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3-Hydroxyazetidine Carboxylic Acids: Non-Proteinogenic Amino Acids for Medicinal Chemists

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The formation from D-glucose of both enantiomers of 2,4-dideoxy-2,4-iminoribonic acid is the first chemical synthesis of unprotected 3-hydroxyazetidine carboxylic acids. The long-term stability of 3-hydroxyazetidine amides is established at acidic and neutral pH and implies their value as non-proteinogenic amino acid components of peptides, providing medicinal chemists with a new class of peptide isosteres. The structure of *N*,3-*O*-dibenzyl-2,4-dideoxy-2,4-imino-D-ribonic acid was established by X-ray crystallographic analysis. An *N*-methylazetidine amide derivative is a specific inhibitor of β-hexosaminidases at the micromolar level, and is only the second example of potent inhibition of any glycosidase by an amide of a sugar amino acid related to an iminosugar.

Introduction

Proline **1**, containing a pyrrolidine ring, has a smaller loss of conformational entropy upon folding than other proteinogenic amino acid constituents and is an important determinant in the structural features of proteins (Figure 1).[1] Therefore, the use of modified proline isosteres[2] incorporated into peptidomimetics is of considerable value to medicinal chemists in the invention of new pharmacophores.[3] L-Azetidine-2-carboxylic acid (Aze) **4**[4,5] is a naturally occurring non-proteinogenic amino acid, first isolated from *Convallaria majalis* in 1955;[6] Aze is a constituent of nicotianamine and mugineic acid derivatives, which are iron transporters in plants.[7] Aze occurs in many other plants, including sugar beet,[8] and in rhizomes of *Polygonatum sibiricum* and *Polygonatum odoratum* used as supplements in many foods, including tea.[9] Aze is readily misincorporated into proteins as a substitute for proline **1** in many species, including humans,[10] and causes numerous toxic effects as well as congenital malformations.[11] There are recent reports of Aze **4** and its analogues as key components of SAR studies on azetidine-containing dipeptides as HCMV inhibitors[12] and as modulators of sphingosine phosphate receptor-1 as a suppressant of autoimmunity,[13] among many other uses.[14] The rigidity of the four-membered ring makes azetidine carboxylic acids attractive as a family of monomers for foldamers[15,16] to complement the use of oxetane amino acids[17] in the generation of novel secondary structural features in peptidomimetics. There is therefore current interest in the synthesis of Aze itself[18] and related azetidine amino acids.[19]

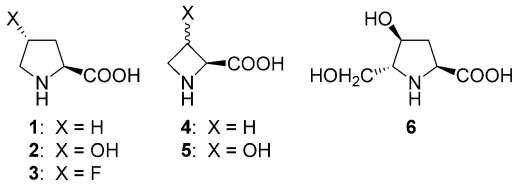

Figure 1. Azetidine-2-carboxylic acid and related amino acids.

The *trans*-4-hydroxylation of proline **1** by prolyl hydroxylases to give a *trans*-4-hydroxyproline **2** (Hyp) in collagen proline residues changes Gly-Pro-Pro repeats to Gly-Pro-Hyp and is crucial for the conformational stability of its triple-helical secondary structure, as studied using collagen-like model peptides.[20] A related family of prolyl hydroxylases (PHDs) regulates the transcriptional complex hypoxia inducible factor (HIF) by introducing an Hyp moiety into HIF. This Hyp residue increases HIF affinity to the von Hippel Lindau tumor suppressor ~1000-fold, leading to proteasomal HIF degradation. Because PHD activity is decreased under hypoxic conditions, HIF remains stable and initiates its transcriptional response as central regulator of mammalian oxygen homeostasis.[21] HIF is activated in a broad array of ischemic/hypoxic and neoplastic diseases; HIF has provided a focus for efforts to understand the underlying mechanisms of oxygen sensing and signal transduc-

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tion.[22] The HIF prolyl hydroxylases are related to the collagen prolyl hydroxylases; structural studies have been used for the design of PHD inhibitors aimed at treating anemia and ischemic disease.[23] The origin of increased stability of collagen by 4-fluoroproline **3** has been studied.[24] Substrate analogue studies with **2** and **3** (and their *cis*-epimers) have shown how PHDs achieve specificity for hydroxyprolyl/prolyl residues for the C4-*exo*/*endo* prolyl conformations, respectively.[25] Despite the interest in hydroxyprolines,[26] the sole reported preparation of 3-hydroxy-Aze **5** is by biohydroxylation of Aze with proline hydroxylases;[27] other azetidine substrates have been biohydroxylated to 3-hydroxyazetidines.[28] There is no previous report of the chemical synthesis of a 3-hydroxyazetidine-2-carboxylic acid with free NH and OH groups in the structure. In the pursuit of a synthesis of 3-epi-hydroxymugineic acid **7**, an N-alkylated derivative was generated (Figure 2A).[29]

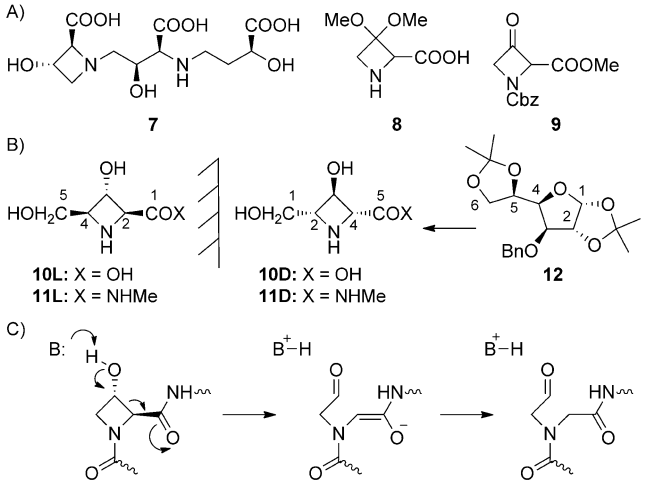


Figure 2. A) Published examples; B) synthesis strategy (numbering refers to the carbon atoms in glucose); C) retro-aldol mechanism.

Herein we report the synthesis of the enantiomers of 2,4-dideoxy-2,4-iminoribonic acid **10** and the corresponding *N*-methylamides **11** from the protected D-glucose **12**, in which the azetidine ring is formed by double nucleophilic displacements between C2 and C4 of a glucopyranoside. The L-enantiomer **10L** is obtained by cleavage of the C5–C6 bond prior to azetidine ring formation, whereas the D-enantiomer **10D** involves cleavage of the C5–C6 bond after formation of the heterocyclic ring (Figure 2B). Protected derivatives of **10** are suitable intermediates for the study of highly functionalized azetidine carboxylic acids as peptidomimetics and as a potential family of foldamer monomers. It is shown that the amides **11** are stable at neutral and low pH for periods of six months, but are vulnerable to aldol cleavage at higher pH (Figure 2C). Similar mechanisms have rendered methylacetal **8**[30] unstable on standing at room temperature, ketone **9**[31] unstable to purification on silica gel, and have only allowed for isolation of C3-hydroxy-protected derivatives.[32] Because Aze **4** is misincorporated for proline **1** into proteins and because proline hydroxylases oxidize Aze **4** to **5**, it may be that the study of incorporation of hydroxyazetidine carboxylic acids (and of their fluoro analogues) would provide further information on the consequences of substitution of proline by Aze and supply compounds of interest to medicinal chemists. It is clear that such a hydroxylation of an Aze protein would render the protein potentially conformationally unstable due to a reverse aldol reaction (Figure 2C).

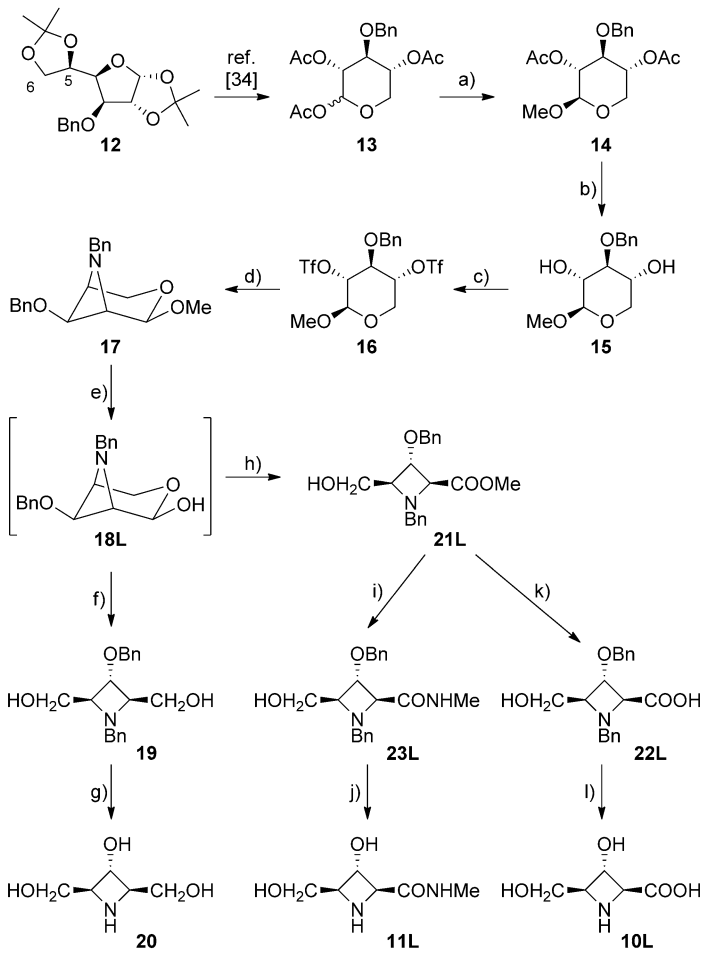
Additionally, the effect of the hydroxylated azetidines on a panel of glycosidases was determined; the *N*-methylamide **11L** is a potent and specific inhibitor of hexosaminidases, and its enantiomer **11D** is a good inhibitor of a β-glucuronidase. Although iminosugars are well established as inhibitors of glycosidases and other sugar-metabolizing enzymes, inhibition of amides of their corresponding amino acids is effectively unknown. It may also be noted that the azetidine acids **10** are related to the amino acid bulgecinine **6**[33] in the same way the hydroxyazetidine **5** is related to hydroxyproline **2** (Figure 1).

Results and Discussion

The synthesis of the L-amino acid **10L** required cleavage of the C5–C6 bond in the protected glucose **12** prior to formation of the azetidine ring (Scheme 1). Selective hydrolysis of the side chain acetonide in **12** followed by periodate cleavage and functional group manipulation gave a mixture of anomers of the protected 3-*O*-benzylxylose **13** in five steps with an overall yield of 52%, as previously described.[34]

Reaction of **13** with hydrogen bromide in acetic acid/dichloromethane afforded the corresponding bromide, which upon treatment with methanol in the presence of silver(I) carbonate formed the β-pyranoside **14** (61%),[35] from which the acetyl groups were removed by sodium methoxide in methanol to afford the diol **15** (100%). Esterification of the remaining hydroxy groups in **15** with trifluoromethanesulfonyl anhydride in dichloromethane in the presence of pyridine formed the ditriflate **16**β (100%), which with benzylamine in acetonitrile gave the bicyclic azetidine **17** (85%). Under similar conditions the corresponding α-pyranoside **16**α did not form any bicyclic product; only β-anomers of such pyranosides cyclized to azetidines in good yield.[36]

Hydrolysis of **17** by aqueous hydrochloric acid in dioxane gave the lactols **18L**. Reduction of **18L** by sodium borohydride, followed by purification via an acetylation–deacetylation sequence to remove the borate complexes, gave the dibenzyl diol **19** (74%). Removal of the benzyl group by hydrogenolysis in aqueous dioxane in the presence of palladium on carbon and hydrochloric acid gave the *meso*-iminoribitol azetidine **20**. Oxidation of **18L** by iodine in methanol in the presence of potassium carbonate[37] produced the methyl ester **21L** (84%). Hydrolysis of **21L** by hydrochloric acid in aqueous dioxane gave the acid **22L** (81%) from which the benzyl groups were removed by hydrogenolysis to afford the unprotected 3-hydroxyazetidine carboxylic acid **10L**. Treatment of the methyl ester **21L** with methylamine in methanol in the presence of anhydrous calcium chloride[38] formed the amide **23L** (70%) which, upon hydrogenolysis, formed the unprotected amide **11L**.



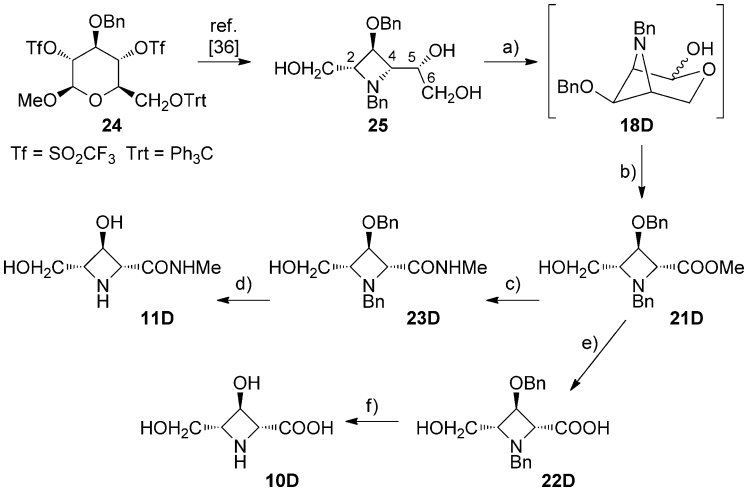
Scheme 1. a) HBr, 5–10 °C, AcOH/CH_2Cl_2 (7:3), 5 h, then Ag_2CO_3, MeOH, RT, 14 h, 61%; b) NaOMe, MeOH, 40 °C, 18 h, 100%; c) Tf_2O, py, CH_2Cl_2, −20 to −10 °C, 1.5 h, 100%; d) $BnNH_2$, CH_3CN, 70 °C, 2 h, 85%; e) 1,4-dioxane/2 M $HCl_{(aq)}$ (1:5), 40 °C, 17.5 h, 100%; f) $NaBH_4$, MeOH/1,4-dioxane (3:1), 1.5 h, then Ac_2O, py, then NaOMe, MeOH, 74%; g) Pd/C, H_2, H_2O/1,4-dioxane (2:1), HCl, 72 h, 100%; h) I_2, K_2CO_3, MeOH, 0 °C, 1 h, 96%; i) $MeNH_2$, $CaCl_2$, 45 °C, 2 h, MeOH, 70%; j) Pd/C, H_2, H_2O/1,4-dioxane (2:1), HCl, 10 h, 100%; k) HCl, H_2O/1,4-dioxane (2:1), 70 °C, 3 d, 81%; l) Pd/C, H_2, H_2O/1,4-dioxane (2:1), HCl, 15 h, 100%.

base catalysis; however, the amide **11** is stable indefinitely under neutral or acidic pH.[41]

Among recent studies on the bioactivity of iminosugar azetidines,[42] potent inhibition of purine nucleoside phosphorylase[43] and specific inhibition of non-mammalian glycosidases[44,45] have been reported. Inhibition by the azetidines **10L**, **11L**, **10D**, **11D**, and **20** of the following glycosidases were studied (Table 1):[46] α-glucosidases (EC 3.2.1.20, rice, yeast, *Aspergillus niger*), β-glucosidases (EC 3.2.1.21, almond, bovine liver, *Aspergillus niger*), α-galactosidase (EC 3.2.1.22, coffee beans), β-galactosidase (EC 3.2.1.23, bovine liver), α-mannosidase (EC 3.2.1.24, Jack bean), β-mannosidase (EC 3.2.1.25, snail), α-L-rhamnosidase (EC 3.2.1.40, *Penicillium decumbens*), α-L-fucosidase (EC 3.2.1.44, bovine kidney), β-glucuronidases (EC 3.2.1.31, *Escherichia coli*, bovine liver), trehalase (EC 3.2.1.28, porcine kidney), amyloglucosidases (EC 3.2.1.3, *Aspergillus niger*, *Rhizopus sp.*), β-*N*-acetylglucosaminidases (EC 3.2.1.52, human placenta, bovine kidney, Jack beans, HL 60, *Aspergillus oryzae*), α-*N*-acetylgalactosaminidases (EC 3.2.1.49, chicken liver, *Charonia lampas*), and β-*N*-acetylgalactosaminidases (EC 3.2.1.53, HL 60, *Aspergillus oryzae*).

Neither of the enantiomeric acids **10L** and **10D** showed any inhibition ($IC_{50} < 50\%$ at 1000 μM) of any glycosidases (Figure 4). The *meso*-azetidine triol **20** showed good inhibition of yeast α-glucosidase (IC_{50} 9.5 μM), good inhibition of trehalase (IC_{50} 30 μM) and rice α-glucosidase (IC_{50} 83 μM), and weak inhibition of *A. niger* α-glucosidase (IC_{50} 693 μM) and amyloglucosidases [*A. niger* (IC_{50} 758 μM), *Rhizopus sp.* (IC_{50} 274 μM)]. The *N*-nonyl derivative **26** is a specific inhibitor of some ceramide-specific glucosyl transferases and glucosidases.[47]

For the enantiomeric acid **10D** and amide **11D**, the azetidine **25** was formed from the glucose-derived ditriflate **24** as previously described (Scheme 2).[36] Oxidation of **25** with sodium periodate in aqueous acetone gave the lactols **18D** which, upon further oxidation by iodine in methanol, formed the methyl ester **21D** (77%). Subsequent transformations on **21D**, identical to those performed on **21L**, allowed access to the 3-hydroxy-D-azetidine carboxylic acid **10D** and the corresponding amide **11D**. The structure of the dibenzyl acid **22D** was firmly established by X-ray crystallographic analysis (Figure 3).[39] NOE studies on the free acid **10L** indicated that deprotection of the benzyl groups had not otherwise changed the stereochemistry of the ring.[40] Azetidine carboxylic acid derivatives with an unprotected hydroxy group at C3, such as the amide **11**, are susceptible to retro-aldol reactions under



Scheme 2. a) $NaIO_4$, H_2O/Me_2CO (2:1), RT, 1 h; b) I_2, K_2CO_3, MeOH, 0 °C, 1 h, 77% over two steps; c) $MeNH_2$, $CaCl_2$, MeOH, 45 °C, 2 h, 72%; d) Pd/C, H_2, H_2O/1,4-dioxane (2:1), 12 h, 100%; e) HCl, H_2O/1,4-dioxane (2:1), RT→70 °C, 7 d, 96%; f) Pd/C, H_2, H_2O/1,4-dioxane (2:1), 18 h, 100%.

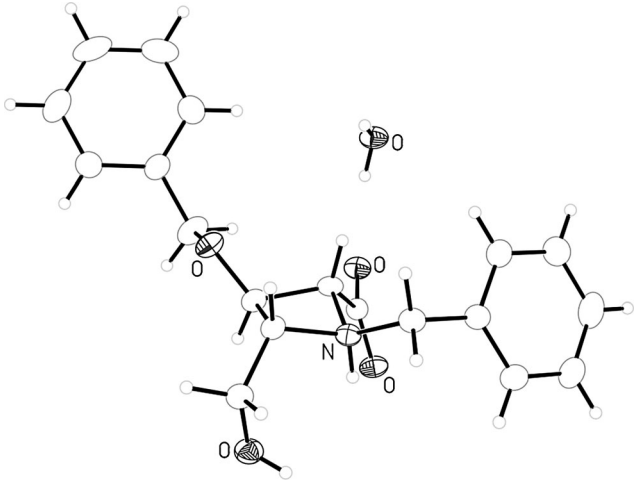


Figure 3. X-ray crystal structure of **22D** with displacement ellipsoids drawn at the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radius. The compound crystallizes as the zwitterion with a molecule of water in the asymmetric unit.

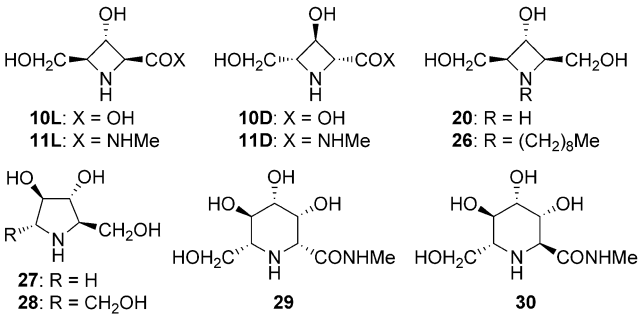


Figure 4. Glycosidase inhibition studies.

The inhibition of yeast α-glucosidase by the azetidine triol **20** is noteworthy. Iminosugars that are good to potent inhibitors of other α-glucosidases generally show no significant inhibition of the yeast enzyme; DAB **27** (IC_{50} 0.15 μM) and DMDP **28** (IC_{50} 0.71 μM) are the only natural iminosugars that are potent inhibitors of yeast α-glucosidase.[48] Early indications[44,45] are that azetidines are selective inhibitors of non-mammalian glycosidases—unlike their pyrrolidine and piperidine counterparts—and may have significance for the development of use of such compounds.

The L-*ribono*-azetidine amide **11L** (IC_{50} 1.4 μM for bovine kidney β-*N*-acetylglucosaminidase) is a potent inhibitor of a number of β-hexosaminidases (Table 1); **11L** is totally specific and shows no inhibition of any of the other glycosidases. The only other reported examples of hexosaminidase inhibition by amides of iminosugar acids is that of the tetrahydroxypipecolic acid amides **29** and **30** (IC_{50} 11 and 0.09 μM, respectively, for bovine liver).[49] These observations indicate that the study of hexosaminidase inhibition by acid amides of iminosugars may provide a class of specific and potent inhibitors. None of the amides **11L**, **29**, or **30** are inhibitors of α-*N*-acetylgalactosaminidases. The enantiomeric amide **11D** shows no inhibition of hexosaminidases, but is a good inhibitor of *E. coli* β-glucuronidase (IC_{50} 59 μM).

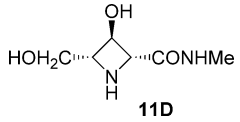
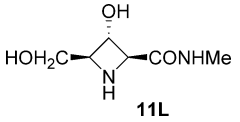
Conclusions

1. This paper reports the first chemical synthesis of 3-hydroxyazetidine carboxylic acids and of protected derivatives suitable for incorporation into peptides. The stability of such moieties is established; the amides, although vulnerable to ring opening by reverse aldol reactions, are stable at neutral and acidic pH at room temperature for substantial periods of time. Because of the value of hydroxyprolines as peptide isosteres, it is almost certain that such hydroxylazetidine carboxylic acids will allow medicinal chemists, for the first time, to access a new range of novel bioactive peptides containing highly functionalized azetidines.
2. The *meso*-azetidine triol **20** is a very rare example of an iminosugar as a good inhibitor (IC_{50} 9.5 μM) of yeast α-glucosidase. There are many iminosugars that are potent inhibitors of mammalian glucosidases, but almost all of them show no significant inhibition ($IC_{50} > 1$ mM) of yeast α-glucosidase. This observation is consistent with the selective inhibition of non-mammalian glycosidases by azetidine iminosugars.[44,45]
3. Although no glycosidase inhibition was observed for the acids **10L** and **10D**, the amide of the azetidine L-ribonic acid **11L** is a potent and specific inhibitor of hexosaminidases, and its enantiomer **11D** is a good inhibitor of a β-glucuronidase. Although many iminosugars have been identified as potent glycosidase inhibitors, the inhibition by the related hydroxyproline and hydroxypipecolic acids has always been modest. The only examples of any enzyme inhibition of amides of such acids reported previously is by the pipecolic acid amides **29** and **30**; the adventitious observation of the micromolar inhibition of the *N*-methylamide of the azetidine acid **11L** indicates that such simple derivatives of polyhydroxylated prolines may be a fertile field for medicinal chemists to investigate the inhibition of sugar-metabolizing enzymes.
4. Further study of such compounds and related azetidines is likely to reveal interesting bioactivity both as monomers and as components of peptidomimetics.

Experimental Section

All commercial reagents were used as supplied. MeOH and pyridine (py) were purchased dry from Aldrich in sure-seal bottles over molecular sieves. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. H_2O was purified by a Milli-Q filtration system. Reactions were performed under an atmosphere of N_2 or Ar unless stated otherwise. Thin-layer chromatography (TLC) was performed on Al sheets coated with 60 F_{254} silica. Sheets were visualized with a spray of 0.2% *w/v* $Ce(SO_4)_2$ and 5% $(NH_4)_2MoO_4$ in 2 M H_2SO_4, a spray of 1% *w/v* $KMnO_4$, 5% *w/v* K_2CO_3, and 0.1% NaOH in H_2O. Flash column chromatography was performed on Sorbsil C_{60} 40/60 silica. Ion-exchange chromatogra-

Table 1. Concentration of iminosugars giving 50% inhibition of various glycosidases.[a,b]

Glycosidase / source	 **11D**	 **11L**
β-*N*-Acetylglucosaminidase		
Human placenta	NI (42.8)	3.3
Bovine kidney	NI (46.8)	1.4
Jack bean	797	2.8
HL 60	NI (34.7)	4.2 [0.892][c]
Aspergillus oryzae	NI (21.4)	48
α-*N*-Acetylgalactosaminidase		
Chicken liver	NI (12.5)	NI (0)
Charonia lampas	NI (13.9)	NI (15.3)
β-*N*-Acetylgalactosaminidase		
HL 60	NI (11.3)	18
Aspergillus oryzae	NI (26.0)	27
β-Glucuronidase		
E. coli	59	NI (9.0)
Bovine liver	NI (12.1)	NI (0)

[a] Values of IC_{50} [μM]. [b] NI: no inhibition (i.e., $<50\%$ inhibition at 1000 μM); values in parentheses: percent inhibition at 1000 μM. [c] K_i value for inhibitor. A complete table of glycosidase inhibition by the azetidines is provided in the Supporting Information.

phy was performed using Dowex (50W-X8, H^+) eluted with 2 M NH_4OH. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a PerkinElmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g(100 mL)$^{-1}$. IR spectra were recorded on a PerkinElmer 1750 IR Fourier transform spectrophotometer using thin films. Only the characteristic peaks are quoted. Low-resolution MS data (*m/z*) were recorded on a Waters LCT Premier spectrometer, and high-resolution MS data (HRMS *m/z*) on a Waters ZMD spectrometer; electrospray ionization (ESI) was the ionization technique used. NMR spectra were recorded on Bruker AMX 500 (^{1}H: 500 MHz; ^{13}C: 125.7 MHz) and Bruker DPX 400 and DQX 400 spectrometers (^{1}H: 400 MHz; ^{13}C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm, and coupling constants (*J*) in Hz. Residual signals from the solvents were used as an internal reference except in the case of D_2O, for which CH_3CN was used as an internal reference. For enantiomeric pairs, the NMR and IR spectra were recorded and found to be identical; hence only the data for one enantiomer is given.

Synthesis started from 1,2,4-tri-*O*-acetyl-3-*O*-benzyl-β-D-xylopyranose **13**, which can be prepared from D-glucose according to published procedures.[34,35,50]

Methyl 2,4-*O*-diacetyl-3-*O*-benzyl-β-D-xylopyranoside (14): HBr (33% wt in AcOH, 0.63 mL, 3.67 mmol) was added dropwise over a 20 min period to a stirred solution of triacetate **13** (500 mg, 1.36 mmol) in 7:3 AcOH/CH_2Cl_2 (5 mL) at 10 °C, and the reaction mixture was then cooled to 5 °C. TLC analysis (1:1 cyclohexane/EtOAc) after 5 h indicated disappearance of the starting material ($R_f=0.65$) and formation of a major product ($R_f=0.79$). The solution was diluted with CH_2Cl_2 (25 mL) and poured into ice water (25 mL). The organic layer was washed with cold saturated $NaCHO_3$ (2×25 mL), H_2O (25 mL), dried ($MgSO_4$), filtered, and evaporated at 20 °C. The crude bromide was dissolved in MeOH (8 mL) in a foil-wrapped flask in the presence of Ag_2CO_3 (637 mg, 2.31 mmol) and stirred in the dark at RT for 14 h. TLC analysis (1:1 cyclohexane/EtOAc) indicated the formation of a major product ($R_f=0.62$); the reaction mixture was filtered through a glass fiber pad and washed with MeOH. The combined filtrates were evaporated, and the residue (384 mg, 83%) was purified by flash column chromatography (8:1→7:1 cyclohexane/EtOAc) to afford the β-pyranoside **14** as a white crystalline solid (280 mg, 61%): mp: 93–95 °C (EtOAc/cyclohexane) [lit. 95.5–96 °C];[35] $[\alpha]_D^{25}=-56.5$ ($c=1.3$, $CHCl_3$) [lit. $[\alpha]_D^{22}=-57$[35] ($c=1.00$, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.04$ (s, 2×3H, $COCH_3$), 3.35 (dd, $J_{4,5}=7.1$ Hz, $J_{5,5'}=12.0$ Hz, 1H, H5′), 3.45 (s, 3H, OCH_3), 3.66 (t, $J_{2,3}=J_{3,4}=7.2$ Hz, 1H, H3), 4.15 (dd, $J_{4,5}=4.4$ Hz, $J_{5,5'}=12.0$ Hz, 1H, H5), 4.40 (d, $J_{1,2}=5.6$ Hz, 1H, H1), 4.68 (s, 2H, CH_2Ph), 4.92 (td, $J_{4,5}=4.4$ Hz, $J_{3,4}=J_{4,5'}=7.1$ Hz, 1H, H4), 4.96 (dd, $J_{1,2}=5.6$ Hz, $J_{2,3}=7.3$ Hz, 1H, H2), 7.37–7.26 ppm (m, 5H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=21.1$ (C=OCH_3), 56.4 (OCH_3), 61.2 (C5), 70.3 (C4), 70.9 (C2), 73.4 (CH_2Ph), 77.0 (C3), 101.3 (C1), 127.8, 127.9, 128.5 (Ph), 138.0 (*ipso*-Ph), 169.6 (C=O), 170.0 ppm (C=O); IR (thin film): $\tilde{\nu}=1745$ cm^{-1} (s, C=O); MS (ESI+): *m/z* (%): 361 (32) [*M*+Na]$^+$, 699 (100) [2*M*+Na]$^+$; HRMS (ESI+): *m/z* [*M*+Na]$^+$ calcd for $C_{17}H_{22}NaO_7$: 361.1258, found: 361.1257.

Methyl 3-*O*-benzyl-β-D-xylopyranoside (15): A solution of the protected β-pyranoside **14** (239 mg, 0.70 mmol) and NaOMe (3.8 mg, 0.07 mmol) in MeOH (4 mL) was stirred at 40 °C. After 14 h, TLC analysis (1:1 cyclohexane/EtOAc) indicated complete disappearance of the starting material ($R_f=0.68$) and formation of a single product ($R_f=0.32$). The reaction mixture was evaporated to dryness. The residue was taken up in EtOAc (25 mL), washed with H_2O (2×25 mL) and brine (25 mL), and the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic solutions were dried ($MgSO_4$) and evaporated to dryness to yield methyl pyranoside **15** as a white crystalline solid (203 mg, 100%): mp: 102–104 °C [lit. 103–104 °C];[35] $[\alpha]_D^{25}=-79.8$ ($c=1.0$, $CHCl_3$) [lit. $[\alpha]_D^{22}=-71.5$[35] ($c=1.00$, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.24$ (d, $J_{4,OH}=3.1$ Hz, 1H, 4-OH), 2.47 (d, $J_{2,OH}=2.7$ Hz, 1H, 2-OH), 3.26 (dd, $J_{4,5'}=9.8$ Hz, $J_{5,5'}=11.6$ Hz, 1H, H5′), 3.37 (apparent t, $J_{2,3}=J_{3,4}=8.5$ Hz, 1H, H3), 3.51 (ddd, $J_{2,OH}=2.6$ Hz, $J_{1,2}=7.2$ Hz, $J_{2,3}=8.8$ Hz, 1H, H2), 3.54 (s, 3H, OMe), 3.72 (dddd, $J_{4,OH}=3.1$ Hz, $J_{4,5}=5.2$ Hz, $J_{3,4}=8.4$ Hz, $J_{4,5'}=9.7$ Hz, 1H, H4), 4.01 (dd, $J_{4,5}=5.2$ Hz, $J_{5,5'}=11.6$ Hz, 1H, H5), 4.17 (d, $J_{1,2}=7.1$ Hz, 1H, H1), 4.74 (d, $J_{gem}=11.7$ Hz, 1H, CH_2Ph′), 4.98 (d, $J_{gem}=11.7$ Hz, 1H, CH_2Ph), 7.41–7.28 ppm (m, 5H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=57.3$ (OMe), 65.3 (C5), 69.4 (C4), 74.0 (C2), 74.6 (CH_2Ph), 83.4 (C3), 104.5 (C1), 128.2, 128.8 (3×Ph), 138.6 ppm (*ipso*-Ph); IR (thin film): $\tilde{\nu}=3409$ cm^{-1} (m, OH); MS (ESI+): *m/z* (%): 377 (100) [*M*+Na]$^+$, 531 (32) [2*M*+Na]$^+$; HRMS (ESI+): *m/z* [*M*+Na]$^+$ calcd for $C_{13}H_{18}NaO_5$: 277.1046, found: 277.1045.

Methyl 3-*O*-benzyl-2,4-di-*O*-trifluoromethanesulfonyl-β-D-xylopyranoside (16): Trifluoromethanesulfonic anhydride (0.95 mL, 5.6 mmol) was added slowly to a stirred solution of the pyranoside **15** (357 mg, 1.4 mmol) and py (0.68 mL, 8.4 mmol) in CH_2Cl_2 (10 mL) at −20 °C under N_2. The reaction mixture was stirred at −10 °C; after 1.5 h, TLC analysis (1:1 cyclohexane/EtOAc) indicated complete consumption of the starting material ($R_f=0.27$) and formation of a major species ($R_f=0.78$). The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with $HCl_{(aq)}$ (2 M, 3×20 mL), dried ($MgSO_4$), filtered, and concentrated to dryness to afford the

crude ditriflate **16** as a clear yellow oil (729 mg, 100%): $[\alpha]_D^{25} = -38.2$ ($c = 1.29$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.53$ (s 3H, OMe), 3.62 (dd, $J_{4,5'} = 8.0$ Hz, $J_{5,5'} = 12.4$ Hz, 1H, H5′), 3.91 (app t, $J_{2,3} = J_{3,4} = 7.6$ Hz, 1H, H3), 4.27 (dd, $J_{4,5} = 4.6$ Hz, $J_{5,5'} = 12.4$ Hz, 1H, H5), 4.53 (d, $J_{1,2} = 6.1$ Hz, 1H, H1), 4.64 (dd, $J_{1,2} = 6.2$ Hz, $J_{2,3} = 7.6$ Hz, 1H, H2), 4.76 (d, $J_{gem} = 10.4$ Hz, 1H, CH_2Ph′), 4.80 (d, $J_{gem} = 10.4$ Hz, 1H, CH_2Ph), 4.85 (app td, $J_{4,5} = 4.7$ Hz, $J_{3,4} = J_{4,5'} = 7.7$ Hz, 1H, H4), 7.45–7.29 ppm (m, 5H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 57.4$ (OMe), 61.4 (C5), 75.5 (CH_2Ph), 76.6 (C3), 81.6 (C4), 82.2 (C2), 100.5 (C1), 128.6 128.7, 128.7 (3×Ph), 135.7 ppm (*ipso*-Ph); IR (thin film): ν = fingerprint region only; MS (ESI+): *m/z* (%): 541 (25) $[M+Na]^+$, 1059 (100) $[2M+Na]^+$; HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{15}H_{16}F_6NaO_9S_2$: 541.0032, found: 541.0034.

Methyl *N*,3-*O*-Dibenzyl-2,4-dideoxy-2,4-imino-β-L-ribopyranoside (17): Benzylamine (0.77 mL, 7.0 mmol) was added to the crude ditriflate **16** (729 mg, 1.4 mmol) in CH_3CN (7 mL); the reaction mixture was stirred at 65–70 °C for 2 h when TLC analysis (2:1 cyclohexane/EtOAc) indicated complete disappearance of the starting material ($R_f = 0.71$) and formation of a major species ($R_f = 0.56$). The reaction mixture was left to cool, concentrated in vacuo, and the residue was purified by flash column chromatography (7:1 cyclohexane/EtOAc) to afford the bicyclic azetidine **17** as a light-yellow oil (388 mg, 85%): $[\alpha]_D^{25} = -30.7$ ($c = 1.21$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.45$ (s, 3H, OMe), 3.55 (dt, $J_{4,5} = J_{4,5'} = 1.4$ Hz, $J_{2,4} = 4.2$ Hz, 1H, H4), 3.65 (dd, $J_{1,2} = 0.9$ Hz, $J_{2,4} = 4.2$ Hz, 1H, H2), 3.71 (dd, $J_{4,5'} = 1.1$ Hz, $J_{5,5'} = 10.6$ Hz, 1H, H5′), 3.98 (s, 1H, H3), 4.15 (s, 2H, NCH_2Ph), 4.34 (dd, $J_{4,5} = 1.7$ Hz, $J_{5,5'} = 10.6$ Hz, 1H, H5), 4.64 (d, $J_{gem} = 12.1$ Hz, 1H, OCH_2Ph), 4.64 (d, $J_{1,2} = 0.8$ Hz, 1H, H1), 4.69 (d, $J_{gem} = 12.1$ Hz, 1H, OCH_2Ph), 7.45–7.18 ppm (m, 10H, ArH,); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 51.6$ (NCH_2Ph), 55.9 (OCH_3), 62.4 (C5), 63.3 (C4), 66.2 (C2), 71.6 (OCH_2Ph), 79.9 (C3), 100.9 (C1), 126.7, 128.0, 128.1, 128.3, 128.4, 128.6 (Ph), 137.8, 139.4 ppm (*ipso*-Ph); IR (thin film): ν = fingerprint region only; MS (ESI+): *m/z* (%): 326 (100) $[M+H]^+$, 348 (26) $[M+Na]^+$, 673 (64) $[2M+Na]^+$; HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{24}NO_3$: 326.1751, found: 326.1750.

***N*,3-*O*-Dibenzyl-2,4-dideoxy-2,4-imino-*meso*-ribitol (19)**: Bicyclic azetidine **17** (56 mg, 0.17 mmol) was dissolved in 1,4-dioxane/$HCl_{(aq)}$ (2 M, 1:5, 6 mL) and stirred at 40 °C for 5 h, after which TLC analysis (2:1 cyclohexane/EtOAc; sample quenched with Et_3N) indicated the consumption of the starting material ($R_f = 0.49$) and the presence of a major compound ($R_f = 0.10$). The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated $NaCHO_{3(aq)}$ (25 mL), and the aqueous fraction was extracted with CH_2Cl_2 (2× 30 mL). Evaporation of the combined organic fractions to dryness at 30 °C yielded the lactol **18L** (60 mg, 100%) as a colorless glass, which was used without further purification. The crude lactol **18L** was dissolved in MeOH/1,4-dioxane (3:1, 4 mL), $NaBH_4$ (8 mg, 0.20 mmol) was added, and the reaction mixture was stirred at RT for 1.5 h. At this point TLC analysis (EtOAc) indicated disappearance of the lactol ($R_f = 0.63$) and formation of a new major compound ($R_f = 0.4$, streaks to baseline); MS (ESI+) indicated the sole presence of the desired compound. The reaction mixture was quenched by addition of a few drops of AcOH and was evaporated to dryness to give the crude diol **19** (97 mg, 100%). The residue was dissolved in py/acetic anhydride (1:1 4 mL) and stirred at RT for 19 h. TLC analysis (3:1 cyclohexane/EtOAc) indicated disappearance of the starting material ($R_f = 0.0$) and appearance of a new major compound ($R_f = 0.64$), which was identified by MS (ESI+) as the diacetylated intermediate. The reaction was, on dilution with toluene (4 mL), evaporated to dryness and co-evaporated with toluene (2×4 mL). The residue was dissolved in EtOAc (30 mL), washed with H_2O (2×25 mL), saturated $NaCHO_{3(aq)}$ (25 mL) brine (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude diacetate as colorless oil (65 mg, 0.16 mmol, 96%). The residue was dissolved in anhydrous MeOH (2 mL); NaOMe (4 mg, 0.07 mmol) was added, and the reaction mixture was stirred at RT for 20 h. TLC analysis (EtOAc) indicated consumption of starting material ($R_f = 0.95$) and formation of a major product ($R_f = 0.54$) along with an additional species ($R_f = 0.87$), which was tentatively identified as the monoacetate (by MS), and an additional quantity of NaOMe (4 mg, 0.07 mmol) was added to the reaction mixture. After a total reaction time of 45 h, TLC analysis (1:1 cyclohexane/EtOAc) indicated formation of a major species ($R_f = 0.18$) with only traces of the intermediate ($R_f = 0.65$) remaining, and the reaction mixture was concentrated in vacuo. The crude was dry loaded from MeOH/Et_3N (99:1) and flash column chromatography (cyclohexane/EtOAc/Et_3N 75:29:1→0:99:1) yielded dibenzyl diol **19** as a clear colorless oil (39 mg, 0.13 mmol, 74%): $[\alpha]_D^{25} = +0.23$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.17$ (br s, 2H, OH), 3.23 (dt, $J_{1,2} = J_{1',2} = J_{4,5} = J_{4,5'} = 3.2$ Hz, $J_{2,3} = J_{3,4} = 6.1$ Hz, 2H, H2, H4), 3.29 (dd, $J_{1',2} = J_{4,5'} = 3.4$ Hz, $J_{5,5'} = J_{1,1'} = 11.8$ Hz, 2H, H1′, H5′), 3.34 (dd, $J_{1,2} = J_{4,5} = 3.0$ Hz, $J_{5,5'} = J_{1,1'} = 11.8$ Hz, 2H, H1, H5), 3.75 (s, 2H, NCH_2Ph), 4.02 (t, $J_{2,3} = J_{3,4} = 5.4$ Hz, 1H, H3), 4.50 (s, 2H, OCH_2Ph), 7.40–7.24 ppm (m, 10H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 61.4$ (NCH_2Ph), 61.9 (C1, C5), 71.6 (C2, C4), 71.7 (C3), 72.1 (OCH_2Ph), 127.9, 128.0, 128.1, 128.7, 128.8, 129.1 (10×Ph), 137.9, 138.0 ppm (2×*ipso*-Ph); IR (thin film): $\tilde{\nu} = 3405$ cm^{-1} (s, OH); MS (ESI+): *m/z* (%): 314 (100) $[M+H]^+$, 336 (98) $[M+Na]^+$, 649 (77) $[2M+Na]^+$; MS (ESI-): *m/z* (%): 312 (100) $[M-H]^-$; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}NO_3$: 314.1751, found: 314.1745.

2,4-Dideoxy-2,4-imino-*meso*-ribitol (20): Concentrated HCl (11.6 M, 11 μL, 0.13 mmol) was diluted with H_2O (2 mL), premixed with 1,4-dioxane (1 mL), and added to diol **19** (20 mg, 0.07 mmol). To this solution was added Pd/C (10% wt, 8 mg), and the reaction vessel was degassed and charged with H_2. After 5 h of vigorous stirring, TLC analysis (4:1 EtOAc/MeOH) indicated a trace of remaining starting material ($R_f = 0.81$) along with a major species on the baseline and an intermediate compound ($R_f = 0.36$); similarly, TLC analysis (14:3:1:1:1 EtOH/py/*n*BuOH/AcOH/H_2O) indicated the presence of a major product ($R_f = 0.81$) along with a minor component ($R_f = 0.91$). MS still showed evidence of the starting material along with a monobenzyl intermediate. After having been re-subjected to the reaction conditions for an additional 18 h, only a trace of the monobenzyl species remained by TLC analysis; however, MS still indicated its presence until a total of 72 h had passed. The reaction mixture was then filtered (GF/A glass microfiber), washed with MeOH (2 mL), concentrated in vacuo, and loaded onto a short column of Dowex (50W-X8, H^+) in which the resin had been pretreated by washing with H_2O (until eluent was neutral). The crude was loaded (H_2O/1,4-dioxane 2:1) and washed sequentially with H_2O, 1,4-dioxane, EtOH, and H_2O again. The product was eluted with aqueous ammonia (2 M) and the ammoniacal fractions concentrated in vacuo at RT to yield triol **20** as a viscous gum (11 mg, 100%): $[\alpha]_D^{25} = +0.68$ ($c = 0.29$, MeOH); ^{1}H NMR (400 MHz, D_2O): $\delta = 3.62$ (dd, $J = 1.4$ Hz, $J_{1,2} = J_{4,5} = 4.4$ Hz, 4H, H1, H5), 4.05 (dt, $J_{1,2} = J_{4,5} = 4.4$ Hz, $J_{2,3} = J_{3,4} = 7.1$ Hz, 2H, H2, H4), 4.27 ppm (t, $J_{2,3} = J_{3,4} = 7.1$ Hz, 1H, H3); ^{13}C NMR (63 MHz, D_2O): $\delta = 58.2$ (C1, C5), 64.0 (C3), 66.9 ppm (C2, C4); IR (thin film): $\tilde{\nu} = 3271$ cm^{-1} (s, OH); MS (ESI-): *m/z* (%): 168 (72) $[M+Cl]^-$, 362 (100); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_5H_{12}NO_3$: 134.0812, found: 134.0807.

Methyl *N*,3-*O*-dibenzyl-2,4-dideoxy-2,4-imino-L-ribonate (21L): A solution of the bicyclic azetidine **17** (136 mg, 0.42 mmol) in 1,4-dioxane/$HCl_{(aq)}$ (2 M, 1:5, 6 mL) was stirred at 40 °C for 17.5 h, after

which TLC analysis (2:1 cyclohexane/EtOAc; sample quenched with Et_3N) indicated the absence of starting material ($R_f = 0.49$) and the formation of a major product ($R_f = 0.10$). The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated $NaCHO_{3(aq)}$ (25 mL). The aqueous fraction was extracted with CH_2Cl_2 (2× 30 mL). The combined organic fractions were washed with brine (40 mL) and dried ($MgSO_4$). Evaporation to dryness yielded bicyclic lactol **18L** (147 mg, 100%) as an unstable colorless glass, which was used without further purification. A solution of the crude lactol **18L** (102 mg, 0.30 mmol) and K_2CO_3 (124 mg, 0.90 mmol) in anhydrous MeOH (4 mL) was stirred at 0 °C under an atmosphere of N_2. Iodine (99 mg, 0.39 mmol), dissolved by sonication in anhydrous MeOH (4 mL), was added dropwise to the stirred reaction mixture at 0 °C. MS indicated the formation of the desired product after 1 h reaction time, and TLC analysis (EtOAc) showed consumption of the starting material ($R_f = 0.61$) and formation of a single compound ($R_f = 0.79$). The reaction was quenched by the addition of saturated $Na_2SO_{3(aq)}$ (8 mL). The resultant white precipitate was dissolved in H_2O (32 mL), and the aqueous fraction was extracted with Et_2O (4×50 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated in vacuo to yield the title compound **21L** (98 mg, 96%). The highest yield was obtained when the ester **21L** was used without further purification in the following hydrolysis. However, on one occasion the ester was isolated as follows: in this case the lactol **18L** (147 mg, 0.42 mmol) reacted in the same way as above to give the crude methyl ester **21L** (136 mg, 95%). Purification by flash column chromatography (cyclohexane/EtOAc/Et_3N 80:19:1→66:32:1) gave the methyl ester **21L** (116 mg, 81%) as a clear colorless oil: $[\alpha]_D^{25} = -58.8$ ($c = 0.80$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.54$ (d, $J_{OH,5} = 8.5$ Hz, 1H, OH-5), 3.08 (dd, $J_{4,5'} = 2.8$ Hz, $J_{5,5'} = 11.9$ Hz, 1H, H5′), 3.31–3.22 (m, 2H, H4, H5), 3.66 (s, 3H, OMe), 3.67 (d, $J_{2,3} = 5.3$ Hz, 1H, H2), 3.70 (d, $J_{gem} = 12.5$ Hz, 1H, NCH_2Ph), 3.93 (d, $J_{gem} = 12.4$ Hz, 1H, NCH_2Ph), 4.20 (app t, $J_{2,3} = J_{3,4} = 5.3$ Hz, 1H, H3), 4.47 (d, $J_{gem} = 11.6$ Hz, 1H, OCH_2Ph), 4.62 (d, $J_{gem} = 11.6$ Hz, 1H, OCH_2Ph), 7.37–7.24 ppm (m, 10H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 52.1$ (OMe), 60.6 (C5), 60.9 (NCH_2Ph), 69.7 (C2), 70.6 (C4), 71.9 (OCH_2Ph), 72.8 (C3), 127.9, 128.0, 128.1, 128.6, 129.4 (6×Ph), 136.7, 137.5 (2×*ipso*-Ph), 171.7 ppm (C=O); IR (thin film): $\tilde{\nu} = 3445$ (w, OH), 1737 cm^{-1} (s, C=O); MS (ESI+): *m/z* (%): 342 (56) $[M+H]^+$, 364 (100) $[M+Na]^+$, 705 (88) $[2M+Na]^+$; HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}NNaO_4$: 364.1519, found: 364.1512.

For enantiomer 21D: Synthesis started from *N*,3-*O*-dibenzyl-2,4-dideoxy-2,4-imino-D-talitol 25, prepared according to published procedures:[36] $NaIO_4$ (117 mg, 0.55 mmol) was added to a solution of the triol **25** (159 mg, 0.46 mmol) in aqueous acetone (H_2O/acetone, 2:1, 6 mL), and the reaction mixture was stirred at RT for 1 h. TLC analysis (EtOAc) indicated consumption of the starting material ($R_f = 0.30$) and formation of a single new compound ($R_f = 0.67$). EtOH (24 mL) was added, the reaction was stirred for 45 min, and the resultant precipitate was removed by filtration (GF/A glass microfiber). The filtrate was concentrated in vacuo (only careful heating) to yield lactol **18D** as a clear glass (163 mg, 100%), which was used directly without further purification. The lactol **18D** (70 mg, 0.23 mmol) was dissolved in anhydrous MeOH (3 mL) along with K_2CO_3 (95 mg, 0.69 mmol) and stirred at 0 °C under an atmosphere of N_2. Iodine (76 mg, 0.30 mmol) was dissolved under sonication in anhydrous MeOH (3 mL) and added dropwise to the stirred reaction mixture at 0 °C. MS indicated the formation of the desired product after 45 min of reaction time, and TLC analysis (EtOAc) showed consumption of the starting material ($R_f = 0.61$) and formation of a single compound ($R_f = 0.79$). The reaction was quenched by addition of saturated $Na_2SO_{3(aq)}$ (6 mL). The resultant white precipitate was dissolved in H_2O (16 mL), and the aqueous fraction was extracted with Et_2O (4×30 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to yield the crude title compound **21D** (84 mg, 100%). Purification by flash column chromatography (cyclohexane/EtOAc/Et_3N 80:19:1→66:32:1) gave the methyl ester **21D** (60 mg, 77%) as a clear colorless oil. $[\alpha]_D^{25} = +55.5$ ($c = 0.51$, $CHCl_3$); HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}NNaO_4$: 364.1519, found: 364.1514.

***N*,3-*O*-Dibenzyl-2,4-dideoxy-2,4-imino-L-ribonic acid (22L)**: Concentrated HCl (11.6 M, 11 μL, 0.13 mmol) was diluted with H_2O (4 mL), premixed with 1,4-dioxane (2 mL), added to the methyl ester **21L** (22.5 mg, 0.066 mmol), and stirred at 70 °C without a condenser open to air for three days. The reaction progress was followed by MS (starting material found in +ve, title compound in −ve; on completion the title compound was found in both). Furthermore, TLC analysis (EtOAc) indicated the complete disappearance of starting material ($R_f = 0.79$) and appearance of a new compound ($R_f = 0.0$). On completion the reaction mixture was concentrated in vacuo. The residue was loaded onto a short column of Dowex (50W-X8, H^+) in which the resin had been pretreated by sequential washing with H_2O (until eluent was neutral), 1,4-dioxane and H_2O again. The crude was loaded (H_2O/1,4-dioxane 2:1) and washed sequentially with H_2O, 1,4-dioxane, and H_2O again. The product was eluted with aqueous ammonia (2 M), and the ammoniacal fractions were concentrated in vacuo to afford the carboxylic acid **22L** as white crystalline solid (18 mg, 81%): mp: 172–174 °C; $[\alpha]_D^{25} = -19.4$ ($c = 0.16$, MeOH); ^1H NMR (400 MHz, [D$_5$]py): $\delta = 3.61$ (app q, $J_{3,4} = J_{4,5} = 4.8$ Hz, 1H, H4), 3.76 (d, $J_{4,5} = 4.7$ Hz, 2H, H5, H5′), 3.97 (d, $J_{gem} = 12.9$ Hz, 1H, NCH_2Ph), 4.10 (d, $J_{2,3} = 5.5$ Hz, 1H, H2), 4.30 (d, $J_{gem} = 12.9$ Hz, 1H, NCH_2Ph), 4.72 (app t, $J_{2,3} = J_{3,4} = 5.4$ Hz, 1H, H3), 4.85 (d, $J_{gem} = 11.9$ Hz, 1H, OCH_2Ph), 4.95 (d, $J_{gem} = 11.9$ Hz, 1H, OCH_2Ph), 7.39–7.24 (m, 6H, ArH), 7.57–7.48 ppm (m, 4H, ArH); ^{13}C NMR (126 MHz, [D$_5$]py): $\delta = 62.0$ (NCH_2Ph), 63.5 (C5), 70.9 (C2), 71.8 (OCH_2Ph), 72.1 (C4), 76.1 (C3), 128.1, 128.3, 128.6, 129.0, 129.1, 130.56 (6×Ph), 138.7, 139.4 (2×*ipso*-Ph), 174.9 ppm (C=O); IR (thin film): $\tilde{\nu} = 3326$ (w, OH), 1634 cm^{-1} (s, C=O); MS (ESI+): *m/z* (%): 328 (45) $[M+H]^+$, 350 (100) $[M+Na]^+$; MS (ESI-): *m/z* (%): 326 (100) $[M-H]^-$; HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{21}NNaO_4$: 350.1363, found: 350.1356.

For enantiomer 22D: The protected amino acid **22D** was isolated as a white solid (32 mg, 96%): mp: 177–178 °C; $[\alpha]_D^{25} = +25.1$ ($c = 0.66$, MeOH); HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{21}NNaO_4$: 350.1363, found: 350.1357.

2,4-Dideoxy-2,4-imino-L-ribonic acid (10L): Concentrated HCl (11.6 M, 7 μL, 0.08 mmol) was diluted with H_2O (2 mL), premixed with 1,4-dioxane (1 mL), and added to the protected amino acid **22L** (15 mg, 0.04 mmol). To this solution was added Pd/C (10% wt, 6 mg), and the reaction vessel was degassed and charged with H_2. After 15 h vigorous stirring, TLC analysis (14:3:1:1:1 EtOH/py/*n*BuOH/AcOH/H_2O) indicated the presence of a single product ($R_f = 0.62$). The reaction mixture was filtered (GF/A glass microfiber), concentrated in vacuo at RT, and loaded onto a short column of Dowex (50W-X8, H^+) in which the resin had been pretreated by sequential washing with H_2O (until eluent was neutral), 1,4-dioxane, and H_2O again. The crude was loaded (H_2O/1,4-dioxane 2:1) and washed sequentially with H_2O, 1,4-dioxane, and H_2O again. The product was eluted with aqueous ammonia (2 M), and the ammoniacal fractions were concentrated in vacuo at RT to yield the amino acid **10L** as a viscous gum (7 mg, 100%). Data for HCl salt: $[\alpha]_D^{25} = -9.7$ ($c = 0.11$, DMF); ^1H NMR (500 MHz, CD_3OD): $\delta = 3.83$ (d, $J_{4,5} = J_{4,5'} = 3.6$ Hz, 2H, H5, H5′), 4.28 (dt, $J_{4,5} = J_{4,5'} = 3.5$ Hz, $J_{3,4} = 6.7$ Hz, 1H, H4), 4.66 (app t, $J_{2,3} = J_{3,4} = 6.6$ Hz, 1H, H3), 4.73 ppm (d,

$J_{2,3}$ = 6.6 Hz, 1H, H2); ^{13}C NMR (126 MHz, CD_3OD): δ = 58.8 (C5), 65.3 (C2), 68.4 (C3), 69.5 (C4), 168.8 ppm (C=O); IR (thin film): $\tilde{\nu}$ = 3209 (br m, OH, NH), 1733 (s, C=OOH), 1604 (m, CO_2^-), 1420 cm^{-1} (m, CO_2^-).

For enantiomer 10D: The amino acid **10D** was isolated as an off-white viscous gum (15.1 mg, 100%). Data for HCl salt: $[\alpha]_D^{25}$ = + 6.64 (c = 0.19, DMF).

Methyl *N*,3-*O*-dibenzyl-2,4-dideoxy-2,4-imino-L-ribonamide (23L): To a 15-mL screw-cap vial was added the methyl ester **21L** (51 mg, 0.15 mmol) along with $CaCl_2$ (17 mg, 0.15 mmol) and anhydrous MeOH (5 mL). Methylamine in absolute EtOH (0.37 mL, 3.0 mmol) was added, and the reaction vessel was flushed with a stream of N_2 before being heated at 45 °C for 2 h. TLC analysis (1:1 cyclohexane/EtOAc) indicated complete consumption of the starting material (R_f = 0.44) and the formation of a single new product (R_f = 0.12) along with MS showing only the desired product in the positive ion mode. The reaction mixture was evaporated to dryness, and the residue was dissolved in saturated $NH_4Cl_{(aq)}/H_2O$ (1:3, 4 mL). The resultant mixture was adjusted to pH 5 with $HCl_{(aq)}$ (2 M) and stirred at RT for 20 min. EtOAc (5 mL) was then added to the mixture, which was stirred for an additional 10 min. The aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic fractions were dried ($MgSO_4$), filtered, and evaporated to give the crude reaction product (51 mg, 100%). The crude was loaded in CH_2Cl_2/Et_3N (99:1) and purified by flash column chromatography (cyclohexane/EtOAc/Et_3N 66:33:1→0:99:1) to yield methylamide **23L** as a white crystalline solid (36 mg, 70%): mp: 97–99 °C; $[\alpha]_D^{25}$ = −57.3 (c = 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (s, 1H, OH), 2.63 (d, $J_{NH,Me}$ = 5.0 Hz, 3H, NHMe), 3.44–3.30 (m, 3H, H4, H5, H5′), 3.65 (d, $J_{2,3}$ = 5.1 Hz, 1H, H2), 3.73 (d, J_{gem} = 12.2 Hz, 1H, NCH_2Ph), 3.77 (d, J_{gem} = 12.2 Hz, 1H, NCH_2Ph), 3.92 (app t, $J_{2,3}$ = $J_{3,4}$ = 5.1 Hz, 1H, H3), 4.45 (d, J_{gem} = 11.6 Hz, 1H, OCH_2Ph), 4.83 (d, J_{gem} = 11.7 Hz, 1H, OCH_2Ph), 6.54 (br d, $J_{NH,Me}$ = 4.1 Hz, 1H, NH), 7.38–7.24 ppm (m, 10H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.7 (NHMe), 61.6 (C5), 61.9 (NCH_2Ph), 70.9 (C4), 71.4 (OCH_2Ph), 72.6 (C2), 73.9 (C3), 127.9, 128.1, 128.1, 128.5, 128.9, 129.3 (8×Ph), 136.9, 137.7 (*ipso*-Ph), 171.5 ppm (C1); IR (thin film): $\tilde{\nu}$ = 3343 (m, OH), 1651 (s, C=O, amide I), 1540 cm^{-1} (m, C=O, amide II); MS (ESI+): m/z (%): 341 (100) $[M+H]^+$, 363 (73) $[M+Na]^+$, 703 (57) $[2M+Na]^+$; MS (ESI-): m/z (%): 375 (100) $[M+Cl]^-$; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{20}H_{24}N_2NaO_3$: 363.1679, found: 363.1679.

For enantiomer 23D: Starting from *N*-benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-D-talitol (75 mg, 0.22 mmol), methylamide **23D** was isolated as a white crystalline solid (54 mg, 72%) without intermediate purification. $[\alpha]_D^{25}$ = + 58.5 (c = 1.04, $HCCl_3$); HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{20}H_{24}N_2NaO_3$: 363.1679, found: 363.1680.

Methyl 2,4-dideoxy-2,4-imino-L-ribonamide (11L): Concentrated HCl (11.6 M, 8 μL, 0.10 mmol) was diluted with H_2O (2 mL) premixed with 1,4-dioxane (1 mL) and added to the protected methylamide **23L** (16 mg, 0.05 mmol). To this solution was added Pd/C (10% wt, 6 mg), and the reaction vessel was degassed and charged with H_2. After 10 h vigorous stirring, TLC analysis (14:3:1:1:1 EtOH/py/*n*BuOH/AcOH/H_2O) indicated the presence of a single product (R_f = 0.69). The reaction mixture was filtered (GF/A glass microfiber), washed with MeOH, and the solvent was removed by lyophilization to yield methylamide **11L** as a clear colorless glass (11 mg, 100%): $[\alpha]_D^{25}$ = −12.2 (c = 0.42, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 2.82 (s, 3H, Me), 3.83 (d, $J_{4,5}$ = 4.0 Hz, 2H, H5, H5′), 4.28 (dt, $J_{4,5}$ = $J_{4,5'}$ = 3.9 Hz, $J_{3,4}$ = 7.2 Hz, 1H, H4), 4.53 (app t, $J_{2,3}$ = $J_{3,4}$ = 6.7 Hz, 1H, H3), 4.62 ppm (d, $J_{2,3}$ = 6.6 Hz, 1H, H2); ^{13}C NMR (126 MHz, CD_3OD): δ = 26.5 (Me), 58.9 (C5), 66.1 (C2), 68.6 (C3), 69.6 (C4), 167.2 ppm (C1); IR (thin film): $\tilde{\nu}$ = 3273 (m, OH), 1673 (s, C=O, amide I), 1570 cm^{-1} (m, C=O, amide II); MS (ESI-): m/z (%): 102 (100), 161 (80) $[M+H]^+$, 183 (57) $[M+Na]^+$; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_6H_{12}N_2NaO_3$: 183.0740, found: 183.0742.

For enantiomer 11D: The methylamide **11D** was isolated as a clear colorless glass (33 mg, 100%). $[\alpha]_D^{25}$ = + 7.7 (c = 1.29, MeOH); HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_6H_{12}N_2NaO_3$: 183.0740, found: 183.0740.

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[1] a) A. L. Lehninger, D. L. Nelson, M. M. Cox, *Principles of Biochemistry, 3rd ed.*, W. H. Freeman, New York, ISBN: 1-57259-153-6, **2000**; b) S. C. Lovell, I. W. Davis, W. B. Adrendall, P. I. W. de Bakker, J. M. Word, M. G. Prisant, J. S. Richardson, D. C. Richardson, *Proteins Struct. Funct. Bioinf.* **2003**, *50*, 437–450.

[2] a) A. Choudhary, R. T. Raines, *ChemBioChem* **2011**, *12*, 1801–1807; b) X. D. J. Wang, S. A. Hart, B. L. Xu, M. D. Mason, J. R. Goodell, F. A. Etzkorn, *J. Org. Chem.* **2003**, *68*, 2343–2349; c) X. D. J. Wang, B. L. Xu, A. B. Mullins, F. K. Neiler, F. A. Etzkorn, *J. Am. Chem. Soc.* **2004**, *126*, 15533–15542.

[3] a) F. Benedetti, F. Berti, S. Budal, P. Campaner, F. Dinon, A. Tossi, R. Argirova, P. Genova, V. Atanassov, A. Hinkov, *J. Med. Chem.* **2012**, *55*, 3900–3910; b) J. D. Wade, F. Lin, M. A. Hossain, R. M. Dawson, *Amino Acids* **2012**, *43*, 2279–2283; c) M. P. C. Mulder, P. Fodran, J. Kemmink, E. J. Breukink, J. A. W. Kruijtzer, A. J. Minnaard, R. M. J. Liskamp, *Org. Biomol. Chem.* **2012**, *10*, 7491–7502.

[4] F. Couty, G. Evano, *Org. Prep. Proced. Int.* **2006**, *38*, 427–465.

[5] a) F. Couty, G. Evano, *Synlett* **2009**, 3053–3064; b) T. M. Bott, F. G. West, *Heterocycles* **2012**, *84*, 223–264; c) A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988–4035.

[6] L. Fowden, *Nature* **1955**, *176*, 347–348.

[7] M. Noma, M. Noguchi, E. Tamaki, *Tetrahedron Lett.* **1971**, *12*, 2017–2020.

[8] a) E. Rubenstein, *J. Neuropathol. Exp. Neurol.* **2008**, *67*, 1035–1040; b) E. Rubenstein, T. McLaughlin, R. C. Winant, A. Sanchez, M. Eckart, K. M. Krasinska, A. Chien, *Phytochemistry* **2009**, *70*, 100–104; c) V. Vranova, K. Rejsek, P. Formanek, *Listy Cukrov. Reparske* **2012**, *128*, 22–25.

[9] S. H. Baek, J. G. Lee, S. Y. Park, X. L. Piao, H. Y. Kim, O. N. Bae, J. H. J. Park, *Food Composition Anal.* **2012**, *25*, 137–141.

[10] K. Bessonov, V. V. Bamm, G. Harauz, *Phytochemistry* **2010**, *71*, 502–507.

[11] a) E. Rubenstein, *Medicine* **2000**, *79*, 80–89; b) K. Dasuri, P. J. Ebenezer, R. M. Uranga, E. Gavilan, L. Zhang, S. O. K. Fernandez-Kim, A. J. Bruce-Keller, J. N. Keller, *J. Neurosci. Res.* **2011**, *89*, 1471–1477.

[12] P. Pérez-Faginas, M. T. Aranda, M. T. Garcia-López, R. Snoeck, G. Andrei, J. Balzarini, R. Gonzalez-Muniz, *Bioorg. Med. Chem.* **2011**, *19*, 1155–1161.

[13] T. Nakamura, M. Asano, Y. Sekiguchi, Y. Mizuno, K. Tamaki, F. Nara, Y. Kawase, Y. Yabe, D. Nakai, E. Kamiyama, Y. Urasaki-Kaneno, T. Shimozato, H. Doi-Komuro, T. Kagari, W. Tomisato, R. Inoue, M. Nagasaki, H. Yuita, K. Oguchi-Oshima, R. Kaneko, T. Nishi, *Eur. J. Med. Chem.* **2012**, *51*, 92–98.

[14] a) X. Zhang, H. Hufnagel, T. Markotan, J. Lanter, C. Cai, C. Hou, M. Singer, E. Opas, S. McKenney, C. Crysler, D. Johnson, Z. Sui, *Bioorg. Med.*

Chem. Lett. **2011**, *21*, 5577 – 5582; b) Y. Sun, S. Gou, R. Yin, P. Jiang, *Eur. J. Med. Chem.* **2011**, *46*, 5146 – 5153; c) G. S. T. Smith, M. De Avila, P. M. Paez, V. Spreuer, M. K. B. Wills, N. Jones, J. M. Boggs, G. Harauz, *J. Neurosci. Res.* **2012**, *90*, 28 – 47; d) K. Lu, Y. Jiang, B. Chen, E. M. Eldemenky, G. Ma, M. Packiarajan, G. Chandrasena, A. D. White, K. A. Jones, B. Li, S.-P. Hong, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5310 – 5314; e) M. Perassolo, C. V. Quevedo, A. M. Giulietti, J. R. Talou, *Plant Cell Tissue Organ Cult.* **2011**, *106*, 153 – 159; f) C. V. Quevedo, M. Perassolo, A. M. Giulietti, J. R. Talou, *Biotechnol. Lett.* **2012**, *34*, 571 – 575; g) J. T. Lowe, M. D. Lee IV, L. B. Akella, E. Davoine, E. J. Donckele, L. Durak, J. R. Duvall, B. Gerard, E. B. Holson, A. Joliton, S. Kesavan, B. C. Lemercier, H. Liu, J.-C. Marié, C. A. Mulrooney, G. Muncipinto, M. Welzel-O'Shea, L. M. Panko, A. Rowley, B.-C. Suh, M. Thomas, F. F. Wagner, J. Wei, M. A. Foley, L. A. Marcaurelle, *J. Org. Chem.* **2012**, *77*, 7187 – 7211; h) B. J. Melancon, T. J. Utley, C. Sevel, M. E. Mattmann, Y. Y. Cheung, T. M. Bridges, R. D. Morrison, D. J. Sheffler, C. M. Niswender, J. S. Daniels, P. J. Conn, C. W. Lindsley, M. R. Wood, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5035 – 5040.

[15] T. A. Martinek, F. Fülöp, *Chem. Soc. Rev.* **2012**, *41*, 687 – 702.

[16] a) A. Zukauskaite, S. Mangelinckx, V. Buinauskaite, A. Sackus, N. De Kimpe, *Amino Acids* **2011**, *41*, 541 – 558; b) M. J. L. Baeza, M. A. Bonache, M. T. Garcia-Lopez, R. Gonzalez-Muniz, M. Martin-Martinez, *Amino Acids* **2010**, *39*, 1299 – 1307; c) B. Drouillat, K. Wright, J. Marrot, F. Couty, *Tetrahedron: Asymmetry* **2012**, *23*, 690 – 696.

[17] a) S. F. Jenkinson, G. W. J. Fleet, *Chimia* **2011**, *65*, 71 – 75; b) T. D. W. Claridge, J. M. Goodman, A. Moreno, D. Angus, S. F. Barker, C. Taillefumier, M. P. Watterson, G. W. J. Fleet, *Tetrahedron Lett.* **2001**, *42*, 4251 – 4255; c) S. F. Jenkinson (née Barker), T. Harris, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2004**, *15*, 2667 – 2679; d) T. D. W. Claridge, B. Lopez-Ortega, S. F. Jenkinson, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2008**, *19*, 984 – 988.

[18] a) M. Bouazaoui, J. Martinez, F. Cavelier, *Eur. J. Org. Chem.* **2009**, 2729 – 2732; b) S. P. Fritz, J. F. Moya, M. G. Unthank, E. M. McGarrigle, V. K. Aggarwal, *Synthesis* **2012**, *44*, 1584 – 1590 and references cited therein.

[19] a) V. Declerck, D. J. Aitken, *J. Org. Chem.* **2011**, *76*, 708 – 711; b) L. Kiss, S. Mangelinckx, F. Fülöp, N. De Kimpe, *Org. Lett.* **2007**, *9*, 4399 – 4402; c) J. A. Burkhard, C. Guérot, H. Knust, E. M. Carreira, *Org. Lett.* **2012**, *14*, 66 – 69; d) G. Callebaut, S. Mangelinckx, L. Kiss, R. Sillanpaa, F. Fülöp, N. De Kimpe, *Org. Biomol. Chem.* **2012**, *10*, 2326 – 2338.

[20] K. Inouye, Y. Kobayashi, Y. Kyogoku, Y. Kishida, S. Sakakibara, D. J. Prockop, *Arch. Biochem. Biophys.* **1982**, *219*, 198 – 203.

[21] C. J. Schofield, P. J. Ratcliffe, *Nat. Rev. Mol. Cell Biol.* **2004**, *5*, 343 – 354.

[22] A. C. R. Epstein, J. M. Gleadle, L. A. McNeill, K. S. Hewitson, J. O'Rourke, D. R. Mole, M. Mukherji, E. Metzen, M. I. Wilson, A. Dhanda, Y.-M. Tian, N. Masson, D. L. Hamilton, P. Jaakkola, R. Barstead, J. Hodgkin, P. H. Maxwell, C. W. Pugh, C. J. Schofield, P. J. Ratcliffe, *Cell* **2001**, *107*, 43 – 54.

[23] R. Chowdhury, M. A. McDonough, J. Mecinovic, C. Loenarz, E. Flashman, K. S. Hewitson, C. Domene, C. J. Schofield, *Structure* **2009**, *17*, 981 – 989.

[24] M. D. Shoulders, K. J. Kamer, R. T. Raines, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3859 – 3862.

[25] C. Loenarz, J. Mecinovic, R. Chowdhury, A. McNeill, E. Flashman, C. J. Schofield, *Angew. Chem.* **2009**, *121*, 1816 – 1819; *Angew. Chem. Int. Ed.* **2009**, *48*, 1784 – 1787.

[26] A. Borgogno, P. Ruzza, *Amino Acids* **2013**, *44*, 607 – 614.

[27] T. Shibasaki, W. Sakurai, A. Hasegawa, Y. Uosaki, H. Mori, M. Yoshida, A. Ozaki, *Tetrahedron Lett.* **1999**, *40*, 5227 – 5230.

[28] D. Chang, H.-J. Feiten, K.-H. Engesser, J. B. van Beilen, B. Witholt, Z. Li, *Org. Lett.* **2002**, *4*, 1859 – 1862.

[29] a) F. Matsuura, Y. Hamada, T. Shioiri, *Tetrahedron* **1994**, *50*, 265 – 274; b) F. Matsuura, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1992**, *33*, 7921 – 7924.

[30] S. Mangelinckx, M. Boeykens, M. Vliegen, J. Van der Eycken, N. De Klimpe, *Tetrahedron Lett.* **2005**, *46*, 525 – 529.

[31] M. P. Moyer, P. L. Feldman, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 5223 – 5230.

[32] a) E. Fernández-Megía, M. A. Montaos, F. J. Sardina, *J. Org. Chem.* **2000**, *65*, 6780 – 6783; b) P. Wessig, J. Schwarz, *Helv. Chim. Acta* **1998**, *81*, 1803 – 1814; c) A. Duréault, M. Portal, F. Carreaux, J. C. Depezay, *Tetrahedron* **1993**, *49*, 4201 – 4210.

[33] a) A. Imada, K. Kintaka, M. Nakao, S. Shinagawa, *J. Antibiot.* **1982**, *35*, 1400 – 1403; b) S. Shinagawa, M. Maki, K. Kintaka, A. Imada, M. Asai, *J. Antibiot.* **1985**, *38*, 17 – 23; c) S. Shinagawa, F. Kashara, Y. Wada, S. Harada, M. Asai, *Tetrahedron* **1984**, *40*, 3465 – 3470; d) K. Show, P. K. Upadhyay, P. Kumar, *Tetrahedron: Asymmetry* **2011**, *22*, 1234 – 1238.

[34] S. Mandal, N. Sharma, B. Mukhopadhyay, *Tetrahedron: Asymmetry* **2010**, *21*, 2172 – 2176.

[35] P. Kovac, J. Alfoldi, *Chem. Zvesti* **1979**, *33*, 785 – 791.

[36] G. M. J. Lenagh-Snow, N. Araujo, S. F. Jenkinson, R. F. Martinez, Y. Shimada, C.-Y. Yu, A. Kato, G. W. J. Fleet, *Org. Lett.* **2012**, *14*, 2142 – 2145.

[37] a) N. Mori, T. Togo, *Tetrahedron* **2005**, *61*, 5915 – 5925; b) S. Yamada, D. Morizono, K. Yamamoto, *Tetrahedron Lett.* **1992**, *33*, 4329 – 4332.

[38] M. W. Bundesmann, S. B. Coffey, S. W. Wright, *Tetrahedron Lett.* **2010**, *51*, 3879 – 3882.

[39] A crystal structure of compound **22D** was obtained. Data were collected using synchotron radiation on I19 (EH1) at Diamond Light Source [H. Nowell, S. A. Barnett, K. E. Christensen, S. J. Teat, D. R. Allan, *J. Synchrotron Radiat.* **2012**, *19*, 435 – 441] at low temp [J. Cosier, A. M. Glazer, *J. Appl. Crystallogr.* **1986**, *19*, 105 – 107], and the structure was solved with SuperFlip [L. Palatinus, G. Chapuis, *J. Appl. Crystallogr.* **2007**, *40*, 786 – 790] and refined with the CRYSTALS software suite [P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, *36*, 1487; H-atom refinement: R. I. Cooper, A. L. Thompson, D. J. Watkin, *J. Appl. Crystallogr.* **2010**, *43*, 1100 – 1107]. Full refinement details are given in the Supporting Information CIF file. CCDC 924224 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[40] Details of the NOE experiments on **10L** are given in the Supporting Information.

[41] Spectra of a six-month-old sample of **11L** are given in the Supporting Information.

[42] N. Araújo, S. F. Jenkinson, F. R. Martínez, A. F. G. Glawar, M. Wormald, T. D. Butters, S. Nakagawa, I. Adachi, A. Kato, A. Yoshihara, K. Akimitsu, K. Izumori, G. W. J. Fleet, *Org. Lett.* **2012**, *14*, 4174 – 4177.

[43] G. B. Evans, R. H. Furneaux, B. Greatrex, A. S. Murkin, V. L. Schramm, P. C. Tyler, *J. Med. Chem.* **2008**, *51*, 948 – 956.

[44] G. M. J. Lenagh-Snow, N. Araújo, S. F. Jenkinson, C. Rutherford, S. Nakagawa, A. Kato, C.-Y. Yu, A. C. Weymouth-Wilson, G. W. J. Fleet, *Org. Lett.* **2011**, *13*, 5834 – 5837.

[45] B. Krämer, T. Franz, S. Picasso, P. Pruschek, V. Jäger, *Synlett* **1997**, 295 – 297.

[46] For details of assays, see: a) A. F. G. Glawar, D. Best, B. Ayers, S. Miyauchi, S. Nakagawa, M. Aguilar-Moncayo, J. M. García Fernández, C. O. Mellet, E. V. Crabtree, T. D. Butters, F. X. Wilson, A. Kato, G. W. J. Fleet, *Chem. Eur. J.* **2012**, *18*, 9341 – 9359; b) T. B. Mercer, S. F. Jenkinson, B. Bartholomew, R. J. Nash, S. Miyauchi, A. Kato, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2009**, *20*, 2368 – 2373; c) D. Best, C. Wang, A. C. Weymouth-Wilson, R. A. Clarkson, F. X. Wilson, R. J. Nash, S. Miyauchi, A. Kato, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2010**, *21*, 311 – 319. A complete table of glycosidase inhibition by the azetidines is shown in the Supporting Information.

[47] J. C. Lee, S. Francis, D. Dutta, V. Gupta, Y. Yang, J.-Y. Zhu, J. S. Tash, E. Schonbrunn, G. I. Georg, *J. Org. Chem.* **2012**, *77*, 3082 – 3098.

[48] A. Kato, N. Kato, S. Miyauchi, Y. Minoshima, I. Adachi, K. Ikeda, N. Asano, A. A. Watson, R. J. Nash, *Phytochemistry* **2008**, *69*, 1261 – 1265.

[49] J. P. Shilvock, R. J. Nash, J. D. Lloyd, A. L. Winters, N. Asano, G. W. J. Fleet, *Tetrahedron: Asymmetry* **1998**, *9*, 3505 – 3516.

[50] P. Paquette, L. Barriault, D. Pissarnitski, J. Johnston, *J. Am. Chem. Soc.* **2000**, *122*, 619 – 631.

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