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Stereoselective syntheses of the glycosidase inhibitors hyacinthacine A_2, hyacinthacine A_3 and 5-*epi*-hyacinthacine A_3

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ABSTRACT

Stereoselective syntheses of the naturally occurring glycosidase inhibitors hyacinthacines A_2 and A_3 are reported. In the case of hyacinthacine A_2, the pyrrolizidine system was created from an acyclic precursor via a double cyclization procedure with a one-pot formation of two C–N bonds. In the case of hyacinthacine A_3, the two C–N bonds were created in separate steps. In addition, the non-natural epimer at C-5 of hyacinthacine A_3 was obtained.

1. Introduction

Pyrrolizidine alkaloids have been isolated from species of many terrestrial plants.[1] Polyhydroxylated representatives have been found in genera belonging to the Leguminosae and a few other families. For instance, hyacinthacine A_1 (**1**), hyacinthacine A_2 (**2**) and hyacinthacine A_3 (**3**) (Fig. 1) were isolated in 2000, together with further related alkaloids, from *Muscari armeniacum* Leichtl. ex Baker (Hyacinthaceae).[2] From these, compound **1** showed a strong β-galactosidase activity whereas **2** and, to a lesser extent, **3** were found to be selective inhibitors of the amyloglucosidase from *Aspergillus niger*.

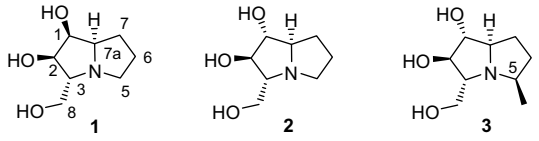
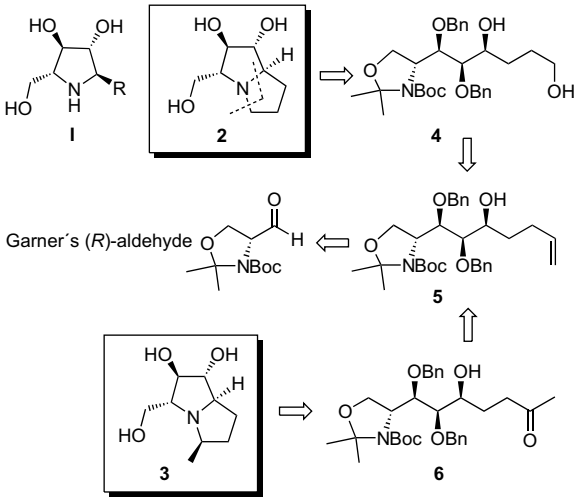


Figure 1. Structures of hyacinthacines A_1 (**1**), A_2 (**2**) and A_3 (**3**).

The diverse array of potentially useful biological activities[3] and the high degree of functionality embedded in these alkaloids make them attractive targets for stereoselective synthesis.[4] As regards the hyacinthacine family, several of its members have been so far the object of total synthesis. In most cases, simple carbohydrates already having several of the final stereocentres were the ultimate source of chirality.[5,6] As for **2** and **3**, five syntheses of the former have appeared in the bibliography, as well as one of the non-natural enantiomer.[7] Four of these syntheses used commercial sugar derivatives as the chirality source,[7a–d] whereas the remaining one relied on the enzymatic resolution of a racemic aminoacid for the preparation of the chiral starting material.[7e] An enzymatic methodology was also used in the synthesis of the enantiomer of hyacinthacine A_2.[7f] With respect to hyacinthacine A_3 (**3**), only one synthesis has been reported so far, with a sugar derivative also being the starting material.[8]

In the present paper, we describe stereoselective syntheses of **2** and **3**. The retrosynthetic plan for **2**, shown in Scheme 1, relies on that followed in our recent syntheses of the natural pyrrolidines broussonetines D and M, because all these compounds share the



Scheme 1. Retrosynthetic analysis of **2** and **3**.

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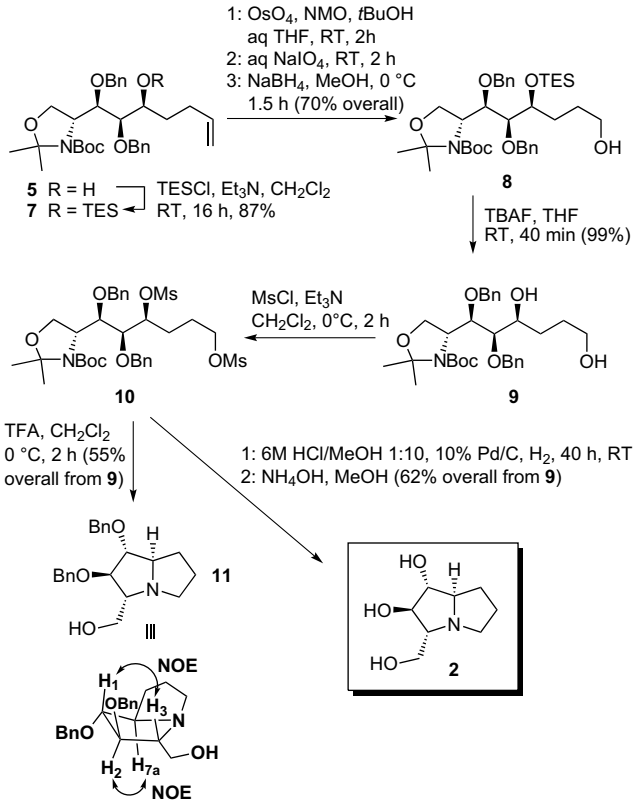
common fragment **I**.[9] Thus, pyrrolizidine **2** may be referred to diol **4** via one-pot or stepwise cleavage of two C–N bonds.[10] In the synthetic sense, this corresponds to activation of the hydroxyl groups and oxazolidine ring opening, followed by two nucleophilic substitutions. Diol **4** in turn should be readily prepared from compound **5**, for which an efficient synthesis from Garner's (*R*)-aldehyde has been recently reported by our group.[9a] Likewise, pyrrolizidine **3** may also be referred to alcohol **5** through a similar sequence of reactions via ketone **6**.

2. Results and discussion

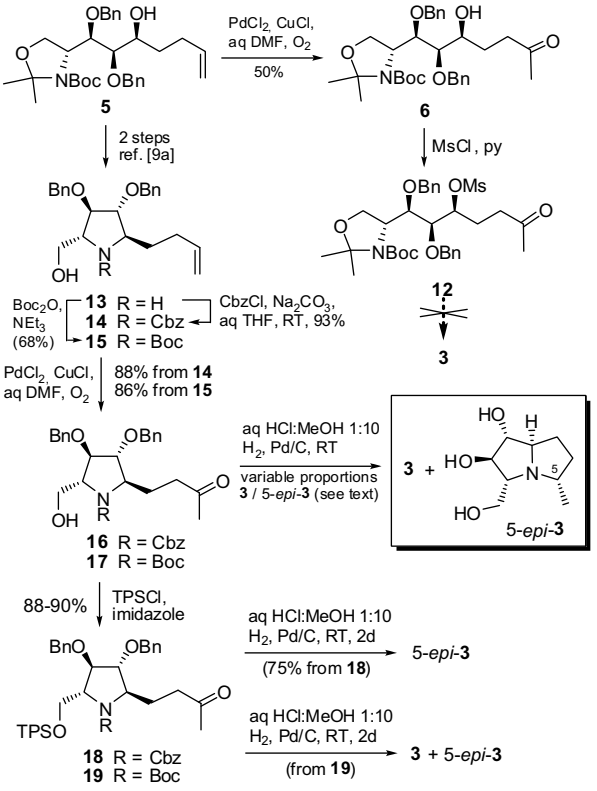
Scheme 2 shows in detail the synthesis of hyacinthacine A_2 (**2**). Compound **5** can be prepared in 6 steps and ca. 59% overall yield from Garner's (*R*)-aldehyde.[9a] Attempts at oxidative cleavage of the olefinic bond in **5** gave unsatisfactory yields. Much better results were observed after protection of the free OH as the triethylsilyl (TES) ether to yield **7**. Thus, oxidative cleavage of the C=C bond in **7** to give alcohol **8** was achieved in 70% overall yield by means of a three-step osmylation/periodate oxidation/$NaBH_4$ reduction procedure.[10] Desilylation of the TES group in **8** with tetra-*n*-butylammonium fluoride (TBAF) furnished diol **9** in almost quantitative yield. The latter reacted with mesyl chloride to give dimesylate **10**.



Scheme 2. Stereoselective synthesis of **2**.

Treatment of **10** with trifluoroacetic acid (TFA) in CH_2Cl_2 at 0 °C provided pyrrolizidine **11** in a one-pot process which encompasses the cleavage of the Boc and the aminoacetal groups followed by the sequential formation of two C–N bonds through intramolecular 5-*exo*-tet nucleophilic substitutions.[11] NOE studies were performed on compound **11** in order to confirm the configuration at the newly formed stereocentre C-7a (Scheme 2). While compound **11** was amenable to conversion into **2** by means of hydrogenolytic deprotection of the two benzyl groups, it proved much more practical to stir crude **10** in an acidic medium under an H_2 atmosphere, followed by alkalinization with aq methanolic ammonia. This yielded pyrrolizidine **2**, which showed spectroscopic data consistent with those reported for both natural[2] and synthetic[7] hyacinthacine A_2.

Scheme 3 depicts the synthesis of hyacinthacine A_3 (**3**). Our initial idea was to convert alcohol **5** into methyl ketone **6**, followed by mesylation to **12** and subsequent cyclization. On the basis of that observed in the previous synthesis of **3**[8] and in our synthesis of radicamine B,[9b] we expected that hydrogenation of **12** in an acidic medium would give rise to cleavage of *N*-protecting groups, intramolecular nucleophilic substitution and reductive ring closure with formation of the pyrrolizidine system of **3**. Indeed, Wacker oxidation[12] of **5** gave moderate yields of ketone **6**, which was then mesylated to **12**. Unfortunately, all attempts at converting **12** into **3** were unsuccessful, mixtures of ill-defined products being the only observed result.



Scheme 3. Stereoselective synthesis of **3** and 5-*epi*-**3**.

In view of these drawbacks, we decided to build up the two required C–N bonds of the pyrrolizidine system in two separate steps. Compound **5** was converted into pyrrolidine **13** in two steps as reported in our recent synthesis of broussonetines D and M.[9a] Conversion of **13** into its *N*-Cbz and *N*-Boc derivatives, **14** and **15**, followed by Wacker oxidation gave methyl ketones **16** or **17**, respectively. When subjected to hydrogenolytic conditions, either of these two ketones gave separable mixtures of hyacinthacine A_3 (**3**) and its epimer at C-5 (5-*epi*-**3**).[13] The relative configuration of the new stereocentre (C-5) was confirmed in both cases with the aid of NOE studies. For **3**, a NOE was observed between H-1 and the methyl group bound to C-5. This NOE was not detected in 5-*epi*-**3** but, in contrast, a NOE was visible between H-7a and the aforementioned methyl group.

The relative proportion of the two pyrrolizidines was markedly dependent on the experimental procedure. For instance, hydrogenolysis under neutral conditions until disappearance of the starting compound (TLC monitoring), followed by addition of acid

(aq HCl/MeOH) and further stirring under a H_2 atmosphere afforded a mixture of **3** and 5-*epi*-**3** with a slight predominance of the former (dr ~1.2:1). In contrast, when the acid was added from the beginning of the hydrogenolysis, 5-*epi*-**3** was practically the sole product detected, even though the formation of small amounts of **3** cannot be completely excluded.

On the basis of that reported in the previous synthesis of **3**,[8] we wondered whether the presence of a free hydroxyl group might exert some influence[14] on the stereochemical outcome of the hydrogenation step. Thus, ketones **16** and **17** were first converted into their respective silylated derivatives **18** and **19** (Scheme 3, TPS=*tert*-butyldiphenylsilyl). Compound **19** showed spectral data coincident with those reported for an intermediate in the previous synthesis of **3**.[8,15] When **18** was subjected to hydrogenolysis under the same conditions described above for **16** and **17** (acid added from the beginning), however, 5-*epi*-**3** was the main product, whereas **19** yielded a mixture of **3** and 5-*epi*-**3** (dr ~1:1). Further variations in the reaction conditions (modification of temperature or reaction time, etc.) caused changes in the relative proportion of 5-*epi*-**3** to **3** but did not give rise to the formation of pure **3**.

The reasons of these stereochemical differences and of the divergence of our results from those reported in the previous synthesis[8] of **3** are not clear. *trans*-2,5-Disubstituted pyrrolidine derivatives with a 3-oxoalkyl chain at C-2 and a further substituent at C-5 (pyrrolidine numbering) have often been shown to undergo ring closure via intramolecular reductive amination to yield a pyrrolizidine system.[16] Furthermore, the stereoisomers formed in a predominant or exclusive manner were found to display the same relative configuration at C-3, C-5 and C-7a as does 5-*epi*-**3**. This has been attributed to a face-selective reduction of the intermediate bicyclic iminium cation controlled by an interplay of stereoelectronic and steric factors.[17] Therefore, preferential formation of 5-*epi*-**3** rather than **3** is the expected result in the present case. However, the fact that small variations in the reaction conditions cause marked changes in the stereoisomer composition suggests that other subtle factors may also play a role.

In summary, the two bioactive, naturally occurring pyrrolizidine alkaloids **2** and **3** and the non-natural alkaloid 5-*epi*-**3** have been prepared in enantiopure form from the commercially available aminoacid D-serine via Garner's aldehyde.[18]

3. Experimental

3.1. General

$^1H/^{13}C$ NMR spectra were recorded at 500/125 MHz in the indicated solvent at 30 °C if not stated otherwise. Molecules with Cbz or Boc protecting groups were measured at higher temperatures in those cases where this was necessary to have reasonably sharp signals. When sharp, separate signals for the two rotamers were observed at 30 °C, the signals of one of the rotamers are indicated in *italics*. The signals of the deuterated solvent were taken as the reference (for DMSO-d_6, δ 2.50 and 39.5 ppm for ^1H and ^{13}C NMR, respectively). For spectra measured in D_2O, sodium 3-(trimethylsilyl)-propanesulfonate-d_6 (DSS) was the reference for δ=0 (^1H and ^{13}C NMR). Carbon atom types (C, CH, CH_2, CH_3) were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact mode (EIMS), by the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) or by the electrospray injection mode (ESMS). IR data are given only for compounds with significant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic, an additional washing with 5% aq $NaHCO_3$ was performed. If the reaction medium was basic, an additional washing with aq NH_4Cl was performed. New washing with brine, drying over anhyd Na_2SO_4 and elimination of the solvent under reduced pressure were followed by chromatography on a silica gel column (60–200 μm) and elution with the indicated solvent mixture. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer.

3.1.1. *tert*-Butyl (*R*)-4-[(1*R*,2*S*,3*S*)-1,2-bis(benzyloxy)-3-(triethylsilyloxy)hept-6-enyl]-2,2-dimethyloxazolidine-3-carboxylate (**7**)

A solution of alcohol **5**[9a] (1.05 g, 2 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C under N_2 and treated with Et_3N (1.12 mL, 8 mmol, 2 equiv) and TESCl (0.4 mL, 2.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 16 h. Work-up (extraction with CH_2Cl_2, 3×15 mL) and column chromatography on silica gel (hexanes/EtOAc, 95:5) afforded 1.11 g (87%) of silyl ether **7**: oil; $[\alpha]_D$ +42.3 (*c* 1.65, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 70 °C): δ=7.35–7.25 (br m, 10H), 5.80 (ddt, *J*=17.2, 10.3, 6.4 Hz, 1H), 5.00 (dd, *J*=17.2, 1.7 Hz, 1H), 4.95 (dd, *J*=10.3, 1.7 Hz, 1H), 4.68 (d, *J*=11.2 Hz, 1H), 4.62 (m, 3H), 4.24 (br s, 1H), 4.10 (dd, *J*=8.6, 4.2 Hz, 1H), 4.06 (m, 1H), 3.90–3.85 (m, 2H), 3.34 (dd, *J*=6.4, 4.9 Hz, 1H), 2.15 (br m, 1H), 2.04 (br m, 1H), 1.80 (br m, 1H), 1.56 (br m, 1H), 1.47 (s, 9H), 1.42 (s, 3H), 1.40 (s, 3H), 0.92 (t, *J*=7.8 Hz, 9H), 0.57 (q, *J*=7.8 Hz, 6H); ^{13}C NMR (125 MHz, DMSO, 70 °C): δ=152.6*, 139.2, 139.1, 94.0*, 80.1 (C_q), 139.3, 128.7 (×2), 128.6 (×2), 128.2 (×2), 128.0, 127.9 (×2), 127.8, 83.9, 78.2*, 72.0, 59.2* (CH), 75.1, 73.9, 63.9*, 32.2*, 30.2, 5.2 (×3) (CH_2), 28.8 (×3), 26.4*, 25.0*, 7.2 (×3) (CH_3) (starred signals are low and broad); IR ν_{max} 3065 (C=C–H), 1692 (C=O) cm^{-1}; HRFABMS *m*/*z* 640.4039 ($M+H^+$). Calcd for $C_{37}H_{58}NO_6Si$: 640.4033.

3.1.2. *tert*-Butyl (*R*)-4-[(1*R*,2*S*,3*S*)-1,2-bis(benzyloxy)-6-hydroxy-3-(triethylsilyloxy)hexyl]-2,2-dimethyloxazolidine-3-carboxylate (**8**)

Compound **7** (448 mg, 0.7 mmol) was dissolved at room temperature in a mixture of THF (1.5 mL), *t*-BuOH (3.75 mL) and water (0.5 mL). The solution was then treated with NMO (100 mg, ca. 0.84 mmol, 1.2 equiv) and OsO_4 (4% aq solution, 0.18 mL, 0.028 mmol, 0.04 equiv) and stirred at room temperature for 2 h. Subsequently, a solution of $NaIO_4$ (214 mg, ca. 1 mmol, 1.4 equiv) in water (1 mL) was added dropwise, followed by further stirring at room temperature for 2 h. The reaction mixture was then treated with satd aq Na_2SO_3 (5 mL), stirred for 5 min and extracted with CH_2Cl_2 (3×20 mL). The organic layers were washed with brine and dried on anhyd Na_2SO_4. After filtration and solvent removal under reduced pressure, the oily residue was used as such in the next step.

The residue from above was dissolved in MeOH (8 mL), cooled to 0 °C and treated with $NaBH_4$ (80 mg, 2.1 mmol, 3 equiv). The reaction mixture was then stirred at 0 °C for 1.5 h. Work-up (extraction with EtOAc, 2×15 mL) and column chromatography on silica gel (hexanes/EtOAc, 8:2) furnished alcohol **8** (316 mg, 70%): oil; $[\alpha]_D$ +46 (*c* 2.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, 55 °C): δ=7.35–7.20 (br m, 10H), 4.75–4.70 (m, 2H), 4.64 (s, 2H), 4.40 (br s, 1H), 4.22 (dd, *J*=8.8, 4.2 Hz, 1H), 4.20 (br s, overlapped, 1H), 3.90 (m, 2H), 3.63 (br t, *J*=5.6 Hz, 2H), 3.38 (dd, *J*=7.2, 4.5 Hz, 1H), 1.90 (br m, 2H), 1.70 (m, 2H), 1.50 (br s, 12H), 1.47 (s, 3H), 0.95 (t, *J*=8 Hz, 9H), 0.57 (q, *J*=8 Hz, 6H) (hydroxyl signal not detected); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): δ=152.8*, 139.1, 138.8, 94.0*, 80.2 (C_q), 128.3 (×2), 128.1 (×2), 127.8 (×2), 127.7 (×2), 127.5, 127.2, 84.7, 78.1*, 72.4, 59.0* (CH), 75.5, 74.3, 63.9*, 63.0, 29.2 (×2), 5.1 (×3) (CH_2), 28.6 (×3), 26.2*,

24.9*, 6.9 (×3) (CH_3) (starred signals are low and broadened); IR ν_{max} 3490 (br, OH), 1691 (C=O) cm^{-1}; HRFABMS *m/z* 644.3998 ($M+H^+$). Calcd for $C_{36}H_{58}NO_7Si$: 644.3982.

3.1.3. *tert-Butyl (R)-4-[(1R,2R,3S)-1,2-bis(benzyloxy)-3,6-dihydroxyhexyl]-2,2-dimethyloxazolidine-3-carboxylate (**9**)*

A solution of compound **8** (258 mg, 0.4 mmol) in dry THF (3 mL) was treated under N_2 with TBAF trihydrate (152 mg, 0.48 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 45 min. Solvent removal under reduced pressure and column chromatography of the residue on silica gel (hexanes/EtOAc, 1:1) provided diol **9** (209 mg, 99%): oil; $[\alpha]_D$ +51.8 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, 55 °C): δ=7.35–7.20 (br m, 10H), 4.78 (d, *J*=11.2 Hz, 1H), 4.76 (d, *J*=11.3 Hz, 1H), 4.67 (d, *J*=11.3 Hz, 1H), 4.58 (d, *J*=11.2 Hz, 1H), 4.32 (br s, overlapped, 1H), 4.30 (dd, *J*=8.8, 3.5 Hz, 1H), 4.15 (br s, 1H), 3.96 (dd, *J*=8.8, 7.5 Hz, 1H), 3.72 (br m, 1H), 3.60 (m, 2H), 3.30 (dd, *J*=6, 3 Hz, 1H), 2.50 (br s, OH, 2H), 1.70–1.50 (br m, overlapped, 4H), 1.57 (s, 3H), 1.51 (s, 9H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): δ=152.9*, 138.5, 138.2, 93.9*, 80.4 (C), 128.3 (×2), 128.2 (×4), 127.9 (×2), 127.7, 127.5, 82.2*, 78.2*, 71.1, 58.8 (CH), 75.0, 74.6*, 63.5, 62.7, 31.4, 29.6 (CH_2), 28.5 (×3), 26.4*, 24.3* (CH_3) (starred signals are low and broadened); IR ν_{max} 3430 (br, OH), 1688 (C=O) cm^{-1}; HRFABMS *m/z* 530.3118 ($M+H^+$). Calcd for $C_{30}H_{44}NO_7$: 530.3117.

3.1.4. *[(1R,2R,3R,7aR)-1,2-Bis(benzyloxy)hexahydro-1H-pyrrolizin-3-yl] methanol (**11**)*

A solution of diol **9** (185 mg, 0.35 mmol) in dry CH_2Cl_2 (3 mL) was cooled to 0 °C under N_2 and treated with DMAP (6 mg, 0.05 mmol), Et_3N (0.3 mL, 2.1 mmol, 6 equiv) and methanesulfonyl chloride (0.11 mL, 1.4 mmol, 4 equiv). The reaction mixture was stirred at 0 °C for 2 h. Work-up (extraction with CH_2Cl_2, 3×10 mL) and removal of all volatiles under reduced pressure gave crude dimesylate **10**, which was divided into two identical aliquots and used as such in the two next reactions.

One of the aliquots of the crude dimesylate from above was dissolved in CH_2Cl_2 (1 mL), cooled to 0 °C and treated with TFA (1 mL). The mixture was stirred at the same temperature for 2 h. After removal of all volatiles under reduced pressure, the residue was dissolved in MeOH (2 mL) and the solution was brought to basic pH with dropwise addition of 33% aq NH_3. After stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The residue was then subjected to column chromatography on silica gel (EtOAc/MeOH, 9:1) to yield pyrrolizidine **11** (34 mg, 55% overall yield from **9**): oil; $[\alpha]_D$ +17.7 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ=7.40–7.25 (br m, 10H), 4.78 (d, *J*=11.2 Hz, 1H), 4.65 (d, *J*=11.2 Hz, 1H), 4.62 (d, *J*=11.8 Hz, 1H), 4.56 (d, *J*=11.8 Hz, 1H), 4.12 (br t, *J*~6 Hz, 1H), 3.82 (br t, *J*~5.8 Hz, 1H), 3.62 (dd, *J*=11.1, 2.3 Hz, 1H), 3.58 (dd, *J*=11.1, 2.8 Hz, 1H), 3.46 (br q, *J*~6.5 Hz, 1H), 2.96 (br dt, *J*~10.5, 6.3 Hz, 1H), 2.85 (m, 1H), 2.80 (br s, 1H, OH), 2.68 (br dt, *J*~10.5, 6.3 Hz, 1H), 2.05–2.00 (m, 1H), 1.90–1.80 (m, 1H), 1.80–1.75 (m, 1H), 1.75–1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.3, 138.1 (C_q), 128.5 (×2), 128.4 (×2), 127.8 (×4), 127.7 (×2), 88.8, 84.5, 69.5, 67.5 (CH), 73.0, 72.0, 60.6, 53.9, 31.9, 25.7 (CH_2); IR ν_{max} 3440 (br, OH) cm^{-1}; HRFABMS *m/z* 354.2076 ($M+H^+$). Calcd for $C_{22}H_{28}NO_3$: 354.2069.

3.1.5. *(1R,2R,3R,7aR)-3-(Hydroxymethyl)hexahydro-1H-pyrrolizine-1,2-diol, hyacinthacine A_2 (**2**)*

The second aliquot of the crude dimesylate **10** was dissolved in MeOH (10 mL) and treated with 6 M HCl (1 mL). The mixture was stirred at room temperature for 30 min. After addition of Degussa-type 10% Pd/C (100 mg), the mixture was stirred at room temperature for 40 h under an H_2 atmosphere. Following this, the mixture was filtered through a pad of Celite (MeOH), and the solvent was removed under reduced pressure. The obtained residue was dissolved in MeOH (3 mL) and the solution was brought to basic pH with dropwise addition of 33% aq NH_3. After stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The residue was then put on the top of a ion-exchange resin column (Dowex® 50Wx4 200–400 mesh, pre-acidified with 0.5 M HCl). Elution with water (50 mL) to remove salts and then with 1 M aq NH_3 until elution of the product (TLC monitoring), followed by removal of the volatiles of the latter fraction under reduced pressure, gave a brownish residue which was subjected to column chromatography on silica gel ($CHCl_3$/MeOH/aq NH_3, gradient from 90:10:1 to 10:10:1). This yielded hyacinthacine A_2 (**2**) (19 mg, 62% overall yield from **9**): oil; $[\alpha]_D$ +12.1 (*c* 0.3, H_2O), lit.[2] $[\alpha]_D$ +20.1 (*c* 0.44, H_2O), lit.[7a] $[\alpha]_D$ +12.5 (*c* 0.4, H_2O), lit.[7b] $[\alpha]_D$ +12.7 (*c* 0.13, H_2O), lit.[7c] $[\alpha]_D$ +10.5 (*c* 0.6, H_2O), lit.[7d] $[\alpha]_D$ +19.9 (*c* 0.97, MeOH), lit.[7e] $[\alpha]_D$ +11.2 (*c* 0.52, H_2O), lit.[7f] for the non-natural enantiomer, $[\alpha]_D$ −11 (*c* 1, MeOH); IR ν_{max} 3470 (br, OH) cm^{-1}. For NMR data and their comparison with literature values for natural and synthetic samples, see Supplementary data.

3.1.6. *tert-Butyl (R)-4-[(1R,2R,3S)-1,2-bis(benzyloxy)-3-hydroxy-6-oxoheptyl]-2,2-dimethyloxazolidine-3-carboxylate (**6**)*

A solution of compound **5** (263 mg, 0.5 mmol) in a 10:1 DMF/H_2O mixture (11 mL) was treated with $PdCl_2$ (35 mg, 0.2 mmol) and CuCl (248 mg, 2.5 mmol). The reaction mixture was then stirred under O_2 at room temperature for 24 h. Work-up (extraction with Et_2O, 3×10 mL) and column chromatography on silica gel (hexanes/EtOAc, 8:2 to 7:3) afforded 135 mg (50%) of methyl ketone **6**: oil; $[\alpha]_D$ +42 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6, 90 °C): δ=7.35–7.20 (br m, 10H), 4.70–4.55 (br m, 4H), 4.45 (br s, 1H), 4.25 (br d, *J*~6.5 Hz, 1H), 4.20–4.00 (br m, 2H), 3.90 (m, 1H), 3.60 (m, 1H), 3.30 (br dd, *J*~6.5, 4 Hz, 1H), 2.60–2.40 (br m, 2H), 2.04 (s, 3H), 1.85–1.60 (br m, 2H), 1.45 (s, 9H), 1.40 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 90 °C): δ=207.8, 151.8, 138.7 (×2), 93.0, 79.1 (C_q) (10 overlapped aromatic CH signals), 83.2, 77.7*, 69.0, 58.3 (CH), 74.0, 73.2, 63.0, ca. 40.5 (overlapped by solvent, CH_2CO), 29.2 (CH_2), 28.0 (×3), 26.7, 25.6 (CH_3) (the starred signal is low and broadened); IR ν_{max} 3440 (br, OH), 1690 (C=O) cm^{-1}; HRESMS *m/z* 564.2944 ($M+Na^+$). Calcd for $C_{31}H_{43}NNaO_7$: 564.2937.

3.1.7. *tert-Butyl (R)-4-[(1R,2R,3S)-1,2-bis(benzyloxy)-3-(methanesulfonyloxy)-6-oxoheptyl]-2,2-dimethyloxazolidine-3-carboxylate (**12**) and attempts at the synthesis of **3***

A solution of compound **6** (108 mg, 0.2 mmol) in dry CH_2Cl_2 (2 mL) was cooled to 0 °C under N_2 and treated with DMAP (1 mg, ca. 0.01 mmol), Et_3N (84 μL, 0.6 mmol) and methanesulfonyl chloride (31 μL, 0.4 mmol). The reaction mixture was stirred at 0 °C for 2 h and then further 30 min at room temperature. Work-up (extraction with CH_2Cl_2, 3×10 mL) and removal of all volatiles under reduced pressure gave crude mesylate **12**.

The crude **12** from above was dissolved in MeOH (10 mL) and treated with 6 M HCl (1 mL). The mixture was stirred at room temperature for 30 min. After addition of Degussa-type 10% Pd/C (100 mg), the mixture was stirred at room temperature under an H_2 atmosphere until no UV-absorbing product was visible in a TLC plate (ca. 48 h). Following this, the mixture was filtered through a pad of Celite (MeOH), and the solvent was removed under reduced pressure. The obtained residue was dissolved in MeOH (3 mL) and the solution was brought to basic pH with dropwise addition of 33% aq NH_3. After stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The residue was then put on the top of a ion-exchange resin column (Dowex® 50Wx4 200–400 mesh, pre-acidified with 0.5 M HCl). Elution with water (50 mL) to remove salts and then with 1 M aq NH_3 until elution of the product (TLC monitoring), followed by removal of the volatiles of the latter fraction under reduced pressure, gave a brownish residue which was subjected to column

chromatography on silica gel ($CHCl_3$/MeOH/aq NH_3, gradient from 90:9:1 to 70:29:1). After solvent removal, NMR examination of the chromatographic fractions showed only ill-defined products but not the desired **3**.

3.1.8. Benzyl [(2R,3R,4R,5R)-3,4-bis(benzyloxy)-2-(but-3-enyl)-5-(hydroxymethyl)]pyrrolidine-1-carboxylate (**14**)

A solution of pyrrolidine **13**[9a] (441 mg, 1.2 mmol) in a 1:1 THF/H_2O mixture (12 mL) was cooled to 0 °C under N_2 and treated with CbzCl (257 μL, 1.8 mmol, 1.5 equiv) and solid Na_2CO_3 (510 mg, 4.8 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 8 h. Work-up (extraction with EtOAc, 3×15 mL) and column chromatography on silica gel (hexanes/EtOAc, 7:3) provided 560 mg (93%) of compound **14**: oil; $[\alpha]_D$ −27 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 30 °C): δ=7.40–7.25 (br m, 15H together, aromatic), 5.78 and 5.62 (ddt, *J*=17.2, 10.3, 6 Hz, 1H; olefinic CH), 5.15 and 5.14 (d, *J*=12.2 Hz, 1H; Cbz CH_2), 5.05 and 5.02 (d, *J*=12.2 Hz, 1H; Cbz CH_2), 5.05–4.85 (br m, 2H together; olefinic CH_2), 4.65–4.50 (br m, 4H together; benzyl CH_2), 4.24 and 4.21 (br s, 1H; C*H*OBn), 3.96 (s, 1H; C*H*OBn), 3.95–3.85 and 3.80–3.70 (m, 3H together; 2C*H*N and CH_2OH), 3.35–3.25 (m, 1H; CH_2OH), 2.10–1.55 (several br m, 4H together; CH_2CH_2) (OH signal not detected); ^{13}C NMR (125 MHz, DMSO-d_6, 30 °C): δ=153.7, 153.5, 138.0, 137.6, 136.8, 136.6 (4C together, C_q), 137.8 (olefinic), 128.4–127.4 (15 overlapped aromatic CH signals), 83.1, 82.4, 81.8, 65.7, 65.1, 64.0, 63.3 (4C together) (CH), 115.1, 114.9 (1×olefinic CH_2), 70.3, 70.2 (2×benzyl CH_2), 66.1, *65.9* (1×Cbz CH_2), 59.7, *58.6*, 30.2, 29.9, *29.8*, *28.6* (3C together) (CH_2); IR ν_{max} 3450 (br, OH), 3065, 3032 (C=C–H), 1698 (C=O) cm^{-1}; HREIMS *m*/*z* (rel int.) 501.2523 (M^+, 1), 471 (4), 426 (6), 91 (100). Calcd for $C_{31}H_{35}NO_5$: 501.2515.

3.1.9. Benzyl [(2R,3R,4R,5R)-3,4-bis(benzyloxy)-2-(but-3-enyl)-5-(hydroxymethyl)]pyrrolidine-1-carboxylate (**15**)

A solution of pyrrolidine **13** (551 mg, 1.5 mmol) in dry THF (5 mL) was cooled to 0 °C under N_2 and treated first with Et_3N (0.42 mL, 3 mmol, 2 equiv) and then dropwise with a solution of Boc_2O (360 mg, 1.65 mmol, 1.1 equiv) in THF (3 mL). The reaction mixture was stirred at room temperature for 18 h. Work-up (extraction with EtOAc, 3×25 mL) and column chromatography on silica gel (hexanes/EtOAc, 7:3) provided 477 mg (68%) of compound **15**: oil; $[\alpha]_D$ +16 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C): δ=7.40–7.25 (br m, 10H), 5.80 (ddt, *J*=17, 10, 6.2 Hz, 1H), 5.00 (br dd, *J*∼17, 1.7 Hz, 1H), 4.94 (br dd, *J*=10, 1.7 Hz, 1H), 4.57 (d, *J*=12 Hz, 2H), 4.52 (d, *J*=12 Hz, 2H), 4.02 (br d, *J*=1.8 Hz, 1H), 4.00 (br d, *J*=1.2 Hz, 1H), 3.80 (br t, *J*=3.5 Hz, 1H), 3.67 (dd, *J*=5, 3.5 Hz, 1H), 3.33 (br dt, *J*=6.5, 3.5 Hz, 1H), 3.05 (m, 1H, overlapped by water signal or hydroxyl signal), 2.15–2.00 (br m, 2H), 1.65–1.40 (br m, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 90 °C): δ=152.7, 138.2, 138.1, 81.1 (C_q), 138.3, 128.0–127.0 (10 overlapped aromatic CH signals), 88.8, 86.1, 67.6, 60.2 (CH), 114.2, 70.8, 70.7, 60.8, 32.7, 30.0 (CH_2), 27.2 (×3) (CH_3); IR ν_{max} 3390 (br, OH), 1686 (C=O) cm^{-1}; HRESMS *m*/*z* 468.2757 (M+H$^+$). Calcd for $C_{28}H_{38}NO_5$: 468.2750.

3.1.10. Benzyl [(2R,3R,4R,5R)-3,4-bis(benzyloxy)-2-(hydroxymethyl)-5-(3-oxobutyl)]pyrrolidine-1-carboxylate (**16**)

A solution of compound **14** (501 mg, ca. 1 mmol) in a 10:1 DMF/H_2O mixture (22 mL) was treated with $PdCl_2$ (71 mg, 0.4 mmol) and CuCl (495 mg, 5 mmol). The reaction mixture was then stirred under O_2 at room temperature for 24 h. Work-up (extraction with Et_2O, 3×20 mL) and column chromatography on silica gel (hexanes/EtOAc, 7:3) afforded 455 mg (88%) of methyl ketone **16**: oil; $[\alpha]_D$ −20.9 (*c* 2, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 30 °C): δ=7.40–7.25 (br m, 15H together, aromatic), 5.13 and *5.06* (br d, *J*∼12.5 Hz, 1H; Cbz CH_2), 5.13 and *5.04* (d, *J*∼12.2 Hz, 1H; Cbz CH_2), 4.90 (br s, 1H; OH), 4.60–4.50 (br m, 4H together; benzyl CH_2), 4.22 and *4.18* (br s, 1H; C*H*–OBn), 3.95–3.85 and *3.75–3.70* (m, 4H together; C*H*OBn, 2C*H*N and CH_2OH), 3.35–3.25 (m, 1H; CH_2OH), 2.45–2.35 (br m, 2H; CH_2CO), 2.15–2.05 (br m, 1H; CH_2CH$_2$CO), 2.04 and *1.94* (two s, 3H together; COMe), 1.80–1.65 (br m, 1H; CH_2CH$_2$CO); ^{13}C NMR (125 MHz, DMSO-d_6, 30 °C): δ=207.6 and *207.4*, 153.8 and *153.7*, 138, 137.9, 136.8 and *136.7* (C_q), 128.3–127.4 (15 overlapped aromatic CH signals), 83.4, *82.6*, 82.4, *81.8*, 65.7, *65.2*, 63.9, *63.4* (CH), 70.3, 70.2 (2×benzyl CH_2), 66.1, *66.0* (Cbz CH_2), 59.6, *58.6* (CH_2OH), ca. 40.5 (overlapped by solvent, CH_2CO), 25.7, *24.3* (CH_2CH_2CO) (CH_2), 29.4, *29.3* (CH_3); IR ν_{max} 3440 (br, OH), 3065, 3032 (C=C–H), 1698 (C=O) cm^{-1}; HRESMS *m*/*z* 540.2363 (M+Na$^+$). Calcd for $C_{31}H_{35}NO_6Na$: 540.2362.

3.1.11. tert-Butyl [(2R,3R,4R,5R)-3,4-bis(benzyloxy)-2-(hydroxymethyl)-5-(3-oxobutyl)]pyrrolidine-1-carboxylate (**17**)

A solution of compound **15** (467 mg, ca. 1 mmol) in a 10:1 DMF/H_2O mixture (22 mL) was treated with $PdCl_2$ (71 mg, 0.4 mmol) and CuCl (495 mg, 5 mmol). The reaction mixture was then stirred under O_2 at room temperature for 24 h. Work-up (extraction with Et_2O, 3×20 mL) and column chromatography on silica gel (hexanes/EtOAc, 7:3) afforded 416 mg (86%) of methyl ketone **17**: oil; $[\alpha]_D$ −32.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C): δ=7.40–7.20 (br m, 10H), 4.70 (br s, 1H, OH), 4.60–4.45 (br m, 4H; 2 benzyl CH_2), 4.15 (br s, 1H), 3.88 (br s, 1H), 3.78 (m, 1H), 3.62 (m, 1H), 3.30 (m, 1H), 3.10 (m, 1H), 2.37 (t, *J*=12 Hz, 2H), 2.03 (s, 3H), 2.05–1.95 (m, 1H), 1.80–1.70 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 90 °C): δ=206.8, 153.0, 137.8, 137.7, 78.5 (C_q), 128.0–127.0 (10 partially overlapped aromatic CH signals), 83.3*, 82.2*, 65.2, 63.3 (CH), 70.2, 70.1, 59.4*, ca. 40.5 (overlapped by solvent), 25.0* (CH_2), 29.0, 27.8 (×3) (CH_3) (starred signals are low and broadened); IR ν_{max} 3450 (br, OH), 3065 (C=C–H), 1689 (C=O) cm^{-1}; HRESMS *m*/*z* 506.2517 (M+Na$^+$). Calcd for $C_{28}H_{37}NNaO_6$: 506.2519.

3.1.12. Benzyl [(2R,3R,4R,5R)-3,4-bis(benzyloxy)-2-(tert-butyldiphenyl-silyloxy)methyl-5-(3-oxobutyl)]pyrrolidine-1-carboxylate (**18**)

A solution of compound **16** (103 mg, 0.2 mmol) in dry DMF (2 mL) was treated with *tert*-butyldiphenylsilyl chloride (62 μL, 0.24 mmol, 1.2 equiv) and imidazole (33 mg, 0.48 mmol). The reaction mixture was then stirred under N_2 at room temperature for 18 h. Work-up (extraction with Et_2O, 3×10 mL) and column chromatography on silica gel (hexanes/EtOAc, 8:2) provided 133 mg (88%) of the silylated derivative **18**: oil; $[\alpha]_D$ −9.7 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 30 °C): δ=7.60–7.10 (several m, 25H together, aromatic), 5.10 and *4.95* (d, *J*=12.5 Hz, 1H together; Cbz CH_2), 4.97 and *4.87* (d, *J*=12 Hz, 1H together; Cbz CH_2), 4.65–4.60 (br m, 2H; benzyl CH_2), 4.50–4.40 (AB system, *J*=12 Hz, 2H; benzyl CH_2), 4.31 and *4.29* (br s, 1H together; C*H*–OBn), 4.12 and *4.06* (br dd, *J*=9, 4.5 Hz, 1H together; C*H*–N), 4.05–3.95 (br m, 1H; C*H*–OBn), 3.91 (br dd, *J*=9, 4.5 Hz, 1H; CH_2OH), 3.70 and *3.67* (br dd, *J*=10, 2.5 Hz; 1H together; C*H*–N), 3.55 (br q, *J*=9 Hz, 1H; CH_2OH), 2.50–2.35 (br m, 2H; CH_2CO), 2.10 and *1.80–1.70* (br m, 2H together; CH_2CH$_2$CO), 2.04 and *1.94* (s, 3H together; COMe), 0.97 and *0.92* (s, 9H together; Si*t*-Bu); ^{13}C NMR (125 MHz, DMSO-d_6, 30 °C): δ=207.7, 153.5, 137.8 (×2), 136.5, 132.8 (×2), 18.7 (C_q), 135.0 (×4), 130.0, 129.9, 128.5 (×4), 128.3 (×4), 128.0–127.4 (11 overlapped aromatic CH signals), 83.3*, 82.5, 82.0, 81.6 (2C together; C*H*–O), 65.1, 64.6, 64.0, 63.6* (2C together; C*H*–N) (CH), 70.5, 70.3 (2×benzyl CH_2), 66.2 and *66.0* (Cbz CH_2), 62.0 and *61.0* (CH_2OH), ca. 40.5 (overlapped by solvent, CH_2CO), 25.8* and *24.2* (CH_2, CH_2CH$_2$CO), 29.6 ($COCH_3$), 26.6 (3×CH_3) (starred signals are low and broadened); IR ν_{max} 3065 (C=C–H), 1701 (C=O) cm^{-1}; HRFABMS *m*/*z* 756.3721 (M+H$^+$). Calcd for $C_{47}H_{54}NO_6Si$: 756.3720.

*3.1.12.1. tert-Butyl [(2R,3R,4R,5R)-3,4-bis(benzyloxy)-2-(tert-butyldiphenyl-silyloxy)methyl-5-(3-oxobutyl)]pyrrolidine-1-carboxylate (**19**).* A solution of compound **17** (97 mg, ca. 0.2 mmol) in dry DMF (2 mL) was treated under N_2 with *tert*-butyldiphenylsilyl chloride (62 μL, 0.24 mmol, 1.2 equiv) and imidazole (33 mg, 0.48 mmol). The reaction mixture was then stirred at room temperature for 24 h. Work-up (extraction with Et_2O, 3×10 mL) and column chromatography on silica gel (hexanes/EtOAc, 8:2) provided 94 mg of the silylated derivative **19** (65%, 90% based on recovered **17**) as well as unreacted **17** (27 mg). The NMR spectra of **19** were coincident with those reported.[8]

*3.1.13. (1R,2R,3R,5R,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2-diol, hyacinthacine A_3 (**3**) and (1R,2R,3R,5S,7aR)-3-(hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2-diol, 5-epi-hyacinthacine A_3 (5-epi-**3**)*

Pyrrolidine **16** (104 mg, ca. 0.2 mmol) was dissolved in MeOH (8 mL). After addition of Degussa-type 10% Pd/C (100 mg), the mixture was stirred at room temperature for 24 h under an H_2 atmosphere until disappearance of the starting compound (TLC monitoring, UV-absorbing products were still present). The mixture was then filtered through a pad of Celite (MeOH), and the solvent was removed under reduced pressure. After this, the residue was dissolved in MeOH (6 mL), followed by addition of 6 M HCl (0.6 mL) and Degussa catalyst (100 mg). The mixture was subsequently stirred for 32 h under an H_2 atmosphere until no UV-absorbing products were observed in TLC plates.

Following this, the mixture was filtered through a pad of Celite (MeOH), and the solvent was removed under reduced pressure. The obtained residue was dissolved in MeOH (2 mL) and the solution was brought to basic pH with dropwise addition of 33% aq NH_3. After stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The residue was then put on the top of a ion-exchange resin column (Dowex® 50Wx4 200–400 mesh, pre-acidified with 0.5 M HCl). Elution with water (50 mL) to remove salts and then with 1 M aq NH_3 until elution of the product (TLC monitoring), followed by removal of the volatiles of the latter fraction under reduced pressure, gave a brownish residue which was subjected to column chromatography on silica gel ($CHCl_3$/MeOH/aq NH_3, gradient from 90:9:1 to 70:29:1). This yielded hyacinthacine A_3 (**3**) (17 mg, 45% yield from **16**) and 5-*epi*-hyacinthacine A_3 (5-*epi*-**3**) (14 mg, 37% yield from **16**).

*3.1.13.1. Compound **3**.* oil; $[\alpha]_D$ +15.1 (*c* 0.35, H_2O), lit.[2] $[\alpha]_D$ +19.2 (*c* 0.43, H_2O), lit.[8] $[\alpha]_D$ +14 (*c* 0.55, H_2O); IR ν_{max} 3370 (br, OH) cm^{-1}; HRESMS *m*/*z* 188.1282 ($M+H^+$). Calcd for $C_9H_{18}NO_3$: 188.1287. For NMR data and their comparison with literature values for natural and synthetic samples, see Supplementary data.

*3.1.13.2. Compound 5-epi-**3**.* oil; $[\alpha]_D$ +22 (*c* 0.3, H_2O), lit.[5c] $[\alpha]_D$ +24.8 (*c* 14, H_2O), lit.[5d] $[\alpha]_D$ −162 (*c* 0.5, H_2O); IR ν_{max} 3390 (br, OH) cm^{-1}; HRESMS *m*/*z* 188.1285 ($M+H^+$). Calcd for $C_9H_{18}NO_3$: 188.1287. For NMR data and their comparison with literature values for previous synthetic samples, see Supplementary data.

*3.1.14. (1R,2R,3R,5S,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2-diol, 5-epi-hyacinthacine A_3 (5-epi-**3**)*

Pyrrolidine **16** (52 mg, ca. 0.1 mmol) was dissolved in MeOH (3 mL) and treated with 6 M HCl (0.3 mL). After addition of Degussa-type 10% Pd/C (50 mg), the mixture was stirred for 48 h at room temperature under an H_2 atmosphere until no UV-absorbing products were observed in TLC plates.

Following this, the mixture was processed in the same way as above. Column chromatography on silica gel ($CHCl_3$/MeOH/aq NH_3, gradient from 90:9:1 to 70:29:1) furnished 5-*epi*-hyacinthacine A_3 (5-*epi*-**3**) (13 mg, 69% yield from **16**).

When the reaction was carried out with pyrrolizidine **17** instead of **16**, a similar result was observed. Under the same reaction conditions, **18** gave 5-*epi*-**3** in 75% yield and **19** afforded a mixture of **3** and 5-*epi*-**3**.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.046.

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18. For **2**, the complete sequence includes 16 steps from D-serine with ca. 21% overall yield. This compares well with the overall yields of the previous syntheses, which were with one exception[7d] in the range 3–11% from commercial precursors. For **3** and 5-*epi*-**3**, the sequence contains 15 steps along the respective synthetic routes **5**→**16**→**3** and **5**→**16**→5-*epi*-**3**. The overall yields were ca. 14% and 21%, respectively.