4.0, irrad. at 3.93 → dd, J = 3.7, 5.9); 4.41 (d, J = 11.8, PhC*H*); 4.43 (d, J = 11.8, PhC*H*); 4.46 (d, J = 11.8, PhC*H*); 4.66 (d, J = 11.8, PhC*H*); 4.74 (d, J = 11.8, PhC*H*); 4.88 (d, J = 11.8, PhC*H*); 6.11 (irrad. at 4.21 → s); 7.15–7.18 (m, 2 arom. H); 7.23–7.37 (m, 13 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7; additionally, 20.73, 21.47 (2br q, (*Me*$_2$CH)$_2$N); 45.81, 46.43 (2br d, (Me$_2$*C*H)$_2$N); 72.82, 73.02, 73.31 (3t, 3Ph*C*H_2); 127.59–128.37 (several d); 137.25, 137.34, 137.68 (3s); 154.45 (s, C=O). HR-MALDI-MS: 636.2789 (<1, $[M+K]^+$, $C_{36}H_{43}KN_3O_5^+$; calcd 636.2840), 620.3084 (17, $[M+Na]^+$, $C_{36}H_{43}N_3NaO_5^+$; calcd 620.3100), 598.3264 (12, $[M+H]^+$, $C_{36}H_{44}N_3O_5^+$; calcd 598.3281), 475.1981 (6, $[M+Na-i\text{-}Pr_2NH-CO_2]^+$, $C_{29}H_{28}N_2$-

NaO_3^+; calcd 475.1997), 453.2168 (100, [M−*i*-Pr_2N−CO_2]$^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178).

4.26.2. Data of 38. R_f (AcOEt) 0.23. $[\alpha]_D^{25} = -41.6$ (*c* 0.43, $CHCl_3$). UV ($CHCl_3$): 259 (2.96), 239 (3.30). IR ($CHCl_3$): 3089w, 3067w, 3031w, 3003m, 2971m, 2934m, 2872m, 1951w, 1879w, 1810w, 1688s, 1603w, 1496m, 1473m, 1454m, 1441m, 1369m, 1346m, 1291s, 1136s, 1107s, 1080s, 1046m, 1028m, 908w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 8; additionally, 1.02–1.32 (m, (Me_2CH)$_2$N); 3.67–3.83 (m, Me_2CH); 4.02–4.16 (m, Me_2CH); 4.05 (irrad. at 4.24 → change, irrad. at 6.58 → d, *J* = 9.3); 4.07 (irrad. at 4.24 → change); 4.39 (d, *J* = 12.8, PhC*H*); 4.43 (d, *J* = 12.8, PhC*H*); 4.55 (d, *J* = 10.9, PhC*H*); 4.59 (d, *J* = 10.6, PhC*H*); 4.94 (d, *J* = 11.2, PhC*H*); 4.97 (d, *J* = 11.2, PhC*H*); 7.20–7.39 (m, 15 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7; additionally, 20.76, 21.57 (2br q, (Me_2CH)$_2$N); 45.45, 46.76 (2br d, (Me_2CH)$_2$N); 71.79, 73.13, 74.84 (3t, 3PhCH_2); 127.53–128.34 (several d); 137.32, 137.62, 137.72 (3s); 154.23 (s, C=O). HR-MALDI-MS: 636.2809 (1, [M+K]$^+$, $C_{36}H_{43}KN_3O_5^+$; calcd 636.2840), 620.3090 (19, [M+Na]$^+$, $C_{36}H_{43}N_3NaO_5^+$; calcd 620.3100), 598.3273 (10, [M+H]$^+$, $C_{36}H_{44}N_3O_5^+$; calcd 598.3281), 475.1985 (4, [M+Na–*i*-Pr_2NH–CO_2]$^+$, $C_{29}H_{28}N_2NaO_3^+$; calcd 475.1997), 453.2171 (100, [M−*i*-Pr_2N–CO_2]$^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178).

4.27. (5*R*,6*R*,7*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-8-one 39

At 0 °C, a soln of **22**[1,24,25] (35 mg, 74.4 μmol) in CH_2Cl_2 (1.5 mL) was treated with 15% soln of Dess–Martin periodinane in CH_2Cl_2 (0.31 mL, 0.149 mmol), stirred at 0 °C for 2 h, treated with a mixture of 10% aq $Na_2S_2O_3$ soln/satd $NaHCO_3$ soln 1:1 (3 mL) and stirred at 23 °C for 10 min. The mixture was diluted with Et_2O (40 mL) and washed with a mixture of 10% aq $Na_2S_2O_3$ soln/satd $NaHCO_3$ soln 1:1 (3 × 25 mL). The combined aq layers were extracted with Et_2O (2 × 20 mL). The combined org. layers were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated. The crude product (34 mg, a single compound according to the ^{1}H NMR spectrum) was precipitated from hexane/AcOEt 2:1 (3 mL) at −50 °C to afford after drying **39** (25 mg, ca. 72%). Colourless solid containing substantial amounts of H_2O. The sample for microanalysis was dried for 5 days at 10^{-4} Torr. R_f (AcOEt) 0.41. Mp 90–93°. $[\alpha]_D^{25} = -12.1$ (*c* 0.97, $CHCl_3$). UV ($CHCl_3$): 292 (4.11). IR ($CHCl_3$): 3375w (br), 3156w, 3089w, 3067w, 3033m, 3012m, 2920w, 2869m, 1953w, 1877w, 1810w, 1696s, 1603w, 1508w, 1497m, 1455s, 1403s, 1364m, 1326w, 1278w, 1219w, 1149m, 1092s, 1043m, 1029m, 922w, 911w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 6; additionally, 3.81 (irrad. at 4.50 → d, *J* = 10.2); 3.87 (irrad. at 4.50 → d, *J* = 10.3); 4.13 (irrad. at 4.22 → change, irrad. at 4.50 → d, *J* = 6.2); 4.22 (irrad. at 4.13 → s); 4.43 (d, *J* = 11.8, PhC*H*); 4.48 (d, *J* = 12.1, PhC*H*); 4.46–4.54 (irrad. at 4.13 → change); 4.53 (d, *J* = 11.8, PhC*H*); 4.67 (d, *J* = 11.5, PhC*H*); 4.75 (d, *J* = 11.5, PhC*H*); 4.96 (d, *J* = 11.8, PhC*H*); 7.14–7.25 (m, 4 arom. H); 7.28–7.40 (m, 11 arom. H). ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7; additionally, 73.39 (t, PhCH_2); 73.47 (t, 2PhCH_2); 127.69–128.44 (several d); 136.67, 136.85, 136.96 (3s). HR-MALDI-MS: 469.2122 (2, [M+H]$^+$, $C_{29}H_{29}N_2O_4^+$; calcd 469.2127), 457.2118 (2), 451.2013 (1, [M−OH]$^+$, $C_{29}H_{27}N_2O_3^+$; calcd 451.2022), 383.1362 (6, [M+Na−BnOH]$^+$, $C_{22}H_{20}N_2NaO_3^+$; calcd 383.1372), 377.1497 (3, [M−Bn]$^+$, $C_{22}H_{21}N_2O_3^+$; calcd 377.1501), 361.1549 (100, [M−BnO]$^+$, $C_{22}H_{21}N_2O_3^+$; calcd 361.1552), 292.0818 (5, [M+Na−BnOH−Bn]$^+$, $C_{15}H_{13}N_2NaO_3^+$; calcd 292.0824), 270.0996 (6, [M−BnO−Bn]$^+$, $C_{15}H_{14}N_2O_3^+$; calcd 270.1004), 253.0968 (4, [M−BnO−BnOH]$^+$, $C_{15}H_{13}N_2O_2^+$; calcd 253.0977). Anal. Calcd for $C_{29}H_{28}N_2O_4 \cdot 0.5H_2O$ (477.56): C, 72.94; H, 6.12; N, 5.87. Found: C, 72.84; H, 5.77; N, 5.87.

4.28. (5*R*,6*R*,7*S*,8*S*)-8-Azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine 40[1,24,25] and (5*R*,6*R*,7*S*,8*R*)-8-azido-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]-pyridine 41[1]

(a) A soln of **22**[1,24,25] (25 mg, 53.1 mol) in toluene (0.5 mL) was treated successively with diphenyl phosphorazidate (= DPPA, 57 μL, 0.264 mmol) and DBU (40 μL, 0.268 mmol), and stirred at 23 °C for 4 h. The brown mixture was diluted with CH_2Cl_2 (30 mL) and washed with satd NH_4Cl soln (3 × 15 mL). The combined aq layers were extracted with CH_2Cl_2 (2 × 20 mL). The combined org. layers were washed with H_2O (35 mL) and brine (35 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 1:0 → 3:1 → 1:1) gave **40** (17 mg, 65%) and **41** (4 mg, 15%).

(b) A soln of **22**[1,24,25] (458 mg, 0.973 mmol) in toluene (9 mL) was treated successively with DPPA (1.05 mL, 4.87 mmol) and DBU (0.73 mL, 4.89 mmol), and stirred at 23 °C for 4.5 h. Workup and FC as described in (a) gave **40** (290 mg, 60%) and a mixture containing mainly **41** and traces of DBU (60 mg). FC (RP-C18 silica gel, MeOH/H_2O 4:1) of this mixture afforded pure **41** (56 mg, 12%).

(c) As (a), but with **22/23** 55:45[1,24,25] (35 mg, 74.4 μmol) instead of **22**. Workup and FC gave **40** (23 mg, 62%) and **41** (4 mg, 11%).

(d) As (a), but with **23**[1,24,25] (13 mg, 27.6 μmol) instead of **22**. Workup and FC afforded **40/41** 85:15 (9 mg, 66%).

(e) As (a), but with di-(*p*-nitrophenyl)phosphorazidate (97 mg, 0.266 mmol) instead of DPPA. Workup and FC gave **40** (14 mg, 53%) and **41** (3 mg, 11%).

(f) A suspension of **22**[1,24,25] (25 mg, 53.1 μmol) and 55% NaH in oil (4.1 mg, 94.0 μmol) was stirred at 23 °C for 1 h, cooled to 0 °C and treated with DPPA (35 μL, 0.162 mmol). The mixture was stirred at 0 °C for 10 min and at 23 °C for 10 h, diluted with Et_2O (30 mL) and washed with satd NH_4Cl soln (3 × 15 mL). The combined aq layers were extracted

with Et_2O (2 × 15 mL). The combined org. layers were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and evaporated. FC (hexane/AcOEt 1:0 → 3:1 → 1:1) gave **40** (7 mg, 27%) and **40/41** 1:1 (3 mg, 11%).

4.28.1. Data of 40. Colourless oil. R_f (hexane/AcOEt 1:1) 0.29. $[\alpha]_D^{25} = +58.6$ (*c* 1.19, $CHCl_3$) (lit.:[24,25] +59.0 ($CHCl_3$)). UV ($CHCl_3$): 258 (2.88), 240 (3.36). IR ($CHCl_3$): 3159w, 3089w, 3067w, 3033w, 3011w, 2955w, 2920w, 2870w, 2109s, 1951w, 1877w, 1810w, 1589w, 1523w, 1496w, 1488w, 1454m, 1362m, 1331w, 1308w, 1282m, 1259w, 1170w, 1142m, 1086m, 1028w, 1011w, 940w, 909w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 6. ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7. HR-MALDI-MS: 607.2436 (16), 518.2166 (5, $[M+Na]^+$, $C_{29}H_{29}N_5NaO_3^+$; calcd 518.2168), 496.2339 (66, $[M+H]^+$, $C_{29}H_{30}N_5O_3^+$; calcd 496.2349), 490.2099 (14, $[M+Na-N_2]^+$, $C_{29}H_{29}N_3NaO_3^+$; calcd 490.2107), 470.2446 (20, $[M+3H-N_2]^+$, $C_{29}H_{32}N_3O_3^+$; calcd 470.2444), 468.2278 (43, $[M+H-N_2]^+$, $C_{29}H_{30}N_3O_3^+$; calcd 468.2287), 455.2328 (65, $[M+2H-N_3]^+$, $C_{29}H_{31}N_2O_3^+$; calcd 455.2235), 453.2170 (100, $[M-N_3]^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178), 361.1541 (11).

4.28.2. Data of 41. Colourless oil. R_f (hexane/AcOEt 1:1) 0.13. $[\alpha]_D^{25} = -49.8$ (*c* 1.00, $CHCl_3$). UV ($CHCl_3$): 258 (2.86), 241 (3.43). IR ($CHCl_3$): 3159w, 3090w, 3067w, 3032w, 3011m, 2930w, 2869m, 2104s, 1951w, 1877w, 1810w, 1603w, 1525w, 1496m, 1454m, 1363m, 1310m, 1268m, 1168w, 1131m, 1102s, 1082s, 1028m, 1013m, 909w. ^{1}H NMR ($CDCl_3$, 300 MHz): see Table 8. ^{13}C NMR ($CDCl_3$, 75 MHz): see Table 7. HR-MALDI-MS: 607.2431 (18), 518.2167 (10, $[M+Na]^+$, $C_{29}H_{29}N_5NaO_3^+$; calcd 518.2168), 496.2338 (89, $[M+H]^+$, $C_{29}H_{30}N_5O_3^+$; calcd 496.2349), 490.2098 (20, $[M+Na-N_2]^+$, $C_{29}H_{29}N_3NaO_3^+$; calcd 490.2107), 470.2442 (55, $[M+3H-N_2]^+$, $C_{29}H_{32}N_3O_3^+$; calcd 470.2444), 468.2276 (72, $[M+H-N_2]^+$, $C_{29}H_{30}N_3O_3^+$; calcd 468.2287), 455.2325 (73, $[M+2H-N_3]^+$, $C_{29}H_{31}N_2O_3^+$; calcd 455.2235), 453.2166 (100, $[M-N_3]^+$, $C_{29}H_{29}N_2O_3^+$; calcd 453.2178), 361.1547 (18).

4.29. (5*R*,6*R*,7*S*,8*R*)-8-Amino-5,6,7,8-tetrahydro-5-(hydroxymethyl)imidazo[1,2-]pyridine-6, 7-diol 8

A soln of **41** (63 mg, 0.127 mmol) in AcOH (3 mL) was treated with 10% Pd/C (60 mg) and hydrogenated at 6 bar for 60 h. The suspension was filtered through Celite, and the residue was washed with MeOH (20 mL). Evaporation of the combined filtrates, co-evaporation with toluene (4 × 5 mL), ion-exchange chromatography (Amberlite CG-120, NH_4^+ form, elution with 0.05 M aq NH_3) and lyophilization afforded **8** (16.5 mg, 65%). Colourless hygroscopic solid. R_f ($CHCl_3$/MeOH/NH_4OH 5:4:1) 0.35. $[\alpha]_D^{25} = -30.1$ (*c* 0.85, H_2O). pK_{HA} = 7.02 (no additional p*K* value was observed in the pH range 2.9–10.3). UV (H_2O): 216 (3.67), 192 (3.61). IR (0.4% in KBr): 3600–2100s (br), 3356s, 3277s, 3162s, 3073s, 2913s, 2841s, 2695s, 1591m, 1484s, 1445s, 1384m, 1336m, 1323m, 1289m, 1277m, 1219w, 1169w, 1154w, 1131w, 1088m, 1061s, 1022s, 959w, 932w, 881m. ^{1}H NMR (D_2O, 300 MHz): see Table 9; additionally, 4.008 (irrad. at 3.88 → d, *J* = 3.1); 4.009 (irrad. at 4.22 → d, *J* = 4.0); 4.14 (irrad. at 3.88 → br t, *J* ≈ 4.1, irrad. at 4.22 → change); 7.02, 7.16 (2d, *J* = 1.2, H–C(2), H–C(3)). ^{1}H NMR (D_2O, 300 MHz, 1 equiv of CF_3CO_2H): see Table 9; additionally, 7.53, 7.67 (2d, *J* = 1.9, H–C(2), H–C(3)). ^{1}H NMR (D_2O, 300 MHz, 2 equiv of CF_3CO_2H): see Table 9; additionally, 7.62, 7.75 (2d, *J* = 2.2, H–C(2), H–C(3)). ^{13}C NMR (D_2O, 75 MHz): 46.77 (d, C(8)); 61.42 (t, CH_2–C(5)); 62.10 (d, C(5)); 68.92, 69.56 (2d, C(6), C(7)); 118.32 (d, C(3)); 127.61 (d, C(2)); 147.06 (s, C(8a)). HR-MALDI-MS: 222.0849 (46, $[M+Na]^+$, $C_8H_{13}N_3O_3^+$; calcd 222.0855), 200.1030 (100, $[M+H]^+$, $C_8H_{14}N_3O_3^+$; calcd 200.1035), 183.0757 (53, $[M-NH_2]^+$, $C_8H_{11}N_2O_3^+$; calcd 183.0757). HR-ESI-MS: 421.1785 (95, $[2M+Na]^+$, $C_{16}H_{26}N_6NaO_6^+$; calcd 421.1812), 222.0852 (18, $[M+Na]^+$, $C_8H_{13}N_3O_3^+$; calcd 222.0855), 200.1027 (100, $[M+H]^+$, $C_8H_{14}N_3O_3^+$; calcd 200.1035).

4.30. Inhibition studies

Determination of the inhibition constants (K_i) or the IC_{50} values was performed with a range of inhibitor concentrations (typically 4–7 concentrations), which bracket the K_i or IC_{50} value, and substrate concentrations, which bracket the K_M of each enzyme (for K_i, typically 5–7 concentrations), or correspond to it (for IC_{50}).

(a) *Inhibition of snail β-mannosidase*. K_M = 0.48–0.56 mM (Ref. 48: K_M = 0.42–0.80 mM). IC_{50} and K_i values were determined at 25 °C at an enzyme concentration of 0.048 units/mL, using a 0.04 M acetate buffer (pH 4.5 or 5.5) and 4-nitrophenyl β-D-mannopyranoside as the substrate. The enzymatic reaction was started after incubation of the enzyme (100 μL) in presence of the inhibitor (50 μL) during 1 h at 25 °C, by the addition of the substrate (50 μL). The enzyme reaction was quenched by addition of 0.2 M borate buffer (pH 9.0, 100 μL) after 5 min and the absorption at 405 nm was taken as rate for the 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 versus 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[60] and plotting them versus the inhibitor concentrations.[61] 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 versus the inhibitor concentrations.[61] After fitting a straight line to the data by linear regression, the negative [I]-intercept of this plot provided the appropriate $\alpha \cdot K_i$ value.

(b) *Inhibition of* Jack *bean α-mannosidase*. K_M = 2.27 mM (Ref. 51: K_M = 2.5 mM; Ref. 48: K_M = 1.8–2.8 mM). As described in (a), inhibition studies were carried out at 37 °C at an enzyme concentration of 0.086 units/mL, using a 0.04 M acetate buffer (pH 4.5),

containing 1.5 mmol of $ZnCl_2$ and 4-nitrophenyl α-D-mannopyranoside as the substrate. The enzymatic reaction was started after the incubation at 37 °C for 1 h.

Acknowledgements

We thank M. Schneider for the pK_{HA} determinations, Dr. M. Linke for a generous sample of **16**, Dr. B. Bernet for modelling and for checking the experimental part and the Swiss National Science Foundation, Oxford Glycosciences Ltd., Abingdon (UK) and F. Hoffmann-La Roche AG, Basel (CH), for generous support.

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