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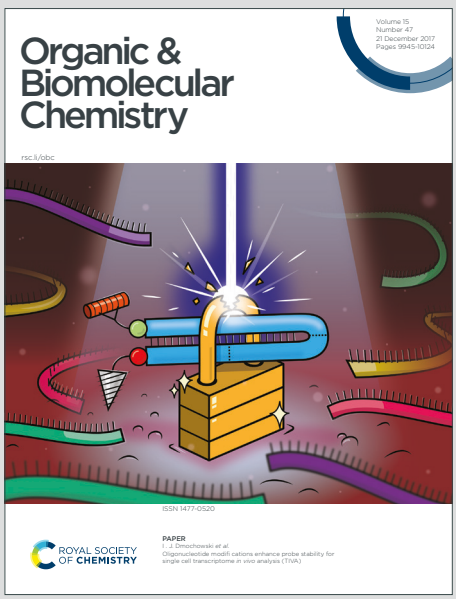

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Regiospecific formation of sugar-derived ketonitrone towards unconventional *C*-branched pyrrolizidines and indolizidines

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The synthesis of unprecedented branched pyrrolizidines and indolizidines was accomplished *via* nitrone chemistry. The required ketonitrone, a known intermediate usually obtained as a mixture of regioisomers, was prepared in a pure form from D-arabinose by a sequence of oximation/reduction/oxidation steps. Nucleophilic vinylation or allylation followed by ring-closing metathesis of the corresponding *N*-allylpyrrolidines furnished the targeted iminosugars, which proved potent and selective inhibitors of alpha-glucosidase from rice (GH31 family).

Introduction

Carbohydrate-derived cyclic nitrones are particularly well-designed building blocks for the construction of complex polyhydroxylated nitrogen heterocycles.[1] Due to their ease of formation, stability and high reactivity, polyalkoxylated aldonitrones have been widely used in the synthesis of five-, six-, or seven-membered iminosugars via nucleophilic addition or 1,3-dipolar cycloaddition.[2,3] In contrast, cyclic *keto*nitrones derived from carbohydrates have been much less used. Beyond a possible drop in reactivity due to the additional substituent at the electrophilic center, the main reason for the underutilization of ketonitrones in iminosugar synthesis is the lack of convenient methods for their preparation.[4] However, six-membered ketonitrones such as **1** have been prepared recently in a straightforward manner by using a ketose, namely L-sorbose, as carbohydrate precursor.[5] Nitrone **1** proved to be a pivotal intermediate in the synthesis of indolizidine **2** and quinolizidine **3** (Figure 1), a new series of constrained analogues of DNJ (**4**).[5,6] Both compounds **2** and **3** were shown highly potent and selective inhibitors of α-glucosidases, especially that from the GH31 family. The significant difference in selectivity, when compared to the standard DNJ (**4**), was predominantly attributed to quaternarization at C-6 (carbohydrate numbering) and to additional interactions in the vicinity of enzyme catalytic site induced by the annulated ring. To gain a better view on the influence of this particular motif we intended to prepare pyrrolizidines **5a,b** and indolizidines **6a,b**, which encompass the same structural outlines as **2** and **3**. Hence, iminosugars **5,6** might be regarded as constrained analogues of DAB **7**, a potent but not selective inhibitor of glycosidases.[7] DAB and its derivatives also display potent inhibition of other biologically relevant enzymes such as *N*-acetylgalactosamine-6-sulfatase,[8] glycogen phosphorylase,[9] arabinofuranosyl transferase,[10] chitin synthase[11] or DNA polymerase.[12] Branched-chain pyrrolizidines and indolizidines such as **5** or **6** are infrequent, contrarily to regioisomers (*i.e.* compound **8**, Figure 1), which have been extensively studied and are widespread in nature.[13]

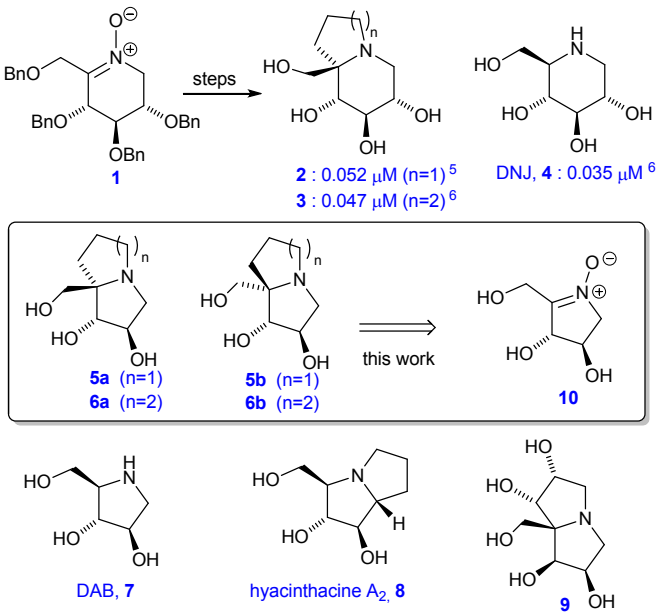

Figure 1 Structures of iminosugars/nitrones **1**-**10** and activities (IC_{50}) against rice α-glucosidase.

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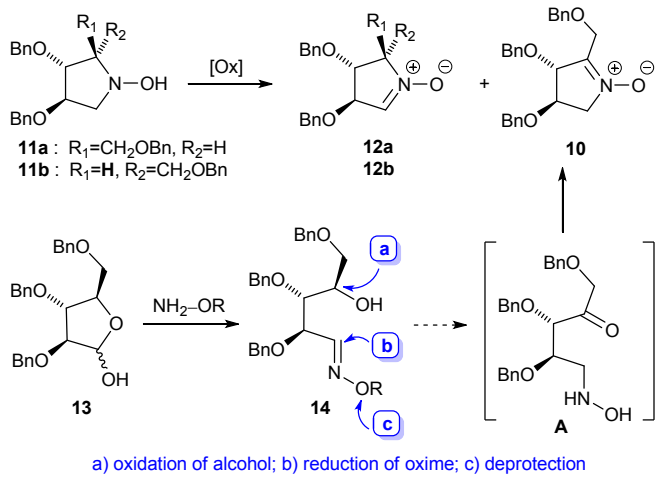
Electronic Supplementary Information (ESI) available: copies of ^{1}H- and ^{13}C-NMR spectra of all compounds, NOESY spectra for **5b**, **6a**, **6b**, **20b** and **21b** See DOI: 10.1039/x0xx00000x

To the best of our knowledge, only a few examples of pyrrolizidines bearing a quaternary center at the ring junction have been described in the literature, such as compound **9** prepared in ten steps from a D-glucose thiocyanate scaffold.[14] Unfortunately, the biological activity of **9** has not been reported. To access targeted compounds **5**,**6**, ketonitrone **10** appeared as an adequate synthon when following a parallel strategy to that used for **2** and **3**. Five-membered ketonitrones such as **10** are invariably prepared by oxidation of the corresponding *N*-hydroxypyrrolidine precursors, a method yielding mixtures of regioisomers.[15,16] In some cases, regioisomeric products are difficult to separate and further transformations must be conducted on the mixture, restraining their use in multistep synthesis.

Thus, we present herein a new synthetic route to nitrone **10**, enabling its isolation as a unique regioisomer, and its transformation into pyrrolizidines **5a,b** and indolizidines **6a,b**. The glycosidase inhibition profile of **5**,**6** as well as that of their monocyclic model **7** was evaluated on a panel of commercial enzymes to provide additional information on the potential of these new constrained iminosugars.[14b,c]

Results and discussion

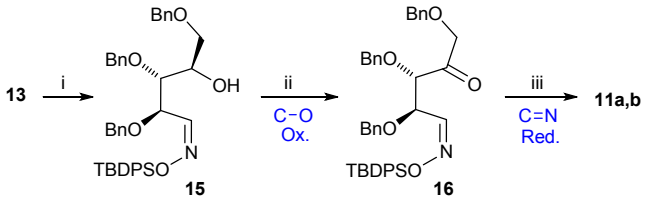
Nitrone **10** has been synthesized in the recent literature by regioselective oxidation of D-*arabino* configured hydroxylamine **11a**.[16] A number of reagents have been evaluated to increase selectivity during dehydrogenation of **11a**. Hypervalent iodine oxidants afford mainly aldonitrone **12a** (5:1 ratio and 89% yield with IBX for instance).[16b] Aerobic-oxidation of **11a** in the presence of a gold catalyst gave a mixture of aldonitrone/ketonitrone in a 39/61 ratio (89% yield).[16c] The L-*xylo* configurated hydroxylamine **11b** is also a possible precursor of **10**.



Scheme 1 possible synthetic access to ketonitrone **10**.

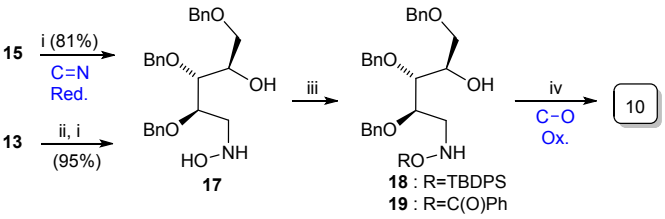
Oxidation of **11b** has not been reported yet, but the treatment of its enantiomer with either hypervalent iodine reagents[16b] or with the system air/Ru catalyst[16a] gave unsatisfactory results with either low ratio of ketonitrone or low yields. For this reason, we focused on a possible new synthetic access to **10**, which would afford the ketonitrone as the only product, to avoid tedious separation of the mixture of regioisomers **12**/**10**. To this goal, we experienced a possible sequence starting from 2,3,5-tri-*O*-benzyl-D-arabinose **13**, involving oximation / oxidation of alcohol / selective reduction of oxime / deprotection steps. The obtained δ-oxo hydroxylamine **A** would spontaneously cyclize to target **10** (Scheme 1). Alternatively, the reduction of oxime could be effected prior to oxidation of the alcohol, affording **A** in a same manner.

O-Protected oxime **15**[17] was obtained in good yield simply by refluxing aldose **13** and TBDPSO-NH_2 in toluene in the presence of $MgSO_4$ and PPTS (Scheme 2). Subsequent oxidation with Dess-Martin periodinane afforded ketone **16** in 84% yield. Selective reduction of the C=N bond proved possible with sodium cyanoborohydride, without affecting C=O. However, the intermediate nitrone **10** which formed in the reaction mixture after spontaneous removal of the silyl group underwent further reduction, so that a 50/50 mixture of hydroxylamines **11a,b** was isolated after standard work-up.



Scheme 2 oxidation/reduction strategy to access nitrone **10**.
Reaction conditions: i) H_2N-OTBDPS, PPTS, PhMe (89%); ii) Dess-Martin periodinane, CH_2Cl_2 (84%); iii) $NaBH_3CN$, MeOH-HCl (60%).

Inversion of oxidation/reduction steps was envisioned next. In a first set of experiments, oxime **15** was reduced with $NaBH_3CN$ in a slightly acidic methanolic solution (Scheme 3). However, various assays at different pH or with a range of co-solvents invariably afforded *O*-deprotected hydroxylamine **17** as the major product, in an optimized 81% yield. Meanwhile, intermediate **17** was obtained in a more efficient manner after direct oximation of tri-*O*-benzyl-arabinose **13** with NH_2OH, HCl and reduction with $NaBH_3CN$ (95% for the two steps). Selective protection of the NH-OH hydroxyl in **17** was effected next in order to minimize the possible oxidation to oxime during upcoming carbonyl formation. Thus, treatment of **17** with either TBDPS-Cl or PhCOOH/CDI afforded hydroxylamines **18** or **19** in 77% and 83% yields, respectively.



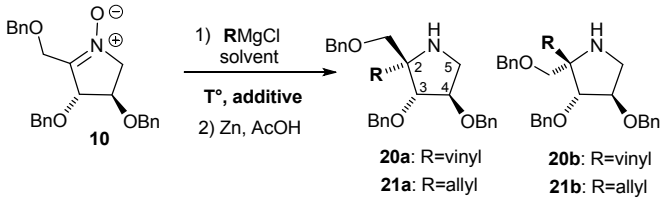
Scheme 3 synthesis of nitrone **10** by reduction/oxidation of oximes.
Reaction conditions: i) $NaBH_3CN$, MeOH-HCl; ii) $NH_2OH.HCl$, MeONa, MeOH; iii) for **18**, TBDPS-Cl, NEt_3, CH_2Cl_2 (77%) and for **19**, PhCOOH, carbonyldiimidazole, CH_2Cl_2 (83%); iv) CrO_3-H_2SO_4 (Jones reagent), acetone, –20 °C (40% from **18**, 54% from **19**).

A number of oxidizing reagents were tested next on **17**, **18** or **19** to produce nitrone **10** or a possible *O*-protected precursor **A** (Scheme 1). Thus, pyridinium dichromate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 2-iodoxybenzoic acid, Dess-Martin periodinane,

tetrapropylammonium perruthenate, or Swern and Moffat oxidation protocols proved unsuccessful to this aim, giving rise either to very low conversion or to oxidation at both the secondary alcohol and the hydroxylamine function. However, to our delight the strongly acidic Jones oxidizing reagent allowed selective oxidation of the secondary alcohol and NH-*O*-deprotection at the same time, affording the expected nitrone **10** in 40% and 54% yield from **18** or **19** respectively. Under these same conditions no nitrone was isolated starting from unprotected hydroxylamine **17**.

Targeted pyrrolizidines **5** and indolizidines **6** might be obtained next starting with ketonitrone **10**, by following the strategy that was exploited for the synthesis of **2** and **3** from ketonitrone **1**.[5,6] A key nucleophilic vinylation or allylation is required as the first step to produce the pivotal quaternary center. To this aim, nitrone **10** was subjected to addition of vinylmagnesium bromide and allylmagnesium bromide under various conditions of temperature and in the presence of a Lewis acid (Table 1).[2i,j]

Table 1 nucleophilic addition of Grignard reagent to nitrone **10**[a]



Entry	R	additive	T (°C)	yield[b]	dr[c] a:b
1	vinyl	none	–78 °C	55%	9 : 91
2	vinyl	none	0 °C	52%	21 : 79
3	vinyl	$ZnCl_2$[d]	–78 °C	–[e]	–
4	vinyl	Et_2AlCl[f]	–78 °C	59%	28 : 72
5	vinyl	Et_2AlCl[f]	–30 °C	55%	31 : 69
6	allyl	none	–78 °C	72%	10 : 90
7	allyl	$ZnCl_2$[d]	–78 °C	75%	13 : 87
8	allyl	Et_2AlCl[f]	–78 °C	80%	18 : 82
9	allyl	Et_2AlCl[f]	–50 °C	78%	23 : 77
10	allyl	Et_2AlCl[f]	–30 °C	83%	35 : 65
11	allyl	Et_2AlCl[d]	–30 °C	–[e]	–
12	allyl	Et_2AlCl[f]	0 °C	37%	34 : 66

[a] Reactions performed in CH_2Cl_2 (without Lewis acid or in the presence of $ZnCl_2$) or in Et_2O (when using Et_2AlCl) with 2.5 equiv. of Grignard reagent. [b] Isolated yield (chromatography on silica gel). [c] Diastereoisomeric ratios were determined from ^{1}H-NMR analysis of the crude reaction mixture. [d] Lewis acid and Grignard reagent were pre-mixed together before addition of **10**. [e] No reaction occurred. [f] Et_2AlCl (4 equiv.) was premixed with **10** in Et_2O at the reaction temperature during 15 min before addition of Grignard reagent.

Due to the instability of the formed hydroxylamines, the reaction sequence combined nucleophilic addition of the organometallic and reduction of N-OH with Zn in acetic acid to afford pyrrolidines **20**,**21**. As shown in Table, both possible stereoisomers were produced, which were separated by silica gel chromatography at this stage (**20a**/**20b**), or more easily at the next step (**21a**/**21b**). The configurations of both isomers were assigned unambiguously by NMR (see SI). Whatever the temperature or the additive used, the 2,3-*trans* isomers **20b** and **21b** were obtained as major products. However, the modulation of the reaction conditions makes it possible to increase the ratio of the 2,3-*cis* epimers **20a** or **21a**. The obtained results lead to the following observations: a) nucleophilic attack occurs mainly from the *Re* face of **10**, affording the 2,3-*trans* isomers **20b** and **21b** as major products; b) unsurprisingly, better control occurs when lowering the temperature (entries 1,2 or 8-10), increasing the ratio of major isomers **b** vs **a**; c) unlike what could be observed with the addition of Grignard reagents to six-membered ketonitrone **1**,[5,6] $ZnCl_2$ as the additive, premixed with the Grignard reagent, had no significant effect on the stereoselectivity of allylation (entry 7) and it completely annihilated the reactivity of vinylmagnesium bromide (entry 3); d) Et_2AlCl as an additive slightly disfavoured the *Re* attack, which improved the yield of isomer **a** (entry 5 or 10); e) a vinyl aluminum is not the reactive species in the presence of Et_2AlCl, since a control experiment including initial transmetallation did not produce any product (entry 11). The stereoselectivity of the reaction observed here is in agreement with former results from the literature. Indeed, although organometallic additions onto six-membered nitrones where reported to favor the formation of a 2,3-*cis* isomer,[18] it is agreed that steric control occurs in all cases with five-membered nitrones, affording the 2,3-*trans* adducts with excellent selectivities.[2,19] Here, in the absence of additive, the C-3 OBn substituent induces direct steric hindrance promoting attack of the Grignard reagent from the *Re* face. In the presence of diethylaluminum chloride, competition may occur between Grignard reagent and Lewis acid to occupy the less hindered side, one situation giving classically the 2,3-*trans* isomer, the other one affording the 2,3-*cis* product.[20] No further attempts were conducted to improve or invert selectivity since each isomer had to be used in the next steps.

Completion of the synthesis of pyrrolizidines **5** and indolizidines **6** was accomplished via *N*-allylation of **20** or **21** with allylbromide to produce pyrrolidines **22** or **23** respectively in good yield (Scheme 4). Subsequent ring-closing metathesis was performed in refluxing dichloromethane using Grubb's II catalyst (5 mol%) to give the sterically congested bicyclic systems **24** and **25**.[21] Finally, hydrogenation of the double bond and removal of benzyl protecting groups were effected at once under hydrogen atmosphere in the presence of Pd/C in an acidic medium. After neutralization with ion exchange resin, pyrrolizidines **5a**,**b** and indolizidines **6a**,**b** were purified by standard chromatography using $CHCl_3$/MeOH/NH_4OH (6/4/1) as the eluent and were subjected next to enzyme inhibition assays.

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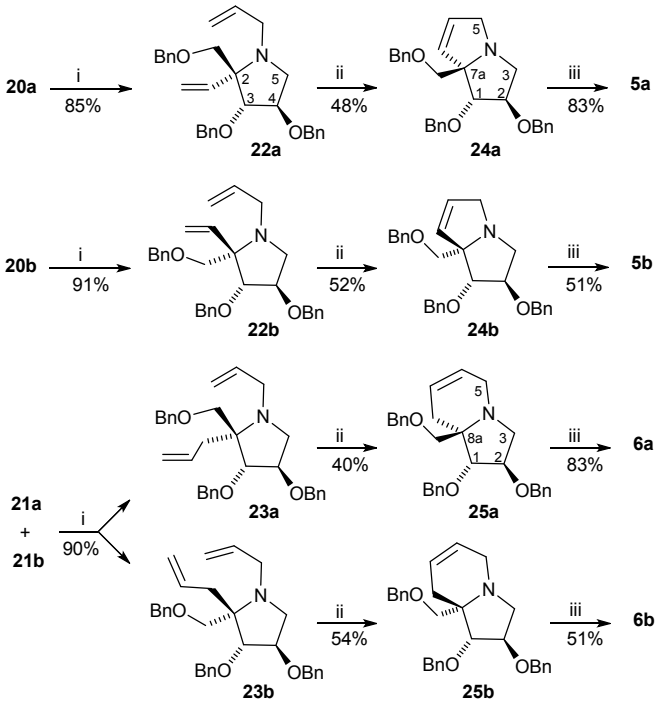
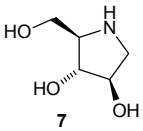
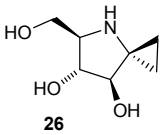
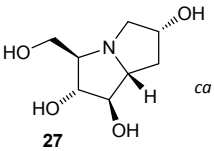
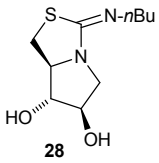


Scheme 4 synthesis of iminosugars **5a,b** and **6a,b**.
Reaction conditions: i) Allyl-Br, K_2CO_3, KI $_{cat.}$, CH_3CN; ii) CH_2Cl_2, Grubbs II cat., reflux; iii) H_2, Pd/C, MeOH-HCl 6M.

Table 2 Reported inhibitory activities of DAB and of some known bicyclic analogues against various α-glucosidases.[a]

α-glucosidase	yeast (IC_{50})	rice (IC_{50})	*A. niger* (IC_{50})
 **7**	0.33 µM [7c] 0.15 µM [7e] 1.2 µM [7f]	120 µM [7f] 250 µM [23] 218 µM [7c]	16 µM [7a] 400 µM [7f]
 **26**	no inhib. [22]	no inhib. [22]	100 µM [22]
 **27**	*ca* 1 mM [11c]	*ca* 1 mM [11c]	4.5 µM [11d]
 **28**	[K_i=183 µM] [7b]	not determined	[K_i=419 µM] [7b]

[a] Corresponding references in brackets.

Biological evaluation

The iminosugar 1,4-dideoxy-1,4-imino-D-arabinitol (DAB, **7**) entails a coveted structural framework due its specific hydroxyl distribution, closely related to that of glucose at C-3,4,6. As a consequence, DAB and some derivatives have strong affinities for enzymes operating with glucosides or glucoconjugates, and strong inhibition has been disclosed towards α-glucosidase from yeast or glycogen phosphorylase for instance.[7,9] However, the flexibility of the five-membered ring as well as structural similarities of DAB with other biologically relevant carbohydrates such as arabinose or mannose induce potent inhibition of other series of enzymes, reducing the potential of **7** as a therapeutic agent due to possible deleterious cross-inhibition.

Thus, introduction of additional substituents into the 5-membered ring is usually achieved with the aim of increasing potency and/or selectivity towards a specific enzymatic activity. Modification of the DAB scaffold towards bicyclic structures has already been envisioned, giving rise to inhibitors with various properties (Table 2). Hence, the spirocyclopropyl substituent in **26** annihilates the inhibition potency of DAB towards α-glucosidases from rice or yeast.[22] A fused cycle such as in pyrrolizidine **27** had likewise a deleterious effect against these same enzymes.[11c-d,17] Surprisingly, an increase in inhibition was observed towards amyloglucosidase from *A. niger*, making pyrrolizidine **27** a powerful and highly selective inhibitor of this isozyme. Incorporation of the hydroxymethyl substituent into a thioimidate cycle as in **28** proved also detrimental for inhibition, irrespective of the glucosidase.[7b]

In turn, the hydroxymethyl substituent is preserved in the structure of **5,6** emerging either on one side of the bicyclic iminosugars (isomers **a**) or on the other (isomers **b**). Enzymatic assays were performed on a series of commercial glycosidases (α-glucosidase from rice and from yeast, β-glucosidase from almond, β-glucosidase and α-rhamnosidase from *A. niger*, β-galactosidase from *A. orizae*, α-mannosidase and β-*N*-acetylglucosaminidase from Jack bean, α-galactosidase from green coffee bean and α-fucosidase from bovine kidney) to assess potency and selectivity of these new compounds (Table 3). Owing to some inhomogeneity in the published inhibition data of DAB, notably towards α-glucosidase from rice (Table 2), a prepared sample of this compound was tested under the same conditions than **5,6** to ensure accurate correlation resulting from strictly identical experimental conditions. To this end, DAB (**7**) was prepared by hydrogenation of nitrone **12a** according to the reported procedure.[24] A first set of biological assays afforded the % inhibition of a given enzyme induced by 1 mM of the tested iminosugar. In cases where inhibition was greater than 95%, IC_{50} values were determined further by assaying decreasing concentrations of inhibitor. Total annihilation (>95%) of enzyme activity at 1 mM concentration is generally a prerequisite for high inhibition potencies, usually in the micromolar range. On the opposite, %inhibition below this threshold are typical of modest or poor inhibitors with half maximal inhibitory concentrations usually above 100 µM. Former results from our laboratories have always followed this empirical rule.

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Table 3 Glycosidase Inhibition potencies of prepared compounds [a,b]

Enzyme	**5a**	**6a**	**5b**	**6b**	**DAB**
α-glucosidase (rice)	98% (**9.3** μM)	99% (**4.2** μM)	53%	90%	99% (**7.8** μM)
α-glucosidase (*Sac. cerevisiae*)	100% (**15** μM)	57%	47%	28%	100% (**0.69** μM)
β-glucosidase (almond)	19%	NI	26%	10%	95% (**79** μM)
β-glucosidase (*Asp. niger*)	18%	11%	9%	37%	96% (**62** μM)
β-galactosidase (*Asp. orizae*)	58%	NI	13%	–22%[c]	76%
α-mannosidase (Jack bean)	15%	23%	9%	11%	97% (**49** μM)
α-rhamnosidase (*Asp. niger*)	30%	29%	7%	24%	34%
α-galactosidase (green coffee)	6%	NI	NI	NI	11%
β-GlcNAc-ase (Jack bean)	8%	–11%[c]	15%	6%	14%
α-fucosidase (bovine kidney)	66%	22%	16%	64%	37%

[a] % inhibition at 1 mM of inhibitor (**IC_{50}** in brackets, determined when >95% inhibition); [b] NI means no impact on enzyme activity (less than 5% inhibition or activation); [c] negative values mean activation of enzyme activity.

In our assay (Table 3), DAB proved to be highly active towards α-glucosidase from rice (>95% at 1 mM, IC_{50}=7.8 μM), significantly more potent than described in some papers (Table 2). The corresponding hydrochloride (obtained by addition of aqueous HCl to DAB, then evaporation) was tested likewise and afforded the same potent inhibition value. Furthermore, another sample of DAB **7**, prepared independently by an alternative method,[25] provided strictly identical performances. This discrepancy with some literature results is puzzling, but might be due to disparity in enzyme sources. In agreement with results from the literature,[7b,c,e,f] DAB proved also very active against other glycosidases. It displayed IC_{50}=0.69 μM against α-glucosidase from yeast, and potent inhibition of ß-glucosidases (almond: IC_{50}=79 μM, *A. niger*: IC_{50}=62 μM) or α-mannosidase (IC_{50}=49 μM). In spite of few structural differences, pyrrolizidines **5a,b** and indolizidines **6a,b** displayed significantly varied behaviour. First of all, the position of the free hydroxymethyl substituent proved crucial to maintain inhibition potency. Indeed **5b** and **6b**, which are structurally related to L-sugars, proved almost inactive against all tested enzymes. Marginal effect was obtained with indolizidine **6b,** which causes 90% inhibition of rice α-glucosidase at 1 mM concentration. But, as expected, this activity decreased rapidly with concentration and only 46% inhibition was maintained at 100 μM (*i.e.*, IC_{50}>100 μM). Epimers **5a**,**6a** for their part, proved to be potent inhibitors of α-glucosidase from rice (IC_{50}=9.3 μM and IC_{50}=4.2 μM respectively), indolizidine **6a** being more active than DAB itself. Interestingly, **6a** showed exclusive inhibition of this enzyme among those tested, all the others being almost unaffected at 1 mM. Pyrrolizidine **5a** showed cross-inhibition of yeast α-glucosidase (IC_{50}=15 μM) but was inactive against all the other tested enzymes. Thus compounds **5a** and **6a** show an activity comparable to DAB towards α-glucosidases, but proved much more selective for these specific hydrolases. This behaviour is very similar to that of homologues **2** and **3** (Figure 1) by analogy with the monocyclic model DNJ. The *C*-branched fused cycle in these compounds seems easily tolerated by α-glucosidases (particularly that from rice) but induces a steric clash in the catalytic site of ß-glucosidases, which might contribute to their excellent selectivity when compared to the monocyclic counterparts. Nevertheless, pyrrolizidine **5a** and indolizidine **6a** are significantly less potent inhibitors of rice α-glucosidase (an enzyme from the GH-31 family) than homologues **2** and **3**. The latter feature an incremental OH group, corresponding to 2-OH of glucose. This additional hydroxyl, also present in the structure of DNJ, is certainly a pivotal binding element that reinforces protein-inhibitor interactions up to two orders of magnitude (IC_{50} *ca.* 50 nM for **2**,**3** or DNJ;[5,6] IC_{50} *ca.* 5-10 μM for **5a**, **6a** or DAB). This is in agreement with results from the literature, where stabilization of protein-inhibitor complex by one binding OH was estimated at 2.5 kcal/mol, decreasing the binding constant by a factor of 70 at 298 K.[26]

Conclusions

In conclusion, we report here the synthesis of a new series of pyrrolizidines **5a,b** and indolizidines **6a,b** as branched bicyclic analogues of the known DAB **7**. As expected, the D-configured iminosugars **5a** and **6a** displayed potent inhibition of rice α-glucosidase (IC_{50}=9.3 μM for **5a** and 4.2 μM for **6a**), comparable to that of DAB (IC_{50}=7.8 μM). Moreover, iminosugars **5a**,**6a** proved much more selective than their monocyclic analogue, DAB being also a potent inhibitor of ß-glucosidases and of α-mannosidase. These results are in agreement with former results from the literature, showing that six-membered homologues with a carbon-branched substituent retain strong inhibition potencies towards α-glucosidase from the GH31 family. Conversely, this distinctive structural feature abolishes recognition by other enzymes, giving rise to highly selective inhibitors. Work is in progress to understand the high selectivity of branched bicyclic iminosugars on a molecular level and to evaluate these compounds on other GH31 α-glucosidases of therapeutic relevance.

Experimental SECTION

General methods

Reactants and reagents were purchased from standard suppliers (Sigma-Aldrich, Alfa-Aesar, Fisher Scientific) and were used without further purification. All reactions were conducted under Ar atmosphere using anhydrous solvents, air- or moisture-sensitive reagents and products were stored at –20°C under Ar. Silica gel F254 (0.2 mm) was used for TLC plates, detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid or an aqueous solution of $KMnO_4$ (2%) / Na_2CO_3 (4%), followed by heating. Reactions were monitored either by TLC. Column chromatography was performed over silica gel M 9385 (40–63 μm) Kieselgel 60. NMR spectra were recorded on Bruker AC 250 (250 MHz for ^{1}H, 62.5 MHz for ^{13}C), 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) or 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C) spectrometers. Chemical shifts are expressed in parts per million (ppm) and were calibrated to deuterated or residual non-deuterated solvent peaks for ^{1}H and ^{13}C spectra. Coupling constants are in Hz and splitting pattern abbreviations are: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. DEPT 1D NMR experiment, COSY, HSQC, and HMBC 2D NMR experiments were used to confirm the NMR peak assignments for all compounds. Optical rotations were determined at 20 °C with a Perkin-Elmer Model 241 polarimeter, in chloroform or in methanol. High Resolution Mass Spectra (HRMS) were performed on Q-TOF Micro micromass positive ESI (CV = 30 V).

(2*R*,3*R*,4*R*)-2,3,5-tris(benzyloxy)-4-hydroxypentanal O-(tert-butyldiphenylsilyl) oxime (15): To a solution of 2,3,5-tri-*O*-benzyl-D-arabinose **13** (12.6 g, 30 mmol, 1.0 equiv.) in dry toluene (120 mL) under argon was added $MgSO_4$ (14.4 g, 120 mmol, 4.0 equiv.). The suspension was heated to reflux and stirred 5 min, then O-*tert*-butyldiphenylsilylhydroxylamine (12.2 g, 45 mmol, 1.5 equiv.) and pyridinium *p*-toluenesulfonate (251 mg, 1 mmol, 0.033 equiv.) were added. The mixture was stirred at this temperature for 30 min then cooled at room temperature. The suspension was passed through a pad of celite and rinsed with toluene. The filtrate was washed with a saturated aqueous solution of sodium bicarbonate (2 x 20 mL) and then brine (20 mL). After drying ($MgSO_4$) and concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:12 to 1:5) to afford known **15**[17,27] (mixture of *Z* an *E* diastereomers, 18 g, 89 %) as a pale-yellow oil.

(2*R*,3*S*)-2,3,5-tris(benzyloxy)-4-oxopentanal O-(tert-butyldiphenylsilyl) oxime (16): To a solution of **15** (2.69 g, 4 mmol, 1.0 equiv.) in dry CH_2Cl_2 (40 mL) under argon was added Dess-Martin periodinane (1.86 g, 4.4 mmol, 1.1 equiv.). The resulting solution was stirred 1h at room temperature then washed with a saturated aqueous solution of sodium bicarbonate (2 x 20 mL) and brine (20 mL). After drying ($MgSO_4$) and concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:19) to afford **16** (mixture of *Z* and *E* diastereomers, 2.25 g, 84 %) as a pale-yellow oil. ν_{max}/cm^{-1} 3066, 3032, 2933, 2859, 1735, 1455, 1428, 1243, 1112; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.17 (9H, s, C(C*H*$_3$)$_3$), 4.16–4.66 (10H, m, H-2, H-3, H-5, 3 x Ph-C*H*$_2$), 7.12–7.40 (21H, m, 20 Ar-H), 7.72–7.81 (5H, m, 5 Ar-H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 19.4 (*C*(CH$_3$)$_3$), 19.5 (*C*(CH$_3$)$_3$), 71.2 (Ph-*C*H$_2$), 73.1 (Ph-*C*H$_2$), 73.4 (Ph-*C*H$_2$), 73.5 (CH), 74.2 (Ph-*C*H$_2$), 74.4 (Ph-*C*H$_2$), 74.5 (Ph-*C*H$_2$), 74.7 (Ph-*C*H$_2$), 75.9 (CH), 84.0 (CH), 84.2 (CH), 127.7-128.7 (25 x Ar-C), 129.9-130.0 (Si-Ar-*C*$_{para}$), 133.0 (Ar-C^{IV}), 133.2 (Ar-C^{IV}), 133.3 (Ar-C^{IV}), 134.9 (Si-Ar-*C*^{IV}), 135.6–135.7 (Si-Ar-*C*$_{meta}$, Si-Ar-*C*$_{ortho}$), 153.2 (C-1), 156.0 (C-1), 206.3 (C=O), 206.4 (C=O); m/z calcd for $C_{42}H_{451}NO_5NaSi$ [M + Na]$^+$ 694.2965, found 694.2961

(2*R*,3*R*,4*R*)-1,3,4-tris(benzyloxy)-5-hydroxyamino-pentan-2-ol (17): To a solution of 2,3,5-tri-*O*-benzyl-D-arabinose **13** (10 g, 23.8 mmol, 1.0 equiv.) in dry methanol (60 mL) under argon was added hydroxylamine hydrochloride (3.31 g, 47.6 mmol, 2 equiv.) and sodium methoxide (1.93 g, 35.7 mmol, 1.5 equiv.). The resulting solution was stirred at room temperature for 2 h then concentrated in vacuum. The residue was dissolved in CH_2Cl_2 (40 mL) and the mixture was washed with water (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in THF (150 mL), and sodium cyanoborohydride (2,99 g, 47,6 mmol, 2 equiv.) was added. Two drops of methyl orange were added as the indicator and a concentrated HCl/methanol (v/v = 1/3) mixture was carefully added to the solution at room temperature to maintain the pH value between 3 and 4. After completion of the reaction (characterized by persistence of the red color of the solution), the resulting mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and washed with 1 N NaOH solution (2 x 10 mL) and then brine (2 x 20 mL). After drying ($MgSO_4$) and concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 12:1 to 1:1) to afford hydroxylamine **17** (9.88g, 95% for 2 steps) as a yellow oil. $[\alpha]_D^{20}$ +19 (c 1 in $CHCl_3$); ν_{max}/cm^{-1} 3399, 3063, 2913, 1737, 1496, 1244, 1210, 1090, 1028; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.10–3.20 (2H, m, H-5, H-5'), 3.65–3.72 (3H, m, H-1, H-1', H-3), 4.00–4.03 (1H, m, H-2), 4.09–4.11 (1H, m, H-4), 4.51–4.71 (6H, m, 3 x Ph-C*H*$_2$), 7.25–7.34 (15H, m, 15 Ar-H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 53.8 (C-5), 70.5 (C-2), 71.3 (C-1), 73.4 (Ph-*C*H$_2$), 73.4 (Ph-*C*H$_2$), 73.7 (Ph-*C*H$_2$), 75.9 (C-4), 78.3 (C-3), 127.7–128.4 (15 x Ar-C), 137.9 (Ar-C^{IV}), 137.9 (Ar-C^{IV}), 138.1 (Ar-C^{IV}); m/z calcd for $C_{26}H_{31}NO_5Na$ [M + Na]$^+$ 460.2100, found 460.2105.

(7*R*,8*R*,9*R*)-7,8,10-tris(benzyloxy)-2,2-dimethyl-3,3-diphenyl-4-oxa-5-aza-3-siladecan-9-ol (18): To a stirred solution of (2*R*,3*R*,4*R*)-2,3,5-tris(benzyloxy)-1-hydroxyamino-pentan-2-ol **17** (1 g, 2.3 mmol, 1 equiv.) in dry CH_2Cl_2 (25 mL) at room temperature under argon was added dropwise triethylamine (690 mg, 2.53 mmol, 1.1 equiv.). The mixture was stirred at this temperature for 1h and *tert*-butyldiphenylchlorosilane (680 mg, 2.2 mmol, 2.2 equiv.) was added. The resulting mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was dissolved in THF (10 mL), passed through a pad of celite and rinsed with THF (3 x 5 mL). EtOAc (25 mL) was added to the filtrate and the mixture was washed with a saturated aqueous solution of ammonium chloride (10 mL) and then brine (10 mL). After drying ($MgSO_4$) and concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:9 to 1:4) to afford **18** (1.19 g, 77 %) as a yellow oil. $[\alpha]_D^{20}$ + 27 (c 1 in $CHCl_3$); ν_{max}/cm^{-1} 3476, 3031, 2931, 2858, 1454, 1428, 1109, 1028; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.11 (9H, s, 3 x CH_3),

2.95–3.16 (2H, m, H-6), 3.64–3.68 (3H, m, H-8, H-10), 3.90–3.97 (1H, m, H-9), 4.20–4.26 (1H, m, H-7), 4.50–4.73 (6H, m, 3 x Ph-CH_2), 7.20–7.42 (21H, m, 21 x Ar-H), 7.65–7.73 (4H, m, 4 x Ar-H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 19.2 (C-2), 27.5 (3 x CH_3), 54.2 (C-6), 70.8 (C-9), 71.1 (C-10), 73.6 (Ph-CH_2), 73.7 (2 x Ph-CH_2), 75.2 (C-7), 77.7 (C-8), 127.6–128.6 (15 x Ar-C), 129.7 (2 x Si-Ar-C_{para}), 133.9 (2 x Si-Ar-C^{IV}), 135.7 (4 x Si-Ar-C_{meta}), 135.8 (4 x Si-Ar-C_{ortho}), 138.0 (Ar-C^{IV}), 138.1 (Ar-C^{IV}), 138.2 (Ar-C^{IV}); m/z calcd for $C_{42}H_{50}NO_5Si$ $[M + H]^+$ 676.3458, found 676.3450.

(2*R*,3*R*,4*R*)-5-(benzoyloxyamino)-1,3,4-tris(benzyloxy)-pentan-2-ol (19): A stirred solution of benzoic acid (307 mg, 2.52 mmol, 1.1 equiv.) in dry CH_2Cl_2 (20 mL) under argon was cooled to 0 °C and carbonyldiimidazole (408 mg, 2.52 mmol, 1.1 equiv.) was added. The mixture was stirred at this temperature for 30 min and **17**•HCl (1.09 g, 2.29 mmol, 1 equiv., previously prepared by addition of a 0,5 M hydrogen chloride solution in MeOH to **17**, stirring for 30 minutes and concentration under reduced pressure) was added. The ice-bath was removed, and the reaction mixture was stirred at room temperature overnight. The resulting mixture was then passed through a pad of celite and rinsed with CH_2Cl_2 (3 x 10 mL). The filtrate was washed with a saturated aqueous solution of sodium bicarbonate (10 mL) and then brine (10 mL). After drying ($MgSO_4$) and concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:9 to 1:4) to afford **19** (1.03 g, 83 %) as a yellow oil. $[\alpha]_D^{20}$ +15.9 (c 1 in $CHCl_3$); ν_{max}/cm^{-1} 3470, 3030, 2867, 1721, 1453, 1271, 1089, 1027; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.26–3.31 (1H, m, H-5), 3.36–3.41 (1H, m, H-5'), 3.60 (1H, dd, *J* = 5.4, 10 Hz, H-1), 3.67–3.70 (2H, m, H-1', H-3), 3.90–3.95 (1H, m, H-2), 4.03–4.07 (1H, m, H-4), 4.52 (2H, d, *J* = 2.6 Hz, Ph-CH_2-O-CH_2), 4.57 (2H, s, Ph-CH_2), 4.64 (2H, s, Ph-CH_2), 5.05 (1H, d, *J* = 6 Hz, OH), 7.25–7.38 (15H, m, 15 x Ar-H), 7.54 (2H, dd, *J* = 7.8, 7.8 Hz, CO-Ar-H_{meta}), 7.68 (1H, dd, *J* = 7.5, 7.5 Hz, CO-Ar-H_{para}), 7.92 (2H, dd, *J* = 8.4, 1.3 Hz, CO-Ar-H_{ortho}), 8.38 (1H, dd, *J* = 6.2, 4.5 Hz, NH); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 52.6 (C-5), 69.3 (C-2), 72.0 (C-1), 72.4 (Ph-CH_2), 72.7 (Ph-CH_2), 73.5 (Ph-CH_2), 75.9 (C-4), 79.8 (C-3), 127.4–128.2 (15 x Ar-C), 128.4 (CO-Ar-C^{IV}), 128.8 (CO-Ar-C_{ortho}), 128.9 (CO-Ar-C_{meta}), 133.4 (CO-Ar-C_{para}), 138.5 (Ar-C^{IV}), 138.6 (Ar-C^{IV}), 138.7 (Ar-C^{IV}), 165.4 (CO); m/z calcd for $C_{23}H_{35}NO_6Na$ $[M + Na]^+$ 564.2362, found 564.2368.

General procedure for the preparation of (3*R*,4*R*)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3,4-dihydro-2H-pyrrole 1-oxide (10): To a stirred solution of alcohol **18** or **19** (1.5 mmol, 1 equiv.) in dry acetone (20 mL) under argon at −20 °C was added dropwise a freshly prepared 1.43 M Jones reagent (1.26 mL, 1.8 mmol, 1.2 equiv. of CrO_3, prepared by addition of 12 mL of concentrated sulfuric acid to a stirred solution of 6 g CrO_3 in 30 mL water). The resulting solution was stirred at this temperature for 1h, then another portion of Jones reagent (0.31 mL, 0.45 mmol, 0.3 equiv.) was added. After 30 min., the solution was quenched with isopropanol (5 mL) and diluted with EtOAc (20 mL). The mixture was successively washed with a 1 N HCl solution (2 x 10 mL), a 1 N NaOH solution (2 x 10 mL) and then brine (10 mL). After drying ($MgSO_4$) and concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:9 to 1:1) to afford **10** as a brown oil. $[\alpha]_D^{20}$ − 62 (c 1 in $CHCl_3$); ν_{max}/cm^{-1} 3412, 3053, 3030, 2860, 1606, 1496, 1453, 1236, 1089; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.90–3.95 (1H, m, H-2), 4.15–4.18 (1H, m, H-3), 4.36–4.42 (2H, m, H-2', H-6), 4.49 (s, 2H, Ph-CH_2), 4.61 (s, 2H, Ph-CH_2), 4.66–4.74 (3H, m, H-6', Ph-CH_2), 4.82–4.84 (1H, m, H-4), 7.27–7.41 (15H, m, 15 x Ar-H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 62.6 (C-6), 67.5 (C-2), 71.7 (Ph-CH_2), 72.6 (Ph-CH_2), 73.7 (Ph-CH_2), 76.6 (C-3), 83.9 (C-4), 127.9–128.7 (15 x Ar-C), 136.9 (Ar-C^{IV}), 137.3 (Ar-C^{IV}), 137.5 (Ar-C^{IV}), 144.3 (C-5); m/z calcd for $C_{26}H_{28}NO_4$ $[M + H]^+$ 418.2018, found 418.2012.

General procedure for the addition of Grignard reagent to nitrone 10 and for the reduction of the obtained hydroxylamine to amine: To a well-stired solution of nitrone **10** (1 equiv.) in dry Et_2O (50 mL) under argon cooled at −30 °C was added dropwise a 1.0 M solution of diethylaluminum chloride in hexanes (4 equiv.). The mixture was stirred at this temperature for 30 min. and the Grignard reagent (2.5 equiv.) was added dropwise. The resulting solution was stirred at the same temperature for 4 h then was quenched with a saturated aqueous solution of ammonium chloride (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford a mixture of two hydroxylamines, which were used in the next step without purification.

To a well-stirred solution of activated zinc powder (10 equiv.) in AcOH (10 mL) was added copper acetate monohydrate (0.1 equiv.). The mixture was stirred at 30 °C for 1 h until copper colour disappeared. A solution of the two diastereomeric hydroxylamines (1 equiv.) in AcOH (10 mL) was added, and the reaction mixture was stirred at 30 °C overnight. Solvent was removed in vacuum, the residue was neutralized with a saturated solution of $NaHCO_3$ and washed three times with EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:19 to 1:4) to afford pyrrolidines as yellow oils.

(2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2-vinylpyrrolidine (20a) and (2*S*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2-vinylpyrrolidine (20b): According to the general method described above, the reaction of vinylmagnesium bromide and nitrone **10** (1.2 g, 2.91 mmol) afforded amines **20a** and **20b** (**20a**:**20b** = 31:69 from NMR analysis of the crude product), which were separated by flash chromatography to afford pure amines **20a** (213 mg) then **20b** (475 mg) as yellow oils. The overall yield for the two steps was 55 %.

(2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2-vinylpyrrolidine (**20a**): $[\alpha]_D^{20}$ − 19.0 (c 0.2 in $CHCl_3$); ν_{max}/cm^{-1} 3336, 3089, 3063, 3030, 2861, 1605, 1496; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.91 (1H, dd, *J* = 4.3, 12.2 Hz, H-5), 3.23–3.35 (2H, m, H-5', BnO-

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CH_aH$_b$), 3.48 (1H, d, *J* = 9.5 Hz, BnO-CH$_a$$H_b$), 4.04–4.10 (1H, m, H-4), 4.15–4.1 8 (1H, m, H-3), 4.41–4.70 (6H, m, 3 x Ph-CH_2), 5.25 (1H, dd, *J* = 1.5, 11 Hz, CH_aH$_b$=CH), 5.47 (1H, dd, *J* = 1.5, 17.5 Hz, CH$_a$$H_b$=CH), 6.04 (1H, dd, *J* = 11, 17.5 Hz, CH$_2$=C*H*), 7.28–7.33 (15H, m, 15 x Ar-H); ^{13}C NMR (CDCl$_3$, 250 MHz) δ 48.5 (C-5), 67.6 (C-2), 72.0 (Ph-*C*H$_2$), 72.5 (BnO-*C*H$_2$), 72.7 (Ph-*C*H$_2$), 73.4 (Ph-*C*H$_2$), 85.4 (C-4), 86.6 (C-3), 115.4 (*C*H$_2$=CH), 127.7–128.5 (15 x Ar-C), 136.5 (CH$_2$=*C*H), 138.2 (Ar-*C*^{IV}), 138.4 (Ar-*C*^{IV}), 138.7 (Ar-*C*^{IV}); *m*/z calcd for $C_{28}H_{32}NO_3$ [M + H]$^+$ 430.2382, found 430.2389.

(2*S*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2-vinylpyrrolidine (**20b**): $[\alpha]_D^{20}$ – 31.0 (c 1 in CHCl$_3$); ν$_{max}$/cm^{-1} 3347, 3089, 3063, 3029, 2862, 1607, 1496; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 2.77 (1H, s br, NH), 2.96 (1H, dd, *J* = 4.5, 11.2 Hz, H-5), 3.34 (1H, dd, *J* = 7.1, 11.2 Hz, H-5'), 3.62 (1H, d, *J* = 9.5 Hz, BnO-CH_aH$_b$), 3.66 (1H, d, *J* = 9.5 Hz, BnO-CH$_a$$H_b$), 4.00 (1H, d, *J* = 4.1 Hz, H-3), 4.14–4.20 (1H, m, H-4), 4.51 (2H, d, *J* = 2.1 Hz, Ph-CH_2), 4.59 (2H, d, *J* = 2.5 Hz, Ph-CH_2), 4.66 (2H, d, *J* = 2.2 Hz, Ph-CH_2), 5.21 (1H, d, *J* = 10.5 Hz, CH_aH$_b$=CH), 5.38 (1H, d, *J* = 17.5 Hz, CH$_a$$H_b$=CH), 6.04 (1H, dd, *J* = 10.5, 17.5 Hz, CH$_2$=C*H*), 7.35 (15H, m, 15 x Ar-H); ^{13}C NMR (CDCl$_3$, 250 MHz) δ 48.8 (C-5), 67.0 (C-2), 71.7 (BnO-*C*H$_2$, Ph-*C*H$_2$), 72.7 (Ph-*C*H$_2$), 73.5 (Ph-*C*H$_2$), 84.5 (C-4), 89.8 (C-3), 114.1 (*C*H$_2$=CH), (127.5–128.4 (15 x Ar-C), 138.3 (Ar-*C*^{IV}), 138.4 (Ar-*C*^{IV}), 138.5 (Ar-*C*^{IV}), 141.3 (CH$_2$=*C*H); *m*/z calcd for $C_{28}H_{32}NO_3$ [M + H]$^+$ 430.2382, found 430.2392.

(2*R*,3*R*,4*R*)-2-allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (21a) and (2S,3R,4R)-2-allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (21b): According to general method, the reaction of allylmagnesium bromide and nitrone **10** (1.2 g, 2.91 mmol) afforded amines **21a and 21b** (**21a:21b** = 35:65 from NMR analysis of the crude); they were partially separated by flash chromatography to afford a mixture of amines **21a** and **21b** (970 mg) then pure amine **21b** (100 mg) as yellow oils. The overall yield for the two steps was 83 %.

(2*R*,3*R*,4*R*)-2-allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (**21a**): (from mixture of **21a**/**21b**) ^{13}C NMR (CDCl$_3$, 250 MHz) δ 36.3 (CH$_2$=CH-*C*H), 48.8 (C-5), 65.5 (C-2), 71.7, 72.4, 72.6, 73.3 (4 x Ph-*C*H$_2$), 85.4 (C-4), 87.3 (C-3), 117.9 (*C*H$_2$=CH), (127.5–128.5 (15 x Ar-C), 134.9 (CH$_2$=*C*H), 138.3 (Ar-*C*^{IV}), 138.4 (Ar-*C*^{IV}), 138.6 (Ar-*C*^{IV}).

(2*S*,3*R*,4*R*)-2-allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (**21b**): $[\alpha]_D^{20}$ – 15 (c 1 in CHCl$_3$); ν$_{max}$/cm^{-1} 3089, 3063, 3030, 2861, 1635, 1496, 1453; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 2.05 (1H, s br, NH), 2.44 (2H, d, *J* = 7.3 Hz, CH$_2$=CH-CH_2), 2.95 (1H, dd, *J* = 4.5, 11.5 Hz, H-5), 3.31 (1H, dd, *J* = 6.5, 11.5 Hz, H-5'), 3.49 (1H, d, *J* = 9.5 Hz, BnO-CH_aH$_b$), 3.55 (1H, d, *J* = 9.5 Hz, BnO-CH$_a$$H_b$), 3.83 (1H, d, *J* = 3.5 Hz, H-3), 4.05–4.11 (1H, m, H-4), 4.41–4.65 (6H, m, 3 x Ph-CH_2), 5.01–5.08 (2H, m, CH_2=CH), 5.72–5.89 (1H, m, CH$_2$=C*H*), 7.24–7.32 (15H, m, 15 x Ar-H); ^{13}C NMR (CDCl$_3$, 250 MHz) δ 40.2 (CH$_2$=CH-*C*H), 48.9 (C-5), 65.6 (C-2), 71.2 (BnO-*C*H$_2$), 71.7 (Ph-*C*H$_2$), 72.5 (Ph-*C*H$_2$), 73.5 (Ph-*C*H$_2$), 84.8 (C-4), 88.0 (C-3), 118.2 (*C*H$_2$=CH), 127.5–128.5 (15 x Ar-C), 134.3 (CH$_2$=*C*H), 138.4 (Ar-*C*^{IV}), 138.7 (Ar-*C*^{IV}), 138.8 (Ar-*C*^{IV}); m/z calcd for $C_{28}H_{32}NO_3$ [M + H]$^+$ 444.2539, found 444.2549.

General procedure for the *N*-allylation of pyrrolidine: To a well-stired solution of pyrrolidines **20** or **21** (1 equiv.) in dry CH$_3$CN (20 mL) under argon was added potassium carbonate (1.7 equiv.), allyl bromide (1.6 equiv.) and a catalytic amount of potassium iodide. The mixture was stirred during 6.5 h at 82 °C then a saturated aqueous solution of sodium bicarbonate was added. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:49) to afford *N*-allyl pyrrolidines as yellow oils.

(2*R*,3*R*,4*R*)-1-allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2-vinylpyrrolidine (22a): According to the above general method, the *N*-allylation of vinylpyrrolidine **20a** (150 mg, 0.35 mmol) afforded *N*-allyl vinylpyrrolidine **22a** (139 mg, 85%) as yellow oil. $[\alpha]_D^{20}$ – 20.0 (c 1 in CHCl$_3$); ν$_{max}$/cm^{-1} 3089, 3062, 3029, 2865, 1638, 1604, 1500, 1451; ^{1}H NMR (CDCl$_3$, 600 MHz) δ 2.83 (1H, dd, *J* = 6, 9.5 Hz, H-5), 3.09–3.16 (3H, m, H-5', CH$_2$=CH-CH_2-N), 3.53 (1H, d, *J* = 9.6 Hz, BnO-CH_aH$_b$), 3.56 (1H, d, *J* = 9.6 Hz, BnO-CH$_a$$H_b$), 4.08–4.11 (1H, m, H-4), 4.22 (1H, d, *J* = 5.6 Hz, H-3), 4.28–4.34 (1H, m, H-4), 4.45–4.53 (4H, m, 2 x Ph-CH_2), 4.57 (1H, d, *J* = 12 Hz, Ph-CH_aH$_b$), 4.62 (1H, d, *J* = 12 Hz, Ph-CH$_a$$H_b$), 5.05 (1H, d, *J* = 10 Hz, CH_aH$_b$=CH-CH$_2$-N), 5.16 (1H, d, *J* = 16 Hz, CH$_a$$H_b$=CH-CH$_2$-N), 5.27–5.30 (2H, m, C$H_2$=CH), 5.79–5.88 (2H, m, CH$_2$=C*H,* CH$_2$=C*H*-CH$_2$-N), 7.28–736 (15H, m, 15 x Ar-H); ^{13}C NMR (CDCl$_3$, 250 MHz) δ 51.8 (CH$_2$=CH-*C*H$_2$-N), 53.8 (C-5), 68.8 (C-2), 70.44 (BnO-*C*H$_2$), 71.8 (Ph-*C*H$_2$), 72.4 (Ph-*C*H$_2$), 73.5 (Ph-*C*H$_2$), 82.4 (C-4), 86.9 (C-3), 116.2 (*C*H$_2$=CH-CH$_2$-N), 116.5 (*C*H$_2$=CH), 127.5–128.4 (15 x Ar-C), 135.7 (CH$_2$=*C*H), 137.0 (CH$_2$=*C*H-CH$_2$-N), 138.4 (Ar-*C*^{IV}), 138.5 (Ar-*C*^{IV}), 138.8 (Ar-*C*^{IV}); *m*/z calcd for $C_{31}H_{36}NO_3$ [M + H]$^+$ 470.2695, found 470.2689.

(2*S*,3*R*,4*R*)-1-allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2-vinylpyrrolidine (22b): According to the above general method, the *N*-allylation of vinylpyrrolidine **20b** (215 mg, 0.5 mmol) afforded *N*-allyl vinylpyrrolidine **22b** (213 mg, 91%) as yellow oil. $[\alpha]_D^{20}$ – 57 (c 1 in CHCl$_3$); ν$_{max}$/cm^{-1} 3087, 3063, 3029, 2863, 1640, 1604, 1498, 1455; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 2.99–3.15 (2H, m, H-5, CH$_2$=CH-CH_aH$_b$-N), 3.22–3.29 (1H, m, H-5'), 3.48 (1H, dm, *J* = 14 Hz CH$_2$=CH-CH$_a$$H_b$-N), 3.71 (1H, d, *J* = 9.8 Hz, BnO-CH_aH$_b$), 3.88 (1H, d, *J* = 9.8 Hz, BnO-CH$_a$$H_b$), 4.06 (1H, d, *J* = 5.6 Hz, H-3), 4.40–4.48 (1H, m, H-4), 4.53–4.61 (4H, m, 2 x Ph-CH_2), 4.75 (2H, s, Ph-CH_2), 5.10–5.36 (4H, m, CH_2=CH, CH_2=CH-CH$_2$-N), 5.82–5.97 (2H, m, CH$_2$=C*H,* CH$_2$=C*H*-CH$_2$-N), 7.32 (15H, m, 15 x Ar-H); ^{13}C NMR (CDCl$_3$, 250 MHz) δ 51.9 (CH$_2$=CH-*C*H$_2$-N), 56.2 (C-5), 68.7 (C-2), 70.05 (BnO-*C*H$_2$), 71.7 (Ph-*C*H$_2$), 72.7 (Ph-*C*H$_2$), 73.6 (Ph-*C*H$_2$), 82.4 (C-4), 91.2 (C-3), 115.3 (*C*H$_2$=CH), 115.8 (*C*H$_2$=CH-CH$_2$-N), 127.3–128.3 (15 x Ar-C), 137.1 (CH$_2$=*C*H-CH$_2$-N), 138.6 (Ar-*C*^{IV}), 138.7 (Ar-*C*^{IV}), 138.8 (Ar-*C*^{IV}), 140.9 (CH$_2$=*C*H); *m*/z calcd for $C_{31}H_{36}NO_3$ [M + H]$^+$ 470.2695, found 470.2687.

(2*R*,3*R*,4*R*)-1,2-diallyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (23a) and (2S,3R,4R)-1,2-diallyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (23b): According to the above general method, the *N*-allylation of the mixture of pyrrolidine **21a** and **21b** (353 mg, 0.8 mmol, **21b**:**22b** = 55:65) afforded *N*-allyl pyrrolidines **23a** and **23b**, which were separated by flash chromatography to afford **23b** (226 mg) then **23a** (123 mg) as yellow oils. The overall yield was 90 %. (**23b** can also be prepared from pure **21b** with comparable yield).

(2*R*,3*R*,4*R*)-1,2-diallyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (**23a**): $[\alpha]_D^{20}$ – 19 (c 1 in $CHCl_3$); ν_{max}/cm^{-1} 3087, 3065, 3031, 2865, 1639, 1604, 1498, 1451; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.30–2.48 (2H, m, CH_2=CH-CH_2), 2.78–2.84 (1H, m, H-5), 3.19–3.25 (1H, m, H-5'), 3.31–3.35 (2H, m, CH_2=CH-CH_2-N), 3.42-3.51 (2H, m, BnO-CH_2), 4.11–4.19 (2H, m, H-4, H-5), 4.42–4.81 (6H, m, 3 x Ph-CH_2), 5.01–5.22 (4H, m, CH_2=CH-CH_2, CH_2=CH-CH_2-N), 5.77–5.93 (1H, m, CH_2=C*H*-CH_2), 5.95–6.12 (1H, m, CH_2=C*H*-CH_2-N), 7.35 (15H, m, 15 x Ar-H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 35.8 (CH_2=CH-*C*H_2), 52.0 (CH_2=CH-*C*H_2-N), 54.2 (C-5), 67.0 (C-2), 71.9 (Ph-*C*H_2), 72.7 (Ph-*C*H_2), 73.1 (BnO-*C*H_2), 73.4 (Ph-*C*H_2), 82.2 (C-4), 87.6 (C-3), 116.0 (*C*H_2=CH-CH_2-N), 116.8 (*C*H_2=CH), 127.4–128.4 (15 x Ar-C), 136.4 (CH_2=*C*H), 137.3 (CH_2=*C*H-CH_2-N), 138.6 (Ar-*C*^{IV}), 138.6 (Ar-*C*^{IV}), 139.0 (Ar-*C*^{IV}); *m*/z calcd for $C_{32}H_{38}NO_3$ [M + H]$^+$ 484.2852, found 484.2847.

(2*S*,3*R*,4*R*)-1,2-diallyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)pyrrolidine (**23b**): $[\alpha]_D^{20}$ – 36 (c 1 in $CHCl_3$); ν_{max}/cm^{-1} 3087, 3064, 3029, 2865, 1639, 1605, 1498, 1450; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.28 (2H, d, *J* = 6.8, CH_2=CH-CH_2), 2.98–3.18 (3H, m, H-5, CH_2=CH-CH_aH$_b$-N), 3.46–3.50 (2H, m, CH_2=CH-CH_aH$_b$-N, BnO-CH_aH$_b$), 3.67 (1H, d, *J* = 10.85 Hz, BnO-CH_aH$_b$), 4.02 (1H, d, *J* = 5.3 Hz, H-3), 4.30–4.37 (1H, m, H-4), 4.45–4.78 (6H, m, 3 x Ph-CH_2), 4.96–5.12 (3H, m, CH_2=CH-CH_2, CH_aH$_b$=CH-CH_2-N), 5.26 (1H, d, *J* = 17 Hz, CH_aH$_b$=CH-CH_2-N), 5.80–5.99 (2H, m, CH_2=C*H*-CH_2, CH_2=C*H*-CH_2-N), 7.28–7.37 (15H, m, 15 x Ar-H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 36.4 (CH_2=CH-*C*H_2), 51.7 (CH_2=CH-*C*H_2-N), 56.0 (C-5), 67.3 (C-2), 71.5 (BnO-*C*H_2), 71.8 (Ph-*C*H_2), 72.3 (Ph-*C*H_2), 73.5 (Ph-*C*H_2), 82.3 (C-4), 86.8 (C-3), 115.9 (*C*H_2=CH-CH_2-N), 117.4 (*C*H_2=CH), 127.3–128.4 (15 x Ar-C), 134.5 (CH_2=*C*H), 137.2 (CH_2=*C*H-CH_2-N), 138.5 (Ar-*C*^{IV}), 139.0 (Ar-*C*^{IV}), 139.1 (Ar-*C*^{IV}); m/z calcd for $C_{32}H_{38}NO_3$ [M + H]$^+$ 484.2852, found 484.2846.

General procedure for the metathesis of pyrrolidine: To a well-stirred solution of pyrrolidine **22** or **23** (1 equiv.) in dry and degazed (30 min of argon bubbling) CH_2Cl_2 (10 mL) under argon was added second generation Grubbs catalyst (0.05 equiv). The mixture was stirred overnight at 40°C then second generation Grubbs catalyst (0.05 equiv) was added additionally. After another 6 h, the resulting mixture was cooled at room temperature, passed through a pad of celite and rinsed with Et_2O (3 x 5 mL). Finally, the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:3) to afford target compounds as yellow oils.

(1*R*,2*R*,7a*R*)-1,2-bis(benzyloxy)-7a-(benzyloxymethyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine (24a): According to general method, the metathesis of vinylpyrrolidine **22a** (112 mg, 0.24 mmol) afforded **24a** (52mg, 48 %) as yellow oil. $[\alpha]_D^{20}$ – 12 (c 0.57 in $CHCl_3$); ν_{max}/cm^{-1} 3063, 3029, 2915, 2854, 1695, 1498, 1455, 1066; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.69 (1H, dd, *J* = 5.0, 11.1 Hz, H-3), 3.12 (1H, dd, *J* = 4.1, 11.1 Hz, H-3'), 3.26–3.30 (2H, m, H-5, BnO-CH_aH$_b$), 3.36 (1H, d, *J* = 8.7 Hz, BnO-CH_aH$_b$), 3.81–3.86 (2H, m, H-5', H-2), 4.00 (1H, d, *J* = 2.8 Hz, H-1), 4.34 (2H, s, Ph-CH_2), 4.39 (1H, d, *J* = 12.1 Hz, PhCH_aH$_b$), 4.45 (1H, d, *J* = 12.1 Hz, PhCH_aH$_b$), 4.54 (2H, s, Ph-CH_2), 5.77 (1H, d, *J* = 5.8 Hz, H-7), 5.85–5.86 (1H, m, H-6), 7.16–7.25 (15H, m, 15 x Ar-H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 58.2 (C-3), 62.6 (C-5), 71.4 (Ph-*C*H_2), 72.2 (Ph-*C*H_2), 73.5 (Ph-*C*H_2), 76.1 (BnO-*C*H_2), 82.8 (C-2), 83.0 (C-7a), 84.8 (C-1), 127.5–128.5 (15 x Ar-C), 128.4 (C-6), 129.8 (C-7), 138.4 (Ar-*C*^{IV}), 138.6 (Ar-*C*^{IV}), 138.7 (Ar-*C*^{IV}); *m*/z calcd for $C_{29}H_{32}NO_3$ [M + H]$^+$ 442.2382, found 442.2369.

(1*R*,2*R*,7a*S*)-1,2-bis(benzyloxy)-7a-(benzyloxymethyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine (24b): According to general method, the metathesis of vinylpyrrolidine **22b** (110 mg, 0.23 mmol) afforded **24b** (54 mg, 52 %) as yellow oil. $[\alpha]_D^{20}$ – 41 (c 1 in $CHCl_3$); ν_{max}/cm^{-1} 3061, 3029, 2916, 2854, 1695, 1499, 1455, 1066; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.55 (1H, dd, *J* = 8.0, 9.4 Hz, H-3), 3.36–3.49 (3H, m, H-3', H-5, BnO-CH_aH$_b$), 3.58 (1H, d, *J* = 9.3 Hz, BnO-CH_aH$_b$), 3.87–3.94 (2H, m, H-5', H-1), 4.25 (1H, m, H-2), 4.54–4.68 (6H, m, 3 x Ph-CH_2), 5.75–5.82 (2H, m, H-6, H-7), 7.28–7.31 (15H, m, 15 x Ar-H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 57.4 (C-3), 63.0 (C-5), 72.3 (Ph-*C*H_2), 73.2 (Ph-*C*H_2), 73.6 (Ph-*C*H_2), 73.8 (BnO-*C*H_2), 80.2 (C-7a), 82.4 (C-2), 87.6 (C-1), 127.3–128.5 (15 x Ar-C), 127.9 (C-6), 131.7 (C-7), 138.6 (Ar-*C*^{IV}), 138.6 (Ar-*C*^{IV}), 138.9 (Ar-*C*^{IV}); *m*/z calcd for $C_{29}H_{32}NO_3$ [M + H]$^+$ 442.2382, found 442.2386.

(1*R*,2*R*,8a*R*)-1,2-bis(benzyloxy)-8a-(benzyloxymethyl)-1,2,3,5,8,8a-hexahydroindolizine (25a): According to general method, the metathesis of pyrrolidine **23a** (126 mg, 0.27 mmol) afforded **25a** (50 mg, 40 %) as yellow oil. $[\alpha]_D^{20}$ – 19.0 (c 0.25 in $CHCl_3$); ν_{max}/cm^{-1} 3063, 3030, 2915, 2853, 1695, 1498, 1455, 1068; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.89 (1H, dm, *J* = 18.1 Hz, H-8), 2.31 (1H, dm, *J* = 18.1 Hz, H-8'), 2.97 (1H, dd, *J* = 3.2, 10.0 Hz, H-3), 3.13 (1H, dm, *J* = 18.0, H-5), 3.26 (1H, dd, *J* = 7.2, 10 Hz, H-3'), 3.36–3.50 (3H, m, H-5', BnO-CH_2), 4.07–4.13 (1H, m, H-2), 4.18 (1H, d, *J* = 3.2 Hz, H-1), 4.40–4.60 (6H, m, 3 x Ph-CH_2), 5.60–5.78 (2H, m, H-6, H-7), 7.26–7.36 (15H, m, 15 x Ar-H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 23.5 (C-8), 45.4 (C-5), 55.2 (C-3), 62.4 (C-8a), 68.2 (BnO-*C*H_2), 71.5 (Ph-*C*H_2), 72.2 (Ph-*C*H_2), 73.4 (Ph-*C*H_2), 82.6 (C-2), 86.9 (C-1), 123.5 (C-6 or C-7), 124.1 (C-6 or C-7), 123.52–128.4 (15 x Ar-C), 138.3 (Ar-*C*^{IV}), 138.6 (Ar-*C*^{IV}), 138.8 (Ar-*C*^{IV}); *m*/z calcd for $C_{30}H_{33}LiNO_3$ [M + Li]$^+$ 462.2620, found 462.2625.

(1*R*,2*R*,8a*S*)-1,2-bis(benzyloxy)-8a-(benzyloxymethyl)-1,2,3,5,8,8a-hexahydroindolizine (25b): According to general method, the metathesis of pyrrolidine **23b** (232 mg, 0.5 mmol) afforded **25b** (120 mg, 54%) as yellow oil. $[\alpha]_D^{20}$ – 17.8 (c 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 3061, 3029, 2914, 2854, 1695, 1499, 1456, 1065;

^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.24 (2H, s br, H-8), 2.98 (1H, dd, *J* = 4.2, 9.3 Hz, H-3), 3.21 (1H, d, *J* = 17.8, H-5), 3.30 (1H, d, *J* = 17.8, H-5'), 3.53 (1H, dd, *J* = 8.0, 9.3 Hz, H-3'), 3.62 (1H, d, *J* = 8.9 Hz, BnO-CH_aH$_b$), 3.80 (1H, d, *J* = 8.9 Hz, BnO-CH$_a$$H_b$), 3.87 (1H, d, *J* = 2.9 Hz, H-1), 4.30–4.36 (1H, m, H-2), 4.50 (2H, s, Ph-CH_2), 4.57 (2H, d, *J* = 1.1 Hz, Ph-CH_2), 4.72 (2H, d, *J* = 2.7 Hz, Ph-CH_2), 5.67–5.80 (2H, m, H-6, H-7), 7.32–7.43 (15H, m, 15 x Ar-H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 28.2 (C-8), 45.9 (C-5), 56.8 (C-3), 62.4 (C-8a), 69.3 (BnO-CH_2), 71.4 (Ph-CH_2), 72.0 (Ph-CH_2), 73.4 (Ph-CH_2), 82.5 (C-2), 89.6 (C-1), 123.7 (C-6 or C-7), 124.0 (C-6 or C-7), 127.2–128.3 (15 x Ar-C), 138.3 (Ar-C^{IV}), 138.6 (Ar-C^{IV}), 138.7 (Ar-C^{IV}); *m*/z calcd for $C_{30}H_{33}LiNO_3$ [M + Li]$^+$ 462.2620, found 462.2628.

General procedure for the hydrogenolysis of unsaturated pyrrolizidines and indolizidines : To a well-stirred solution of unsaturated pyrrolizidines or indolizidines (0.1 mmol) in dry MeOH (5 mL) was added 20% Pd/C (25 mg) and HCl (6 M, 1 mL). The suspension was stirred 48 h under hydrogen (1 atm) then filtered over celite. The celite was rinsed with MeOH and the filtrate was neutralized with Amberlist A-26 (OH^-) resin. Finally, the solution was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, $CHCl_3$/MeOH/NH_4OH 6/4/1) to afford the compounds as brown solids.

(1*R*,2*R*,7a*R*)-7a-(hydroxymethyl)pyrrolizidine-1,2-diol (5a): According to general method, the hydrogenolysis of unsaturated pyrrolizidine **24a** (40 mg, 0.09 mmol) afforded **5a** (13 mg, 83 %) as brown solid. $[\alpha]_D^{20}$ + 11.0 (c 0.36 in MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 1.59–1.64 (1H, m, H-7), 1.75–1.87 (2H, m, H-6), 1.98–2.03 (1H, m, H-7'), 2.77–2.81 (1H, m, H-5), 2.94–3.01 (2H, m, H-3), 3.08–3.13 (1H, m, H-5'), 3.49 (1H, d, *J* = 11.5 Hz, BnO-CH_aH$_b$), 3.55 (1H, d, *J* = 11.5 Hz, BnO-CH$_a$$H_b$), 3.92 (1H, d, *J* = 5.1 Hz, H-1), 4.15–4.19 (1H, m, H-2); ^{13}C NMR (D_2O, 500 MHz) δ 24.6 (C-6), 28.4 (C-7), 55.7 (C-5), 56.2 (C-3), 65.0 (BnO-CH_2), 74.5 (C-2), 77.8 (C-7a), 78.0 (C-1); *m*/z calcd for $C_8H_{16}NO_3$ [M + H]$^+$ 174.1130, found 174.1124.

(1*R*,2*R*,7a*S*)-7a-(hydroxymethyl)pyrrolizidine-1,2-diol (5b): According to general method, the hydrogenolysis of unsaturated pyrrolizidine **24b** (54 mg, 0.12 mmol) afforded **5b** (10 mg, 51 %) as brown solid. $[\alpha]_D^{20}$ + 8.3 (c 0.21 in MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 2.00–2.07 (1H, m, H-7), 2.13–2.25 (3H, m, H-7', H-6), 3.08 (1H, dd, *J* = 7.2, 12.4 Hz, H-3), 3.38–3.42 (1H, m, H-5), 3.54–3.59 (1H, m, H-5'), 3.68 (1H, d, *J* = 12.5, BnO-CH_aH$_b$), 3.86 (1H, dd, *J* = 6.1, 12.4 Hz, H-3') 3.96 (1H, d, *J* = 12.5, BnO-CH$_a$$H_b$), 4.13 (1H, d, *J* = 6.1 Hz, H-1), 4.39–4.43 (1H, m, H-2); ^{13}C NMR (D_2O, 500 MHz) δ 23.6 (C-6), 32.3 (C-7), 55.4 (C-3), 56.5 (C-5), 60.9 (BnO-CH_2), 73.8 (C-2), 80.0 (C-1), 81.1 (C-7a); *m*/z calcd for $C_8H_{16}NO_3$ [M + H]$^+$ 174.1130, found 174.1134.

(1*R*,2*R*,8a*R*)-8a-(hydroxymethyl)indolizidine-1,2-diol (6a): According to general method, the hydrogenolysis of unsaturated indolizidine **25a** (45 mg, 0.10 mmol) afforded **6a** (15 mg, 83 %) as brown solid. $[\alpha]_D^{20}$ + 6 (c 0.5 in MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 1.31–1.43 (3H, m, H-8, H-6), 1.46–1.55 (1H, m, H-7), 1.64–1.75 (2H, m, H-6', H-7'), 2.62–2.70 (2H, m, H-5, H-3), 2.79 (1H, td, *J* = 3.0, 13.5 Hz, H-5'), 3.54 (1H, dd, *J* = 9.2, 11.3 Hz, H-3'), 3.70 (2H, s, BnO-CH_2), 3.95 (1H, d, *J* = 5.7 Hz, H-1), 4.25–4.29 (1H, m, H-2), ^{13}C NMR (D_2O, 500 MHz) δ 17.5 (C-6), 18.5 (C-7), 20.7 (C-8), 43.7 (C-5), 53.2 (C-3), 60.4 (BnO-CH_2), 63.6 (C-8a), 74.1 (C-2), 82.0 (C-1); *m*/z calcd for $C_9H_{18}NO_3$ [M + H]$^+$ 188.1287, found 188.1289.

(1*R*,2*R*,8a*S*)-8a-(hydroxymethyl)indolizidine-1,2-diol (6b): According to general method, the hydrogenolysis of unsaturated indolizidine **25b** (95 mg, 0.21 mmol) afforded **6b** (20 mg, 51 %) as brown solid. $[\alpha]_D^{20}$ – 11.7 (c 0.4 in MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 1.39–1.42 (1H, m, H-6), 1.53–1.72 (5H, m, H-6', H-7, H-8), 2.74–2.77 (1H, m, H-5), 2.82–2.88 (1H, m, H-5'), 2.95–2.99 (1H, m, H-3), 3.20–3.25 (1H, m, H-3'), 3.74 (1H, d, *J* = 11.8 Hz, BnO-CH_aH$_b$), 3.78–3.83 (2H, m, H-1, BnO-CH$_a$$H_b$), 4.18–4.22 (1H, m, H-2); ^{13}C NMR (D_2O, 500 MHz) δ 18.9 (C-6), 19.0 (C-7), 25.0 (C-8), 44.9 (C-5), 54.7 (C-3), 59.2 (BnO-CH_2), 64.5 (C-8a), 76.1 (C-2), 84.4 (C-1); *m*/z calcd for $C_9H_{18}NO_3$ [M + H]$^+$ 188.1287, found 188.1279.

Enzymatic assay: all the enzymes were purchased from Sigma Chemical Co. In a typical experiment, the glycosidase (0.013 U/mL) was pre-incubated at 33 °C for 5 min in the presence of the inhibitor in 50 mM acetate buffer (pH 5.6, except for rice α-glucosidase pH 5.1 and yeast α-glucosidase pH 6.2). The reaction was started by addition of the appropriate substrate (*p*-nitrophenyl glycoside, 1 mM concentration) to a final volume of 250 µl. The reaction was stopped after 10-15 min (depending on the enzyme) by addition of 350 µL of 0.4 M Na_2CO_3. The released *p*-nitrophenolate was quantified spectrophotometrically at 415 nm with a microplate reader (300 µL of the reaction mixture in a well, OD *ca* 0.7 for the control, without inhibitor). In cases where inhibition was greater than 95%, IC_{50} values were determined further after assaying decreasing concentrations of inhibitor (typically 5 concentrations around IC_{50}). All the assays were done in duplicate (less than 10% variability in each case).

Conflicts of interest

"There are no conflicts to declare".

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