Efficient synthesis of (+)-1,8,8a-tri-*epi*-swainsonine, (+)-1,2-di-*epi*-lentiginosine, (+)-9a-*epi*-homocastanospermine and (−)-9-deoxy-9a-*epi*-homocastanospermine from a D-glucose-derived aziridine carboxylate, and study of their glycosidase inhibitory activities†

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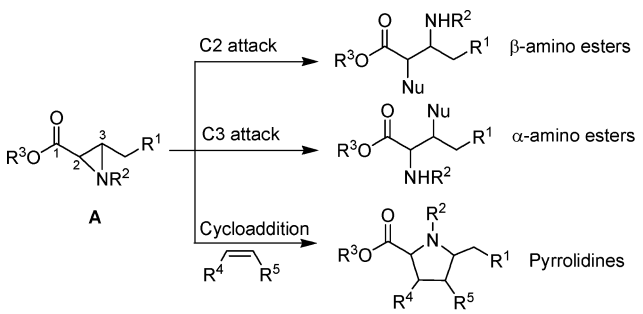
Received 17th August 2007, Accepted 16th October 2007
First published as an Advance Article on the web 3rd January 2008
DOI: 10.1039/b712753g

The utility of a D-glucose-derived aziridine carboxylate was demonstrated for the synthesis of polyhydroxylated quinolizidine and indolizidine alkaloids. The chemoselective reduction of **1** followed by two-carbon homologation by the Wittig reaction afforded γ,δ-aziridino-α,β-unsaturated ester **9**, which on regioselective nucleophilic aziridine ring opening either by using water as a nucleophile or hydrogenation afforded δ-lactams **11/16**—true synthons for the synthesis of four structurally different iminosugars, namely quinolizidine alkaloids **5b/5c**, swainsonine **6b** and lentiginosine **7b** analogues. Glycosidase inhibitory activities of these iminosugars were investigated.

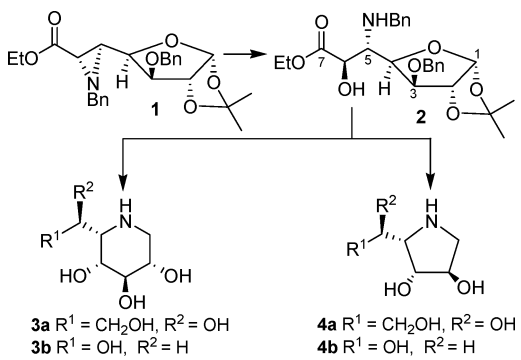
Introduction

Among the functionalized three-membered cyclic compounds, aziridines and aziridine carboxylates have been considered to be prominent precursors in the synthesis of natural and unnatural amino compounds due to their inherent ability to undergo regio- and chemo-selective reactions as well as cycloaddition pathways.[1] For example, aziridine carboxylates of type **A** are prone to regio-controlled nucleophilic ring opening either at C2 or at C3, leading to the formation of β- or α-amino esters,[2a–l,r,s] while cycloaddition reactions with doubly activated olefins afford pyrrolidines[2m–q,t] (Scheme 1). In addition, the presence of two electrophilic functionalities (aziridine and ester) in **A** offers flexibility to achieve chemoselective transformations under diverse reaction conditions.



Scheme 1 Reactivity of aziridine carboxylates of type **A**.

In general, it is observed that aziridine carboxylates in which the ring nitrogen is activated by an electron-withdrawing group (R^2 = electron withdrawing group like Cbz, tosyl *etc.*) react more rapidly with hydride donors like $LiAlH_4$ and DIBAL-H than non-activated aziridines (*e.g.* those having a benzyl group on nitrogen).[3,4h] In such cases, chemoselective reduction of the carboxylate group to an alcohol/aldehyde functionality, keeping the aziridine functionality intact, could be achieved under kinetically controlled reaction conditions. This type of chemoselective functional group transformation protocol, with initial reaction at the carboxylate functionality, followed by regio-selective aziridine ring opening giving access to distinct building blocks that are necessary for the synthesis of complex natural products, has received limited attention.[4,5] Recently, we reported the synthesis of D-glucose-derived aziridine carboxylate **1**, and demonstrated that exclusive aziridine ring opening at the C2 position, using water as a nucleophile in the presence of TFA, resulted in the formation of α-hydroxy β-amino ester **2**, which was then elaborated to the piperidine and pyrrolidine iminosugars **3a/3b** and **4a/4b**, respectively (Scheme 2).[5c,d]



Scheme 2 Piperidine and pyrrolidine alkaloids.

Iminosugars,[6] in particular polyhydroxylated indolizidine[7] and quinolizidine alkaloids, namely naturally occurring (+)-castanospermine **5a**, (−)-swainsonine **6a** and (+)-lentiginosine **7a** (Fig. 1), are promising glycosidase inhibitors[8] and show exceptional ability to inhibit the glycoprotein-processing enzymes useful in studies on

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, and copies of ^1H and ^{13}C NMR spectra of compounds **5b**, **5c**, **6b**, **7b** and **8–19**. See DOI: 10.1039/b712753g

the effect of oligosaccharide structure on glycoprotein function.[8e–g] In the search for better inhibitors toward specific classes of hydrolytic enzymes, a number of stereochemically different hydroxyl-substituted and ring-expanded analogues[9] of these iminosugars have been synthesized and evaluated for glycosidase inhibitory and immunosupressive activities.[8h–k] As a continuation of our interest in this area,[10] we envisioned that the presence of a non-activated aziridine functionality in **1** will allow us to explore kinetically controlled chemoselective transformations at the carboxylate functionality to obtain γ,δ-aziridino-α,β-unsaturated ester **9** (Scheme 3).

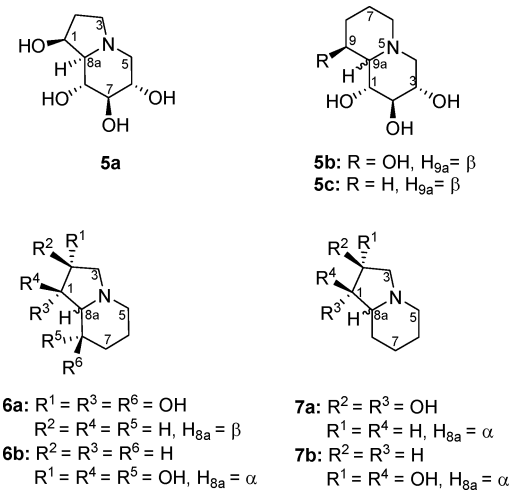
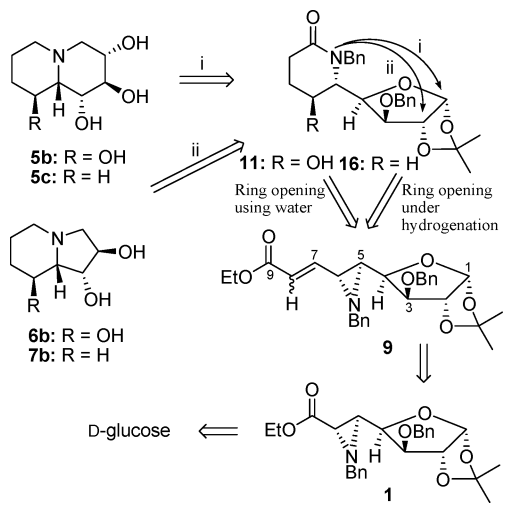


Fig. 1 Indolizidine and quinolizidine alkaloids.

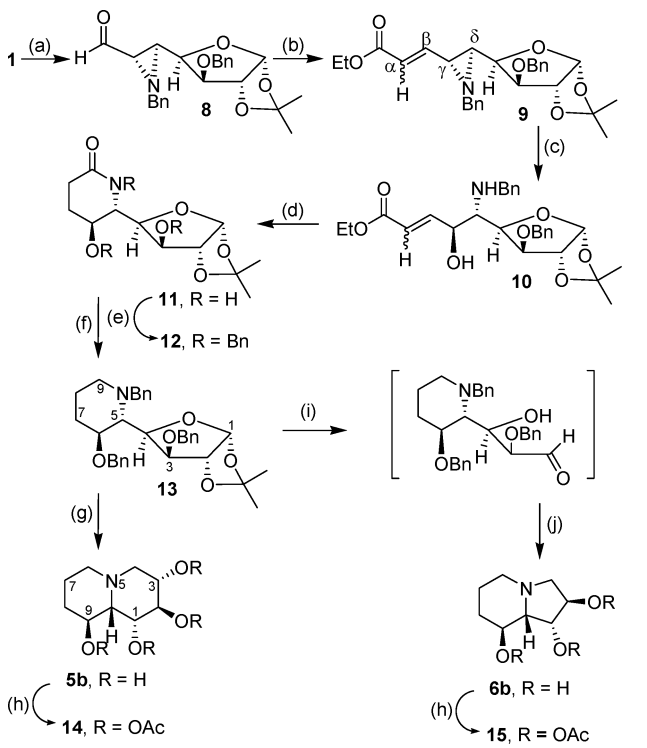


Scheme 3 Retrosynthetic analysis.

The regioselective aziridine ring opening at C6 either by a hydroxyl- or hydrogen-equivalent will give access to two different δ-lactams **11** and **16**, with a sugar appendage required to generate the polyhydroxylated framework. Lactams **11** and **16** can be common intermediates for the synthesis of polyhydroxylated quinolizidine **5b** and **5c** and indolizidine alkaloids **6b** and **7b**. A few reports are available on the use of sugar aziridines in the synthesis of iminosugars;[11] however, the applicability of aziridine carboxylate **1** in the synthesis of quinolizidine and indolizidine alkaloids of the following types: 8a-*epi*-homocastanospermine **5b**; 1-deoxy-8a-*epi*-homocastanospermine **5c**; 1,8,8a-tri-*epi*-swainsonine **6b**; and 1,2-di-*epi*-lentiginosine **7b**; to the best of our knowledge, has not been reported so far. Our efforts in this direction are discussed herein.

Results and discussion

Aziridine carboxylate **1** was prepared from D-glucose as reported earlier by us.[5c] Treatment of **1** with DIBAL-H in CH_2Cl_2 at −78 °C resulted in the chemoselective formation of aziridine aldehyde **8**, which was subjected to the two-carbon homologation using $Ph_3P{=}CHCOOEt$ to afford an inseparable *E*/*Z* mixture of γ,δ-aziridino-α,β-unsaturated ester **9** in the ratio 8.5 : 1.5 as evident from the ^1H NMR of the crude product (Scheme 4). A mixture of **9** was treated with TFA (2 equiv.) in CH_3CN–H_2O (8 : 1) to afford γ-hydroxy-δ-amino-α,β-conjugated ester **10** as the major *E*-isomer in 74% yield.[12] Assignment of structure **10** was made by using ^1H NMR data and decoupling experiments, wherein H5 showed a doublet of doublets ($J_{5,6} = 8.8$ Hz and $J_{4,5} = 3.5$ Hz) at δ 3.39 while H6 appeared at δ 4.45 as a doublet of doublet of doublets (J = 8.8, 3.8, and 2.2 Hz). This indicated that aziridine ring opening in **9** took place regioselectively at C6 leading to the formation of δ-amino ester **10**.



Scheme 4 *Reagents and conditions*: (a) DIBAL-H, CH_2Cl_2, −78 °C, 2.5 h, 79%; (b) $Ph_3P{=}CHCOOEt$, CH_3CN, 30 °C, 6 h, 77%; (c) TFA (2 equiv.), CH_3CN–H_2O (8 : 1), 15 °C to 30 °C, 6 h, 80%; (d) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 3 h, 90%; (e) NaH, BnBr, THF, 0 °C to reflux, 2.5 h, 90%; (f) LAH, THF, 0 °C to reflux, 3 h, 85%; (g) i) TFA–H_2O (7 : 3), 0 °C to 20 °C, 3 h; ii) H_2 (80 psi), 10% Pd/C, MeOH, 24 h, 96%; (h) Ac_2O, Py, DMAP, 30 °C, 6 h; (i) i) TFA–H_2O (7 : 3), 0 °C to 20 °C, 3 h; ii) $NaIO_4$, acetone–water (4 : 1); (j) H_2 (80 psi), 10% Pd/C, MeOH, 30 °C, 24 h, 81%.

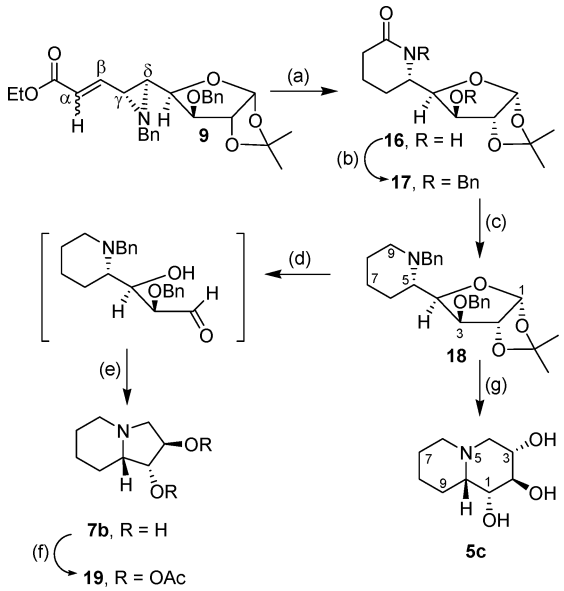
The observed stereo- and regioselectivity in **10** (with a 5*S*,6*R* absolute configuration) could be explained by the preferential S_N2 attack at the C6 carbon atom of the aziridine ring, rather than at C5, which is hindered due to the β-oriented C3-*O*Bn group. In the next step, δ-amino ester **10** was subjected to hydrogenation using 10% Pd/C in methanol to give δ-lactam **11** in quantitative yield. Formation of δ-lactam was confirmed by IR (C=O, 1628 cm^{-1}) and NMR spectral data.[13] This one-pot three-step process involves reduction of C=C, removal of *N*/*O*-benzyl groups and cyclization. Subsequently, reaction of **11** with benzyl bromide and sodium hydride in THF gave tribenzylated lactam **12**, which on treatment with $LiAlH_4$ in THF afforded tribenzylated piperidine **13** in good yield. Finally, opening of the 1,2-acetonide functionality in **13** with TFA–H_2O (7 : 3) to give a hemiacetal followed by hydrogenation using 10% Pd/C in MeOH and purification by chromatography afforded quinolizidine alkaloid **5b** as a white solid. The structure of **5b** was confirmed by converting it to peracetylated derivative **14**. The analytical and spectral data of both the compounds were found to be in accordance with the assigned structures **5b** and **14**. With the indolizidine alkaloid target **6b** in mind, compound **13** was treated with TFA–H_2O (to cleave the 1,2-acetonide group) to give a hemiacetal, and oxidative cleavage with $NaIO_4$ afforded the one-carbon-degraded product (as evident from the NMR of the crude product), which was immediately subjected to hydrogenation with 10% Pd/C in MeOH to give 1,8,8a-tri-*epi*-swainsonine **6b** as a thick liquid. Peracetylation of **6b** using Ac_2O in pyridine gave triacetyl derivative **15**. The analytical and spectral data were found to be in agreement with the assigned structures **6b** and **15**.

It is known that small structural modifications of the natural indolizidine alkaloids such as swainsonine and lentiginosine induce significant changes in their specificity and potency to inhibit various glycosidases.[7r,x] In view of this, the synthetic potentiality of γ,δ-aziridino ester **9** was further demonstrated by transforming it to 1,2-di-*epi*-lentiginosine and 9-deoxy-9a-*epi*-homocastanospermine (Scheme 5).

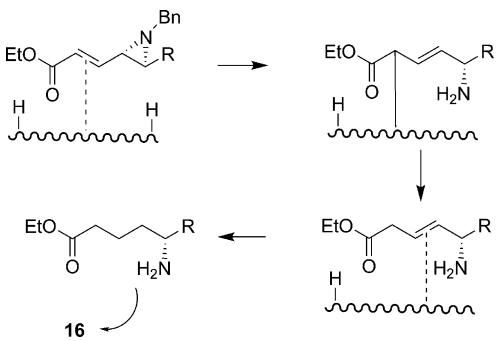
At this stage, we thought of reductive aziridine ring opening in **9**, keeping the ester functionality intact. There exists a possibility to achieve this transformation under hydrogenation conditions. In general, hydrogenation of aziridine carboxylates of type **A** occurs at C3, affording α-amino esters in good yield.[14] However, compound **9**, on hydrogenation (10% Pd/C, MeOH)[15] followed by treatment with sodium acetate in methanol, afforded δ-lactam **16** and not the γ-lactam. This two-step process probably involves reduction of C=C, *N*/*O*-debenzylation, regioselective aziridine ring opening at C6 and the formation of the δ-lactam. The spectral and analytical data of **16** was found to be identical to that reported by us previously [mp 156–157 °C; lit.[9d] mp 157 °C; $[a]_D = -12.3$ (*c* 2.51, $CHCl_3$), lit.[9d] $[a]_D = -11.5$ (*c* 2.35, $CHCl_3$)].

The formation of the δ-lactam rather than the γ-lactam is interesting. We believe that the reductive aziridine ring opening is assisted by the conjugated double bond,[16] wherein initial abstraction of the hydrogen is followed by migration of the double bond and aziridine ring opening to give an allylamine. This is further reduced to a δ-amino ester and cyclizes to give the δ-lactam **16**, as shown in Scheme 6.

We previously reported the transformation of δ-lactam **16** to quinolizidine alkaloid **5c** using reduction of the lactam functionality followed by *N*-Cbz protection.[9d] However, at this stage we



Scheme 5 *Reagents and conditions*: (a) H_2 (80 psi), 10% Pd/C, MeOH, 30 °C, 12 h, then, NaOAc, MeOH, reflux, 1.5 h, 74% (over two steps); (b) NaH, BnBr, THF, 0 °C to reflux, 2.5 h, 96%; (c) LAH, THF, 0 °C to reflux, 3 h, 89%; (d) i) TFA–H_2O (7 : 3); ii) $NaIO_4$, acetone–water (4 : 1); (e) H_2 (80 psi), 10% Pd/C, MeOH, 30 °C, 24 h, 69%; (f) Ac_2O, Py, DMAP (cat.), 30 °C, 6 h; (g) i) TFA–H_2O (7 : 3), 0 °C to 20 °C, 3 h; ii) H_2 (80 psi), 10% Pd/C, MeOH, 24 h, 96%.



Scheme 6 Plausible pathway for the hydrogenation reaction.

thought of using benzyl protection of δ-lactam **16** (to give a product benzylated on the nitrogen and C3 oxygen), to give access to quinolizidine as well as indolizidine alkaloids.[17]

Thus, as shown in Scheme 5, benzylation of **16** with benzyl bromide (using NaH in THF) afforded piperidone **17**, which on $LiAlH_4$ reduction afforded dibenzylated piperidine compound **18**. In the subsequent steps, 1,2-acetonide cleavage (TFA–H_2O) followed by hydrogenation (10% Pd/C, MeOH) and purification by chromatography afforded quinolizidine alkaloid **5c** as a thick liquid. The analytical and ^1H NMR and ^{13}C NMR data of **5c** were in consonance with the reported data [$[a]_D = -75.9$ (*c* 0.13, MeOH), lit.[9d] $[a]_D = -80.0$ (*c* 0.1, MeOH)]. On the other hand, 1,2-acetonide deprotection followed by oxidative cleavage ($NaIO_4$) and hydrogenation (10% Pd/C, MeOH) afforded 1,2-di-*epi*-lentiginosine **7b** as a crystalline solid in good yield. The spectral and analytical data of **7b** was found to be identical with

Table 1 Inhibition potencies of quinolizidines **5b** and **5c** and indolizidines **6b** and **7b**

Enzyme	IC_{50}/mM			
	5b	**5c**	**6b**	**7b**
α-Amylase (ex-porcine)	—[a]	NI[b]	629	1109
β-Glucosidase (sweet almonds)	79.80	372	1.23	0.75
α-Mannosidase (jack bean)	NI[b]	—[a]	NI[b]	NI[b]
β-Xylanase (*Thermomyces lanuginosus*)	1.80	0.26	10.70	6.50

[a] Inhibition was not studied. [b] No inhibition under the assay conditions.

that reported [mp 133–135 °C; lit.[7w,10e] mp (not reported); $[\alpha]_D$ = +3.8 (*c* 0.43, MeOH), lit.[7w,10e] $[\alpha]_D$ = +4.2 (*c* 0.51, MeOH)]. The dihydroxy indolizidine **7b** was further characterized as its diacetyl derivative **19**.

Glycosidase inhibitory activity

Using standardized assay techniques,[18] the inhibitory activities of **5b**, **5c**, **6b**, and **7b** were screened with different enzymes, namely α-amylase (ex-porcine), β-glucosidase (sweet almonds), α-mannosidase (jack bean), and β-xylanase (*Thermomyces lanuginosus*) and results are summarized in Table 1. The data clearly indicates that quinolizidines **5b**/**5c** and indolizidines **6b**/**7b** are weak inhibitors of α-amylase. 9-Deoxyquinolizidine analogue **5c** was found to be a selective inhibitor of β-xylanase, with a ~10-fold increase in activity compared to that of **5b**. Thus, the presence of a hydroxyl functionality in the six-membered ring of quinolizidine **5b** reduces the activity (towards β-xylanase) and also the specificity of the inhibitor as noted from the structure–activity relationship with **5c**. This observation is analogous to that of Pearson and coworkers,[9a] who found that ring homologues of swainsonine were found to be poor inhibitors of glycosidases. Natural (−)-swainsonine **6a** is a potent inhibitor of α-D-mannosidase and mannosidase II, while the antipode (+)-swainsonine is a selective and potent inhibitor of naringinase (L-rhamnosidase).[8f–l] However, the new analogue 1,8,8a-tri-*epi*-swainsonine **6b** did not show any inhibition towards α-mannosidase, probably due to the *anti*-orientation of the hydroxyl functionalities at C1 and C3 in the pyrrolidine ring of the indolizidine skeleton.

Interestingly, **6b** showed moderate inhibition toward β-glucosidase as well as β-xylanase. Lentiginosine analogue **7b** displayed similar activity to that of **6b** (in the millimolar range), indicating that the presence of the C8 hydroxyl functionality in **6b** has little influence on the specificity and potency.

Conclusion

In conclusion, we have demonstrated chemo- and regio-selective transformations of D-glucose-derived aziridine carboxylate **1** and its versatility in the efficient synthesis of iminosugars of biological interest, namely (+)-1,8,8a-tri-*epi*-swainsonine **6b**, (+)-1,2-di-*epi*-lentiginosine **7b**, (+)-9a-*epi*-homocastanospermine **5b**, and its 9-deoxy analogue **5c**. A structure–activity relationship study of target molecules indicates that the small structural changes have a noticeable effect on the potency as well as the specificity of the inhibitor.

Experimental

General methods

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with an FTIR spectrometer as a thin film, in Nujol mull, or using KBr pellets, and are expressed in cm^{-1}. δ_H (300 MHz) and δ_C (75 and 100 MHz) NMR spectra were recorded using $CDCl_3$ or D_2O/CD_3OD as a solvent. Chemical shifts were reported in δ units (ppm) with reference to TMS as an internal standard, and *J* values are given in Hz. Decoupling and DEPT experiments confirmed the assignments of the signals. Elemental analyses were carried out with a C,H-analyzer. Optical rotations were measured using a polarimeter at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh). The reactions were carried out in oven-dried glassware under dry N_2. Methanol, pyridine, THF, were purified and dried before use. The n-hexane used was the fraction distilling between 40–60 °C. TFA and 10% Pd/C were purchased from Aldrich and/or Fluka. After decomposition of the reaction with water, the work-up involves: washing of combined organic layers with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent under reduced pressure.

General procedure for inhibition assay

Inhibition potencies of **5b**/**5c**, and **6b**/**7b** were determined by measuring the residual hydrolytic activities of the glycosidases.[18] The substrates (purchased from Sigma Chemicals Co., USA), namely *p*-nitrophenyl-α-D-glucopyranoside and *p*-nitrophenyl-β-D-glucopyranoside, of 2 mM concentration, were prepared in 0.025 M citrate buffer with pH 6.0. *p*-Nitrophenyl-α-D-mannopyranoside of 2 mM concentration was prepared in 0.025 M citrate buffer with pH 4.0. The test compound was preincubated with the respective enzyme buffered at their optimal pH, for 1 h at 25 °C. The enzyme reaction was initiated by the addition of 100 μL substrate. Controls were run simultaneously in the absence of test compound. The reaction was terminated after 10 min by the addition of 0.05 M borate buffer (pH 9.8), and absorbance of the liberated *p*-nitrophenol was measured at 405 nm using a spectrophotometer. One unit of glycosidase activity is defined as the amount of enzyme hydrolyzing 1 μmol of (*p*-nitrophenyl)pyranoside in 1 min at 25 °C. The xylanase assay was carried out at pH 6.0 by mixing 2 mM of the enzyme with 0.5 cm^3 of oat spelt xylan (10 mg cm^{-3}) in 1 cm^3 of reaction mixture and incubation at 50 °C for 30 min; the reducing sugar released was determined by the dinitrosalicylic method.[18b] One unit of xylanase activity is defined as the amount of enzyme producing 1 μmol of xylose equivalent per unit using oat spelt xylan as the substrate under assay conditions.

1,2-*O*-Isopropylidine-3-*O*-benzyl-5,6-dideoxy-5,6-*N*-benzyl-*E*-aziridino-β-L-*ido*-1,4-furan-7-al (8)

To a solution of aziridine ester **1** (1.41 g, 3.09 mmol) in dry dichloromethane (20 cm^3) at −78 °C was added DIBAL-H (20% solution in hexane) (4.35 cm^3, 6.18 mmol) over 15 min, and the mixture stirred for 2.5 h. The reaction mixture was quenched using

ethyl acetate (5 cm^3) and sat. NH_4Cl (1 cm^3) and filtered through Celite, concentrated, adsorbed on silica and purified by column chromatography (n-hexane–ethyl acetate = 9 : 1), to give **8** as a white solid (1.01 g, 79.3%): mp 95–96 °C; (found: C, 70.31; H, 6.49. Calc. for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65); $R_f = 0.40$ (n-hexane–ethyl acetate = 7 : 3); $[\alpha]_D = -29.10$ (*c* 0.05, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2920, 1726, 1666, 1074, 1022; δ_H (300 MHz, $CDCl_3$) (the ^1H and ^{13}C NMR spectra showed additional signals corresponding to aldehydes and aziridine protons and carbons—we are unable to explain these features) 1.24 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.54 (1H, bs, H-5), 2.91 (1H, bs, H-6), 3.91 (2H, bs, NCH_2Ph), 4.12–4.40 (2H, m, H-4, H-3), 4.46 (1H, d, $J = 11.0$ Hz, OCH_2Ph), 4.65 (1H, d, $J = 3.8$ Hz, H-2), 4.67 (1H, d, $J = 11.0$ Hz, OCH_2Ph), 6.00 (1H, d, $J = 3.8$ Hz, H-1), 7.14–7.27 (10H, m, Ar*H*), 9.40 (1H, s, C*H*O); δ_C (75 MHz, $CDCl_3$) 26.2, 26.8 (2 × CH_3), 43.2 (C-6), 48.7 (C-5), 56.3 (N*C*H_2Ph), 71.8 (O*C*H_2Ph), 75.7 (C-3), 82.0 (C-2), 82.7 (C-4), 105.3 (C-1), 111.7 (O*C*O), 127.1 (ArC), 127.7 (ArC), 128.0 (ArC), 128.3 (strong, 4 × ArC), 128.4 (strong, 3 × ArC), 137.8 (ArC), 197.2 (CHO).

(*E*)-Ethyl-3-*O*-benzyl-5,6-dideoxy-5,6-*N*-benzyl-*E*-aziridino-1,2-*O*-isopropylidine-β-L-*ido*-nona-7-eno-furanuronate (9)

To a solution of aziridine aldehyde **8** (0.97 g, 2.37 mmol) in dry acetonitrile (15 cm^3) was added (carboethoxymethylene)triphenylphosphorane (1.07 g, 3.08 mmol), and the reaction mixture was stirred for 6 h at 30 °C. The acetonitrile was evaporated and the reaction mixture was adsorbed on silica. Purification by column chromatography (n-hexane–ethyl acetate = 9 : 1) gave **9** (mixture of *E* and *Z* isomers) as a thick liquid (0.87 g, 77.7%): (found: C, 69.97; H, 6.86. Calc. for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94); $R_f = 0.40$ (n-hexane–ethyl acetate = 7 : 3); ν_{max}(neat)/cm^{-1} 1718, 1624, 1217, 1076; δ_H (300 MHz, $CDCl_3$) (the ^1H and ^{13}C NMR spectra showed an additional signal due to the minor *Z*-isomer (~15%)) 1.31 (3H, t, $J = 7.1$ Hz, OCH_2CH_3), 1.32 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.45 (1H, dd, $J = 7.1$ and 3.0 Hz, H-5), 2.59 (1H, dd, $J = 9.9$ and 3.0 Hz, H-6), 3.72 (1H, d, $J = 14.0$ Hz, NCH_2Ph), 3.86 (1H, d, $J = 3.3$ Hz, H-3), 3.96 (1H, d, $J = 14.0$ Hz, NCH_2Ph), 4.15–4.27 (3H, m, OCH_2CH$_3$, H-4), 4.44 (1H, d, $J = 12.1$ Hz, OCH_2Ph), 4.61 (1H, d, $J = 3.8$ Hz, H-2), 4.66 (1H, d, $J = 12.1$ Hz, OCH_2Ph), 5.98 (1H, d, $J = 3.8$ Hz, H-1), 6.04 (1H, d, $J = 15.4$ Hz, H-8), 6.89 (1H, dd, $J = 15.4$ and 9.9 Hz, H-7), 7.16–7.37 (10H, m, ArH); δ_C (75 MHz, $CDCl_3$) δ 14.3 (OCH_2CH_3), 26.3 (CH_3), 26.8 (CH_3), 39.9 (C-5), 47.0 (C-6), 56.9 (N*C*H_2Ph), 60.5 (O*C*H_2CH$_3$), 71.7 (O*C*H_2Ph), 81.9 (C-3), 82.0 (C-2), 82.7 (C-4), 105.2 (C-1), 111.6 (O*C*O), 125.2 (C-8), 126.8 (ArC), 127.7 (strong, 2 × ArC), 127.8 (strong, 2 × ArC), 127.9 (ArC), 128.1 (strong, 2 × ArC), 128.3 (strong, 2 × ArC), 136.8 (ArC), 138.4 (ArC), 142.9 (C-7), 165.2 (*C*OOCH$_2$CH$_3$).

(*E*)-Ethyl-3-*O*-benzyl-5-*N*-(benzyl)amino-1,2-*O*-isopropylidine-β-L-*glycero*-L-*ido*-nona-7-eno-furanuronate (10)

To a solution of aziridine ester **9** (0.85 g, 1.77 mmol) in acetonitrile–water (8 : 1, 20 cm^3) at 15 °C was added TFA (0.40 cm^3, 3.54 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 6 h, and neutralized with Indion-860 resin. Filtration, evaporation of solvent at rotary evaporator and column chromatography (n-hexane–ethyl acetate = 4 : 1) afforded **10** (0.72 g, 80.4%) as a thick liquid: (found: C, 67.83; H, 7.05. Calc. for $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09); $R_f = 0.30$ (n-hexane–ethyl acetate = 7 : 3); $[\alpha]_D = -11.53$ (*c* 0.26, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3080–3700 (broad), 1714, 1654; δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, $J = 6.8$ Hz, OCH_2CH_3) 1.33 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.80 (2H, bs, exchanges with D_2O, N*H*Bn, O*H*) 3.39 (1H, dd, $J =$ 8.8 and 3.5 Hz, H-5), 3.87 (1H, d, $J = 3.0$ Hz, H-3), 3.89 (2H, ABq, $J = 12.0$ Hz, NCH_2Ph), 4.19 (1H, dd, $J = 3.5$ and 3.0 Hz, H-4), 4.20 (2H, q, $J = 6.8$ Hz, OCH_2CH$_3$), 4.45 (1H, ddd, $J =$ 8.8, 3.8 and 2.2 Hz, H-6), 4.58 (2H, ABq, $J = 11.2$ Hz, OCH_2Ph), 4.65 (1H, d, $J = 3.8$ Hz, H-2), 5.89 (1H, d, $J = 3.8$ Hz, H-1), 6.22 (1H, dd, $J = 15.6$ and 2.2 Hz, H-8), 6.90 (1H, dd, $J = 15.6$ and 3.5 Hz, H-7), 7.22–7.42 (10H, m, ArH); δ_C (75 MHz, $CDCl_3$) δ 14.3 (OCH_2CH_3), 26.3 (CH_3), 26.7 (CH_3), 52.0 (C-5), 59.6 (NCH_2Ph), 60.4 (O*C*H_2CH$_3$), 68.0 (OCH_2Ph), 71.2 (C-3), 78.5 (C-6), 81.9 (strong, C-2 and C-4), 103.8 (C-1), 111.6 (O*C*O), 121.3 (C-8), 127.1 (ArC), 127.6 (strong, 2 × ArC), 127.9 (ArC), 128.2 (strong, 2 × ArC), 128.3 (strong, 2 × ArC), 128.4 (strong, 2 × ArC), 137.0 (ArC), 139.1 (ArC), 146.0 (C-7), 166.1 (*C*OOCH$_2$CH$_3$).

1,2-*O*-Isopropylidine-3,6-di-hydroxy-5,7,8-tri-deoxy-β-L-*glycero*-5,9-imino-β-L-*ido*-furan-9-ulose (11)

To a stirred solution of hydroxyl amino ester **10** (0.66 g, 1.32 mmol) in methanol (15 cm^3) at reflux was added ammonium formate (0.41 g, 6.63 mmol) and 10% Pd/C (100 mg), and the mixture refluxed for 3 h. The reaction mixture was filtered through Celite, concentrated and purified by column chromatography (n-hexane–ethyl acetate = 2 : 8) to afford **11** as a white solid (0.30 g, 90%); mp 182 °C: (found: C, 52.61; H, 7.30. Calc. for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01); $R_f = 0.83$ ($CHCl_3$–MeOH = 7 : 3); $[\alpha]_D = -5.40$ (*c* 0.36, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3325, 1628, 1076 cm^{-1}; δ_H (300 MHz, CD_3OD) 1.30 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.79–1.92 (1H, m, H-7a), 1.99–2.08 (1H, m, H-7b) 2.27–2.50 (2H, m, H-8), 3.57 (1H, dd, $J = 6.7$ and 3.5 Hz, H-5), 3.88 (1H, ddd, $J = 9.1$, 6.7 and 3.2 Hz, H-6), 4.20 (1H, d, $J = 2.7$ Hz, H-3), 4.25 (1H, t, $J =$ 3.5 Hz, H-4), 4.49 (1H, d, $J = 3.8$ Hz, H-2), 4.62 (1H, bs, N*H*), 5.91 (1H, d, $J = 3.8$ Hz, H-1) (Note: In the ^1H NMR spectrum OH protons are exchanged with CD_3OD); δ_C (75 MHz, CD_3OD) 26.4 (CH_3), 27.1 (CH_3), 28.8 (C-7), 28.9 (C-8), 59.5 (C-5), 66.3 (C-6), 77.3 (C-3), 79.8 (C-2), 86.8 (C-4), 105.9 (C-1), 112.7 (OCO), 174.3 (*C*OOCH$_2$CH$_3$).

1,2-*O*-Isopropylidine-3,6-di-*O*-benzyl-5,7,8-tri-deoxy-β-L-*glycero*-5,9-*N*-(benzyl)imino-β-L-*ido*-furan-9-ulose (12)

To a slurry of NaH (0.29 g, 0.74 mmol) in dry THF (5 cm^3) at 0 °C was added a solution of lactam **11** (0.50 g, 0.18 mmol) in THF (10 cm^3), and the mixture stirred for five minutes. Benzyl bromide (0.86 cm^3, 0.74 mmol) in THF (5 cm^3) was added dropwise, and stirred well while warming to room temperature, before being refluxed for 2.5 h. Usual workup and purification by column chromatography (n-hexane–ethyl acetate = 8.5 : 1.5) yielded **12** as a thick liquid (0.90 g, 90%): (found: C, 73.11; H, 7.02. Calc. for $C_{33}H_{37}NO_6$: C, 72.91; H, 6.86); $R_f = 0.43$ (n-hexane–ethyl acetate = 6.5 : 3.5); $[\alpha]_D = +50.00$ (*c* 0.2, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2925, 1627, 1217, 1078; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.79–2.12 (2H, m, H-8), 2.48 (1H, dd, $J = 18.1$ and 7.4 Hz,

H-7), 2.67–2.79 (1H, m, H-7), 3.49 (1H, bs, H-6), 3.79 (1H, d, J = 2.7 Hz, H-3), 3.89 (2H, s, OCH_2Ph), 3.99 (1H, bd, J = 9.3 Hz, H-5), 4.13 (1H, dd, J = 9.3 and 2.7 Hz, H-4), 4.23 (1H, d, J = 15.1 Hz, NCH_2Ph), 4.29 (1H, d, J = 12.1 Hz, OCH_2Ph), 4.61 (1H, d, J = 3.8 Hz, H-2), 4.62 (1H, d, J = 12.1 Hz, OCH_2Ph), 5.66 (1H, d, J = 15.1 Hz, NCH_2Ph), 5.99 (1H, d, J = 3.8 Hz, H-1), 6.92–6.95 (2H, m, ArH), 7.11–7.30 (13H, m, ArH); δ_C (75 MHz, $CDCl_3$) 23.5 (C-7), 26.0 (CH_3), 26.6 (CH_3), 27.0 (C-8), 49.0 (C-5), 56.1 (NCH_2Ph), 69.2 (C-6), 70.5 (OCH_2Ph), 71.2 (OCH_2Ph), 80.5 (C-3), 81.5 (C-2), 83.1 (C-4), 104.5 (C-1), 111.5 (OCO), 126.4 (strong, ArC), 126.5 (ArC), 127.0 (ArC), 127.3 (strong, 2 × ArC), 127.9 (ArC), 128.0 (strong, 2 × ArC), 128.1 (strong, 2 × ArC), 128.2 (strong, 2 × ArC), 128.3 (strong, 2 × ArC), 136.3 (ArC), 137.5 (ArC), 137.8 (ArC), 169.5 (*C*ONH).

1,2-*O*-Isopropylidine-3,6-di-*O*-(benzyl)-5,7,8-tri-deoxy-β-L-*glycero*-5,9-*N*-(benzyl)imino-β-L-*ido*-1,4-furanose (13)

To an ice-cooled suspension of LAH (0.02 g, 0.04 mmol) in dry THF (4 cm^3) was added tribenzylated lactam **12** (0.09 g, 0.16 mmol) in dry THF (10 cm^3) at 0 °C, and the mixture stirred for 10 min. The reaction mixture was slowly warmed to room temperature, refluxed for 3 h and quenched with ethyl acetate (10 cm^3), followed by an aqueous solution of ammonium chloride (2 cm^3). Filtration through Celite, concentration under vacuum and purification by column chromatography (n-hexane–ethyl acetate = 9 : 1) gave **13** as a thick liquid (0.06 g, 85.0%): (found: C, 74.71; H, 7.33. Calc. for $C_{33}H_{39}NO_5$: C, 74.83; H, 7.42); R_f = 0.82 (n-hexane–ethyl acetate = 7 : 3); $[\alpha]_D$ = +13.33 (*c* 0.15, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1610, 1416; δ_H (300 MHz, $CDCl_3$) 1.20–1.74 (2H, m, H-8), 1.32 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.79–2.00 (2H, m, H-7), 2.46–2.65 (1H, m, H-9), 2.66–2.84 (1H, m, H-9), 3.42 (1H, bd, J = 3.3 Hz, H-6), 3.60 (1H, dd, J = 9.3 and 2.7 Hz, H-5), 3.79 (1H, d, J = 2.7 Hz, H-3), 3.86 (1H, d, J = 14.3 Hz, NCH_2Ph), 4.05 (1H, d, J = 14.3 Hz, NCH_2Ph), 4.31 (1H, d, J = 11.8 Hz, OCH_2Ph), 4.36 (1H, d, J = 12.1 Hz, OCH_2Ph), 4.42 (1H, d, J = 11.8 Hz, OCH_2Ph), 4.52–4.66 (3H, m, H-2, H-4, OCH_2Ph), 5.97 (1H, d, J = 3.8 Hz, H-1), 7.13–7.32 (13H, m, ArH), 7.41 (2H, d, J = 7.1 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 19.4 (C-8), 26.2 (CH_3), 26.8 (CH_3), 26.9 (C-7), 44.9 (C-9), 58.4 (C-5), 58.5 (NCH_2Ph), 69.6 (OCH_2Ph), 71.3 (OCH_2Ph), 73.0 (C-6), 76.2 (C-3), 81.2 (C-2), 82.7 (C-4), 104.3 (C-1), 111.1 (OCO), 126.1 (ArC), 126.9 (strong, 2 × ArC), 127.2 (strong, 2 × ArC), 127.6 (strong, 2 × ArC), 127.7 (strong, 2 × ArC), 127.9 (strong, 2 × ArC), 128.2 (strong, 2 × ArC), 128.4 (strong, 2 × ArC), 137.1 (ArC), 138.9 (ArC), 140.9 (ArC).

1,2-*O*-Isopropylidine-5,6,7,8-tetra-deoxy-5,9-imino-β-L-*ido*-1,4-furan-9-ulose (16)

A solution of aziridine ester **9** (0.62 g, 1.29 mmol) and 10% Pd/C (70 mg) in methanol (15 cm^3) was hydrogenated (80 psi) at 30 °C for 12 h. The reaction mixture was filtered through Celite. Sodium acetate (0.12 g, 1.55 mmol) was added to the filtrate and the mixture refluxed for 1.5 h. The reaction mixture was concentrated under vacuum, extracted using $CHCl_3$ (3 × 15 cm^3) and dried over anhydrous sodium sulfate. The combined organic layer was concentrated and purified by column chromatography (n-hexane–ethyl acetate = 7 : 3) to give **16** as a white solid (0.25 g, 74%): [mp 156–157 °C; lit.[9d] mp 157 °C]; (found: C, 56.29; H, 7.57. Calc. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44); R_f = 0.35 (n-hexane–ethyl acetate = 5 : 5); [$[\alpha]_D$ = −12.3 (*c* 2.51, $CHCl_3$), lit.[9d] $[\alpha]_D$ = −11.5 (*c* 2.35, $CHCl_3$)]; ν_{max}(KBr)/cm^{-1} 1624, 1076; δ_H (300 MHz, $CDCl_3$) 1.28 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.64–1.79 (2H, m, H-7), 1.80–1.98 (2H, m, H-6), 2.26–2.38 (2H, m, H-8), 3.72–3.79 (1H, m, H-5), 3.93 (1H, dd, J = 3.2 and 2.7 Hz, H-4), 4.22 (1H, d, J = 2.7 Hz, H-3), 4.50 (1H, d, J = 3.6 Hz, H-2), 5.50–5.89 (1H, bs, exchangable with D_2O, OH), 5.93 (1H, d, J = 3.6 Hz, H-1), 7.10–7.16 (1H, bs, exchangable with D_2O, NH); δ_C (75 MHz, $CDCl_3$) 20.1 (CH_3), 26.2 (CH_3), 26.5 (C-7), 27.1 (C-6), 31.2 (C-8), 52.9 (C-5), 76.0 (C-3), 81.6 (C-4), 85.5 (C-2), 104.9 (C-1), 111.8 (OCO), 173.4 (*C*ONH).

1,2-*O*-Isopropylidine-3-*O*-benzyl-5,6,7,8-tetradeoxy-β-L-*glycero*-5,9-*N*-(benzyl)imino-β-L-*ido*-1,4-furan-9-ulose (17)

To a suspension of NaH (0.07 g, 1.71 mmol) in dry THF (3 cm^3) at 0 °C were added a solution of lactam **16** (0.20 g, 0.77 mmol) in THF (10 cm^3) and benzyl bromide (0.19 cm^3, 1.71 mmol) in THF (3 cm^3) successively. The reaction was refluxed for 3 h. Usual workup and purification by column chromatography (n-hexane–ethyl acetate = 8.5 : 1.5) yielded dibenzylated lactam **17** as a thick liquid (0.33 g, 96%): (found: C, 71.18; H, 7.20. Calc. for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14); R_f = 0.58 (n-hexane–ethyl acetate = 4 : 6); $[\alpha]_D$ = +12.84 (*c* 0.19, $CHCl_3$); ν_{max}($CDCl_3$)/cm^{-1} 2925, 1627, 1217, 1073; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.52–1.85 (4H, m, H-6, H-7), 2.48–2.52 (2H, m, H-8), 3.74–3.78 (1H, m, H-5), 3.85 (1H, d, J = 3.0 Hz, H-4), 4.25 (1H, d, J = 15.4 Hz, NCH_2Ph), 4.31 (1H, dd, J = 6.7 and 3.0 Hz, H-3), 4.38 (1H, d, J = 11.8 Hz, NCH_2Ph), 4.59 (1H, d, J = 3.8 Hz, H-2), 4.64 (1H, d, J = 11.8 Hz, OCH_2Ph), 5.56 (1H, d, J = 15.4 Hz, NCH_2Ph), 5.98 (1H, d, J = 3.8 Hz, H-1), 7.16–7.29 (10H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.9 (C-7), 25.1 (C-6), 26.1 (CH_3), 26.6 (CH_3), 31.2 (C-8), 49.3 (C-5), 53.6 (N*C*H$_2$Ph), 71.4 (OCH_2Ph), 80.6 (C-3), 81.6 (C-2), 83.2 (C-4), 104.9 (C-1), 111.5 (OCO), 126.6 (ArC), 127.5 (strong, 2 × ArC), 127.8 (strong, 2 × ArC), 127.9 (ArC), 128.1 (strong, 2 × ArC), 128.3 (strong, 2 × ArC), 136.5 (ArC), 138.6 (ArC), 169.9 (*C*ONH).

1,2-*O*-Isopropylidine-3-*O*-benzyl-5,6,7,8-tetradeoxy-β-L-*glycero*-5,9-*N*-(benzyl)imino-β-L-*ido*-1,4-furanose (18)

To an ice-cooled suspension of LAH (0.24 g, 6.40 mmol) in dry THF (4 cm^3) was added dibenzylated lactam **17** (0.70 g, 1.60 mmol) in dry THF (10 cm^3) at 0 °C, and the mixture stirred for 10 min. The reaction mixture was slowly warmed to room temperature and refluxed for 3 h. The reaction was quenched by adding ethyl acetate (10 cm^3) and an aqueous solution of ammonium chloride (2 cm^3), and was then filtered through Celite. The filtrate was concentrated under vacuum and purified by column chromatography (n-hexane–ethyl acetate = 9 : 1) to give **18** as a thick liquid (0.61 g, 89%): (found: C, 73.85; H, 7.78. Calc. for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85); R_f = 0.61 (n-hexane–ethyl acetate = 6 : 4); $[\alpha]_D$ = −33.33 (*c* 2.15, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1620, 1410; δ_H (300 MHz, $CDCl_3$) 1.31 (3H, s, CH_3), 1.36–1.66 (6H, m, H-6, H-7, H-8), 1.49 (3H, s, CH_3), 2.26–2.33 (1H, m, H-9), 2.69–2.74 (1H, m, H-9), 3.09–3.13 (1H, m, H-5), 3.63 (1H, d, J = 13.7 Hz, NCH_2Ph), 3.86 (1H, d, J = 2.7 Hz, H-3), 4.08 (1H, d, J = 13.7 Hz,

NCH_2Ph), 4.42 (1H, d, J = 11.5 Hz, OCH_2Ph), 4.47 (1H, dd, J = 6.5 and 2.7 Hz, H-4), 4.57 (1H, d, J = 3.8 Hz, H-2), 4.66 (1H, d, J = 11.5 Hz, OCH_2Ph), 5.96 (1H, d, J = 3.8 Hz, H-1), 7.13–7.35 (10H, m, ArH); δ_C (75 MHz, $CDCl_3$) 22.8 (C-7), 24.2 (C-8), 26.3 (C-6), 26.6 (CH_3), 26.7 (CH_3), 48.7 (C-9), 57.8 (C-5), 58.9 (NCH_2Ph), 71.4 (OCH_2Ph), 79.6 (C-3), 80.6 (C-4), 82.6 (C-2), 104.7 (C-1), 111.1 (OCO), 126.1 (ArC), 127.4 (strong, 2 × ArC), 127.6 (ArC), 127.7 (strong, 2 × ArC), 128.2 (strong, 2 × ArC), 128.6 (strong, 2 × ArC), 137.1 (ArC), 140.7 (ArC).

(+)-(1*R*,2*R*,3*S*,9*S*,9a*S*)-1,2,3,9-Tetrahydroxyquinolizidine (5b)

A solution of **13** (0.03 g, 0.14 mmol) in TFA–H_2O (3 cm^3, 2 : 1) was stirred at 15 °C for 3 h. The trifluoroacetic acid was co-evaporated with benzene to furnish a thick liquid. A solution of this liquid in methanol (5 cm^3) and 10% Pd/C (0.05 g) was hydrogenated at 80 psi for 24 h. The catalyst was filtered through Celite, washed with methanol, and the filtrate concentrated to give **5b** as a solid (0.015 g, 96%): mp 207 °C; (found: C, 53.50; H, 8.70 Calc. for $C_9H_{17}NO_4$: C, 53.19; H, 8.43); R_f = 0.27 (chloroform–methanol = 4 : 6); $[\alpha]_D$ = +66.66 (*c* 0.15, MeOH); ν_{max}(neat)/cm^{-1} 3400–3600 (broad); δ_H (300 MHz, D_2O) 1.48–1.64 (1H, m, H-7a), 1.65–1.84 (1H, m, H-7b), 1.86–1.98 (1H, bd, J = 14.3 Hz, H-8a), 2.07–2.19 (1H, bd, J = 12.1 Hz, H-8b) 2.88–3.34 (2H, m, H-4a, H-6b), 3.25–3.44 (3H, m, H-4b, H-6a, H-9a), 3.83–3.94 (1H, m, H-9), 3.98 (1H, bs, H-3), 4.03 (1H, bs, H-2), 4.20 (1H, bs, H-1); δ_C (75 MHz, D_2O) 20.4 (C-1), 30.9 (C-8), 54.8 (C-6), 55.9 (C-4), 63.8 (C-9a), 64.8 (C-9), 65.7 (C-3), 66.3 (C-1), 67.1 (C-2).

(−)-(1*R*,2*R*,3*S*,9a*S*)-1,2,3-Trihydroxyquinolizidine (5c)

Reaction of **18** (0.25 g, 0.57 mmol) with TFA–H_2O (6 cm^3, 7 : 3) and hydrogenation as in the case of **5b** afforded **5c** as a thick liquid (0.08 g, 80%): R_f = 0.27 (chloroform–methanol = 4 : 6); [$[\alpha]_D$ = −75.9 (*c* 0.13, MeOH), lit.[9d] $[\alpha]_D$ = −80.0 (*c* 0.1, MeOH)]; ν_{max}(neat)/cm^{-1} 3190–3645 (broad); δ_H and δ_C values were in agreement with those reported.

(+)-1,8,8a-Tri-*epi*-swainsonine (6b)

A solution of **13** (0.25 g, 0.47 mmol) in TFA–H_2O (6 cm^3, 7 : 3) was stirred at 15 °C for 4 h. The trifluoroacetic acid was co-evaporated with benzene to give a thick liquid (0.17 g, 0.34 mmol), which was dissolved in acetone–water (5.00 cm^3, 4 : 1) at 0 °C, treated with sodium metaperiodate (0.09 g, 0.41 mmol) and stirred at 15 °C for 1 h. The reaction was quenched using ethylene glycol (0.01 cm^3), concentrated, extracted with CH_2Cl_2 (3 × 10 cm^3) and dried over sodium sulfate. The combined organic layer was concentrated and dried to afford aldehyde (1.28 g, 0.27 mmol). The crude aldehyde was dissolved in methanol (15 cm^3), and hydrogenated at 80 psi using 10% Pd/C (40 mg) at 30 °C for 24 h. The reaction mixture was filtered through Celite, concentrated, and purified by column chromatography to afford 1,8,8a-tri-*epi*-swainsonine **6b** as a thick liquid (0.04, 81%): (found: C, 55.11; H, 8.51.Calc. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73); R_f = 0.40 (chloroform–methanol 7 : 3); $[\alpha]_D$ = +42.42 (*c* 0.66, MeOH); ν_{max}(neat)/cm^{-1} 3390–3610 (broad); δ_H (300 MHz, D_2O) 1.46–1.59 (1H, m, H-6a), 1.65–1.81 (1H, m, H-7a), 1.98–2.02 (1H, bd, J = 12.1 Hz, H-7b), 2.16–2.60 (1H, m, H-6b), 2.83–2.95 (2H, m, H-3, H-5a), 3.35 (1H, bd, J = 11.8 Hz, H-5b), 3.42 (1H, dd, J = 10.1 and 2.7 Hz, H-8a), 3.76–3.90 (2H, m, H-1, H-3), 4.14–4.19 (2H, m, H-8, H-2); δ_C (75 MHz, D_2O) 21.9 (C-6), 31.0 (C-7), 51.9 (C-5), 59.8 (C-3), 64.0 (C-8a), 71.1 (C-8), 73.4 (C-2), 74.2 (C-1).

(1*R*,2*R*,3*S*,9*S*,9a*S*)-1,2,3,9-Tetraacetoxyquinolizidine (14)

A solution of quinolizidine alkaloid **5b** (0.017 g, 0.08 mmol) in pyridine (1.50 cm^3), acetic anhydride (0.06 cm^3, 0.66 mmol) and DMAP (cat.) was stirred for 6 h. The reaction mixture was concentrated under vacuum and purified by column chromatography (n-hexane–ethyl acetate = 3 : 7) to afford tetraacetoxyquinolizidine alkaloid **14** as a semi-solid (0.023 g, 74%): (found: C, 55.30; H, 7.11. Calc. for $C_{17}H_{25}NO_8$: C, 54.98; H, 6.79); R_f = 0.30 (ethyl acetate); $[\alpha]_D$ = +40.0 (*c* 0.15, $CHCl_3$); ν_{max}($CDCl_3$)/cm^{-1} 1727, 1210; δ_H (300 MHz, $CDCl_3$) 1.21–1.82 (4H, m, H-7, H-8), 2.03 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.63–2.78 (1H, dt, J = 12.9 and 3.0 Hz, H-3), 3.56 (1H, dd, J = 10.1 and 4.1 Hz, H-6), 4.42–4.54 (3H, m, H-9a, H-4), 4.58 (1H, dd, J = 12.6 and 4.1 Hz, H-6), 4.59–4.69 (1H, dt, J = 11.0 and 4.9 Hz, H-9), 4.56–5.41 (1H, m, H-2), 5.66 (1H, d, J = 4.1 Hz, H-1); δ_C (75 MHz, $CDCl_3$) 20.6 (CH_3), 20.7 (CH_3), 20.9 (CH_3), 22.3 (CH_3), 29.4 (C-7), 44.3 (C-8), 60.4 (C-6), 61.3 (C-4), 61.6 (C-9a), 67.6 (C-9), 69.3 (C-3), 74.0 (C-2), 77.2 (C-1), 169.9 (*C*OCH_3), 170.0 (*C*OCH_3), 170.2 (*C*OCH_3), 170.4 (*C*OCH_3).

1,8,8a-Triacetoxy-tri-*epi*-swainsonine (15)

Reaction of tri-*epi*-swainsonine **6b** (0.023 g, 0.13 mmol) with pyridine (2 cm^3), acetic anhydride (0.09 cm^3, 0.93 mmol) and DMAP (cat.) for 6 h afforded triacetoxy-tri-*epi*-swainsonine **15** as a thick liquid (0.033 g, 82%): (found: C, 55.94; H, 6.89. Calc. for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07); R_f = 0.35 (n-hexane–ethyl acetate = 6 : 4); $[\alpha]_D$ = −25.8 (*c* 0.13, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1721, 1204; δ_H (300 MHz, $CDCl_3$) 1.54–1.62 (2H, m, H-6), 1.68–1.78 (2H, m, H-7), 1.98 (3H, s, CH_3), 2.06 (6H, s, 2 × CH_3), 2.07–2.14 (2H, m, H-3), 2.31 (1H, dd, J = 9.3 and 4.4 Hz, H-8a), 3.01 (1H, d, J = 9.7 Hz, H-5), 3.69 (1H, dd, J = 9.3 and 8.9 Hz, H-5), 4.82 (1H, m, H-8), 4.94 (1H, t, J = 6.6 Hz, H-2), 5.33 (1H, d, J = 4.4 Hz, H-1); δ_C (75 MHz, $CDCl_3$) 20.8 (CH_3), 21.1 (CH_3), 23.6 (CH_3), 29.9 (C-6), 44.8 (C-7), 51.7 (C-5), 59.5 (C-3), 67.9 (C-8a), 68.3 (C-8), 75.6 (C-2), 76.8 (C-1), 169.7 (*C*OCH_3), 169.8 (*C*OCH_3), 169.9 (*C*OCH_3).

(+)-1,2-Di-*epi*-lentiginosine (7b)

Reaction of **18** (0.60 g, 1.43 mmol) with TFA–H_2O (6 cm^3, 7 : 3), as in the case of **6b**, followed by treatment with $NaIO_4$ (0.55 g, 1.38 mmol) in acetone–water (8 cm^3, 4 : 1) afforded an aldehyde (0.49 g, 1.30 mmol). The aldehyde, on hydrogenation using 10% Pd/C (50 mg) and column purification, afforded 1,2-di-*epi*-lentiginosine **7b** as a white solid (0.15 g, 69%): [mp 133–135 °C; lit.[7w,10e] mp (not reported)]; R_f = 0.26 (chloroform–methanol 7 : 3); [$[\alpha]_D$ = +3.8 (*c* 0.43, MeOH), lit.[10e] $[\alpha]_D$ = +4.2 (*c* 0.51, MeOH), lit.[7w] $[\alpha]_D$ = +3.4 (*c* 0.51, MeOH)]; ν_{max}(neat)/cm^{-1} 3390–3609 (broad); the δ_H and δ_C values are in agreement with those reported by us[10e] and Shibasaki *et al.*[7w]

1,2-Diacetoxy-di-*epi*-lentiginosine (19)

Acetylation of di-*epi*-lentiginosine **7b** (0.02 g, 0.13 mmol) with pyridine (2 cm^3), acetic anhydride (0.04 cm^3, 0.38 mmol) and DMAP (cat.) as in case of **15**, after purification by column chromatography (n-hexane–ethyl acetate = 8 : 2) afforded diacetoxy-di-*epi*-lentiginosine **19** as a thick liquid (0.025 g, 83%): (found: C, 60.01; H, 8.20. Calc. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94); $R_f = 0.20$ (n-hexane–ethyl acetate = 6 : 4); $[a]_D = -37.7$ (*c* 0.26, $CHCl_3$); ν_{max}(neat)/cm^{-1}1725, 1210; δ_H (300 MHz, $CDCl_3$) 1.20–1.40 (2H, m, H-7, H-6), 1.42–1.84 (4H, m, H-6, H-7, H-8), 2.06 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.12–2.27 (3H, m, H-3, H-5), 3.11 (1H, bd, J = 11.0 Hz, H-3), 3.64 (1H, dd, J = 9.9 and 7.1 Hz, H-8a), 4.99 (1H, t, J = 7.4 Hz, H-2), 5.16 (1H, d, J = 4.6 Hz, H-1); δ_C (75 MHz, $CDCl_3$) 20.9 (strong, C-6 and C-7), 23.7 (C-8), 24.8 (CH_3), 24.9 (CH_3), 53.1 (C-5), 59.7 (C-3), 65.7 (C-8a), 76.9 (C-1), 78.8 (C-2), 169.9 ($COCH_3$), 170.2 ($COCH_3$).

Acknowledgements

We are thankful to Dr MalaRao, Head of the Biochemical Division, and Dr V. P. Vinod of the National Chemical laboratory (NCL), Pune, for carrying out glycosidase inhibitory activity studies of our target molecules. We are grateful to Prof. M. S. Wadia and Dr K. G. Marathe for helpful discussion. AKKS is thankful to CSIR, New Delhi, for a Research Fellowship. We gratefully acknowledge DST, New Delhi, for the research fund SR/S1/OC-21/2005.

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13 This observation also supports the aziridine ring opening in **9** occurring exclusively at the C6 position.

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15 The product after hydrogenation was a mixture of δ-amino saturated ester (80%) and cyclized δ-lactam (~20%) as indicated by the ^{1}H NMR spectra. The mixture was therefore subjected to sodium acetate in methanol to afford δ-lactam as the only product.

16 Our assumption was supported by the fact that when aziridine carboxylate **1** was subjected to hydrogenation, under conditions identical to those for **9**, an *N*/*O*-debenzylated aziridine ester was obtained, indicating high stability of the aziridine ring in **1** to the hydrogenation. For mechanistic aspects in hydrogenation, see: I. Horiuti and M. Polanyi, *Trans. Faraday Soc.*, 1934, **30**, 1164–1167.

17 Protection of C3–OH group is essential for the removal of the C1 carbon atom required for the synthesis of indolizidine alkaloids.

18 (*a*) Y.-T. Li and S.-C. Li in *Methods in Enzymology*, ed. V. Ginsberg, Academic Press, New York, 1972, vol. 28, Part B, p. 702; (*b*) G. L. Miller, *Anal. Chem.*, 1959, **31**, 426–428.