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Total Synthesis of (+)-Hyacinthacine A_1, (+)-7a-*epi*-Hyacinthacine A_1, (6*R*)-6-Hydroxyhyacinthacine A_1 and (6*S*)-6-Hydroxy-7a-*epi*-hyacinthacine A_1

Giampiero D'Adamio,[a] Andrea Goti,*[a] Camilla Parmeggiani,[a] Elena Moreno-Clavijo,[b] Inmaculada Robina,[b] and Francesca Cardona*[a]

Keywords: Natural products / Total synthesis / Alkaloids / Nitrogen heterocycles / Cycloaddition / Enzyme inhibitors / Biological activity

The total synthesis of natural (+)-hyacinthacine A_1 (**6**), (+)-7a-*epi*-hyacinthacine A_1 (**7**) and their 6-hydroxy analogues **21** and **16** was achieved using a nitrone cycloaddition strategy with D-ribose-derived cyclic nitrone **8** as the dipole and *tert*-butyl acrylate as the dipolarophile. After separation of the adducts, reductive cleavage of the N–O bond followed by lactam reduction and deprotection afforded the two non-natural hydroxy analogues in excellent yields. The synthesis of (+)-hyacinthacine A_1 (**6**) and of (+)-7a-*epi*-hyacinthacine A_1 (**7**), which required deoxygenation at C(6), was accomplished by DIBAL-H reduction of mesylate derivatives of the pyrrolizidinols **20** and **15**, respectively. Evaluation of the synthesized compounds against a panel of 12 commercially available glycosidases showed that hyacinthacine A_1 (**6**) and its (6*R*)-hydroxy analogue **21** are good inhibitors of amyloglucosidase; the non-natural compound **21** is also a strong inhibitor of β-glucosidase, while **6** showed only moderate inhibition. The non-natural (+)-7a-*epi*-hyacinthacine A_1 (**7**) is a moderate inhibitor of amyloglucosidase and α-L-fucosidase; the presence of the (6*S*)-hydroxy group in **16** led to diminished activity.

Introduction

In 1988, Fleet and co-workers reported the isolation of alexine (**1**, Figure 1) from the seedpods of *Alexia leiopetala*,[1] the first example of a novel type of polyhydroxylated pyrrolizidine alkaloid bearing a carbon substituent at C(3). Since then, several related polyhydroxylated pyrrolizidines have been isolated from various plant families (*eg*, compounds **2**–**4**, Figure 1), and this structural motif has proven to be a rich source of glycosidase inhibitors.[2] Iminosugar glycosidase inhibitors are valuable targets for synthesis[3] since they are the focus of growing attention as possible therapeutic agents for the treatment of tumor metastasis, viral infections, as antidiabetic agents and in the oral treatment of lysosomal storage disorders.[4] Our group recently achieved the total synthesis of a number of these natural alkaloids, including hyacinthacine A_2 (**2**), casuarine (**3**), (–)-uniflorine A (**4**) and their structural analogues using a nitrone cycloaddition strategy[3d] and a D-arabinose derived nitrone **5** (Scheme 1) as the key building block.[5] Their activity as inhibitors of commercial and human glycosidases and trehalases have been evaluated.[6]

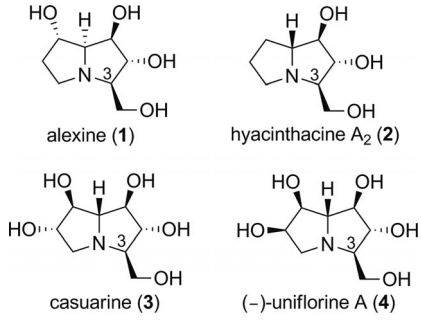
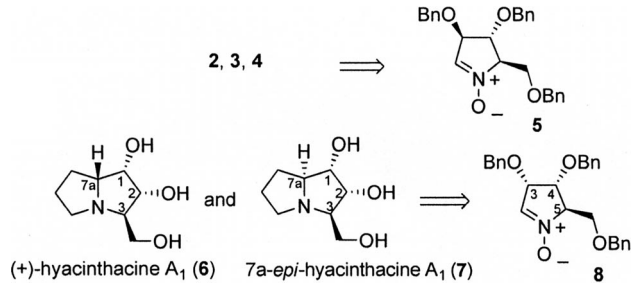


Figure 1. Naturally occurring pyrrolizidine alkaloids.



Scheme 1. Nitrone **8** as the key building block for the synthesis of (+)-hyacinthacine A_1 (**6**) and 7a-*epi*-hyacinthacine A_1 (**7**).

[a] Dipartimento di Chimica "Ugo Schiff", Università di Firenze, Polo Scientifico e Tecnologico,
via della Lastruccia 3–13, 50019 Sesto Fiorentino, Firenze, Italia
Fax: 39-055-457-3531
E-mail: francesca.cardona@unifi.it
[b] Departmento de Química Orgánica, Facultad de Química, Universidad de Sevilla,
c/ Prof. García González 1, 41012 Sevilla, Spain

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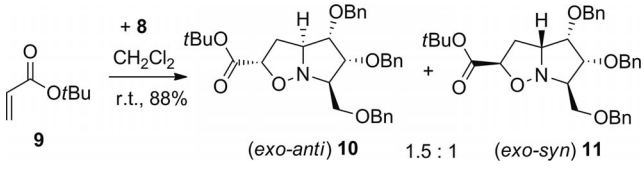
The natural product (+)-hyacinthacine A_1 (**6**, Scheme 1) was isolated in 2000 from the bulbs of *Muscari armeniacum* (Hyacinthaceae) in less than 0.0005% yield.[2a] Since then, several total syntheses of this alkaloid have been reported, either using the chiral pool approach[7] or the enantioselective non chiron approach.[8,9] This alkaloid was found to be a good inhibitor of β-galactosidase from rat intestinal lactase (IC_{50} = 4.4 μM) and a moderate inhibitor of α-L-fucosidase from rat epididymis (IC_{50} = 46 μM).[2a] It also is a moderate inhibitor of amyloglucosidase from *Aspergillus niger* (IC_{50} = 25 μM)[2a] although in our hands, potent inhibition of the latter enzyme was measured (see below).

Based on our previous findings in the total synthesis of indolizidine and pyrrolizidine alkaloids, we envisaged that the nitrone cycloaddition strategy could be suited for the total synthesis of pyrrolizidine alkaloids bearing the C(1)–C(2) *cis* stereochemistry of (+)-hyacinthacine A_1 if the D-ribose derived nitrone **8** was employed (Scheme 1).[10]

The main challenge of this synthetic strategy rested in the stereoselectivity of the cycloaddition reaction to nitrone **8**, which had not been investigated before. We report here our results leading to the total synthesis of (+)-hyacinthacine A_1 (**6**), 7a-*epi*-hyacinthacine A_1 (**7**), and two new 6-hydroxy analogues **16** and **21**. The biological activity of the synthesized compounds was then evaluated using a panel of 12 commercially available glycosidases.

Results and Discussion

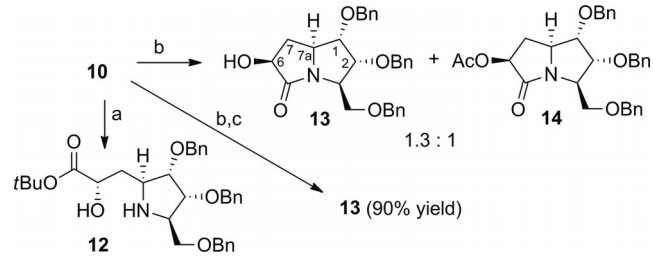
Nitrone **8** was synthesized from commercially available 2,3,5-tri-*O*-benzyl-D-ribofuranose as recently reported in the literature.[10a] The cycloaddition reaction of nitrone **8** was performed in dichloromethane at room temperature using *tert*-butylacrylate (**9**) as the dipolarophile (Scheme 2). As reported for analogous cycloadditions to nitrone **5**,[5] the reaction was completely regioselective and only 5-substituted isoxazolidines were generated. However, in considering the issue of stereoselectivity, two main adducts **10** and **11** were formed; both result from an *exo*-approach of the dipolarophile (Scheme 2).



Scheme 2. The cycloaddition reaction.

Major adduct **10**, whose structure was confirmed on the basis of 1D NOESY NMR spectra, results from an *exo* approach of acrylate *anti* to the vicinal OBn of the nitrone. Significant formation of adduct **11**, resulting from an *exo-syn* approach of the dipolarophile to nitrone **8**, was observed. A similar *syn* approach had not been observed before in cycloadditions to nitrone **5**. This result can be explained by the peculiar stereochemistry of **8**. Indeed, a *syn* approach to the vicinal OBn at C(3) of the nitrone occurs *anti* with respect to the CH_2OBn substituent at C(5), which clearly plays a crucial role in determining stereoselectivity on steric grounds. The two adducts **10** and **11** were obtained in a 1.5:1 ratio,[11,12] and were isolated in 50% and 38% yield, respectively. Their structures were unambiguously assigned on the basis of ^1H NMR, ^{13}C NMR, COSY, HSQC and 1D NOESY spectra.

This modest diastereoselectivity[13] proved, nevertheless, to be convenient for the synthesis of both 7a-*epi*-hyacinthacine A_1 (**7**), (+)-hyacinthacine A_1 (**6**) and their structural analogues. Reductive N-O ring cleavage, performed by heating a mixture of **10** with Zn in CH_3COOH/H_2O, 9:1 as reported for similar cycloadducts to nitrone **5**,[5,6] gave erratic results. Indeed, using the usual temperature conditions (60–65 °C), only formation of the open chain pyrrolidine **12** was observed, as clearly shown by the ^1H NMR spectrum (Scheme 3). Ring closure and formation of desired lactam **13** was achieved by refluxing the mixture for 3 d, but concomitant formation of acetylated lactam **14** was also observed (see Supporting Information). Treatment of the crude mixture with the strongly basic resin Ambersep 900 OH afforded, in good overall yield, target compound **13** in 90% yield from **10** (Scheme 3). The structure of **13**, confirmatory of the structure of its precursor **10**, was assigned on the basis of ^1H NMR, ^{13}C NMR, COSY, HSQC and 1D NOESY spectra. In particular, 1D NOESY spectra showed strong NOESY correlation peaks between H(6) and H(7a) and between H(1) and one of the two hydrogen atoms at C(7).



Scheme 3. Synthesis of lactam **13**. Reaction conditions: a) Zn, CH_3COOH/H_2O, 9:1, 60–65 °C, 3 h; b) Zn, CH_3COOH/H_2O, 9:1, reflux, 3 d; c) Ambersep 900 OH, MeOH, room temp., 10 h, 90% over two steps from **10**.

Reduction of the C=O bond of **13** was achieved with $LiAlH_4$ in refluxing THF, to afford protected pyrrolizidine **15** in 82% yield (Scheme 4); subsequent removal of the benzyl groups, performed by catalytic hydrogenolysis under acidic conditions, afforded non-natural (6*S*)-6-hydroxy-7a-*epi*-hyacinthacine A_1 (**16**) in excellent overall yield after ion exchange chromatography of the corresponding ammonium salt (Scheme 4).

Deoxygenation at C(6) of lactam **13**, required for the synthesis of 7a-*epi*-hyacinthacine A_1 (**7**), was not trivial. First, a radical deoxygenation, namely the Barton–McCombie reaction,[14] previously useful in our hands for the deoxygenation of indolizidine alkaloids,[15] was attempted on a thiocarbonylimidazolide derivative, readily obtained from **13** in 97% yield (see Supporting Information). However, treat-

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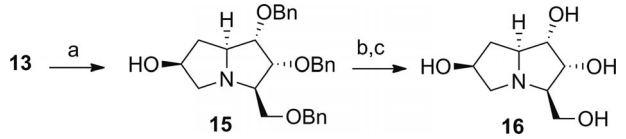
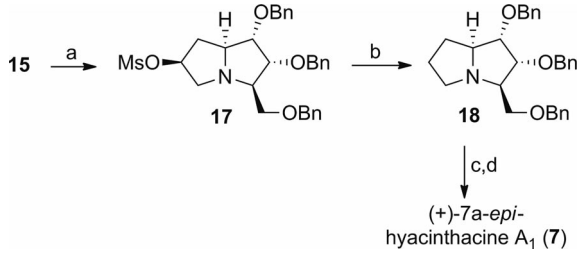


Scheme 4. Synthesis of (6*S*)-6-hydroxy-7a-*epi*-hyacinthacine A_1 (**16**). Reaction conditions: a) $LiAlH_4$, dry THF, reflux, 2 h, 82%; b) H_2, MeOH, HCl, room temp., 3 d; c) DOWEX 50WX8–200, 100% over two steps.

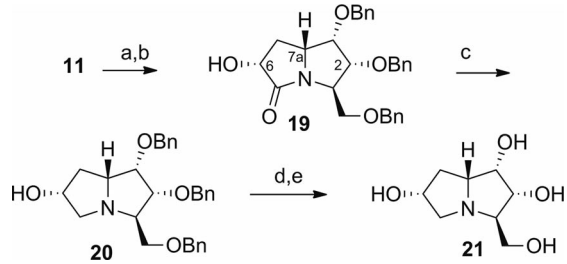
ment of the thiocarbonylimidazolide with Bu_3SnH in refluxing THF afforded only a complex mixture of products. Attempts to deoxygenate the corresponding mesylate obtained from **13** in 82% yield (see Supporting Information) with $LiAlH_4$ in refluxing THF, successful for the deoxygenation of similar pyrrolizidines,[5,6e] failed, giving predominantly alcohol **15**. Inspired by these observations we then changed our strategy by first reducing the double bond to afford secondary alcohol **15** which was then transformed into corresponding mesylate derivative **17** in 88% yield (Scheme 5).



Scheme 5. Synthesis of (+)-7a-*epi*-hyacinthacine A_1 (**7**). Reaction conditions: a) MsCl, NEt_3, CH_2Cl_2, room temp., 2 h, 88%; b) DIBAL-H, toluene, reflux, 3 h, 27%; c) H_2, MeOH, HCl, room temp., 2 d, 100% over two steps; d) DOWEX 50WX8–200.

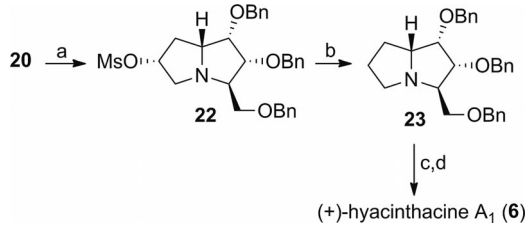
Reduction of mesylate **17** with the less reactive DIBAL-H in refluxing toluene afforded desired pyrrolizidine **18**, albeit in 27% yield. Final catalytic hydrogenation gave (+)-7a-*epi*-hyacinthacine A_1 (**7**) as its hydrochloride salt in quantitative yield. Due to the limited amount of compound available, only a small portion of the hydrochloride salt was passed on ion exchange resin DOWEX 50WX8–200 obtaining analytically pure **7** for biological tests (Scheme 5).[16,17]

Starting from minor *exo-syn* cycloadduct **11**, an analogous reaction sequence gave (6*R*)-6-hydroxyhyacinthacine A_1 (**21**) (Scheme 6). N-O reductive cleavage of the isoxazolidine adduct and ring closure to lactam **19** was easier, requiring heating in a refluxing 9:1 CH_3COOH/H_2O mixture for only 24 h instead of the 3 d required for the major adduct **10**; using these conditions, compound **19** was obtained in 92% isolated yield after treatment with the strongly basic resin Ambersep 900 OH. Such treatment was found to be convenient since, as previously observed with major isomer **10** (Scheme 3), partial acetylation of **19** occurred under the reaction conditions. The structure of **19** (and thus, indirectly, of cycloadduct **11**) was assigned on the basis of ^1H NMR, ^{13}C NMR, COSY, HSQC and 1D NOESY spectra. In particular, 1D NOESY spectra showed strong NOESY correlation peaks between H(6) and H(7a) and between H(7a) and H(2). Reduction of the lactam C=O in **19** and further catalytic hydrogenolysis of compound **20** afforded (6*R*)-6-hydroxyhyacinthacine A_1 (**21**) in 96% yield after ion exchange chromatography of the corresponding ammonium salt (Scheme 6).



Scheme 6. Synthesis of (6*R*)-6-hydroxyhyacinthacine A_1 (**21**). Reaction conditions: a) Zn, CH_3COOH/H_2O, 9:1, reflux, 24 h; b) Ambersep 900 OH, MeOH, room temp., 10 h, 92% over two steps from **11**; c) $LiAlH_4$, dry THF, reflux, 2 h, 79%; d) H_2, MeOH, HCl, room temp., 3 d; e) DOWEX 50WX8–200, 96% over two steps.

In a fashion analogous to previous observations with lactam **13**, mesylation of lactam **19** (see Supporting Information) and subsequent treatment with $LiAlH_4$ in refluxing THF afforded predominantly pyrrolizidinol **20**. Thus, the total synthesis of (+)-hyacinthacine A_1 (**6**) was undertaken from pure **20**. Reaction of **20** with MsCl and NEt_3 in dry CH_2Cl_2 gave mesylate **22** in 100% yield (Scheme 7). Reaction with DIBAL-H in toluene at reflux afforded compound **23** in 56% yield. Finally, catalytic hydrogenation and treatment with the basic resin gave (+)-hyacinthacine A_1 (**6**) in 95% yield (Scheme 7). The spectroscopic data and physicochemical properties of the synthesized compound were identical to those of natural (+)-hyacinthacine A_1 (**6**). Synthetic **6** showed a specific optical rotation of $[\alpha]_D^{24}$ = +35.6 (*c* = 0.32, H_2O) that is in good agreement with that reported for the natural sample: $[\alpha]_D$ = +38.2 (*c* = 0.23, H_2O).[2a]



Scheme 7. Synthesis of (+)-7a-hyacinthacine A_1 (**6**). Reaction conditions: a) MsCl, NEt_3, CH_2Cl_2, room temp., 2 h, 100%; b) DIBAL-H, toluene, reflux, 3 h, 56%; c) H_2, MeOH, HCl, room temp., 2 d; d) DOWEX 50WX8–200, 95% over two steps.

Biological Evaluation of Hyacinthacine Derivatives towards Glycosidases

(+)-Hyacinthacine A_1 (**6**), 7a-*epi*-hyacinthacine A_1 (**7**), and the two new structural analogues **16** and **21** were assayed for their ability to inhibit 12 commercially available

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glycosidases.[18] At 1 mM concentration and under enzyme-optimized pH none of the compounds inhibited α-galactosidase from coffee beans, β-galactosidase from *Escherichia coli*, α-glucosidase from yeast and rice, α-mannosidase from Jack beans, β-mannosidase from snail, β-xylosidase from *Aspergillus niger* and β-*N*-acetylglucosaminidase from Jack beans. Table 1 summarizes the inhibitory activity measured towards α-L-fucosidase from bovine kidney, β-galactosidase from *Aspergillus orizae*, amyloglucosidase from *Aspergillus niger* and β-glucosidase from almonds. (+)-Hyacinthacine A_1 (**6**) showed a strong mixed type of inhibition (see Supporting Information for Lineweaver–Burk plot) towards amyloglucosidase from *Aspergillus niger*. The much better inhibitory activity for **6** found relative to that described previously by Asano and co-workers[2a] (IC_{50} one order of magnitude lower) may be attributable to the use of different assay conditions. Compound **6** also displayed moderate inhibitory activity against β-glucosidase from almonds and weak inhibitory activity against α-L-fucosidase and β-galactosidase. The non-natural (6*R*)-hydroxy analogue **21** was also found to be a strong inhibitor of amyloglucosidase from *A. niger*; competitive inhibition was observed in this case. Compound **21** also was found to display potent competitive inhibition of β-glucosidase from almonds.

Table 1. Inhibitory activities of hyacinthacine derivatives **6**, **7**, **16** and **21** against 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]

Entry	Comp.	α-L-Fuc-ase	β-Gal-ase	Amyloglucosidase	β-Glc-ase
1	**6**	17	43	99 (2.3); **3.9** (M)	84; (180)
2	**7**	64	–	75 (346)	–
3	**16**	60	–	58	–
4	**21**	–	–	99 (7.7); **3.6** (C)	99 (14.5); **7.7** (C)

[a] For conditions of measurements see ref.[18] and the Supporting Information. [b] (C): competitive inhibition (M): mixed type of inhibition from Lineweaver–Burk plots, ni: no inhibition at 1 mM concentration of the inhibitor. [c] α-L-Fuc-ase: α-L-fucosidase from bovine kidney, β-Gal-ase: β-galactosidase from *Aspergillus orizae*, amyloglucosidase is from *Aspergillus niger*, β-Glc-ase: β-glucosidase from almonds.

The inversion of configuration at C-7a in **6** to give 7a-*epi*-hyacinthacine A_1 (**7**) diminished inhibitory potential against amyloglucosidase from *Aspergillus niger*, abolished activity against β-glucosidase from almonds, and slightly improved activity against α-L-fucosidase. The presence of the hydroxy group at C-6 (compound **16**) was found to be detrimental for activity against amyloglucosidase from *Aspergillus niger*, while slight inhibition against α-L-fucosidase was found to be retained.

Conclusions

In conclusion, the total synthesis of (+)-hyacinthacine A_1 (**6**), (+)-7a-*epi*-hyacinthacine A_1 (**7**) and two new 6-hydroxy analogues **16** and **21** was achieved by the nitrone cycloaddition strategy employing a D-ribose-derived nitrone **8** and *tert*-butyl acrylate (**9**) as dipolarophile. In our assays, (+)-hyacinthacine A_1 (**6**) showed a strong mixed inhibition of amyloglucosidase from *Aspergillus niger* and moderate inhibitory activity against β-glucosidase from almonds. Its non-natural (6*R*)-hydroxy analogue **21** was a strong competitive inhibitor of both amyloglucosidase from *Aspergillus niger* and β-glucosidase from almonds. The C-7a epimer, 7a-*epi*-hyacinthacine A_1 (**7**) displayed only moderate inhibition of amyloglucosidase from *Aspergillus niger*. The presence of the hydroxy group at C-6 (compound **16**) in this case was detrimental to enzyme inhibition activity.

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}) and column chromatography was carried out on Silica Gel 60 (32–63 μm). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. ^{1}H NMR spectra were recorded with a Varian Mercury-400 or Varian INOVA-400. ^{13}C NMR spectra were recorded with a Varian Gemini-200. Infrared spectra were recorded with a Perkin–Elmer Spectrum BX FT-IR System spectrophotometer. Mass spectra were recorded with a QMD 1000 Carlo Erba instrument by direct inlet; relative percentages are shown in brackets. ESI full MS were recorded with a Thermo LTQ instrument by direct inlet; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer. Optical rotation measurements were performed with a JASCO DIP370 polarimeter.

Cycloaddition of Nitrone 8 to Dipolarophile 9: A solution of nitrone **8** (700 mg, 1.68 mmol) and *tert*-butylacrylate (**9**, 366 μL, 2.52 mmol) in 1.7 mL CH_2Cl_2 was stirred at room temp. under nitrogen atmosphere for 3 d, monitoring the reaction by TLC analysis (AcOEt/PE, 3:1). At completion of the reaction, the solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (eluent AcOEt/PE, 1:3) affording pure **10** (R_f = 0.23, 463 mg, 0.85 mmol, 50% yield) as a white solid, and pure **11** (R_f = 0.14, 346 mg, 0.63 mmol, 38% yield) as a colourless oil.

***tert*-Butyl (2*S*,3a*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)-methyl]-hexahydro-pyrrolo[1,2-*b*]isoxazole-2-carboxylate (10):** M.p. 58–59 °C. $[\alpha]_D^{24}$ = +43.6 (*c* = 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 15 H, Ar), 4.71–4.60 (AB system, *J* = 12.2 Hz, 2 H, Bn), 4.61–4.51 (AB system, *J* = 11.7 Hz, 4 H, Bn), 4.28 (dd, *J* = 8.3, 4.8 Hz, 1 H, 2-H), 4.00 (dd, *J* = 7.8, 5.9 Hz, 1 H, 5-H), 3.95 (dd, *J* = 9.2, 3.9 Hz, 1 H, 8-Ha), 3.85–3.76 (m, 2 H, 3a-H, 6-H), 3.80 (dd, *J* = 9.2, 5.4 Hz, 1 H, 8-Hb), 3.70 (dd, *J* = 5.9, 4.4 Hz, 1 H, 4-H), 2.74 (ddd, *J* = 12.7, 7.8, 4.9 Hz, 1 H, 3-Ha), 2.31 (ddd, *J* = 12.7, 8.8, 2.4 Hz, 1 H, 3-Hb), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.4 (s, C=O), 138.5, 138.0, 137.8 (s, C-Ar), 128.4–127.3 (d, 15 C, C-Ar), 81.8 (d, C-4), 81.8 (s, O*t*Bu), 79.3 (d, C-5), 75.0 (d, C-2), 73.2, 72.5, 72.2 (t, C-Bn), 70.8 (d, C-6), 69.9 (d, C-3a), 67.9 (t, C-8), 37.7 (t, C-3), 28.2 (q, 3 C, *t*Bu) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3518, 3088, 3065, 3032, 3004, 2869, 1741, 1454, 1368, 1241, 1153, 1027 cm^{-1}. MS (ESI): *m*/*z* (%) = 568.24 (51) $[M + Na]^+$. $C_{33}H_{39}NO_6$ (545.67): calcd. C 72.64, H 7.20, N 2.57; found C 72.69, H 7.36, N 2.56.

***tert*-Butyl (2*R*,3a*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)-methyl]-hexahydro-pyrrolo[1,2-*b*]isoxazole-2-carboxylate (11):** $[\alpha]_D^{24}$ = –20.8 (*c* = 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 15 H, Ar), 4.71 (d, *J* = 12.2 Hz, 1 H, Bn), 4.61–4.49 (m, 5 H, Bn), 4.56 (t, *J* = 7.8 Hz, 1 H, 2-H), 3.99 (t, *J* = 5.4 Hz, 1 H,

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4-H), 3.91 (t, *J* = 5.4 Hz, 1 H, 5-H), 3.92–3.86 (m, 1 H, 3a-H), 3.65 (dd, *J* = 9.8, 3.9 Hz, 1 H, 8-Ha), 3.57 (dd, *J* = 9.8, 5.4 Hz, 1 H, 8-Hb), 3.44–3.41 (m, 1 H, 6-H), 2.91 (ddd, *J* = 12.2, 7.3, 4.4 Hz, 1 H, 3-Ha), 2.21 (ddd, *J* = 12.2, 9.3, 2.9 Hz, 1 H, 3-Hb), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.4 (s, C=O), 138.2, 138.0, 137.9 (s, C-Ar), 128.4–127.5 (d, 15 C, C-Ar), 81.8 (s, O*t*Bu), 78.5 (d, C-5) 77.8 (d, C-4), 76.5 (d, C-2), 73.5, 73.0, 72.4 (t, C-Bn), 70.5 (d, C-6), 69.9 (t, C-8), 65.9 (d, C-3a), 34.6 (t, C-3), 28.2 (q, 3 C, *t*Bu) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3472, 3018, 2997, 1738, 1521, 1453, 1368, 1219, 1156, 1047 cm^{-1}. MS (ESI): *m*/*z* (%) = 568.25 (100) $[M + Na]^+$. $C_{33}H_{39}NO_6$ (545.67): calcd. C 72.64, H 7.20, N 2.57; found C 72.34, H 7.63, N 2.47.

N–O Ring Cleavage of Cycloadduct 10: To a solution of **10** (162 mg, 0.30 mmol) in 4 mL of a 9:1 CH_3COOH/H_2O mixture, Zn dust (78 mg, 1.12 mmol) was added. The suspension was heated at reflux and stirred for 3 d then a TLC analysis (AcOEt/PE, 3:1) showed the disappearance of the starting material (R_f = 0.80) and formation of two new products (R_f = 0.30 and 0.58). After cooling to room temp. and filtration through cotton the mixture was concentrated at reduced pressure and then saturated aqueous solution of $NaHCO_3$ was added at 0 °C until basic pH. After extraction with AcOEt (3 × 25 mL), the organic layers were dried on Na_2SO_4 and concentrated at reduced pressure affording a crude brown oil (140 mg) that resulted, after ^{1}H NMR 200 MHz spectra analysis, in a mixture of the desired product **13** and its acetylated derivative in 1.5:1 ratio. This crude was then stirred at room temp. with Ambersep 900 OH (500 mg) in 20 mL of MeOH for 10 h, then a TLC analysis (AcOEt/PE, 3:1) showed conversion of the two products (R_f = 0.30 and 0.58) in **13** (R_f = 0.30). The resin was filtered off and the solvent removed under reduced pressure affording **13** (128 mg, 0.27 mmol, 90% yield over two steps) as a pale yellow oil enough pure to be used in the next steps. A small amount of the product was purified by flash column chromatography (eluent AcOEt/PE, 2:1) affording analytically pure material.

(1*S*,2*R*,3*R*,6*S*,7a*S*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]-6-hydroxyhexahydro-5*H*-pyrrolizin-5-one (13): $[\alpha]_D^{24}$ = –62.0 (*c* = 0.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 15 H, Ar), 4.63–4.39 (m, 7 H, Bn, 6-H), 4.09 (d, *J* = 4.4 Hz, 1 H, 2-H), 4.03 (dd, *J* = 9.8, 4.4 Hz, 1 H, 8-Ha), 3.98 (dd, *J* = 9.3, 4.9 Hz, 1 H, 7a-H), 3.87–3.85 (m, 1 H, 3-H), 3.74 (dd, *J* = 9.3, 4.4 Hz, 1 H, 1-H), 3.69 (dd, *J* = 9.8, 2.4 Hz, 1 H, 8-Hb), 2.68 (ddd, *J* = 11.7, 6.8, 4.9 Hz, 1 H, 7-Ha), 1.63 (dt, *J* = 11.2, 9.8 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4 (s, C=O), 137.7, 137.6, 137.5 (s, C-Ar), 128.4–127.7 (d, 15 C, C-Ar), 82.1 (d, C-2), 82.0 (d, C-1), 73.7 (d, C-6) 73.5, 72.2, 72.1 (t, C-Bn), 65.8 (t, C-8), 61.0 (d, C-3), 58.7 (d, C-7a), 37.0 (t, C-7) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3354, 3088, 3066, 3031, 3009, 2926, 2867, 1690, 1454, 1261, 1116, 1027 cm^{-1}. MS (ESI): *m*/*z* (%) = 496.42 (61) $[M + Na]^+$. $C_{29}H_{31}NO_5$ (473.56): calcd. C 73.55, H 6.60, N 2.96; found C 73.24, H 7.04, N 3.36.

(1*S*,2*R*,3*R*,6*R*,7a*S*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]-6-hydroxyhexahydro-1*H*-pyrrolizine (15): A solution of **13** (145 mg, 0.31 mmol) in 10 mL of dry THF was stirred under nitrogen atmosphere at 0 °C and $LiAlH_4$ (1 M solution in THF, 1.22 mL, 1.22 mmol) was added drop wise. The mixture was raised to room temp. and refluxed for 2 h, until TLC analysis (AcOEt/PE, 3:1) showed the disappearance of the starting material (R_f = 0.33) and the formation of a new product (R_f = 0.00). Reaction was then quenched with 2 mL of a saturated aqueous solution of Na_2SO_4 at 0 °C, filtered through Celite® and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (CH_2Cl_2/MeOH, 10:1), affording pure **15** (R_f = 0.22, 116 mg, 0.25 mmol, 82% yield) as a white solid; m.p. 146–146.5 °C. $[\alpha]_D^{22}$ = +38.3 (*c* = 0.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 15 H, Ar), 4.62–4.48 (AB system, *J* = 12.2 Hz, 2 H, Bn), 4.60–4.52 (AB system, *J* = 11.7 Hz, 2 H, Bn), 4.53–4.44 (AB system, *J* = 11.7 Hz, 2 H, Bn), 4.36–4.31 (m, 1 H, 6-H), 4.06 (t, *J* = 5.4 Hz, 1 H, 2-H), 3.79 (t, *J* = 4.9 Hz, 1 H, 1-H), 3.77–3.73 (m, 1 H, 8-Ha), 3.68–3.62 (m, 1 H, 7a-H), 3.60–3.54 (m, 2 H, Hb-8, 3-H), 3.04 (dd, *J* = 10.7, 4.9 Hz, 1 H, 5-Ha), 2.96–2.90 (m, 1 H, 5-Hb), 2.55 (br. s, 1 H, OH), 2.24 (ddd, *J* = 13.6, 8.3, 5.8 Hz, 1 H, 7-Ha), 1.52 (dt, *J* = 13.2, 5.4 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.1 (s, 2 C, C-Ar), 137.5 (s, C-Ar), 128.4–127.6 (d, 15 C, C-Ar), 81.5 (d, C-1) 78.8 (d, C-2), 73.4 (t, C-Bn), 72.6 (d, C-6), 72.3, 71.7 (t, C-Bn), 67.9 (d, C-7a), 67.4 (t, C-8), 63.6 (d, C-3), 55.6 (t, C-5) 39.3 (t, C-7) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3426, 3090, 3064, 3031, 2913, 2866, 1453, 1358, 1206, 1114, 1045 cm^{-1}. MS (ESI): *m*/*z* (%) = 460.32 (50) $[M + H]^+$. $C_{29}H_{33}NO_4$ (459.24): calcd. C 75.79, H 7.24, N 3.05; found C 75.37, H 7.31, N 3.56.

(1*S*,2*R*,3*R*,6*R*,7a*S*)-1,2,6-Trihydroxy-3-(hydroxymethyl)-hexahydro-1*H*-pyrrolizine (16): To a solution of **15** (67 mg, 0.15 mmol) in MeOH (20 mL), 10% Pd on carbon (35 mg) and 37% HCl (2 drops) were added while stirring under nitrogen atmosphere, then the mixture was stirred under hydrogen atmosphere at room temp. for 3 d. After that a TLC analysis (CH_2Cl_2/MeOH, 3:1) showed the disappearance of starting material (R_f = 0.76) and formation of a new product (R_f = 0.17), the mixture was filtered through Celite® and the solvent was removed under reduced pressure affording a crude yellow oil (40 mg). The free amine was obtained by passing the hydrochloride salt through a Dowex 50WX8 ion-exchange resin. Elution with ammonia 6% afforded free base **16** (29 mg, 0.15 mmol, 100% yield over two steps) as a pale yellow solid; m.p. 111–112 °C. $[\alpha]_D^{26}$ = +35.5 (*c* = 1.22, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.25 (pseudo quint, *J* = 6.3 Hz, 1 H, 6-H), 4.02 (dd, *J* = 8.3, 5.4 Hz, 1 H, 2-H), 3.88 (t, *J* = 5.4 Hz, 1 H, 1-H), 3.86 (dd, *J* = 11.7, 3.9 Hz, 1 H, 8-Ha), 3.79 (dd, *J* = 12.2, 7.8 Hz, 1 H, 8-Hb), 3.36 (td, *J* = 7.8, 3.4 Hz, 1 H, 7a-H), 3.16 (td, *J* = 8.3, 3.9 Hz, 1 H, 3-H), 3.00 (dd, *J* = 9.8, 5.4 Hz, 1 H, 5-Ha), 2.77 (dd, *J* = 9.8, 6.3 Hz, 1 H, 5-Hb), 2.32 (ddd, *J* = 13.2, 8.3, 6.3 Hz, 1 H, 7-Ha), 1.55 (dt, *J* = 13.2, 7.3 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 75.1 (d, C-1) 70.5 (d, C-2), 70.2 (d, C-6), 68.0 (d, C-7a), 65.2 (d, C-3), 58.9 (t, C-8), 52.9 (t, C-5) 36.9 (t, C-7) ppm. ^{1}H NMR (400 MHz, D_2O): δ = 4.19 (dq, *J* = 7.8, 6.3 Hz, 1 H, 6-H), 3.99 (dd, *J* = 9.3, 5.4 Hz, 1 H, 2-H), 3.88 (dd, *J* = 5.4, 2.9 Hz, 1 H, 1-H), 3.78–3.69 (m, 2 H, 8-Ha, 8-Hb), 3.25 (td, *J* = 7.8, 2.9 Hz, 1 H, 7a-H), 3.03 (ddd, *J* = 9.3, 7.8, 5.4 Hz, 1 H, 3-H), 2.93 (dd, *J* = 9.8, 5.9 Hz, 1 H, 5-Ha), 2.55 (dd, *J* = 9.8, 8.3 Hz, 1 H, 5-Hb), 2.32 (dt, *J* = 13.2, 7.3 Hz, 1 H, 7-Ha), 1.44 (dt, *J* = 13.2, 7.8 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 75.7 (d, C-1), 70.9 (d, C-2), 70.6 (d, C-6), 67.9 (d, C-7a), 64.8 (d, C-3), 59.6 (t, C-8), 52.8 (t, C-5), 36.9 (t, C-7) ppm. MS (ESI): *m*/*z* (%) = 190.17 (100) $[M + H]^+$. $C_8H_{15}NO_4$ (189.21): calcd. C 50.78, H 7.99, N 7.40; found C 50.43, H 8.26, N 7.22.

(1*S*,2*R*,3*R*,6*S*,7a*S*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]-6-(methylsulfonyloxy)-hexahydro-1*H*-pyrrolizine (17): To a stirred solution of **15** (56 mg, 0.12 mmol) in dry CH_2Cl_2 (10 mL), NEt_3 (50 μL, 0.36 mmol) was added under nitrogen atmosphere, and, at 0 °C, MsCl (12 μL, 0.16 mmol) was added dropwise. The solution was left stirring at room temp. for 2 h. TLC analysis (CH_2Cl_2/MeOH, 3:1) showed disappearance of the starting material (R_f = 0.63) and formation of a new product (R_f = 0.75). Then 20 mL of H_2O were added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the organic layers were dried on Na_2SO_4. Filtration on cotton and evaporation under reduced pressure afforded crude **17** that was purified by flash column chromatography (eluent

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CH_2Cl_2/MeOH, 10:1) affording pure **17** as a yellow oil, (R_f = 0.37, 57 mg, 0.11 mmol, 88% yield). $[\alpha]_D^{26}$ = +23.7 (c = 1.04, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 15 H, Ar), 5.10 (ddd, J = 12.2, 11.2, 5.9 Hz, 1 H, 6-H) 4.65–4.50 (AB system, J = 12.2 Hz, 2 H, Bn), 4.57–4.46 (AB system, J = 12.2 Hz, 2 H, Bn), 4.53–4.50 (AB system, J = 11.7 Hz, 2 H, Bn), 3.91 (dd, J = 6.3, 5.9 Hz, 1 H, 2-H), 3.72 (t, J = 5.4 Hz, 1 H, 1-H), 3.64 (dd, J = 10.2, 3.4 Hz, 1 H, 8-Ha), 3.56 (dd, J = 10.2, 6.3 Hz, 1 H, 8-Hb), 3.51–3.49 (m, 1 H, 7a-H), 3.48 (dt, J = 3.9, 2.9 Hz, 1 H, 3-H), 3.12 (d, J = 5.4 Hz, 2 H, 5-H), 2.81 (s, 3 H, Ms), 2.43 (ddd, J = 13.7, 7.8, 6.8 Hz, 1 H, 7-Ha), 1.80 (dt, J = 13.7, 6.3 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.0, 137.9, 137.8 (s, 3 C, C-Ar), 128.7–127.7 (d, 15 C, C-Ar), 80.9 (d, C-6) 80.9 (d, C-1), 78.5 (d, C-2), 73.3, 72.2, 71.9 (t, C-Bn), 68.2 (t, C-8), 67.3 (d, C-7a), 63.9 (d, C-3), 52.8 (t, C-5), 38.1 (q, Ms), 36.2 (t, C-7) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3087, 3065, 3031, 2867, 1495, 1453, 1362, 1177, 1118, 1027 cm^{-1}. MS (ESI): m/z (%) = 538.33 (100) $[M + H]^+$. $C_{30}H_{35}NO_6S$ (537.22): calcd. C 67.02, H 6.56, N 2.61; found C 67.03, H 6.51, N 2.68.

(1*S*,2*R*,3*R*,7a*S*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]hexahydro-1*H*-pyrrolizine (18): A solution of **17** (57 mg, 0.11 mmol) in 4 mL of dry toluene was stirred under nitrogen atmosphere at 0 °C and DIBAL-H (1 M solution in CH_2Cl_2, 0.53 mL, 0.53 mmol) was added dropwise. The mixture was raised to room temp. and refluxed for 3 h, until TLC analysis (AcOEt) showed the disappearance of the starting material (R_f = 0.32) and formation of a new product (R_f = 0.00). Reaction was then quenched with 0.5 mL of a saturated aqueous solution of Na_2SO_4 at 0 °C, filtered through Celite® and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 10:1), affording pure **18** (R_f = 0.41, 13 mg, 0.03 mmol, 27% yield) as a yellow oil. $[\alpha]_D^{26}$ = +49.1 (c = 0.87, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.19 (m, 15 H, Ar), 4.56–4.39 (m, 6 H, Bn), 3.89 (dd, J = 8.3, 4.9 Hz, 1 H, 2-H), 3.86–3.80 (m, 1 H, 7a-H), 3.76 (dd, J = 11.2, 2.4 Hz, 1 H, 8-Ha), 3.74–3.71 (m, 1 H, 3-H), 3.61 (dd, J = 11.2, 5.9 Hz, 1 H, 8-Hb), 3.58 (dd, J = 4.9, 2.9 Hz, 1 H, 1-H), 3.16–3.06 (m, 1 H, 5-Ha), 2.92–2.82 (m, 1 H, 5-Hb), 2.09–2.02 (m, 1 H, 7-Ha), 1.84–1.78 (m, 2 H, Ha-6 and Hb-6), 1.35–1.25 (m, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.3 (s, Ar), 137.2 (s, 2 C, Ar), 128.1–127.4 (d, 15 C, C-Ar), 79.1 (d, C-1) 77.4 (d, C-2), 73.1 (d, C-Bn), 71.9 (t, C-Bn), 71.3 (t, C-Bn), 68.4 (d, C-7a), 66.3 (t, C-8), 62.1 (d, C-3), 48.4 (t, C-5), 29.7 (t, C-7), 26.2 (t, C-6) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3153, 3088, 3065, 3030, 2901, 2868, 1467, 1454, 1381, 1207, 1097 cm^{-1}. MS (ESI): m/z (%) = 444.50 (100) $[M + H]^+$. $C_{29}H_{33}NO_3$ (443.58): calcd. C 78.52, H 7.50, N 3.16; found C 78.67, H 7.12, N 3.01.

(1*S*,2*R*,3*R*,7a*S*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2-diol (7): To a solution of **18** (26 mg, 0.06 mmol) in 20 mL of MeOH 13 mg of 10% Pd on carbon and 2 drops of 37% HCl were added while stirring under a nitrogen atmosphere, then the mixture was stirred under a hydrogen atmosphere at room temp. for 2 d. After that a TLC analysis (CH_2Cl_2/MeOH, 5:1) showed the disappearance of starting material (R_f = 0.71) and formation of a new product (R_f = 0.00), the mixture was filtered through Celite® and the solvent was removed under reduced pressure affording quantitatively the hydrochloride salt of **7** (13 mg, 0.06 mmol, 100% yield over two steps) as a waxy yellow solid. $[\alpha]_D^{30}$ = +56.5 (c = 0.12, H_2O). ^1H NMR (400 MHz, CD_3OD): δ = 4.16 (dd, J = 10.2, 4.3 Hz, 1 H, 2-H), 4.04–3.96 (m, 2 H, 1-H, 7a-H), 3.97 (dd, J = 12.4, 3.1 Hz, 1 H, 8-Ha), 3.86 (dd, J = 12.4, 9.3 Hz, 1 H, 8-Hb), 3.75 (td, J = 10.1, 3.5 Hz, 1 H, 3-H), 3.49 (ddd, J = 11.7, 6.7, 2.0 Hz, 1 H, 5-Ha), 3.38 (td, J = 11.3, 5.8 Hz, 1 H, 5-Hb), 2.39–2.32 (m, 1 H, 7-Ha), 2.18–2.11 (m, 1 H, 6-Ha), 1.93–1.79 (m, 1 H, 6-Hb), 1.71 (dtd, J = 12.9, 10.9, 6.6 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 72.3 (d, C-7a) 72.1 (d, C-1), 68.7 (d, C-2), 64.3 (d, C-3), 56.0 (t, C-8), 47.8 (t, C-5) 27.3 (t, C-7), 24.5 (t, C-6) ppm. ^1H NMR (400 MHz, D_2O): δ = 4.17 (dd, J = 10.5, 4.3 Hz, 1 H, 2-H), 4.07 (d, J = 4.3 Hz, 1 H, 1-H), 4.02–3.98 (m, 1 H, 7a-H), 3.93 (dd, J = 13.3, 3.5 Hz, 1 H, 8-Ha), 3.83 (dd, J = 13.3, 9.3 Hz, 1 H, 8-Hb), 3.70 (td, J = 9.7, 3.5 Hz, 1 H, 3-H), 3.46–3.42 (m, 1 H, 5-Ha), 3.18 (td, J = 11.7, 5.9 Hz, 1 H, 5-Hb), 2.33–2.25 (m, 1 H, 7-Ha), 2.09–2.00 (m, 1 H, 6-Ha), 1.76 (ddd, J = 12.9, 11.7, 6.6 Hz, 1 H, 6-Hb), 1.60 (ddd, J = 12.8, 11.3, 6.6 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 72.1 (d, C-7a), 72.0 (d, C-1), 68.5 (d, C-2), 63.3 (d, C-3), 56.3 (t, C-8), 48.2 (t, C-5), 27.7 (t, C-7), 24.6 (t, C-6) ppm. MS-EI (70 eV): m/z (%) = 142 (99), 96 (100), 70 (68). The free amine **7** was obtained by passing the hydrochloride salt through a Dowex 50WX8 ion-exchange resin, eluting with 6% ammonia. $C_8H_{15}NO_3$ (173.21): calcd. C 55.47, H 8.73, N 8.09; found C 55.36, H 8.71, N 7.96.

N–O Ring Cleavage of Cycloadduct 11: To a solution of **11** (224 mg, 0.41 mmol) in 4 mL of a 9:1 CH_3COOH/H_2O mixture, Zn dust (107 mg, 1.64 mmol) was added. The suspension was heated at reflux and stirred for 24 h then a TLC analysis (AcOEt/PE, 3:1) showed the disappearance of the starting material (R_f = 0.84) and formation of two new products (R_f = 0.28 and 0.68). After cooling to room temp. and filtration through cotton the mixture was concentrated at reduced pressure and then saturated aqueous solution of $NaHCO_3$ was added at 0 °C until basic pH. After extraction with AcOEt (3 × 25 mL), the organic layers were dried on Na_2SO_4 and concentrated at reduced pressure affording a crude brown oil (194 mg) resulting, after ^1H NMR 200 MHz spectra analysis, a mixture of the desired product **19** and of its acetylated derivative. This crude material was stirred at room temp. with Ambersep 900 OH (600 mg) in 20 mL of MeOH for 10 h, then a TLC analysis (AcOEt/PE, 3:1) showed conversion of the two products (R_f = 0.38 and 0.60) in **19** (R_f = 0.38). The resin was filtered off and the solvent removed under reduced pressure affording **19** (178 mg, 0.38 mmol, 92% yield over two steps) as a colourless oil sufficiently pure to be used in subsequent steps. A small amount of the product was purified by flash column chromatography (eluent AcOEt/PE, 2:1).

(1*S*,2*R*,3*R*,6*R*,7a*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-6-hydroxyhexahydro-5*H*-pyrrolizin-5-one (19): $[\alpha]_D^{25}$ = +19.7 (c = 1.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.12 (m, 15 H, Ar), 4.71–4.54 (AB system, J = 12.2 Hz, 2 H, Bn), 4.51–4.29 (AB system, J = 11.7 Hz, 2 H, Bn), 4.42–4.35 (AB system, J = 12.2 Hz, 2 H, Bn), 4.43–4.37 (m, 1 H, 6-H), 4.28 (dd, J = 9.3, 2.9 Hz, 1 H, 2-H), 3.88–3.80 (m, 2 H, 3-H, Ha-8), 3.82 (dd, J = 9.8, 2.9 Hz, 1 H, 1-H), 3.70–3.65 (m, 1 H, 7a-H), 3.51 (dd, J = 10.2, 2.0 Hz, 1 H, 8-Hb), 2.36–2.29 (m, 1 H, 7-Ha), 2.20–2.10 (m, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.0 (s, C=O), 137.9, 137.8, 137.6 (s, C-Ar), 128.4–127.5 (d, 15 C, C-Ar), 82.0 (d, C-2), 74.9 (d, C-1), 73.5, 73.4, 72.9 (t, C-Bn), 71.5 (d, C-6), 67.5 (t, C-8), 59.0 (d, C-7a), 57.2 (d, C-3), 30.6 (t, C-7) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3373, 3088, 3066, 3030, 2868, 1693, 1454, 1361, 1120, 1044 cm^{-1}. MS (ESI): m/z (%) = 496.36(12) $[M + Na]^+$. $C_{29}H_{31}NO_5$ (473.56): calcd. C 73.55, H 6.60, N 2.96; found C 73.28, H 6.89, N 2.73.

(1*S*,2*R*,3*R*,6*S*,7a*R*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]-6-hydroxyhexahydro-1*H*-pyrrolizine (20): A solution of **19** (178 mg, 0.38 mmol) in 12 mL of dry THF was stirred under nitrogen atmosphere at 0 °C and $LiAlH_4$ (1 M solution in THF, 1.52 mL, 1.52 mmol) was added dropwise. The mixture was raised to room temp. and refluxed for 2 h, until TLC analysis (AcOEt/PE, 3:1) showed the disappearance of the starting material (R_f = 0.29) and

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formation of a new product (R_f = 0.00). The reaction was then quenched with 2 mL of a saturated aqueous solution of Na_2SO_4 at 0 °C, filtered through Celite® and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (CH_2Cl_2/MeOH, 10:1), affording pure **20** (R_f = 0.35, 138 mg, 0.30 mmol, 79% yield) as a white solid. mp: 98.5–99 °C. $[\alpha]_D^{22}$ = +35.3 (*c* = 0.89, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.19 (m, 15 H, Ar), 4.86 (d, *J* = 12.2 Hz, 1 H, Bn), 4.54 (d, *J* = 11.7 Hz, 2 H, Bn), 4.55–4.43 (AB system, *J* = 11.7 Hz, 2 H, Bn), 4.43 (d, *J* = 12.2 Hz, 1 H, Bn), 4.20 (d, *J* = 9.8 Hz, 1 H, OH), 4.13–4.07 (m, 1 H, 6-H), 3.93 (dd, *J* = 9.3, 3.4 Hz, 1 H, 2-H), 3.87 (t, *J* = 3.9 Hz, 1 H, 1-H), 3.66 (dt, *J* = 9.3, 3.4 Hz, 1 H, 7a-H), 3.56 (dd, *J* = 9.8, 3.4 Hz, 1 H, 8-Ha), 3.46 (dd, *J* = 9.8, 4.9 Hz, 1 H, 8-Hb), 3.36 (ddd, *J* = 8.7, 4.9, 2.9 Hz, 1 H, 3-H), 2.99 (dd, *J* = 12.7, 3.9 Hz, 1 H, 5-Ha), 2.91 (d, *J* = 12.7 Hz, 1 H, 5-Hb), 1.99 (dt, *J* = 14.1, 1.5 Hz, 1 H, 7-Ha), 1.92 (ddd, *J* = 14.1, 9.3, 4.9 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.4, 137.7, 137.3 (s, C-Ar), 128.5–127.4 (d, 15 C, C-Ar), 82.4 (d, C-2) 77.5 (d, C-1), 74.0, 73.4, 73.3 (t, C-Bn), 73.2 (d, C-6), 71.2 (t, C-8), 67.8 (d, C-3), 65.2 (d, C-7a), 63.0 (t, C-5) 34.9 (t, C-7) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3423, 3088, 3065, 3031, 2939, 2862, 1496, 1453, 1362, 1208, 1136, 1066 cm^{-1}. MS (ESI): *m*/*z* (%) = 460.39 (100) [M + H]$^+$, 482.38 (75) [M + Na]$^+$. $C_{29}H_{33}NO_4$ (459.24): calcd. C 75.79, H 7.24, N 3.05; found C 76.03, H 7.52, N 3.44.

(1*S*,2*R*,3*R*,6*S*,7a*R*)-1,2,6-Trihydroxy-3-(hydroxymethyl)-hexahydro-1*H*-pyrrolizine (21): To a solution of **20** (107 mg, 0.23 mmol) in 20 mL of MeOH, 54 mg of 10% Pd on carbon and 2 drops of HCl 37% were added while stirring under nitrogen atmosphere, then the mixture was stirred under hydrogen atmosphere at room temp. for 3 d. After that a TLC analysis (CH_2Cl_2/MeOH, 10:1) showed the disappearance of starting material (R_f = 0.57) and formation of a new product (R_f = 0.00), the mixture was filtered through Celite® and the solvent was removed under reduced pressure affording a crude yellow oil (72 mg). The free amine was obtained by passing the hydrochloride salt through a Dowex 50WX8 ion-exchange resin. Elution with ammonia 6% afforded free base **21** (41 mg, 0.22 mmol, 96%) as a yellow oil. $[\alpha]_D^{26}$ = +50.5 (*c* = 1.03, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 4.28 (dq, *J* = 5.4, 4.9 Hz, 1 H, 6-H), 3.87 (dd, *J* = 7.8, 3.9 Hz, 1 H, 1-H), 3.84 (dd, *J* = 9.8, 3.9 Hz, 1 H, 2-H), 3.78 (dd, *J* = 11.2, 3.4 Hz, 1 H, 8-Ha), 3.64 (dt, *J* = 8.8, 3.9 Hz, 1 H, 7a-H), 3.55 (dd, *J* = 11.2, 6.3 Hz, 1 H, 8-Hb), 3.08 (dd, *J* = 11.7, 4.4 Hz, 1 H, 5-Ha), 2.99 (ddd, *J* = 9.8, 6.3, 3.4 Hz, 1 H, 3-H), 2.83 (ddd, *J* = 11.7, 3.4, 1.5 Hz, 1 H, 5-Hb), 2.13 (dtd, *J* = 13.7, 3.9, 1.5 Hz, 1 H, 7-Ha), 1.98 (ddd, *J* = 14.1, 9.3, 5.4 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 74.5 (d, C-2) 72.4 (d, C-6), 72.0 (d, C-1), 70.2 (d, C-3), 64.9 (d, C-7a), 63.0 (t, C-8), 61.7 (t, C-5) 32.5 (t, C-7) ppm. ^{1}H NMR (400 MHz, D_2O): δ = 4.27 (dq, *J* = 5.4, 3.9 Hz, 1 H, 6-H), 3.90 (t, *J* = 3.9 Hz, 1 H, 1-H), 3.81 (dd, *J* = 9.8, 3.9 Hz, 1 H, 2-H), 3.70 (dd, *J* = 11.7, 3.4 Hz, 1 H, 8-Ha), 3.55–3.51 (m, 1 H, 7a-H), 3.49 (dd, *J* = 11.7, 6.8 Hz, 1 H, 8-Hb), 3.03 (dd, *J* = 11.2, 4.4 Hz, 1 H, 5-Ha), 2.87 (ddd, *J* = 10.2, 6.8, 3.4 Hz, 1 H, 3-H), 2.62 (dd, *J* = 11.2, 4.9 Hz, 1 H, 5-Hb), 1.99–1.89 (m, 2 H, Ha-7, Hb-7) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 74.5 (d, C-2), 72.4 (d, C-6), 71.6 (d, C-1), 69.4 (d, C-3), 64.2 (d, C-7a), 63.4 (t, C-8), 61.1 (t, C-5) 31.9 (t, C-7) ppm. MS (ESI): *m*/*z* (%) = 190.12 (100) [M + H]$^+$, 212.10 (54) [M + Na]$^+$. $C_8H_{15}NO_4$ (189.21): calcd. C 50.78, H 7.99, N 7.40; found C 50.74, H 8.04, N 7.42.

(1*S*,2*R*,3*R*,6*R*,7a*R*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]-6-(methylsulfonyloxy)-hexahydro-1*H*-pyrrolizine (22): To a stirred solution of **20** (157 mg, 0.34 mmol) in dry CH_2Cl_2 (10 mL), NEt_3 (142 µL, 1.02 mmol) was added under nitrogen atmosphere, and, at 0 °C, MsCl (34 µL, 0.44 mmol) was added dropwise. The solution was left stirring for 2 h at room temp. TLC analysis (CH_2Cl_2/MeOH, 10:1) showed disappearance of the starting material (R_f = 0.13) and formation of a new product (R_f = 0.68). Then 20 mL of H_2O were added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the organic layers were dried on Na_2SO_4. Filtration on cotton and evaporation under reduce pressure afforded crude **22** that was purified by flash column chromatography (eluent AcOEt) affording pure **22** as a yellow oil, (R_f = 0.27, 183 mg, 0.34 mmol, quantitative yield). $[\alpha]_D^{27}$ = +40.8 (*c* = 1.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 15 H, Ar), 5.23 (dq, *J* = 13.6, 7.3 Hz, 1 H, 6-H) 4.78–4.57 (AB system, *J* = 12.2 Hz, 2 H, Bn), 4.58–4.47 (AB system, *J* = 12.2 Hz, 2 H, Bn), 4.58–4.44 (AB system, *J* = 11.7 Hz, 2 H, Bn), 3.93–3.89 (m, 2 H, 1-H, 2-H), 3.59 (dd, *J* = 9.8, 3.4 Hz, 1 H, 8-Ha), 3.60–3.55 (m, 1 H, 7a-H), 3.45 (dd, *J* = 9.8, 5.9 Hz, 2 H, Hb-8, Ha-5), 3.24 (ddd, *J* = 7.8, 5.4, 3.4 Hz, 1 H, 3-H), 3.12 (dd, *J* = 9.8, 6.8 Hz, 1 H, 5-Hb), 2.90 (s, 3 H, Ms), 2.45 (dt, *J* = 12.7, 7.8 Hz, 1 H, 7-Ha), 2.19 (ddd, *J* = 12.7, 8.8, 7.3 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.0, 137.9, 137.5 (s, C-Ar), 128.1–127.2 (d, 15 C, C-Ar), 82.2 (d, C-2), 80.7 (d, C-6), 76.1 (d, C-1), 73.1, 72.9, 72.4 (t, C-Bn), 70.7 (t, C-8), 66.9 (d, C-3), 63.5 (d, C-7a), 58.7 (t, C-5), 37.9 (q, Ms), 30.7 (t, C-7) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3087, 3065, 3030, 2863, 1495, 1453, 1360, 1331, 1176, 1134, 1027 cm^{-1}. MS (ESI): *m*/*z* (%) = 538.42 (100) [M + H]$^+$, 560.17 (76) [M + Na]$^+$. $C_{30}H_{35}NO_6S$ (537.67): calcd. C 67.02, H 6.56, N 2.61; found C 66.72, H 6.86, N 2.55.

(1*S*,2*R*,3*R*,7a*R*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]-hexahydro-1*H*-pyrrolizine (23): A solution of **22** (128 mg, 0.24 mmol) in 10 mL of dry toluene was stirred under nitrogen atmosphere at 0 °C and DIBAL-H (1 M solution in CH_2Cl_2, 2.40 mL, 2.40 mmol) was added dropwise. The mixture was raised to room temp. and refluxed for 3 h, until TLC analysis (AcOEt) showed the disappearance of the starting material (R_f = 0.27) and formation of a new product (R_f = 0.00). The reaction was then quenched with 0.5 mL of a saturated aqueous solution of Na_2SO_4 at 0 °C, filtered through Celite® and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 15:1), affording pure **23** (R_f = 0.23, 59 mg, 0.13 mmol, 56% yield) as a yellow oil. $[\alpha]_D^{25}$ = +33.2 (*c* = 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 15 H, Ar), 4.76 (d, *J* = 11.7 Hz, 1 H, Bn), 4.62–4.54 (m, 4 H, Bn), 4.47 (d, *J* = 11.7 Hz, 1 H, Bn), 3.98–3.92 (m, 2 H, 2-H, 1-H), 3.90–3.80 (m, 1 H, 7a-H), 3.75 (pq, *J* = 8.6 Hz, 1 H, 8-Ha), 3.70 (dd, *J* = 9.8, 3.3 Hz, 1 H, 8-Hb), 3.32 (dq, *J* = 5.5, 4.9 Hz, 1 H, 5-Ha), 3.25 (td, *J* = 9.8, 3.5 Hz, 1 H, 3-H), 2.79–2.73 (m, 5-Hb), 2.11 (dq, *J* = 11.7, 7.2 Hz, 1 H, 7-Ha), 2.01–1.86 (m, 2 H, Ha-6, Hb-6), 1.77 (ddd, *J* = 11.9, 7.2, 5.9 Hz, 1 H, 7-Hb) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.9, 137.2 (s, 3 C, C-Ar), 128.1–127.2 (d, 15 C, C-Ar), 82.2 (d, C-2) 75.9 (d, C-1), 73.2, 73.1, 72.6 (t, C-Bn), 70.0 (t, C-8), 66.8 (d, C-3), 65.9 (d, C-7a), 55.4 (t, C-5), 26.8 (t, C-6), 24.5 (t, C-7) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3087, 3065, 3031, 2909, 2870, 1496, 1453, 1365, 1208, 1143, 1124, 1095, 1027 cm^{-1}. MS (ESI): *m*/*z* (%) = 444.44 (100) [M + H]$^+$. $C_{29}H_{33}NO_3$ (443.58): calcd. C 78.52, H 7.50, N 3.16; found C 78.27, H 7.58, N 2.67.

Synthesis of (1*S*,2*R*,3*R*,7a*R*)-3-Hydroxymethylhexahydro-1*H*-pyrrolizine-1,2-diol (+)-Hyacinthacine A_1 (6): To a solution of **23** (50 mg, 0.11 mmol) in 20 mL of MeOH 25 mg of 10% Pd on carbon and 2 drops of HCl 37% were added while stirring under nitrogen atmosphere, then the mixture was stirred under hydrogen atmosphere at room temp. for 2 d. After TLC analysis (CH_2Cl_2/MeOH, 10:1) showed the disappearance of starting material (R_f = 0.33) and formation of a new product (R_f = 0.00), the mixture was filtered through Celite® and the solvent was removed under reduced pressure affording a crude yellow oil (60 mg). The free amine was ob-

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tained by passing the hydrochloride salt through a Dowex 50WX8 ion-exchange resin. Elution with ammonia 6% afforded free base **6** (18 mg, 0.10 mmol, 95% yield over two steps) as a waxy yellow solid. $[\alpha]_D^{24}$ = +35.6 (*c* = 0.32, H_2O). ^1H NMR (400 MHz, CD_3OD): δ = 3.90–3.87 (m, 2 H, 1-H, 2-H), 3.81 (dd, *J* = 11.2, 3.4 Hz, 1 H, 8-Ha), 3.59 (dd, *J* = 11.2, 6.3 Hz, 1 H, 8-Hb), 3.53–3.49 (m, 1 H, 7a-H), 3.11–3.06 (m, 1 H, 5-Ha), 2.83–2.77 (m, 1 H, 3-H), 2.68 (ddd, *J* = 10.2, 7.8, 6.3 Hz, 1 H, 5-Hb), 2.10 (dq, *J* = 11.7, 6.8 Hz, 1 H, 7-Ha), 1.96 (ddd, *J* = 10.7, 5.3, 4.3 Hz, 1 H, 6-Ha), 1.83–1.65 (m, 2 H, Hb-6, Hb-7) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 74.1 (d, C-2) 70.4 (d, C-1), 68.7 (d, C-3), 65.0 (d, C-7a), 61.7 (t, C-8), 54.5 (t, C-5), 25.7 (t, C-6) 22.9 (t, C-7) ppm. ^1H NMR (400 MHz, D_2O): δ = 3.92 (t, *J* = 3.9 Hz, 1 H, 1-H), 3.86 (dd, *J* = 9.7, 3.9 Hz, 1 H, 2-H), 3.70 (dd, *J* = 11.7, 3.5 Hz, 1 H, 8-Ha), 3.53 (dd, *J* = 11.7, 6.9 Hz, 1 H, 8-Hb), 3.45–3.39 (m, 1 H, 7a-H), 3.02–2.94 (m, 1 H, 5-Ha), 2.73 (ddd, *J* = 9.7, 6.3, 3.4 Hz, 1 H, 3-H), 2.52–2.46 (m, 1 H, 5-Hb), 1.90–1.78 (m, 2 H, Ha-6, Ha-7), 1.70–1.60 (m, 2 H, Hb-6, Hb-7) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 74.1 (d, C-2) 70.4 (d, C-1), 67.8 (d, C-3), 64.5 (d, C-7a), 61.9 (t, C-8), 54.6 (t, C-5), 26.0 (t, C-6), 22.7 (t, C-7) ppm. MS-EI (70 eV): *m*/*z* (%) = 142 (100), 96 (44), 70 (40), 41 (30). $C_8H_{15}NO_3$ (173.21): calcd. C 55.47, H 8.73, N 8.09; found C 55.15, H 8.54, N 7.63.

Supporting Information (see footnote on the first page of this article): Characterization of compound **14**, syntheses of compounds **24**–**26**, ^1H and ^{13}C NMR spectra of compounds **6** and of the hydrochloride salt of **7**, **10**–**11** and **13**–**26**, and glycosidase inhibition assays.

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