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Synthesis and Glycosidase Inhibition Studies of 5-Methyl-Substituted Tetrahydroxyindolizidines and -pyrrolizidines Related to Natural Hyacinthacines B

Daniele Martella,[a,b] Francesca Cardona,[a] Camilla Parmeggiani,[a,c] Francisco Franco,[b] Juan A. Tamayo,*[b] Inmaculada Robina,[d] Elena Moreno-Clavijo,[d] Antonio J. Moreno-Vargas,[d] and Andrea Goti*[a]

Dedicated to Marek Chmielewski on the occasion of his 70th birthday

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The synthesis of three tetrahydroxyindolizidines and one tetrahydroxypyrrolizidine related to natural hyacinthacines B and their biological evaluation as glycosidase inhibitors is reported. The target molecules were obtained through highly stereoselective cycloadditions between sugriched allylic and homoallylic alcohols. This allowed the installation of a methyl group at C5 – a common feature of many natural hyacinthacines – with high control over the stereoselectivity. The new compounds inhibit amyloglucosidase from *Aspergillus niger* and β-glucosidase from almonds. Compound **1** is a competitive inhibitor of amyloglucosidase and shows a fair selectivity towards this enzyme. The presence of C5-Me substitution in indolizidines **2** and **3** slightly diminishes the inhibitory activity towards amyloglucosidase whereas it improves the inhibitory properties towards β-glucosidase.

Introduction

Hyacinthacines are polyhydroxylated pyrrolizidine alkaloids bearing hydroxymethyl groups at C3 and in several cases also methyl or hydroxymethyl groups at C5. Although they were discovered only recently, around twenty of these compounds were identified during the period 1999–2007, by isolation from the Hyacinthaceae family of plants.[1] They have been classified as A, B, or C on the basis of their degrees of oxygenation (three, four, or five hydroxy groups, respectively, Figure 1).

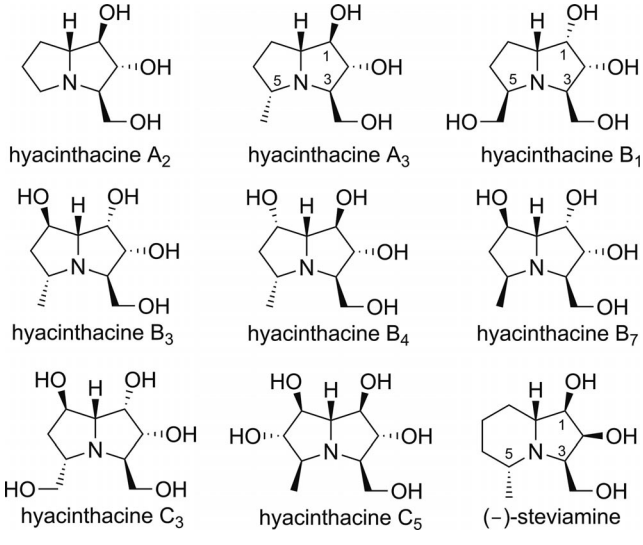

Figure 1. Examples of hyacinthacine alkaloids and the structurally related steviamine.

Only in 2010 was the first example of an indolizidine analogue bearing a methyl group at C5 – namely (–)-steviamine – identified, in *Stevia rebaudiana* Betoni (Asteraceae) and in *Veltheimia capensis* Hyacinthaceae (sand lily).[2]

[a] Dipartimento di Chimica "Ugo Schiff", Università di Firenze, Polo Scientifico e Tecnologico,
Via della Lastruccia 3–13, 50019 Sesto Fiorentino (FI), Italy
Fax: +39-055-4573531
E-mail: andrea.goti@unifi.it
[b] Departamento de Química Farmacéutica y Orgánica, Facultad de Farmacia, Universidad de Granada,
Campus de la Cartuja s/n., 18071 Granada, Spain
E-mail: jtamayo@ugr.es
[c] CNR-INO and European Laboratory for Non-Linear Spectroscopy (LENS), University of Florence,
Via N. Carrara 1, Sesto Fiorentino (FI), Italy
[d] Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla,
c/ Prof. García González 1, 41012, Sevilla, Spain
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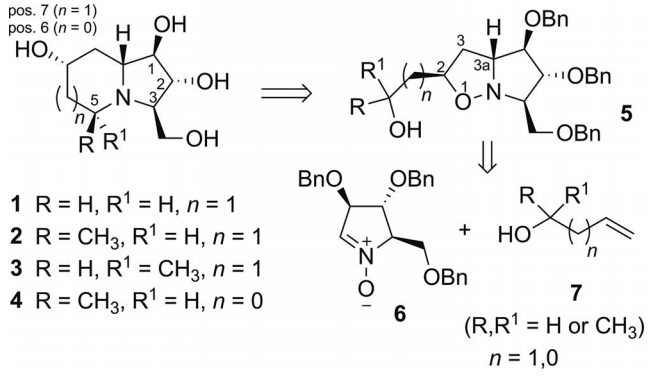
These natural iminosugars and their unnatural analogues behave as glycosidase inhibitors and so are promising candidates as multipurpose drugs in the treatment of different pathologies.[3] For this reason, synthetic efforts to develop general strategies to afford these compounds have been enormous during recent years.[4] New synthetic methods to access such compounds are important not only for confirmation of the structures of the natural samples,[5] but also to provide new analogues for structure–activity relationship studies.

Our groups have a longstanding interest in the total synthesis of pyrrolizidine and indolizidine alkaloids and analogues.[6,7] In particular, Goti and co-workers have widely exploited the use of polyhydroxylated nitrones as dipoles in 1,3-dipolar cycloaddition chemistry[6a,6b,4e] and as electrophiles towards organometallics,[6c,6d] whereas Tamayo and co-workers have recently expanded the scope of cycloadditions for the synthesis of unnatural pentahydroxypyrrolizidines and -indolizidines with hydroxymethyl groups at C5 by use of chemoenzymatically prepared but-3-ene-1,2-diol derivatives as dipolarophiles.[8]

Here we report a general strategy for the synthesis of novel tetrahydroxyindolizidines and -pyrrolizidines, therefore related to hyacinthacines B,[9] each bearing a methyl group at C5 (see **2**–**4**, Scheme 1). This is also a common structural motif of these natural compounds (e.g., hyacinthacines A_3, B_3, B_4, B_7, C_5, steviamine, Figure 1).[10] To provide information about the role of the methyl group for the inhibitory activity, model compound **1** was also synthesized.

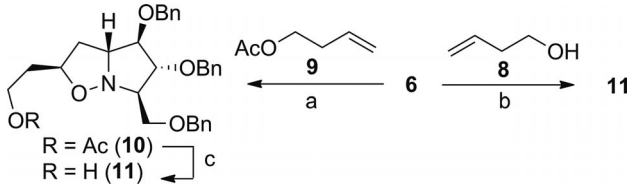


Scheme 1. General strategy for the synthesis of tetrahydroxyindolizidine and -pyrrolizidine alkaloids.

The general strategy is outlined in Scheme 1. Target compounds **1**–**4** were obtained through highly regio- and stereoselective cycloadditions between a D-*arabino*-configured nitrone **6** and a suitable allylic or homoallylic alcohol **7** as the key step. We chose nitrone **6** for two main reasons: firstly, many hyacinthacines (e.g., hyacinthacines A_2, A_3, B_4, C_5, Figure 1) have a common structural motif represented by a pyrrolidine ring with three contiguous stereocenters with the *R* configuration, which corresponds to a D-*arabino* substitution pattern, and secondly, the use of nitrone **6** allowed very high regio- and stereoselectivity in the cycloaddition reaction, which is not the case with nitrones possessing different configurations at the stereogenic centers.[6b] This allowed control of the relative configurations at C2 and C3a of the isoxazolidine intermediates **5** and therefore at C7 (or C6 in the case of pyrrolizidines) and at the bridgehead carbon atoms in the target molecules. Finally, the relative configuration at C5 depended on the enantiomer of the alcohol **7**, obtained through chemoenzymatic resolution and used in the cycloaddition. Complete control of all stereocenters could thus be achieved with high selectivity.

Results and Discussion

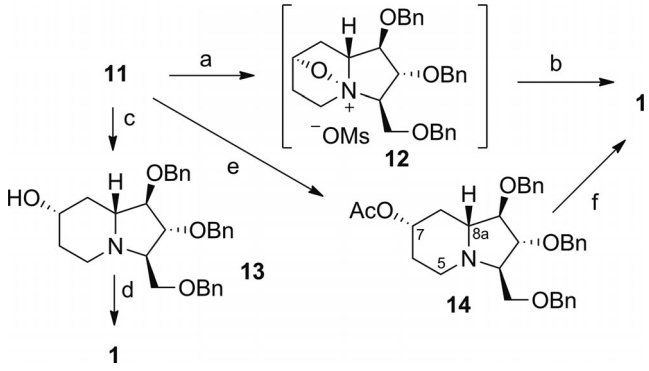
The first step for the synthesis of the model compound **1** involved cycloaddition between **6**[11] and but-3-en-1-ol (**8**, Scheme 2). Previous work in our group had shown that this dipolarophile required prolonged reaction times with different cyclic nitrones,[12] but that these reaction times could be greatly reduced (and stereoselectivity improved) under microwave (MW) irradiation conditions.[13] We therefore first attempted the reaction under microwave irradiation conditions, with the aim of keeping the reaction times short. However, the reaction between **6** and **8** under MW heating conditions failed both in dichloromethane and in toluene as solvents, affording only partial conversion of the starting material. We then treated **6** with the *O*-acetyl derivative **9**, obtained from **8** by treatment with acetic anhydride in pyridine at room temperature (see the Supporting Information) and used without further purification. After MW heating in toluene at 120 °C for two hours, the single adduct **10** (Scheme 2) was recovered in 81% yield after purification by flash column chromatography (FCC). Removal of the acetyl group was achieved by treatment with the strongly basic resin Ambersep 900 OH at room temp. in MeOH.[6b] Compound **11** was obtained by this two-step sequence in 78% overall yield. Alternatively, conventional heating of **6** with **8** in toluene at 60 °C for 4 d directly afforded **11** as a single isomer in 89% yield. The structures of **10** and **11**, confirmed after subsequent transformation (vide infra), confirmed our expectation that both cycloadditions proceeded through an *exo* approach of **8** or **9** *anti* to the vicinal OBn of the nitrone. This stereochemical outcome is in accord with other reactions between nitrone **6** and different dipolarophiles.[6a,14]



Scheme 2. Synthesis of isoxazolidines **10** and **11**. Reaction conditions: a) toluene, MW, 120 °C, 2 h, 81%; b) toluene, 60 °C, 4 d, 89%; c) Ambersep 900 OH, MeOH, 96%.

Two different strategies to afford the indolizidine skeleton were investigated, as outlined in Scheme 3. Mesylation of the primary alcohol in **11** (MsCl, triethylamine) gave the intermediate salt **12**, formed by intramolecular mesylate

substitution with the nitrogen atom.[12a,15] Catalytic hydrogenolysis under acidic conditions resulted in N–O bond cleavage and concomitant removal of the benzyl groups, leading directly to the target compound **1** in 37% yield over two steps.



Scheme 3. Synthesis of tetrahydroxyindolizidine **1**. Reaction conditions: a) MsCl, NEt_3, dry CH_2Cl_2; b) H_2, Pd/C, MeOH, HCl, 37% over two steps; c) I_2, ImH, PPh_3, dry THF, $Na_2S_2O_3$, 35%; d) H_2, Pd/C, MeOH, HCl, 84%; e) I_2, ImH, PPh_3, dry THF, $Na_2S_2O_3$, then Ac_2O/Py; f) H_2, Pd/C, MeOH, HCl, 81% yield from **11**.

Alternatively, treatment of the primary alcohol in **11** with iodine and imidazole (ImH) in the presence of PPh_3, followed by $Na_2S_2O_3$ treatment, resulted in a quite unexpected outcome: indolizidine **13** was obtained in 35% yield. At this stage, a plausible explanation for the formation of **13** involved intramolecular nucleophilic displacement of the intermediate iodide by the nitrogen atom, followed by N–O bond cleavage occurring during the reductive quenching with $Na_2S_2O_3$. To the best of our knowledge, however, there is no report of such cleavage in similar isoxazolidines or their salt derivatives. Subsequent catalytic hydrogenolysis gave **1** in 84% yield. Because purification of **13** from the triphenylphosphane oxide formed in the reaction of **11** was troublesome, we decided to perform direct acetylation of **13** to afford **14**, which was directly subjected to catalytic hydrogenolysis under acidic conditions, leading to **1** in 81% yield over three steps from **11**.

The structure of **1**, which also confirmed that of its precursor **11**, was assigned on the basis of ^1H NMR, ^{13}C NMR, COSY, HSQC, and 1D NOESY spectra of its tetraacetyl derivative, obtained by treatment of **1** with a mixture of Ac_2O and pyridine (see the Supporting Information). In particular, 1D NOESY spectra showed strong NOE correlation peaks between H(7) and H(8a) and between H(7) and one of the two hydrogen atoms at C5 (Figure 2).

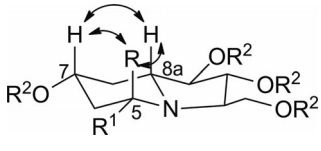
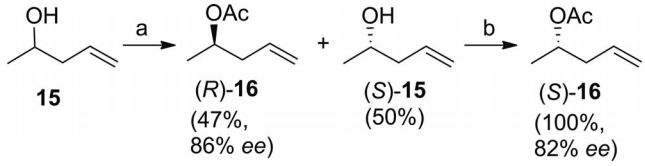


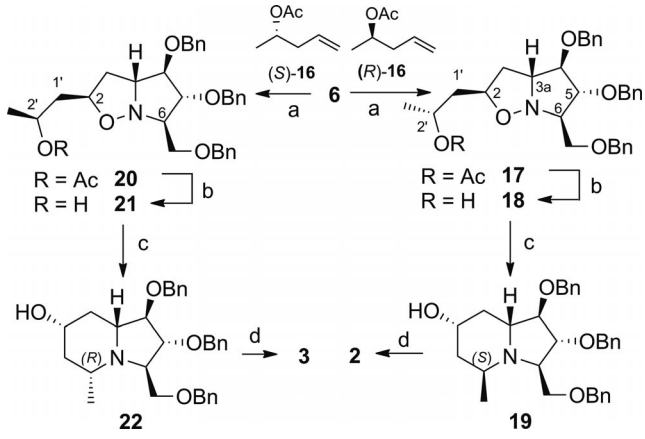
Figure 2. Diagnostic NOE correlation peaks in in tetraacetates of indolizidines **1**, **2**, and in **3**.

To access the indolizidines with methyl substitution at C5, the enantiomeric pent-4-en-2-ols were required as dipolarophiles. Chemoenzymatic kinetic resolution of racemic pent-4-en-2-ol (**15**, Scheme 4) was achieved by stirring in diethyl ether at room temperature for 14 h in the presence of *Candida antarctica* lipase Chirazyme L-2, c.-f., C2 and vinyl acetate as acyl donor, as reported for different racemic alcohols.[16] Under these conditions, acetate (*R*)-**16** was recovered in 47% yield and 86% *ee*,[17] together with unreacted (*S*)-**15** in 50% yield. The *ee* of unreacted **15** was determined after separation from (*R*)-**16** by FCC and acetylation in Ac_2O and Py, which afforded (*S*)-**16** quantitatively and with 82% *ee* (Scheme 4).[17]



Scheme 4. Chemoenzymatic preparation of (*R*)-**16** and (*S*)-**16** from racemic **15**. Reaction conditions: a) Chirazyme L-2, c.-f., C2, vinyl acetate, diethyl ether, room temp., 14 h; b) Ac_2O, Py, room temp.

Cycloaddition between **6** and enantioenriched (*R*)-**16** in toluene under microwave irradiation conditions at 120 °C for three hours afforded the isoxazolidine **17** (Scheme 5) regio- and stereoselectively in 74% yield, as a consequence of the preferred *exo* approach of the dipolarophile *anti* with respect to the vicinal OBn of the nitrone. The structure of **17** was assigned on the basis of its ^1H NMR, ^{13}C NMR, COSY, HSQC, and 2D NOESY spectra. In particular, the NOESY spectrum showed strong correlation peaks (Figure 3) between H(2) and H(6) and between H(3a) and H(5). Treatment of **17** with the strongly basic resin Ambersep 900 OH in MeOH at room temp. led to **18** in 82% yield. Treatment of the secondary alcohol with I_2, imidazole, and



Scheme 5. Synthesis of tetrahydroxyindolizidines **2** and **3**. Reaction conditions: a) (*R*)-**16**, toluene, MW, 120 °C, 3 h, 74% for **17**, 51% for **20**; b) Ambersep 900 OH, MeOH, 82% for **18**, 75% for **21**; c) I_2, ImH, PPh_3, dry THF, $Na_2S_2O_3$, 64% for **19**, 73% for **22**; d) H_2, Pd/C, MeOH, HCl, 95% for **2**, 70% for **3**.

PPh_3 in dry THF directly gave the indolizidine **19** in 64% yield. As described above, the N–O bond cleavage probably occurred during the reductive quenching with $Na_2S_2O_3$. Final catalytic hydrogenolysis of **19** furnished the indolizidine **2** in 95% yield (Scheme 5). The 2D NOESY spectrum of the acetate of **2**, obtained by treatment of **2** with a mixture of Ac_2O and pyridine (see the Supporting Information), showed strong NOE correlation peaks (Figure 2) of the methyl group at C5 with H(7) and H(8a), suggesting the *S* configuration at C5. The formation of indolizidine **19** from isoxazolidine **18** would therefore have occurred with a single inversion of configuration at C2′, contrary to our above hypothesis of intermediate iodide formation.

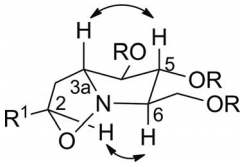


Figure 3. Diagnostic NOE correlation peaks in isoxazolidines **17**, **20**, and **25**.

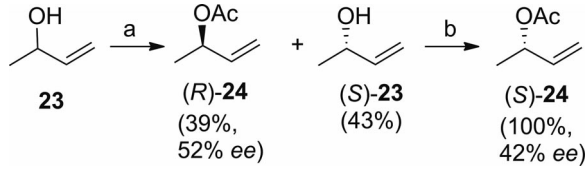
Cycloaddition between **6** and enantioenriched (*S*)-**16** in toluene under MW conditions at 120 °C for three hours gave isoxazolidine **20** in 51% yield, and this was deacetylated by treatment with Ambersep 900 OH in MeOH to afford **21** in 75% yield (Scheme 5). The structure of **20**, originating from an *exo* approach of the dipolarophile *anti* with respect to the vicinal OBn of the nitrone, was assigned on the basis of a strong NOE correlation peak between H(2) and H(6) in the 2D NOESY spectrum (Figure 3).

The similar results of the above cycloadditions with enantioenriched (*R*)-**16** and (*S*)-**16** demonstrated that an additional stereogenic center at C2 of the dipolarophile has virtually no influence on the stereoselectivity of the reactions, which is governed by substrate control by the nitrone.

Treatment of **21** with I_2, ImH, and PPh_3, together with reductive quenching conditions, afforded the indolizidine **22** in 73% yield from **21**. While this manuscript was in preparation, compound **22** was also synthesized through an imine cycloaddition strategy.[18] The ^1H and ^{13}C NMR spectra of **22** were identical to those reported, thus demonstrating the *R* configuration at C5 unequivocally. Final catalytic hydrogenolysis of **22** furnished the indolizidine **3** in 70% yield (Scheme 5).

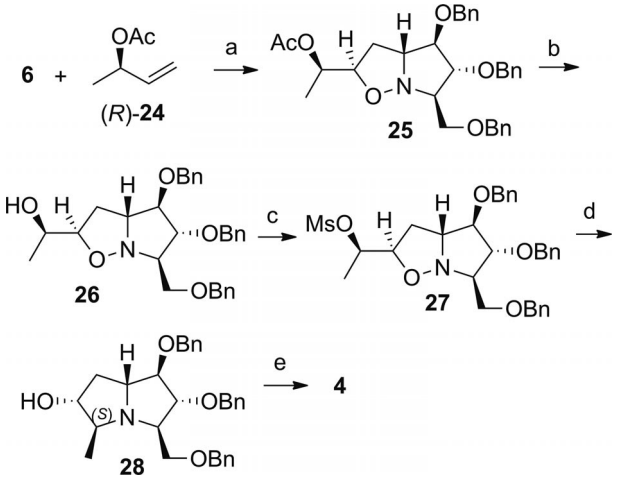
As a further confirmation of the structures of the final tetrahydroxyindolizidines, comparison of the ^1H NMR spectra of **2** and **3** showed a signal at around 3.3 ppm for the equatorial H(5) in **2** and a more shielded signal at around 2.6 ppm for the axial H(5) in **3**. The formation of indolizidines **19** and **22** from isoxazolidines **18** and **21** thus occurred with a single inversion of configuration at C2′ in each case. This result can be reasonably explained by assuming that treatment of cycloadducts **18**, **21**, and **11** with an excess of I_2 and PPh_3 in the presence of imidazole does not afford an intermediate iodide, but that intramolecular nucleophilic substitution by the nitrogen atom of the hydroxy group activated by PPh_3/I_2 occurs more rapidly than intermolecular iodide attack, to form isoxazolidine salts analogous to **12**. Such strained intermediates, in the presence of excess PPh_3, are prone to reductive N–O bond cleavage by $Na_2S_2O_3$ during the quenching procedure, ultimately affording the observed indolizidines **19**, **22**, and **13**, respectively. Support for this hypothesis was gained by treatment of the indolizidine salt **12** under the same reaction conditions (PPh_3, I_2, ImH, then $Na_2S_2O_3$): the indolizidinol **13** was clearly detected in the crude reaction mixture, whereas no reaction was observed on quenching only with $Na_2S_2O_3$.

The synthesis of pyrrolizidines with methyl substitution at C5 required enantioenriched but-3-en-2-ol derivatives as dipolarophiles. Unfortunately, the chemoenzymatic kinetic resolution of racemic but-3-en-2-ol (**23**, Scheme 6), performed with *Candida antarctica* lipase Chirazyme L-2, c.-f., C2 in the presence of vinyl acetate as acyl donor, was less enantioselective. The reaction required only 5 h of stirring at room temp. in diethyl ether to achieve 50% conversion and furnished acetate (*R*)-**24** in 39% yield but only 52% *ee*,[19] together with unreacted (*S*)-**23** in 43% yield (Scheme 6). The *ee* of unreacted **23** was determined after separation from (*R*)-**24** by FCC; acetylation in Ac_2O and Py afforded (*S*)-**24** in 100% yield but with a low 42% *ee* (Scheme 6).[19] Use of different enzymes for the selective acetylation of racemic **23** was also tried,[20] but no better results were achieved. Moreover, attempted chemoenzymatic deacetylation of the acetate of **23** with Chirazyme L-2, c.-f., C2 was unsuccessful.



Scheme 6. Chemoenzymatic preparation of (*R*)-**24** and (*S*)-**24** from racemic **23**. Reaction conditions: a) Chirazyme L-2, c.-f., C2, vinyl acetate, diethyl ether; b) Ac_2O, Py, room temp.

However, cycloaddition between **6** and an excess (5 equiv.) of enantioenriched (*R*)-**24** in toluene under MW conditions at 120 °C for three hours afforded a reasonable 61% yield of the major *exo-anti* diastereoisomer **25** (Scheme 7), which was isolated from the reaction mixture by FCC. The structure of **25** was assigned on the basis of a strong NOE correlation peak between H(2) and H(6) in the 2D NOESY spectrum (Figure 3). Treatment with the strongly basic resin Ambersep 900 OH in MeOH at room temp. led to **26** in quantitative yield. Treatment of **26** with I_2, ImH, and PPh_3 in THF or toluene, though, was unsuccessful, even with prolonged reaction times or heating at 60–80 °C. This observation confirmed the difficulties inherent in the use of external iodide to effect displacement reactions with secondary alcohols of this kind. On the other hand, internal displacement by nitrogen is in this case precluded by the high strain of the putative product.



Scheme 7. Synthesis of tetrahydroxypyrrolizidine **4**. Reaction conditions: a) toluene, MW, 120 °C, 3 h, 61%; b) Ambersep 900 OH, MeOH, 100%; c) MsCl, dry CH_2Cl_2, Py, 95%; d) Zn powder, AcOH/H_2O (9:1), 47%; e) H_2, Pd/C, MeOH, HCl, 80%.

We then decided to obtain the pyrrolizidine skeleton in a two-step sequence based on mesylation of the secondary alcohol **26** followed by N–O bond cleavage. Accordingly, **26** was treated with mesyl chloride and pyridine in dry CH_2Cl_2 to afford compound **27** (Scheme 7) in 95% yield. Subsequent treatment with Zn in an AcOH/H_2O mixture (9:1) gave the pyrrolizidine **28** in 47% yield. Compound **28** was assigned the *S* configuration at C5, as the result of a single inversion of configuration occurring during the intramolecular nucleophilic substitution by the nitrogen atom after N–O bond cleavage. This assignment was supported by the strong NOE correlation peak between H(5) and H(3) in the 2D NOESY spectrum of **28** (Figure 4). Final catalytic hydrogenolysis of **28** furnished the pyrrolizidine **4** in 80% yield (Scheme 7).

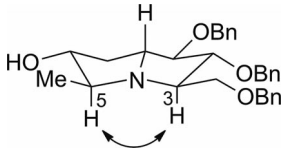


Figure 4. Diagnostic NOE correlation peaks in pyrrolizidine **28**.

Biological Evaluation of Compounds 1–4 with Glycosidases

Synthesized compounds **1**–**4** were assayed for their inhibitory activity towards 11 commercially available glycosidases.[21] At 1 mM concentration and under enzyme-optimal pH they did not inhibit β-galactosidase from *Aspergillus orizae* or from *Escherichia coli*, α-glucosidase from rice, α-mannosidase from Jack beans, or β-*N*-acetylglucosaminidase from Jack beans. Table 1 summarizes the inhibitory activities measured with α-L-fucosidase from bovine kidney, α-galactosidase from coffee beans, amyloglucosidase from *Aspergillus niger*, α-glucosidase from yeast, β-glucosidase from almonds, and β-mannosidase from snail.

Table 1. Inhibitory activities of compounds **1**, **2**, **3**, and **4** with glycosidases. Percentage inhibition at 1 mM, IC_{50} (in parenthesis, μM) and K_i (bold, μM) if measured. Optimal pH, 37 °C.[a,b,c]

	α-L-Fuc-ase	α-Gal-ase	Amylo Glc-ase	α-Glc-ase	β-Glc-ase	β-Man-ase
1	32	n.i.	95 (20.6) **18** (C)	n.i.	21	15
2	n.i.	n.i.	83	n.i.	88 (122)	n.i.
3	n.i.	n.i.	96 (35) **34.8**	n.i.	87 (144)	18
4	n.i.	17	95 (39) **32.1**	18	27	n.i.

[a] For conditions of measurements see ref.[21] and the Supporting Information. [b] (C): competitive inhibition, n.i.: no inhibition at 1 mM concentration of the inhibitor. [c] α-L-Fuc-ase: α-L-fucosidase from bovine kidney. α-Gal-ase: α-galactosidase from coffee beans. AmyloGlc-ase: amyloglucosidase from *Aspergillus niger*. α-Glc-ase: α-glucosidase from yeast. β-Glc-ase: β-glucosidase from almonds. β-Man-ase: β-mannosidase from snail.

Compound **1** showed the best inhibitory activity towards amyloglucosidase from *Aspergillus niger* with a competitive type of inhibition (see the Supporting Information for Lineweaver–Burk plot). This compound also showed weak inhibitory properties with α-L-fucosidase, β-glucosidase, and β-mannosidase. The presence of a methyl group at C5 somewhat decreased the inhibitory properties with amyloglucosidase from *Aspergillus niger*, as was also observed for compounds **2**, **3**, and **4**. The methyl group in compound **2** thus diminished the inhibitory potential towards amyloglucosidase from *Aspergillus niger* and increased the activity against β-glucosidase from almonds to IC_{50} = 122 μM. The methyl groups in compounds **3** and **4** reduced the activity to K_i 34.8 μM and K_i 32.1 μM, respectively. Indolizidine **3** also showed moderate to weak inhibitory activity with β-glucosidase from almonds (IC_{50} = 144 μM), whereas pyrrolizidine **4** showed weak inhibitory properties. Compound **3** also exhibited weak inhibitory activity against β-mannosidase from snail. Compound **4** is also a weak inhibitor of α-galactosidase and α- and β-glucosidases.

In summary, the presence of a methyl group at C5 (compounds **2**, **3**, and **4**) slightly reduces the inhibitory activity towards amyloglucosidase from *Aspergillus niger*. It does, however, improve the inhibitory properties towards β-glucosidase from almonds for indolizidines **2** and **3**, but not for pyrrolizidine **4**.

Conclusions

In conclusion, the straightforward synthesis of three new compounds related to natural hyacinthacines B was achieved by means of highly regio- and stereoselective 1,3-dipolar cycloadditions between a carbohydrate-derived nitrone and suitable chemoenzymatically prepared enantioenriched allylic and homoallylic alcohols. This strategy allowed stereoselective introduction of methyl substitution at C5 in the target molecules. Biological evaluation with a set of commercially available glycosidases revealed that these new compounds mainly inhibit amyloglucosidase form *As-*

pergillus niger and β-glucosidase from almonds. The best inhibitor in this series is compound **1**, which preferentially inhibits amyloglucosidase from *Aspergillus niger*. The methyl substitution at C5 in indolizidines **2** and **3** slightly diminishes inhibition of amyloglucosidase, but improves the activity against β-glucosidase. Pyrrolizidine **4** has inhibitory properties towards amyloglucosidase similar to those of compound **3**, although its activity against β-glucosidase is lower.

Experimental Section

General Methods: Commercial reagents were used as received. All reactions were magnetically stirred and monitored by TLC on 0.25 mm silica gel plates (Merck F_{254}); column chromatography was carried out on silica gel 60 (32–63 μm), yields refer to spectroscopically and analytically pure compounds unless otherwise stated. Small-scale microwave-assisted synthesis was carried out with an Initiator 2.0 single-mode microwave instrument producing controlled irradiation at 2.450 GHz (Biotage AB, Upsala). These parameters were established by the basic principles of microwave-assisted organic synthesis. The temperature was measured with an IR sensor on the outside of the reaction vessel. NMR spectra were recorded with Varian INOVA-400, Bruker AMX-300, or Bruker ARX-400 instruments. Infrared spectra were recorded with a Perkin–Elmer FTIR Spectrum One spectrophotometer. Mass spectra were recorded with Micromass Model Platform II and Autospec-Q instruments; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer. Optical rotation measurements were performed with a JASCO DIP-370 polarimeter. GLC was performed with a gas chromatograph equipped with split/splitless injector and a flame-ionization detector. The He flow rate was 1:1 mL min^{-1}, the injection port and the zone-detector temperatures were 275 °C; β-DEXTM 325 (Supelco TM) capillary column (30 × 0.25 mm i.d. × 0.25 mm film thickness) at 80 °C.

(2*R*,3a*R*,4*R*,5*R*,6*R*)-2-(2-Acetyloxyethyl)-4,5-dibenzyloxy-6-(benzyloxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (10): A solution of nitrone **6** (495 mg, 1.19 mmol) and **9** (1.35 mg, 11.8 mmol) in toluene (2 mL) was heated at 120 °C under microwave irradiation conditions in a sealed tube. After 2 h, TLC (AcOEt/hexane 3:1) revealed the presence of a new compound of higher R_f (= 0.74). The solvent was removed, and the residue was flash chromatographed (AcOEt/hexane 1:2, R_f = 0.22) to afford **10** (629 mg, 81%) as a brown oil. $[\alpha]_D^{27}$ = –31.9 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 15 H, Ar), 4.63–4.54 (m, 6 H, Bn), 4.18–4.15 (m, 2 H, 2-H, C*H*$_2$OAc), 4.13–4.08 (m, 1 H, C*H*$_2$OAc), 4.05 (t, *J* = 5.7 Hz, 1 H, 5-H), 3.91 (t, *J* = 4.8 Hz, 1 H, 4-H), 3.76 (br. s, 1 H, 3a-H), 3.69 (dd, *J* = 9.7, 4.1 Hz, 1 H, C*H*$_2$OBn), 3.63 (dd, *J* = 9.7, 4.8 Hz, 1 H, C*H*$_2$OBn), 3.30 (br. s, 1 H, 6-H), 2.21–2.17 (m, 1 H, 3-H$_a$), 2.06–2.04 (m, 1 H, 3-H$_b$), 2.02 (s, 3 H, C*H*$_3$CO), 1.96–1.93 (m, 1 H, C*H*$_2$CH$_2$OAc), 1.89–1.85 (m, 1 H, C*H*$_2$CH$_2$OAc) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (s, CH$_3$*C*O), 140.9, 140.6, 140.4 (s, Ar), 131.1–130 (d, 15 C, Ar), 90.2 (d, C-4), 85.6 (d, C-5), 76.1, 75.2, 74.6 (d, *t*, 4 C, C-2, Bn), 72.4 (t, *C*H$_2$OBn), 72.1 (d, C-6), 70.5 (d, C-3a), 64.3 (t, *C*H$_2$OAc), 42.9 (t, C-3), 35.0 (t, *C*H$_2$CH$_2$OAc), 23.6 (q, *C*H$_3$CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 2866, 1738, 1454, 1365, 1242 cm^{-1}. HRMS (ES): calcd. for $C_{32}H_{37}NO_6Na$ [M + Na]$^+$ 554.2519; found 554.2516.

(2*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6-(benzyloxymethyl)-2-(2-hydroxyethyl)- hexahydropyrrolo[1,2-*b*]isoxazole (11): Ambersep 900 (OH$^-$ form, 1.5 g) was added to a solution of **10** (435 mg, 0.82 mmol) in MeOH (75 mL), and the mixture was stirred overnight. TLC monitoring (AcOEt/hexane 3:1) revealed a new slower-running compound (R_f = 0.38). The mixture was filtered, washed with MeOH, and concentrated to give **11** (386 mg, 96%) as a yellow oil. $[\alpha]_D^{25}$ = –36.3 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 15 H, Ar), 4.62–4.53 (m, 6 H, Bn), 4.32–4.25 (m, 1 H, 2-H), 4.04 (dd, *J* = 6.8, 4.9 Hz, 1 H, 5-H), 3.92 (t, *J* = 4.9 Hz, 1 H, 4-H), 3.77–3.71 (m, 3 H, 3a-H, C*H*$_2$OH), 3.67 (dd, *J* = 9.8, 4.9 Hz, 1 H, C*H*$_2$OBn), 3.62 (dd, *J* = 10.0, 5.6 Hz, 1 H, C*H*$_2$OBn), 3.33 (dt, *J* = 5.9, 5.4 Hz, 1 H, 6-H), 2.21 (ddd, *J* = 12.2, 6.3, 3.9 Hz, 1 H, 3-H$_a$), 2.13–2.06 (m, 1 H, 3-H$_b$), 1.92–1.77 (m, 2 H, C*H*$_2$CH$_2$OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 140.7, 140.4 (s, Ar), 131.1–130.2 (d, 15 C, Ar), 90.4 (d, C-4), 87.8 (d, C-5), 77.6 (d, C-2), 76.1, 75.1, 74.6 (t, Bn), 72.4 (t, *C*H$_2$OBn), 72.1 (d, C-6), 70.4 (d, C-3a), 63.0 (t, *C*H$_2$OH), 42.8 (t, C-3), 38.3 (t, *C*H$_2$CH$_2$OH) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3538, 3032, 2868, 2248, 1496, 1454, 1364 cm^{-1}. HRMS (ES): calcd. for $C_{30}H_{35}NO_5Na$ [M + Na]$^+$ 512.2413; found 512.2426.

(2*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6-(benzyloxymethyl)-2-(2-hydroxyethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (11): A solution of **6** (150 mg, 0.36 mmol) and but-3-en-1-ol (153 μL, 1.79 mmol) in toluene (1.5 mL) was heated at 60 °C. After 48 h the solvent was removed and the residue was flash chromatographed (AcOEt/petroleum ether 2:1, R_f = 0.32) to afford **11** (156 mg, 0.32 mmol, 89%) as a yellow oil.

(1*R*,2*R*,3*R*,7*S*,8a*R*)-1,2-Dibenzyloxy-7-hydroxy-3-(benzyloxymethyl)indolizidine (13): Iodine (179 mg, 0.69 mmol), triphenylphosphane (161 mg, 0.61 mmol), and imidazole (96 mg, 1.14 mmol) were added under Ar to a stirred solution of **11** (230 mg, 0.47 mmol) in dry THF (30 mL). The mixture was stirred at room temperature for 2 h. TLC monitoring (AcOEt/hexane 3:1) showed the appearance of a new product (R_f = 0.21). A saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (20 mL) was added, and the mixture was stirred at room temperature for 15 min. It was then extracted with CH_2Cl_2 (3× 100 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was flash chromatographed (AcOEt/hexane 4:1, R_f = 0.18) and then retained on a column of Dowex 50WX8 (200–400 mesh). The column was washed with MeOH (100 mL), water (100 mL), and then with NEt_3 (10%) in MeOH to afford pure **13** (78 mg, 35%) as a yellow oil. $[\alpha]_D^{25}$ = –20.1 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 15 H, Ar), 4.58–4.46 (m, 6 H, Bn), 3.89 (t, *J* = 2.7 Hz, 1 H, 2-H), 3.70 (dd, *J* = 4.6, 2.6 Hz, 1 H, 1-H), 3.63–3.57 (m, 2 H, 7-H, C*H*$_2$OBn), 3.50 (dd, *J* = 9.5, 6.0 Hz, 1 H, C*H*$_2$OBn), 3.36–3.34 (m, 1 H, 3-H), 3.10–3.08 (m, 1 H, 5-H$_a$), 2.98–2.96 (m, 1 H, 8a-H), 2.67 (td, *J* = 12.0, 2.0 Hz, 1 H, 5-H$_b$), 2.02–2 (m, 1 H, 8-H$_a$), 1.78–1.76 (m, 1 H, 6-H$_a$), 1.53 (qd, *J* = 11.9, 4.2 Hz, 1 H, 6-H$_b$), 1.38 (q, *J* = 11.5 Hz, 1 H, 8-H$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.1, 132.0, 131.9 (s, Ar), 128.8–127.6 (d, 15 C, Ar), 88.1 (d, C-1), 86.6 (d, C-2), 73.3, 71.7, 71.6 (t, Bn), 69.3 (t, *C*H$_2$OBn), 69.2 (d, C-7), 64.4 (d, C-3), 62.7 (d, C-8a), 44.7 (t, C-5), 37.6 (t, C-8), 32.3 (t, C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3379, 3059, 2923, 2852, 1590, 1437 cm^{-1}. HRMS [nanostructure-assisted laser desorption/ionization time of flight (NALDI-TOF)]: calcd. for $C_{30}H_{36}NO_4$ [M + H]$^+$ 474.2644; found 474.2649.

(1*R*,2*R*,3*R*,7*S*,8a*R*)-1,2,7-Trihydroxy-3-(hydroxymethyl)indolizidine (1): A solution of **13** (73 mg, 0.15 mmol) in MeOH (15 mL) was acidified (conc. HCl, five drops) and hydrogenated (60 psi H_2) in the presence of Pd/C (10%, 30 mg) for 72 h. The catalyst was filtered off, washed with MeOH, and concentrated to give a residue

that was retained on a column of Dowex 50WX8 (200–400 mesh). The column was thoroughly washed with MeOH (75 mL), water (75 mL) and then with NH_4OH (1 M, 100 mL) to afford pure **1** (26 mg, 84%) as a viscous yellow oil. $[\alpha]_D^{24}$ = +2.2 (*c* = 0.91, MeOH), ^{1}H NMR (400 MHz, D_2O): δ = 3.81 (t, *J* = 4.8 Hz, 1 H, 2-H), 3.69 (dd, *J* = 11.8, 5.0 Hz, 1 H, C*H*$_2$OH), 3.65–3.59 (m, 2 H, 1-H, C*H*$_2$OH), 3.57–3.53 (m, 1 H, 7-H), 2.94–2.86 (m, 2 H, 5-H$_a$, 3-H), 2.68 (ddd, *J* = 11.5, 6.3, 3 Hz, 1 H, 8a-H), 2.55 (dt, *J* = 12.7, 2.9 Hz, 1 H, 5-H$_b$), 1.97–1.92 (m, 1 H, 8-H$_a$), 1.75–1.71 (m, 1 H, 6-H$_a$), 1.34 (qd, *J* = 12.5, 4.6 Hz, 1 H, 6-H$_b$), 1.15 (q, *J* = 11.7 Hz, 1 H, 8-H$_b$) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 80.1 (d, C-1), 78.7 (d, C-2), 67.4 (d, C-7), 65.4 (d, C-3), 62.5 (d, C-8a), 59.1 (t, *C*H$_2$OH), 42.7 (t, C-5), 34.6 (t, C-6), 30.1 (t, C-8) ppm. HRMS (NALDI-TOF): calcd. for $C_9H_{18}NO_4$ $[M + H]^+$ 204.1236; found 204.1239.

(1*R*,2*R*,3*R*,7*S*,8a*R*)-1,2,7-Trihydroxy-3-(hydroxymethyl)indolizidine (1): NEt_3 (73 μL, 0.52 mmol) was added under nitrogen to a stirred solution of **11** (170 mg, 0.35 mmol) in dry CH_2Cl_2 (3 mL). MsCl (30 μL, 0.38 mmol) was added dropwise at 0 °C. The solution was stirred at room temp. for 45 min. TLC analysis (AcOEt/petroleum ether 3:1) showed disappearance of the starting material. The solvent was removed, and the residue was dissolved in MeOH (9 mL). The solution was acidified (conc. HCl, five drops) and hydrogenated in the presence of Pd/C (10%, 110 mg) for 72 h. The catalyst was filtered off, with washing with MeOH, and the solution was concentrated to give a residue that was retained on a column of Dowex 50WX8 (200–400 mesh). The column was thoroughly washed with MeOH (20 mL), water (10 mL), and then with NH_4OH (6%, 40 mL) to afford pure **1** (25.9 mg, 0.13 mmol, 37%) as a viscous yellow oil.

(1*R*,2*R*,3*R*,7*S*,8a*R*)-1,2,7-Trihydroxy-3-(hydroxymethyl)indolizidine (1): Iodine (119 mg, 0.46 mmol), triphenylphosphane (104 mg, 0.40 mmol), and imidazole (63 mg, 0.92 mmol) were added under N_2 to a stirred solution of **11** (152 mg, 0.31 mmol) in dry THF (20 mL). The mixture was stirred at room temp. for 2 h. TLC monitoring (AcOEt/hexane 3:1) showed the appearance of a new product (R_f = 0.21). A saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (20 mL) was added, and the mixture was stirred at room temp. for 15 min. It was then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was stirred in the presence of acetic anhydride (3 mL) and dry pyridine (12 mL) at room temp. for 18 h. The solvent was removed, and the residue was purified by FCC (AcOEt/petroleum ether 1:2, R_f = 0.5) to afford crude **14**, which was dissolved in MeOH (9 mL). The solution was acidified (conc. HCl, five drops) and hydrogenated in the presence of Pd/C (10%, 60 mg) for 72 h. The catalyst was filtered off and washed with MeOH, and the solution was stirred for 14 h with Ambersep 900 (OH^- form, 300 mg). The mixture was filtered, washed with MeOH, and concentrated to give **1** (51 mg, 0.25 mmol, 81%) as a yellow oil.

Enzymatic Acetylation of Racemic Pent-4-en-2-ol: Chirazyme L-2, c.-f., C2 (245 mg) was added to a gently stirred solution of (*R*,*S*)-pent-4-en-2-ol (3.5 g, 40.6 mmol) and vinyl acetate (3.76 mL, 40.6 mmol) in Et_2O (45 mL), and the mixture was stirred at room temp. The reaction was monitored by GLC analysis, and after 14 h the enzyme was removed by filtration with thorough washing with ether. After evaporation of the solvent, the residue was subjected to chromatography (Et_2O/pentane 1:2) to afford (*R*)-2-*O*-acetyl-pent-4-en-2-ol [(*R*)-**16**, 2.45 g, 47%, R_f = 0.65, t_R = 12.92 min, 86% *ee*] and (*S*)-pent-4-en-2-ol [(*S*)-**15**, 1.7 g, 50%, R_f = 0.25, t_R = 6.58 min]. Conventional acetylation of (*S*)-**15** in anhydrous pyridine (5 mL) and Ac_2O (4.7 mL) gave (*S*)-2-*O*-acetyl-pent-4-en-2-ol [(*S*)-**16**, 2.67 g, 100%, t_R = 10.90 min; 82% *ee*].

(2*R*,2′*R*,3a*R*,4*R*,5*R*,6*R*)-2-(2-Acetyloxypropyl)-4,5-dibenzyloxy-6-(benzyloxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (17): A solution of **6** (471 mg, 1.13 mmol) and (*R*)-**16** (1.44 g, 11.3 mmol) in toluene (2 mL) was heated at 120 °C under microwave irradiation conditions in a sealed tube. After 3 h, TLC (AcOEt/hexane 3:1) revealed the presence of a new compound (R_f = 0.79). The solvent was removed, and the residue was flash chromatographed (AcOEt/hexane 1:2, R_f = 0.30) to afford **17** (456 mg, 74%) as a yellow oil. $[\alpha]_D^{24}$ = –37.9 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 15 H, Ar), 5.00–4.94 [m, 1 H, C*H*(CH$_3$)OAc], 4.63–4.52 (m, 6 H, Bn), 4.14–4.09 (m, 1 H, 2-H), 4.03 (dd, *J* = 6.7, 4.6 Hz, 1 H, 5-H), 3.90 (t, *J* = 4.6 Hz, 1 H, 4-H), 3.76–3.73 (m, 1 H, 3a-H), 3.70 (dd, *J* = 9.7, 4.1 Hz, 1 H, C*H*$_2$OBn), 3.63 (dd, *J* = 9.7, 6.2 Hz, 1 H, C*H*$_2$OBn), 3.29 (pseudo q, *J* = 5.6 Hz, 1 H, 6-H), 2.16 (ddd, *J* = 12.3, 6.2, 3.7 Hz, 1 H, 3-H$_a$), 2.05–2.01 (m, 1 H, 3-H$_b$), 1.99 [s, 3 H, CH(C*H*$_3$)OAc], 1.84–1.80 [m, 2 H, C*H*$_2$CH(CH$_3$)-OAc], 1.23 (d, *J* = 6.3 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (s, CH$_3$*C*O) 138.6, 138.3, 138.1 (s, Ar), 128.5–127.6 (d, 15 C, Ar), 88.0 (d, C-4), 83.4 (d, C-5), 73.6 (t, Bn), 73.1 (d, C-2) 72.6, 72.0 (t, Bn), 70.3 (t, *C*H$_2$OBn), 69. 8 (d, C-6), 69.2 [d, *C*H(CH$_3$)OAc], 68.1 (d, C-3a), 40.9 (t, C-3), 39.9 [t, *C*H$_2$CH(CH$_3$)OAc], 21.3 (q, *C*H$_3$CO), 20.6 [q, CH(*C*H$_3$)OAc] ppm. IR ($CHCl_3$): ṽ = 3031, 2934, 2869, 1738, 1455, 1372, 1244 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{33}H_{40}NO_6$ $[M + H]^+$ 546.2856; found 546.2861.

(2*R*,2′*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6-(benzyloxymethyl)-2-(2-hydroxypropyl)-hexahydropyrrolo[1,2-*b*]isoxazole (18): Ambersep 900 (OH^- form, 1.6 g) was added to a solution of **17** (456 mg, 0.84 mmol) in anhydrous MeOH (70 mL), and the mixture was stirred overnight. TLC (AcOEt/hexane 3:1) revealed a new slower-running compound (R_f = 0.67). The mixture was filtered and washed with MeOH. The solvent was removed. The residue was flash chromatographed (AcOEt/hexane 3:2, R_f = 0.45) to yield **18** (344 mg, 82%) as a yellow oil. $[\alpha]_D^{27}$ = –36.2 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.18 (m, 15 H, Ar), 4.56–4.46 (m, 6 H, Bn), 4.30–4.23 (m, 1 H, 2-H), 3.98 (dd, *J* = 6.8, 5.1 Hz, 1 H, 5-H), 3.94–3.89 [m, 1 H, C*H*(CH$_3$)OH], 3.85 (t, *J* = 4.9 Hz, 1 H, 4-H), 3.69–3.65 (m, 1 H, 3a-H), 3.60 (dd, *J* = 9.9, 4.5 Hz, 1 H, C*H*$_2$OBn), 3.55 (dd, *J* = 9.9, 5.3 Hz, 1 H, C*H*$_2$OBn), 3.26 (dt, *J* = 11.4, 5.1 Hz, 1 H, 6-H), 2.11 (ddd, *J* = 12.4, 6.6, 3.9 Hz, 1 H, 3-H$_a$), 2.05–2.00 (m, 1 H, 3-H$_b$), 1.68–1.63 [m, 2 H, C*H*$_2$CH(CH$_3$)OH], 1.10 [d, *J* = 6.5 Hz, 3 H, CH(C*H*$_3$)OH] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.0, 140.7, 140.5 (s, Ar), 131.1–130.2 (d, 15 C, Ar), 90.5 (d, C-4), 85.7 (d, C-5), 76.2 (d, C-2), 76.0, 75.2, 74.6 (t, Bn), 72.4 (t, *C*H$_2$OBn), 72.0 (d, C-6), 70.5 (d, C-3a), 67.6 [d, *C*H(CH$_3$)OH], 44.3 [t, *C*H$_2$CH(CH$_3$)OH], 42.6 (t, C-3), 26.4 [q, CH(*C*H$_3$)OH] ppm. IR ($CHCl_3$): ṽ = 3412, 3031, 2931, 2866, 1455, 1103 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{31}H_{38}NO_5$ $[M + H]^+$ 504.2750; found 504.2755.

(1*R*,2*R*,3*R*,5*S*,7*S*,8a*R*)-1,2-Dibenzyloxy-3-(benzyloxymethyl)-7-hydroxy-5-methylindolizidine (19): Iodine (221 mg, 0.87 mmol), triphenylphosphane (198 mg, 0.75 mmol), and imidazole (118 mg, 1.74 mmol) were added under Ar to a stirred solution of **18** (292 mg, 0.58 mmol) in dry THF (25 mL). The mixture was stirred at room temperature for 18 h. TLC monitoring (AcOEt/hexane 3:1) showed the appearance of a new product (R_f = 0.46). A saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (20 mL) was added, and the mixture was stirred at room temperature for 15 min. It was then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were dried with Na_2SO_4, filtered, and concentrated under

reduced pressure. The residue was flash chromatographed (AcOEt/hexane 2:1, R_f = 0.3) to afford **19** (181 mg, 64%) as a yellow oil still containing some impurities. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 15 H, Ar), 4.70–4.56 (m, 6 H, Bn), 3.94–3.89 (m, 1 H, 7-H), 3.85 (br., 1 H, 2-H), 3.78–3.75 (m, 1 H, 1-H), 3.61–3.51 (m, 2 H, CH_2OBn), 3.43–3.41 (m, 2 H, 5-H, 8a-H), 3.29–3.27 (m, 1 H, 3-H), 1.68–1.52 (m, 4 H, 6-H_a, 6-H_b, 8-H_a, 8-H_b) 1.19 (d, J = 6.2 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 141.0, 140.9 (s, Ar), 131.1–130.2 (d, 15 C, Ar), 89.5 (d, C-1), 89.5 (d, C-2), 75.9 (t, Bn), 75.1 (t, *C*H_2OBn), 74.2, 73.9 (t, Bn), 67.8 (d, C-3), 67.6 (d, C-7), 61.3 (d, C-8a), 51.9 (d, C-5), 37.2 (t, 2 C, C-6, C-8), 23.0 (q, Me) ppm. HRMS (NALDI-TOF): calcd. for $C_{31}H_{38}NO_4$ [M + H]$^+$ 488.2801; found 488.2804.

(1*R*,2*R*,3*R*,5*S*,7*S*,8a*R*)-1,2,7-Trihydroxy-3-hydroxymethy-5-methylindolizidine (2): A solution of **19** (98 mg, 0.20 mmol) in MeOH (15 mL) was acidified (conc. HCl, five drops) and hydrogenated (60 psi H_2) in the presence of Pd/C (10%, 30 mg) for 72 h. The catalyst was filtered off, washed with MeOH, and concentrated to give a residue that was retained on a column of Dowex 50WX8 (200–400 mesh). The column was thoroughly washed with MeOH (75 mL), water (75 mL), and then with NH_4OH (1 M, 100 mL) to afford pure **2** (42 mg, 95%) as a viscous yellow oil. $[\alpha]_D^{31}$ = –25.5 (c = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 3.90–3.87 (m, 1 H, 7-H), 3.85–3.84 (m, 1 H, 1-H), 3.72 (dd, J = 5.5, 3.5 Hz, 1 H, 2-H), 3.65 (dd, J = 11.2, 4.3 Hz, 1 H, CH_2OH), 3.60 (dd, J = 11.2, 4.0 Hz, 1 H, CH_2OH), 3.31–3.29 (m, 1 H, 5-H), 3.18–3.15 (m, 1 H, 8a-H), 2.96 (pseudo q, J = 4.3 Hz, 1 H, 3-H), 1.70 (dtd, J = 12.8, 4.2, 1.5 Hz, 8-H_a), 1.64–1.60 (m, 1 H, 6-H_a), 1.56–1.52 (m, 2 H, 6-H_b, 8-H_b), 1.16 (d, J = 6.8 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 84.0 (d, C-1), 83.4 (d, C-2), 70.9 (d, C-3), 66.6 (d, C-7), 64.1 (t, *C*H_2OH), 63.9 (d, C-8a), 50.9 (d, C-5), 36.4 (t, C-6), 36.1 (t, C-8), 21.7 (q, Me) ppm. HRMS (NALDI-TOF): calcd. for $C_{10}H_{20}NO_4$ [M + H]$^+$ 218.1392; found 218.1399.

(2*R*,2′*S*,3a*R*,4*R*,5*R*,6*R*)-2-(2-Acetyloxypropyl)-4,5-dibenzyloxy-6-(benzyloxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (20): A solution of **6** (318 mg, 0.76 mmol) and (*S*)-**16** (0.97 g, 7.6 mmol) in toluene (1.5 mL) was heated at 120 °C under microwave irradiation conditions in a sealed tube. After 3 h, TLC (AcOEt/hexane 3:1) revealed the presence of a new compound of higher R_f (0.67). The solvent was removed, and the residue was flash chromatographed (AcOEt/hexane 1:2, R_f = 0.32) to afford **20** (415 mg, 51%) as a brown oil. $[\alpha]_D^{26}$ = –21.9 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 15 H, Ar), 5.02–4.98 [m, 1 H, C*H*(CH_3)-OAc], 4.63–4.52 (m, 6 H, Bn), 4.13–4.10 (m, 1 H, 2-H), 4.03 (dd, J = 7.5, 4.7 Hz, 1 H, 5-H), 3.88 (t, J = 4.6 Hz, 1 H, 4-H), 3.73 (br. s, 1 H, 3a-H), 3.68 (dd, J = 9.4, 4.7 Hz, 1 H, CH_2OBn), 3.62 (dd, J = 9.5, 4.8 Hz, 1 H, CH_2OBn), 3.29–3.26 (m, 1 H, 6-H), 2.17 (ddd, J = 12.2, 5.9, 3.4 Hz, 1 H, 3-H_a), 2.07–2.01 (m, 1 H, 3-H_b), 1.98 (s, 3 H, CH_3CO), 1.96–1.93 [m, 1 H, CH_2CH(CH_3)OAc], 1.71 [ddd, J = 14.0, 6.3, 4.8 Hz, 1 H, CH_2CH(CH_3)OAc], 1.24 [d, J = 5.7 Hz, 3 H, CH(CH_3)OAc] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (s, CH_3*C*O) 141.0, 140.7, 140.4 (s, Ar), 131.1–130.1 (d, 15 C, Ar), 90.3 (d, C-4), 85.3 (d, C-5), 76.08 (t, Bn), 75.4 (d, C-2) 75.3, 74.6 (t, Bn), 72.4 (t, *C*H_2OBn), 71.8 (d, C-6), 71.3 [d, *C*H(CH_3)OAc], 70.2 (d, C-3a), 43.4 (t, C-3), 41.7 [t, *C*H_2CH(CH_3)OAc], 24.0 (q, *C*H_3CO), 23.0 [q, CH(*C*H_3)OAc] ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3031, 2934, 2860, 1738, 1455, 1373, 1247 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{33}H_{40}NO_6$ [M + H]$^+$ 546.2856; found 546.2861.

(2*R*,2′*S*,3a*R*,4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6-(benzyloxymethyl)-2-(2-hydroxypropyl)-hexahydropyrrolo[1,2-*b*]isoxazole (21): Ambersep 900 (OH^- form, 750 mg) was added to a solution of **20** (214 mg, 0.39 mmol) in anhydrous MeOH (70 mL), and the mixture was stirred overnight. TLC (AcOEt/hexane 3:1) revealed a new slower-running compound (R_f = 0.69). The mixture was filtered and washed with MeOH. The solvent was removed, and the residue was flash chromatographed (AcOEt/hexane 3:2, R_f = 0.46) to yield **21** (147 mg, 75%) as a yellow oil. $[\alpha]_D^{28}$ = –40.3 (c = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 15 H, Ar), 4.62–4.52 (m, 6 H, Bn), 4.28–4.23 (m, 1 H, 2-H), 4.06 (dd, J = 7.0, 5.0 Hz, 1 H, 5-H), 3.96–3.91 [m, 2 H, 4-H, C*H*(CH_3)OH], 3.75–3.72 (m, 1 H, 3a-H), 3.67 (dd, J = 9.5, 4.4 Hz, 1 H, CH_2OBn), 3.63 (dd, J = 9.5, 5.1 Hz, 1 H, CH_2OBn), 3.34–3.31 (m, 1 H, 6-H), 2.20 (ddd, J = 12.3, 6.2, 3.8 Hz, 1 H, 3-H_a), 2.05 (dt, J = 12.3, 8.8 Hz, 1 H, 3-H_b), 1.73–1.70 [m, 2 H, CH_2CH(CH_3)OH], 1.19 [d, J = 6.0 Hz, 3 H, CH(CH_3)OH] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 140.7, 140.4 (s, Ar), 131.1–130.1 (d, 15 C, Ar), 90.3 (d, C-4), 85.6 (d, C-5), 78.2 (d, C-2), 76.1, 75.2, 74.6 (t, Bn), 72.3 (t, *C*H_2OBn), 72.2 (d, C-6), 70.1 (d, C-3a), 69.7 [d, *C*H(CH_3)OH], 45.0 [t, *C*H_2CH(CH_3)OH], 43.5 (t, C-3), 23.0 [q, CH(*C*H_3)OH] ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 2931, 2866, 1455, 1104 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{31}H_{38}NO_5$ [M + H]$^+$ 504.2750; found 504.2749.

(1*R*,2*R*,3*R*,5*R*,7*S*,8a*R*)-1,2-Dibenzyloxy-3-(benzyloxymethyl)-7-hydroxy-5-methylindolizidine (22): Iodine (111 mg, 0.44 mmol), triphenylphosphane (99 mg, 0.38 mmol), and imidazole (59 mg, 0.87 mmol) were added under Ar to a stirred solution of **21** (147 mg, 0.29 mmol) in dry THF (15 mL). The mixture was stirred at room temperature for 18 h. TLC monitoring (AcOEt/hexane 3:1) showed the appearance of a new product (R_f = 0.47). A saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (20 mL) was added, and the mixture was stirred at room temperature for 15 min. It was then extracted with CH_2Cl_2 (3× 100 mL). The combined organic fractions were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC (AcOEt/hexane 2:1, R_f = 0.21) to afford pure **22** (102 mg, 73%) as a yellow oil. $[\alpha]_D^{27}$ = –28.2 (c = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.18 (m, 15 H, Ar), 4.62–4.38 (m, 6 H, Bn), 3.90–3.88 (m, 1 H, 2-H), 3.66–3.65 (m, 1 H, 1-H), 3.63–3.60 (m, 1 H, CH_2OBn), 3.52–3.47 (m, 2 H, 3-H, 7-H), 3.41–3.37 (m, 1 H, CH_2OBn), 2.68–2.64 (m, 1 H, 8a-H), 2.59–2.55 (m, 1 H, 5-H), 2.19–2.16 (m, 1 H, 8-H_a), 1.81–1.78 (m, 1 H, 6-H_a), 1.20–1.13 (m, 2 H, 6-H_b, 8-H_b), 1.10 (d, J = 6.0 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 144.0, 143.9 (s, Ar), 134.1–133.3 (d, 15 C, Ar), 95.1 (d, C-1), 91.8 (d, C-2), 79.3, 77.7, 77.1 (t, Bn), 74. 6 (d, C-7), 71.4 (t, *C*H_2OBn), 68.2 (d, C-8a), 68.0 (d, C-3), 55.1 (d, C-5), 49.2 (t, C-6), 45.5 (t, C-8), 25.8 (q, Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3401, 2930, 2865, 1367, 1455 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{31}H_{38}NO_4$ [M + H]$^+$ 488.2801; found 488.2805.

(1*R*,2*R*,3*R*,5*R*,7*S*,8a*R*)-1,2,7-Trihydroxy-3-hydroxymethyl-5-methylindolizidine (3): A solution of **22** (92 mg, 0.19 mmol) in MeOH (15 mL) was acidified (conc. HCl, five drops) and hydrogenated (60 psi H_2) in the presence of Pd/C (10%, 30 mg) for 72 h. The catalyst was filtered off, washed with MeOH, and the solution was concentrated to give a residue that was retained on a column of Dowex 50WX8 (200–400 mesh). The column was thoroughly washed with MeOH (75 mL), water (75 mL), and then with NH_4OH (1 M, 100 mL) to afford pure **3** (29 mg, 70%) as a viscous yellow oil. $[\alpha]_D^{29}$ = –28.5 (c = 1.25, MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 3.92–3.91 (m, 1 H, 2-H), 3.75 (dd, J = 11.7, 3.8 Hz, 1 H, CH_2OH), 3.59–3.51 (m, 3 H, 1-H, 7-H, CH_2OH), 2.97–2.95 (m, 1 H, 3-H), 2.67–2.64 (m, 1 H, 5-H), 2.59 (dt, J = 11.0, 2.1 Hz, 1 H, 8a-H), 2.06–2.04 (m, 1 H, 8-H_a), 1.84–1.81 (m, 1 H, 6-H_a, 1.07–1.00 (m, 2 H, 6-H_b, 8-H_b), 0.99 (d, J = 5.9 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 84.6 (d, C-1), 82.4 (d, C-2), 70.3 (d, C-7), 68.0 (d, C-3), 65. 7 (d, C-8a), 60.5 (t, *C*H_2OH), 51.6 (d, C-

5), 44.0 (t, C-6), 39.5 (t, C-8), 21.1 (q, Me) ppm. HRMS (NALDI-TOF): calcd. for $C_{10}H_{20}NO_4$ [M + H]$^+$ 218.1392; found 218.1385.

Enzymatic Acetylation of Racemic But-3-en-2-ol: Chirazyme L-2, c.-f., C2 (35 mg) was added to a gently stirred solution of (*R*,*S*)-but-3-en-2-ol (1 g, 13.87 mmol) and vinyl acetate (0.64 mL, 6.9 mmol) in dry Et_2O (8 mL), and the mixture was maintained at room temp. with stirring. The reaction was monitored by GLC analysis, and after 5 h the enzyme was removed by filtration, with thorough washing with ether, and the solvent was evaporated. The residue was subjected to FCC (Et_2O/pentane 1:4) to afford (*R*)-2-*O*-acetyl-but-3-en-2-ol [(*R*)-**24**, 611 mg, 39%, R_f = 0.74, t_R = 6.22 min, 52% *ee*] and (*S*)- but-3-en-2-ol [(*S*)-**23**, 214 mg, 43%, R_f = 0.22, t_R = 3.84 min]. Conventional acetylation of (*S*)-**23** (162 mg, 2.25 mmol) in anhydrous pyridine (1 mL) and Ac_2O (318 μL) gave (*S*)-2-*O*-acetyl-but-3-en-2-ol [(*S*)-**24**, 257 mg, 100%, t_R = 6.11 min, 40% *ee*].

(1′*R*,2*R*,3a*R*,4*R*,5*R*,6*R*)-2-(1-Acetyloxyethyl)-4,5-dibenzyloxy-6-(benzyloxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (25): A solution of **6** (167 mg, 0.40 mmol) and (*R*)-**24** (229 mg, 2 mmol) in toluene (0.8 mL) was heated at 120 °C under microwave irradiation conditions in a sealed tube. After 3 h, TLC (AcOEt/hexane 3:1) revealed the presence of a new compound of higher R_f (0.73). The solvent was removed, and the residue was flash chromatographed (AcOEt/hexane 1:4, R_f = 0.13) to yield **25** (130 mg, 61%) as a colorless syrup. $[\alpha]_D^{27}$ = –18.6 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 15 H, Ar), 5.00–4.95 [m, 1 H, C*H*(CH_3)-OAc], 4.63–4.54 (m, 6 H, Bn), 4.23 (td, *J* = 7.6, 5.5 Hz, 1 H, 2-H), 4.07 (dd, *J* = 6.0, 3.1 Hz, 1 H, 5-H), 3.96 (pseudo t, *J* = 3.7 Hz, 1 H, 4-H), 3.76–3.74 (m, 2 H, 3a-H, CH_2OBn), 3.65 (dd, *J* = 9.9, 6.5 Hz, 1 H, CH_2OBn), 3.35 (td, *J* = 5.9, 5.3 Hz,1 H, 6-H), 2.16–2.13 (m, 2 H, 3-H_a, 3-H_b), 2.05 (s, 3 H, CH_3CO), 1.25 [d, *J* = 6.5 Hz, 3 H, CH(CH_3)OAc] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (s, CH_3*C*O), 138.5, 138.1, 137.9 (s, Ar), 128.5–127.6 (d, 15 C, Ar), 87.2 (d, C-4), 83.3 (d, C-5), 77.9 (d, C-2) 73.5, 72.4, 71.9 (t, Bn), 70.5 [d, *C*H(CH_3)OAc], 70.2 (t, *C*H_2OBn), 69.9 (d, C-6), 68.3 (d, C-3a), 36.2 (t, C-3), 21.3 (q, *C*H_3Ac), 16.5 [q, CH(*C*H_3)-OAc] ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2920, 2859, 1743, 1454, 1242 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{32}H_{38}NO_6$ [M + H]$^+$ 532.2699; found 532.2703.

(1′*R*,2*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6-benzyloxymethyl-2-(1-hydroxyethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (26): Ambersep 900 (OH^- form, 750 mg) was added to a solution of **25** (215 mg, 0.40 mmol) in anhydrous MeOH (70 mL), and the mixture was stirred overnight. TLC (AcOEt/hexane 3:1) then revealed a new slower-running compound (R_f = 0.48). The mixture was filtered and washed with MeOH. The solvent was removed, and the residue was purified by FCC (AcOEt/hexane 1:1, R_f = 0.21) to yield **26** (198 mg, 100%) as a colorless oil. $[\alpha]_D^{29}$ = –48.9 (*c* = 0.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 15 H, Ar), 4.62–4.50 (m, 6 H, Bn), 4.07 (dd, *J* = 5.8, 4.3 Hz, 1 H, 5-H), 4.02 (td, *J* = 6.9, 5.8 Hz, 1 H, 2-H), 3.96 (pseudo t, *J* = 4.3 Hz, 1 H, 4-H), 3.77–3.74 (m, 1 H, 3a-H), 3.70–3.66 [m, 2 H, CH_2OBn, C*H*(CH_3)OH], 3.62–3.59 (m, 1 H, 6-H), 3.38–3.35 (m, 1 H, CH_2OBn), 2.20–2.17 (m, 2 H, 3-H_a, 3-H_b), 1.18 [d, *J* = 6.4 Hz, 3 H, CH(CH_3)OH] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 140.6, 140.4 (s, Ar), 131.1–130.2 (d, 15 C, Ar), 90.2 (d, C-4), 86.6 (d, C-5), 83.7 (d, C-2), 76.0, 75.0, 74.5 (t, Bn), 72.5 (d, C-6), 72.3 (t, *C*H_2OBn), 71.9 [d, *C*H(CH_3)OH], 71.2 (d, C-3a), 39.2 (t, C-3), 22.3 [q, CH(*C*H_3)OH] ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3437, 2929, 2867, 1455, 1366, 1103 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{30}H_{36}NO_5$ [M + H]$^+$ 490.2593; found 490.2597.

(1′*R*,2*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6-(benzyloxymethyl)-2-(1-methylsulfonyloxyethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (27): Pyridine (1.9 mL) and MsCl (51 μL, 0.64 mmol) were added to a stirred solution of **26** (155 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (7 mL). The reaction mixture was stirred at room temp. for 18 h. TLC (AcOEt/hexane 3:1) showed the absence of **26** and the presence of a faster-moving compound (R_f = 0.84). MeOH (5 mL) was added, and the reaction mixture was stirred for 20 min and then concentrated to a residue that was subjected to FCC (AcOEt/hexane 1:2) to give **27** (170 mg, 95%) as a white syrup. $[\alpha]_D^{31}$ = –14.4 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 15 H, Ar), 4.65 [pseudo quint, *J* = 6.6 Hz, 1 H, C*H*(CH_3)OMs], 4.57–4.49 (m, 6 H, Bn), 4.20 (q, *J* = 7.3 Hz, 1 H, 2-H), 4.03 (dd, *J* = 5.6, 4.3 Hz, 1 H, 5-H), 3.95 (t, *J* = 4.3 Hz, 4-H), 3.78–3.74 (m, 1 H, 3a-H), 3.64 (dd, *J* = 9.9, 5.4 Hz, 1 H, CH_2OBn), 3.57 (dd, *J* = 9.9, 5.7 Hz, 1 H, CH_2OBn), 3.37 (pseudo q, *J* = 5.5 Hz, 1 H, 6-H), 3.00 (s, 3 H, Ms), 2.25–2.08 (m, 2 H, 3-H_a, 3-H_b), 1.37 [d, *J* = 6.5 Hz, 3 H, CH(CH_3)OMs] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 137.8, 137.6 (s, Ar), 128.5–127.6 (d, 15 C, Ar), 87.4 (d, C-4), 83.8 (d, C-5), 79.5 [d, *C*H(CH_3)OMs], 78.4 (d, C-2), 73.4, 72.0, 72.3 (t, Bn), 70.1 (d, C-6), 69.9 (t, *C*H_2OBn), 68.3 (d, C-3a), 38.3 (q, Ms) 36.4 (t, C-3), 18.7 [q, CH(*C*H_3)OMs] ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2925, 2856, 1454, 1357, 1101 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{31}H_{38}NO_7S$ [M + H]$^+$ 568.2369; found 568.2360.

(1*R*,2*R*,3*R*,5*S*,6*R*,7a*R*)-1,2-Dibenzyloxy-3-(benzyloxymethyl)-6-hydroxy-5-methylpyrrolizidine (28): A mixture of **27** (162 mg, 0.28 mmol) and Zn dust (148 mg) in AcOH/H_2O 9:1 (3 mL) was heated to 60 °C for 4 h. TLC monitoring (AcOEt/hexane 2:1) showed the absence of **27** and the presence of a lower R_f (= 0.22) compound. The reaction mixture was filtered through cotton with washing with AcOEt. The solvent was washed with a saturated solution of Na_2CO_3 and then evaporated. The residue was purified by FCC (AcOEt/hexane 2:1) to afford **28** (63 mg, 47%). $[\alpha]_D^{27}$ = +1.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 15 H, Ar), 4.65–4.50 (m, 6 H, Bn), 4.13 (t, *J* = 4.3 Hz, 1 H, 2-H), 4.06 (t, *J* = 4.3 Hz, 1 H, 1-H), 3.89 (q, *J* = 6.2 Hz, 1 H, 6-H), 3.61–3.56 (m, 1 H, 7a-H), 3.51 (d, *J* = 6.4 Hz, 2 H, CH_2OBn), 3.38 (td, *J* = 6.4, 4.5 Hz, 1 H, 3-H), 3.01 (quint, *J* = 6.2 Hz, 1 H, 5-H), 2.36 (ddd, *J* = 12.8, 7.9, 6.3 Hz, 1 H, 7-H_a), 1.80 (dt, *J* = 12.9, 6.3 Hz, 1 H, 7-H_b), 1.12 (d, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5 138.2, 138.0 (s, Ar), 128.4–127.5 (d, 15 C, Ar), 89.8 (d, C-1), 86.1 (d, C-2), 78.6 (d, C-6), 73.2, 72.1, 71.8 (t, 4 C, Bn, *C*H_2OBn), 69.3 (d, C-5), 68.9 (d, C-3), 66.2 (d, C-7a), 38.9 (t, C-7), 19.5 (q, Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3396, 3063, 2865, 1454, 1101 cm^{-1}. HRMS (NALDI-TOF): calcd. for $C_{30}H_{36}NO_4$ [M + H]$^+$ 474.2644; found 474.2650.

(1*R*,2*R*,3*R*,5*S*,6*R*,7a*R*)-1,2,6-Trihydroxy-3-hydroxymethyl-5-methylpyrrolizidine (4): A solution of **28** (59 mg, 0.12 mmol) in MeOH (10 mL) was acidified (conc. HCl, five drops) and hydrogenated (60 psi H_2) in the presence of Pd/C (10%, 25 mg) for 48 h. The catalyst was filtered off, washed with MeOH, and the solution was concentrated to give a residue that was retained on a column of Dowex 50WX8 (200–400 mesh). The column was thoroughly washed with MeOH (50 mL), water (50 mL), and then with NH_4OH (1 M, 75 mL) to afford pure **4** (20 mg, 80%) as a viscous yellow oil. $[\alpha]_D^{24}$ = +7.0 (*c* = 0.70, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.87 (pseudo t, *J* = 8.1 Hz, 1 H, 1-H), 3.77 (q, *J* = 6.7 Hz; 1 H, 6-H), 3.69 (pseudo t, *J* = 8.1 Hz, 1 H, 2-H), 3.55 (dd, *J* = 11.7, 4.8 Hz, 1 H, CH_2OH), 3.48 (dd, *J* = 11.7, 5.9 Hz, 1 H, CH_2OH), 3.05 (td, *J* = 8.3, 5.9 Hz, 1 H, 7a-H), 2.83 (dt, *J* = 8.3, 5.4 Hz, 1 H, 3-H), 2.79–2.74 (m, 1 H, 5-H), 2.23 (ddd, *J* = 13.1, 7.9, 6.8 Hz, 1 H, 7-H_a), 1.68–1.62 (m, 1 H, 7-H_b), 0.94 (d, *J* = 6.4 Hz, 3 H, Me) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 80.5 (d, C-1), 77.8 (d, C-2), 77.0 (d, C-6), 68.8 (d, C-3), 67.5 (d, C-5), 63.3 (d, C-7a), 62.1

(t, CH_2OH), 35.2 (t, C-7), 16.5 (q, Me) ppm. HRMS (NALDI-TOF): calcd. for $C_9H_{18}NO_4$ $[M + H]^+$ 204.1236; found 204.1237.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H NMR and ^{13}C NMR spectra of all new compounds, the synthesis of compounds **9**, and tetraacetates **1a** and **2a** of indolizidines **1** and **2**, respectively, GLC analyses of enzymatic acetylation, and glycosidase inhibition assays.

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[1] a) A. Kato, I. Adachi, M. Miyauchi, K. Ikeda, T. Komae, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, M. R. Wormald, G. W. J. Fleet, N. Asano, *Carbohydr. Res.* **1999**, *316*, 95–103; b) N. Asano, H. Kuroi, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, I. Adachi, A. A. Watson, R. J. Nash, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1–8; c) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; d) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295; e) T. Yamashita, K. Yasuda, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, G. W. J. Fleet, N. Asano, *J. Nat. Prod.* **2002**, *65*, 1875–1881; f) N. Asano, K. Ikeda, M. Kasahara, Y. Arai, H. Kizu, *J. Nat. Prod.* **2004**, *67*, 846–850; g) A. Kato, N. Kato, I. Adachi, J. Hollinshead, G. W. J. Fleet, C. Kuriyama, K. Ikeda, N. Asano, R. J. Nash, *J. Nat. Prod.* **2007**, *70*, 993–997.

[2] A. Michalik, J. Hollinshead, L. Jones, G. W. J. Fleet, C.-Y. Yu, X.-G. Hu, R. Van Well, G. Horne, F. X. Wilson, A. Kato, S. F. Jenkinson, R. J. Nash, *Phytochemistry Lett.* **2010**, *3*, 136–138.

[3] a) P. Compain, O. R. Martin (Eds.), *Iminosugars: from synthesis to therapeutic applications*, Wiley-VCH, Weinheim, Germany **2007**; b) G. Horne, F. X. Wilson, *Prog. Med. Chem.* **2011**, *50*, 135–176.

[4] Reviews: a) H. Yoda, *Curr. Org. Chem.* **2002**, *6*, 223–243; b) T. Ayad, Y. Genisson, M. Baltas, *Curr. Org. Chem.* **2004**, *8*, 1211–1233; c) S. G. Pyne, M. Tang, *Curr. Org. Chem.* **2005**, *9*, 1393–1418; d) B. G. Davis, *Tetrahedron: Asymmetry* **2009**, *20*, 652–671; e) A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Eur. J.* **2009**, *15*, 7808–7821; f) B. L. Stocker, E. D. Dangerfield, A. L. Win-Mason, G. W. Haslett, M. S. M. Timmer, *Eur. J. Org. Chem.* **2010**, 1615–1637; g) T. Ritthiwigrom, C. W. G. Au, S. G. Pyne, *Curr. Org. Synth.* **2012**, *9*, 583–612.

[5] Unambiguous total syntheses of some hyacinthacines have served in some cases to establish their structures, replacing previous incorrect structural assignments. For relevant examples, see: a) T. J. Donohoe, R. E. Thomas, M. D. Cheeseman, C. L. Rigby, G. Bhalay, D. Linney, *Org. Lett.* **2008**, *10*, 3615–3618; b) T. Sengoku, Y. Satoh, M. Takahashi, H. Yoda, *Tetrahedron Lett.* **2009**, *50*, 4937–4940; c) C. W. G. Au, R. J. Nash, S. G. Pyne, *Chem. Commun.* **2010**, *46*, 713; d) W. Zhang, K. Sato, A. Kato, Y.-M. Jia, X.-G. Hu, F. X. Wilson, R. van Well, G. Horne, G. W. J. Fleet, R. J. Nash, C.-Y. Yu, *Org. Lett.* **2011**, *13*, 4414–4417.

[6] a) F. Cardona, C. Parmeggiani, E. Faggi, C. Bonaccini, P. Gratteri, L. Sim, T. M. Gloster, S. Roberts, G. J. Davies, D. R. Rose, A. Goti, *Chem. Eur. J.* **2009**, *15*, 1627–1636; b) G. D'Adamio, A. Goti, C. Parmeggiani, E. Moreno-Clavijo, I. Robina, F. Cardona, *Eur. J. Org. Chem.* **2011**, 7155–7162; c) F. Cardona, G. Moreno, F. Guarna, P. Vogel, C. Schuetz, P. Merino, A. Goti, *J. Org. Chem.* **2005**, *70*, 6552–6555; d) I. Delso, T. Tejero, A. Goti, P. Merino, *Tetrahedron* **2010**, *66*, 1220–1227; e) ref.[4e], and references cited therein.

[7] a) J. A. Tamayo, F. Franco, F. Sánchez-Cantalejo, *Eur. J. Org. Chem.* **2011**, 7182–7188; b) J. A. Tamayo, F. Franco, F. Sánchez-Cantalejo, *Tetrahedron* **2010**, *66*, 7262–7267, and references cited therein.

[8] J. A. Tamayo, F. Franco, D. Lo Re, F. Sánchez-Cantalejo, *J. Org. Chem.* **2009**, *74*, 5679–5682.

[9] For other recent syntheses of hyacinthacines B, see: a) T. Sengoku, T. Satoh, M. Ashima, M. Takahashi, H. Yoda, *Tetrahedron* **2008**, *64*, 8052–8058; b) P. V. Reddy, P. Koos, A. Veyron, A. E. Greene, P. Delair, *Synlett* **2009**, *7*, 1141–1143; c) ref.[4g]; d) see ref.[5c].

[10] For different synthetic strategies affording 5-methylated pyrrolizidines and indolizidines, see: a) C. Ribes, E. Falomir, M. Carda, J. A. Marco, *Tetrahedron* **2009**, *65*, 6965–6971; b) X.-G. Hu, Y.-M. Jia, J. Xiang, C.-Y. Yu, *Synlett* **2010**, 982–986; c) W.-J. Liu, J.-L. Ye, P.-Q. Huang, *Org. Biomol. Chem.* **2010**, *8*, 2085–2091; d) X.-G. Hu, B. Bartholomew, R. J. Nash, F. X. Wilson, G. W. J. Fleet, S. Nakagawa, A. Kato, Y.-M. Jia, R. van Well, C.-Y. Yu, *Org. Lett.* **2010**, *12*, 2562–2565; e) ref.[5a]; f) ref.[5c–5d]; g) ref.[7].

[11] F. Cardona, E. Faggi, F. Liguori, M. Cacciarini, A. Goti, *Tetrahedron Lett.* **2003**, *44*, 2315–2318.

[12] a) F. Cardona, A. Goti, S. Picasso, P. Vogel, A. Brandi, *J. Carbohydr. Chem.* **2000**, *19*, 585–601; b) F. M. Cordero, P. Bonanno, B. B. Khairnar, F. Cardona, A. Brandi, B. Macchi, A. Minutolo, S. Grelli, A. Mastino, *ChemPlusChem* **2012**, *77*, 224–233.

[13] A. D. Morozov, I. A. Kirilyuk, D. A. Komarov, A. Goti, I. Y. Bagryanskaya, N. V. Kuratieva, I. A. Grigor'ev, *J. Org. Chem.* **2012**, *77*, 10688–10698.

[14] F. Cardona, G. Isoldi, F. Sansone, A. Casnati, A. Goti, *J. Org. Chem.* **2012**, *77*, 6980–6988.

[15] J. J. Tufariello, *Acc. Chem. Res.* **1979**, *12*, 396–403.

[16] a) I. Izquierdo, M. T. Plaza, M. Rodriguez, J. A. Tamayo, *Tetrahedron: Asymmetry* **2000**, *11*, 1749–1756; b) Y. Naoshima, M. Kamezawa, T. Kimura, F. Okimoto, M. Watanabe, H. Tachibana, T. Ohtani, *Recent Res. Dev. Org. Bioorg. Chem.* **2001**, *4*, 1–16; c) I. Izquierdo, M. T. Plaza, M. Rodriguez, J. A. Tamayo, *Synthesis* **2003**, 1357–1360; d) I. Izquierdo, M. T. Plaza, M. Rodriguez, J. A. Tamayo, *Eur. J. Org. Chem.* **2002**, 309–317; e) S. Adachi, *Handbook of Industrial Biocatalysis*, Taylor & Francis/CRC, Boca Raton, FL, **2005**, pp. 10/1–10/15; f) I. Izquierdo, M. T. Plaza, J. A. Tamayo, F. Franco, F. Sánchez-Cantalejo, *Tetrahedron* **2008**, *64*, 4993–4998.

[17] The *ee* values of (*R*)-*O*-acetyl-pent-4-en-2-ol [(*R*)-**16**, 86%] and (*S*)-*O*-acetyl-pent-4-en-2-ol [(*S*)-**16**, 82%] were determined by chiral GLC (see the Supporting Information).

[18] J. Shao, J.-S. Yang, *J. Org. Chem.* **2012**, *77*, 7891–7900.

[19] The *ee*s of (*R*)-*O*-acetyl-but-3-en-2-ol [(*R*)-**24**, 52%] and (*S*)-*O*-acetyl-but-3-en-2-ol [(*S*)-**24**, 42%] were determined by chiral GLC (see the Supporting Information).

[20] PLF from *Pseudomonas fluorescens*, Chirazyme L-3, c. f., C2 from *Candida rugosa*.

[21] a) R. Saul, J. P. Chambers, R. J. Molyneux, A. D. Elbein, *Arch. Biochem. Biophys.* **1983**, *221*, 593–597; b) A. Brandi, S. Cicchi, F. M. Cordero, R. Frignoli, A. Goti, S. Picasso, P. Vogel, *J. Org. Chem.* **1995**, *60*, 6806–6812.

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