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Total Synthesis of (+)-Hyacinthacine A_2 Based on SmI_2-Induced Nitrone Umpolung

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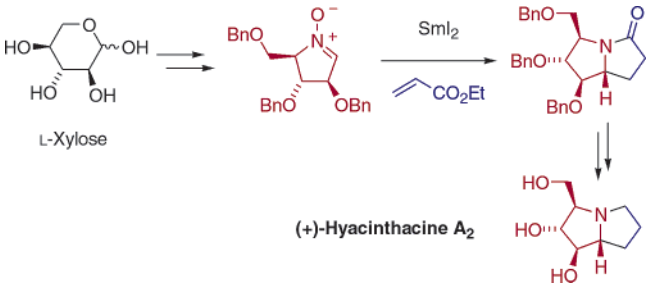
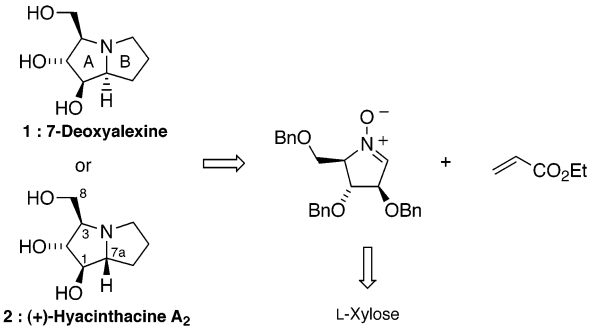


A concise total synthesis of (+)-hyacinthacine A_2, a polyhydroxylated pyrrolizidine alkaloid, is described using our recently discovered inversion of the C−N bond polarity in nitrones. In the key step, the diastereoselective reductive coupling of a L-xylose-derived cyclic nitrone with ethyl acrylate allowed the assembly of the bicyclic core of the target molecule, by way of a tandem formation of the C−C and C−N bonds. The method opens a novel, short, and general route for the synthesis of other pyrrolizidine alkaloids.

Owing to the importance of carbohydrate processing enzymes in pathologies such as diabetes, cancer, or AIDS, selective inhibition of these enzymes represents a promising therapeutic strategy.[1] Iminosugars have rapidly emerged as candidates of choice for inhibiting both glycosidases[2] and glycosyltransferases.[3] In particular, a great deal of attention has been focused on their bicyclic, conformationally constrained analogues, which often exhibit better selectivity toward specific enzymes.[2] As the natural polyhydroxylated pyrrolizidines and their synthetic analogues are part of this class of potential inhibitors, many synthetic efforts have been directed toward their preparation.[4,5] However, most of the reported methodologies are lengthy and/or lead to low selectivity.

SCHEME 1. Retrosynthetic Approach to Polyhydroxylated Pyrrolizidines



We have recently described the first samarium diiodide-induced *umpolung* of nitrones, which become able to undergo reductive coupling with carbonyl derivatives[6] and α,β-unsaturated esters.[7] The latter methodology opens a direct route to γ-*N*-hydroxylamino esters. As in principle γ-lactams should be easily obtained from the corresponding γ-*N*-hydroxylamino esters, we became interested in using sugar-derived cyclic nitrones to develop a new access to functionalized pyrrolizidines, following the retrosynthetic approach outlined in Scheme 1. Our strategy relied on the assembly of the sugar-derived A-ring of pyrrolizidines (including the nitrogen atom) with the three carbons necessary to complete B-ring formation, in a tandem process. Although it could be anticipated that in the key step the chain would be introduced preferentially on the less hindered α-face, the stereochemical outcome of this still uninvestigated reaction was of interest.[8] Depending on the selectivity of the reductive coupling step, a new route to either alexines or hyacinthacines would be designed.

While 7-deoxyalexine (**1**)[9] is a synthetic product for which biological activity has not been investigated yet, hyacinthacine A_2 (**2**) is a representative member of the

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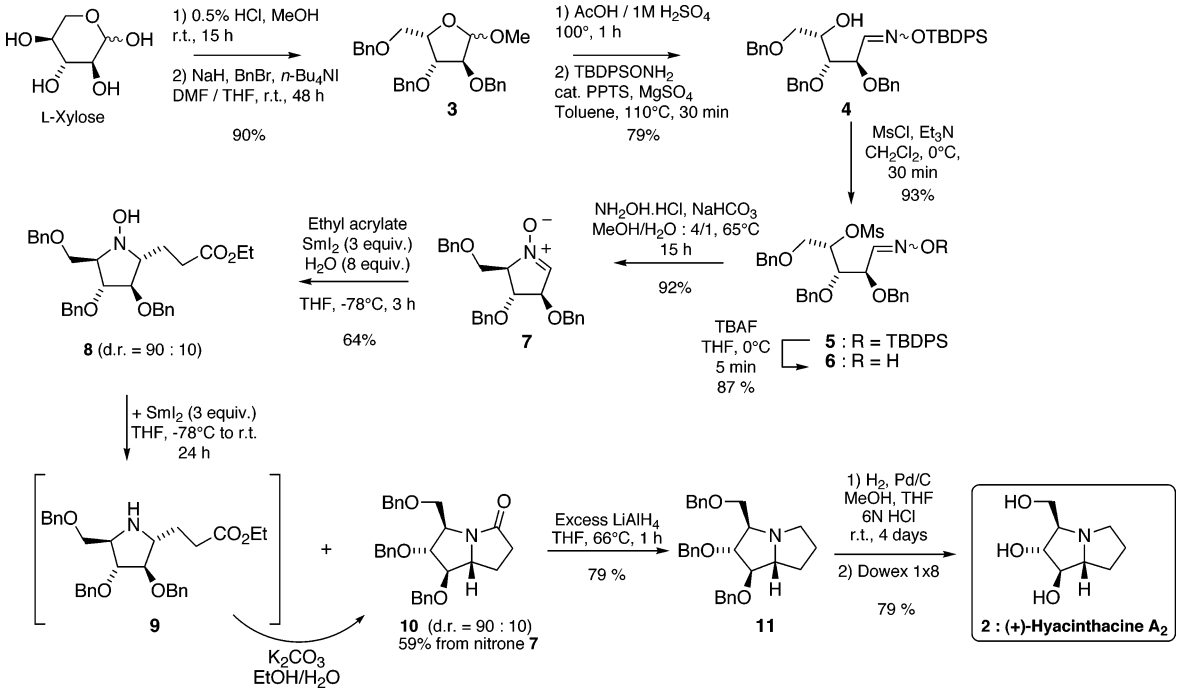
SCHEME 2



natural pyrrolizidine alkaloids family. It was isolated from the bulbs of *Muscari armeniacum* (Hyacinthaceae)[10] and exhibits selective inhibition of amyloglucosidase from *Aspergillus niger* (IC_{50} 8.6 μM). The first synthesis of hyacinthacine A_2 was accomplished in 2001.[11] Then two other syntheses appeared in the literature during the course of our work,[12] and yet another approach targeted an advanced synthetic intermediate to hyacinthacine A_2.[13] The synthetic strategies by the groups of Goti[12a] and Tamura[13] also involved a cyclic sugar-derived nitrone as the key intermediate that was used in a 1,3-dipolar cycloaddition process.

Herein, we wish to highlight a novel aspect of the reactivity of such nitrones in the presence of SmI_2, i.e., their ability to be transformed into α-azanucleophilic species.

Our synthesis started with the preparation of nitrone **7**[12a,14] from L-xylose, an unnatural but not too expensive sugar. Thus, 2,3,5-tri-*O*-benzyl-L-xylofuranose[15] was sequentially reacted with *O*-*tert*-butyldiphenylsilylhydroxylamine[16] and then with mesyl chloride, with the aim of using Tamura's method for selective cyclization of γ-mesyloxy oximes.[13,17] However, in our hands this method proved poorly reproducible, and treatment of the γ-mesyloxy oxime **5** with tetrabutylammonium triphenyldifluorosilicate (TBAT)[18] often led to substantial amounts of unprotected oxime **6** as a side product, even when using freshly opened bottles of TBAT or previously dried material (P_2O_5, desiccator). Next, we found that heating (methanol reflux) the mesyloxy oxime **6** in the presence of hydroxylamine hydrochloride and sodium hydrogen carbonate offered better results in terms of yields and reproducibility and led to nitrone **7** as a white, crystalline product, in 92% yield (Scheme 2).

This nitrone was then treated with SmI_2 [19] and ethyl acrylate in THF at −78 °C, in the presence of water, under conditions previously optimized for the reductive coupling of nitrones with α,β-unsaturated esters.[7a] Under these conditions, the expected *N*-hydroxypyrrolidine **8** was smoothly obtained, in 64% yield and with good stereoselectivity (dr = 90:10). Considering the well-known propensity of *N*-hydroxylamines to be reduced to amines in the presence of SmI_2,[20] we next thought to prepare pyrrolizidinone **10** in a single step. Thus, when TLC control showed total consumption of the starting nitrone (ca. 3 h), excess SmI_2 was added to the reaction mixture, which was then warmed to room temperature. Under these conditions, a mixture of amine **9** and lactam **10** was obtained, in variable proportions. Treating the crude mixture with potassium carbonate in EtOH/H_2O induced total conversion of **9** to **10** which, after purification by chromatography, was isolated in 59% overall yield.

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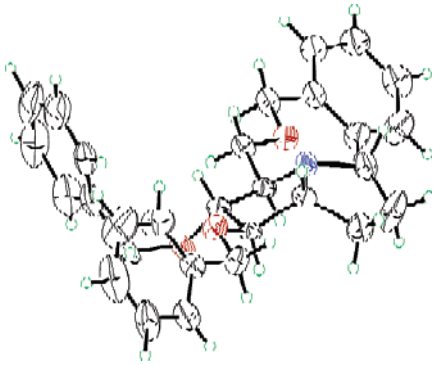

FIGURE 1. ORTEP diagram for compound **11**.

At this stage of the synthesis, the configuration of the new stereocenter in the molecule (C-7a) had to be determined, but NOE experiments on either **8**, **9**, or **10** did not prove informative. Fortunately, reduction of **10** to the corresponding pyrrolizidine **11** by $LiAlH_4$ afforded a nicely crystalline product which could be analyzed by X-ray diffraction[21] (Figure 1). This analysis showed unambiguously that the reductive addition took place on the face opposite to the C-2 and C-4 substituents in the nitrone, affording the product with a trans configuration, i.e., related to the hyacinthacine family.

Deprotection of the benzyl groups was then accomplished as previously described[11] to afford after proper neutralization (+)-hyacinthacine A_2, in 19% overall yield from L-xylose. The synthetic product exhibited physical and spectral properties identical to the data reported for the natural product.

In conclusion, the synthesis of hyacinthacine A_2 described herein illustrates the potential of our novel, convergent methodology based on nitrone *umpolung*. This method complements favorably the well-known 1,3-cycloaddition processes and *opens the field for the synthesis of other polyhydroxypyrrolizidines* starting from a variety of sugar-derived cyclic nitrones. In particular, it should be useful for the preparation of new analogues of the natural pyrrolizidine alkaloids bearing substituents at C-7 that, to the best of our knowledge, have not been accessible via 1,3-cycloaddition. The preparation of new B-ring substituted hyacinthacines is currently under investigation in our laboratories, and their biological evaluation will hopefully lead to a better understanding of the structural requirements for glycosidase and glycosyltransferase inhibition.

Experimental Section

2,3,5-Tri-*O*-benzyl-L-xylofuranose *O*-*tert*-Butyldiphenylsilyloxime (4). Methyl 2,3,5-tri-*O*-benzyl-α,β-L-xylofuranoside **3**[22] (12.3 g, 28.3 mmol) in acetic acid (160 mL) and 1 M aqueous H_2SO_4 (40 mL) was heated at 100 °C for 1 h. After cooling, the mixture was diluted with CH_2Cl_2 (250 mL), and the organic layer was washed with 5 N NaOH and then with brine, dried over $MgSO_4$, and concentrated under vacuum to yield 2,3,5-tri-*O*-benzyl-L-xylofuranose as an oil, which was used without purification in the next step. To a solution of 2,3,5-tri-*O*-benzyl-L-xylofuranose (3.2 g, 7.62 mmol) in dry toluene (31 mL) was added $MgSO_4$ (3.7 g) under argon. The suspension was stirred at reflux temperature for 5 min, and then *O*-*tert*-butyldiphenylsilylhydroxylamine (3.1 g, 11.42 mmol) and pyridinium *p*-toluenesulfonate (60 mg) were added. The reaction mixture was heated at the same temperature for 30 min, and then it was filtered. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ and with brine and dried over $MgSO_4$ to give a residue, which upon column chromatography over silica gel (pentane/AcOEt 9/1, 4/1, then 1/1) yielded the oxime **4** (4.05 g, 79%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H), 2.41 (d, 1H, J = 6.5 Hz), 3.39 (d, 2H, J = 6 Hz), 3.71 (dd, 1H, J = 3, 6 Hz), 3.95−4.04 (m, 1H), 4.18 (dd, 1H, J = 6, 8 Hz), 4.24 (d, AB system, 1H, J = 12 Hz), 4.40 (s, 2H), 4.51 (d, AB system, 1H, J = 12 Hz), 4.52 (d, AB system, 1H, J = 12 Hz), 4.69 (d, AB system, 1H, J = 12 Hz), 7.15−7.35 (m, 21H), 7.65−7.73 (m, 4H); 7.79 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) d 19.7, 27.5, 70.0, 71.4, 73.7, 74.6, 76.8, 79.1, 128.0−128.8, 130.2, 133.8, 133.9, 136.0, 137.9, 138.3, 138.4, 154.7; MS (DCI) *m/z* 674 (100) $[M + H]^+$; IR ν (cm^{-1}) 3551, 3476, 3461, 3069, 3037, 2931, 2857, 1959, 1878, 1804, 1722, 1582, 1495, 1453, 1110. Anal. Calcd for $C_{42}H_{47}O_5NSi$: C, 74.85; H, 7.03; N, 2.08. Found: C, 74.68; H, 6.99; N, 2.08.

2,3,5-Tri-*O*-benzyl-4-methanesulfonyl-L-xylofuranose Oxime (6). To a solution of oxime **4** (4.05 g, 6.02 mmol) in CH_2Cl_2 (18 mL) placed at 0 °C under argon atmosphere were added successively triethylamine (1.3 mL, 9.34 mmol) and mesyl chloride (556 μL, 7.03 mmol). The solution was stirred for 30 min, and then water (5 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give a residue, which upon column chromatography over silica gel (pentane/AcOEt 9/1, 4/1, then 1/1) yielded the mesylate **5** (4.205 g, 93%: 3/1 mixture of *E*/*Z* isomers) as an oil. To a solution of mesylate **5** (4.87 g, 5.60 mmol) in THF (180 mL) placed at 0 °C under argon was added tetrabutylammonium fluoride (6.6 mL, 1 M solution in THF, 6.6 mmol). The reaction mixture was stirred for 5 min at 0 °C, and then the solvent was removed under vacuum. The residue was dissolved in ethyl acetate, water was added, and the aqueous layer was extracted three times with ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give a residue, which upon column chromatography over silica gel (pentane/AcOEt 9/1, 4/1, then 1/1) yielded the oxime **6** (2.5 g, 87%: 2/1 mixture of *E*/*Z* isomers) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.86 (s, 0.9H), 2.91 (s, 2.1H), 3.44 (dd, 0.33H, J = 5.5, 11.5 Hz), 3.53 (dd, 0.66H, J = 5.5, 11.0 Hz), 3.90 (t, 0.66H, J = 5.5 Hz), 4.08−4.21 (m, 1.33H), 4.25−4.69 (m, 6H), 4.86−4.95 (m, 1.33H), 6.94 (d, 0.33H, J = 5.5 Hz), 7.23−7.29 (m, 15H), 7.45 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 38.1, 38.3, 68.6, 71.1, 71.9, 73.3, 75.0, 75.2, 75.2, 77.7, 78.7, 80.7, 81.5, 127.8−128.5, 136.6−137.3, 149.0, 151.0; MS (DCI) *m/z* 514 (100) $[M + H]^+$, 531 (92) $[M + NH_4]^+$, 418 (29) $[M - OMs]^+$; IR ν (cm^{-1}) 3425, 3090, 3061, 3032, 2937, 2865, 1962, 1897, 1824, 1605, 1496, 1453, 1365, 1169, 1067.

Nitrone 7[12a,14] **((2*R*,3*R*,4*R*)-3,4-Bis-benzyloxy-2-benzyloxymethyl-3,4-dihydro-2*H*-pyrrole 1-Oxide).** To a solution of oxime **6** (170 mg, 0.33 mmol) in a 4:1 mixture of methanol and water (3.75 mL) were added $NaHCO_3$ (233 mg, 2.77 mmol) and hydroxylamine hydrochloride (184 mg, 2.65 mmol). The reaction mixture was heated overnight at reflux temperature. After concentration under vacuum, the residue was dissolved in CH_2Cl_2, and water was added. The aqueous layer was extracted three times with CH_2Cl_2, and the organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give a residue, which upon column chromatography over silica gel (pentane/AcOEt 9/1, 4/1, then 1/1) yielded the nitrone **7** (124 mg, 92%) as a white solid: mp 91−93 °C (lit.[14] mp 88−90 °C); $[\alpha]^{20}_D$ −42 (*c* 1.3, $CHCl_3$) (lit.[14] $[\alpha]^{20}_D$ −41.7 (*c* 1.00, CH_2Cl_2)); ^{1}H NMR ($CDCl_3$) δ 3.80 (dd, 1H, J = 3, 10 Hz), 4.04 (m, 1H), 4.08 (dd, 1H, J = 5, 10 Hz), 4.41 (dd, 1H, J = 2, 3.5 Hz), 4.54 (d, AB system, 1H, J = 12 Hz), 4.57 (d, 2H, J = 3 Hz), 4.58 (s, 2H), 4.64 (d, AB system, 1H, J = 12 Hz), 4.69 (t, 1H, J = 2 Hz), 6.91 (s, 1H); 7.30−7.38 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 66.6, 72.1, 72.3, 73.9, 77.9, 80.8, 83.2, 128.1−129.0, 133.1, 137.5, 137.7, 138.1; MS (DCI) *m/z* 418 (100) $[M + H]^+$,

(21) See Supporting Information.

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420 (31) $[M + H - O]^+$; IR ν (cm^{-1}) 3045, 2873, 1959, 1878, 1820, 1589, 1497, 1453, 1088. Anal. Calcd for $C_{26}H_{27}O_4N$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.59; H, 6.56; N, 3.28.

3-((2*R*,3*R*,4*R*,5*R*)-3,4-Bis-benzyloxy-5-benzyloxymethylpyrrolidin-2-yl)propionic Acid Ethyl Ester (8). A stirred and carefully deoxygenated solution of the nitrone **7** (102 mg, 0.245 mmol) in dry THF (5 mL) was cooled to −78 °C under argon. Freshly distilled ethyl acrylate (37 μL, 0.34 mmol), degassed water (35 μL, 1.96 mmol), and a 0.088 M solution of SmI_2 in THF (8.4 mL, 0.74 mmol) were then added. The temperature was kept at −78 °C during 3 h, and then air was introduced until disappearance of the blue color of the reaction mixture, whereupon a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and ethyl acetate (15 mL) were added. The yellow mixture was extracted with AcOEt (3 × 20 mL), and the combined organic layers were washed with a saturated aqueous solution of NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the resulting residue by chromatography on silica gel (pentane/AcOEt 4/1, then 1/1) afforded the expected *N*-hydroxypyrrolidine ester **8** (82 mg; 64%: 90:10 mixture of diastereomers) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, J = 7 Hz), 1.83−1.97 (m, 1H), 2.07−2.19 (m, 1H), 2.40 (t, 2H, J = 7 Hz), 3.15 (lq, 1H, J = 6.5 Hz), 3.52−3.60 (m, 2H), 3.78 (m, 1H), 3.85 (dd, 1H, J = 3, 6.5 Hz), 3.97 (t, 1H, J = 3 Hz), 4.09 (q, 2H, J = 7 Hz), 4.43 (d, AB system, 1H, J = 12 Hz), 4.50 (s, 2H), 4.52 (s, 2H), 4.57 (d, AB system, 1H, J = 12 Hz), 6.39 (s, 1H), 7.27−7.31 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.9, 31.0, 60.3, 68.0, 69.0, 70.0, 71.5, 71.7, 73.2, 84.6, 86.1, 127.6−128.3, 137.9, 138.0, 138.1, 174.0; MS (DCI) *m/z* 520 (100) $[M + H]^+$; IR ν (cm^{-1}) 3428, 3087, 3062, 3028, 2930, 2873, 1730, 1091. Anal. Calcd for $C_{31}H_{37}O_6N$: C, 71.65; H, 7.18; N, 2.70. Found: C, 71.66; H, 7.02; N, 2.73.

(5*R*,6*R*,7*R*,7a*R*)-6,7-Bis-benzyloxy-5-benzyloxymethylhexahydropyrrolizin-3-one (10). A stirred and carefully deoxygenated solution of the nitrone **7** (380 mg, 0.91 mmol) in dry THF (18.5 mL) was cooled to −78 °C under argon. Freshly distilled ethyl acrylate (139 μL, 1.28 mmol), degassed water (136 μL, 7.56 mmol), and a 0.1 M solution of SmI_2 in THF (28 mL, 2.8 mmol) were then added. The temperature was kept at −78 °C during 3 h, and after checking by TLC that the starting nitrone had been completely converted, excess samarium diiodide was added (28 mL, 2.8 mmol) and the temperature was allowed to reach room temperature overnight. The reaction was then quenched by introduction of air, and then a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and ethyl acetate (30 mL) was added. The yellow mixture was extracted with AcOEt (3 × 30 mL), and the combined organic layers were washed with a saturated aqueous solution of NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue, containing a mixture of pyrrolidine **9** and pyrrolizidinone **10**, was dissolved in ethanol (20 mL) and treated with a solution of potassium carbonate (150 mg, 1.17 mmol) in water (5 mL) during 2 days. The mixture was then concentrated in vacuo, and the residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the resulting residue by chromatography on silica gel (CH_2Cl_2/MeOH: 99/1, then 95/5) afforded the expected pyrrolizidinone **10** (246 mg; 59%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.70−1.88 (m, 1H), 2.17−2.42 (m, 2H), 2.56 (td, 1H, J = 10, 16 Hz), 3.50−3.63 (m, 2H), 3.70 (dd, 1H, J = 5, 7 Hz), 3.88 (q, 1H, J = 7 Hz), 4.05−4.12 (m, 1H), 4.32 (dd, 1H, J = 4, 5 Hz), 4.45−4.61 (m, 6H), 7.27−7.30 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 25.6, 33.0, 58.4, 63.5, 69.1, 72.0, 72.1, 73.0, 86.9, 88.9, 127.3, 128.3, 137.6−138.0, 174.6; MS (DCI) *m/z* 458 (100) $[M + H]^+$; IR ν (cm^{-1}) 3090, 3063, 3031, 2857, 1967, 1878, 1820, 1698, 1101. Anal. Calcd for $C_{29}H_{31}O_4N$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.25; H, 6.88; N, 3.11.

(1*R*,2*R*,3*R*,7a*R*)-1,2-Bis-benzyloxy-3-benzyloxymethylhexahydropyrrolizine (11). A solution of pyrrolizidinone **10** (60 mg, 0.13 mmol) in THF (5 mL) was cooled to 0 °C under argon, and then lithium aluminum hydride (9 mg, 0.25 mmol) was added. The reaction mixture was stirred during 5 h at reflux temperature, and then it was quenched with water (9 μL), an aqueous 15% solution of NaOH (9 μL), and water (36 μL) and stirred for 1 h. Then sodium sulfate was added, the mixture was stirred for 1 h and filtered through Celite, and the filtrate was concentrated under vacuum to give a residue, which upon column chromatography over alumina (pentane/AcOEt 9/1, 4/1, then 1/1) yielded the pyrrolizidine **11** (46 mg, 79%) as a white solid: mp 47.5 °C; $[\alpha]^{20}_D$ −5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.61−2.01 (m, 4H), 2.76 (td, 1H, J = 7, 10 Hz), 2.94 (td, 1H, J = 5, 7 Hz), 3.05 (td, 1H, J = 6, 10 Hz), 3.45 (dt, 1H, J = 6, 7 Hz), 3.51 (dd, 1H, J = 7, 10 Hz), 3.59 (dd, 1H, J = 5, 10 Hz), 3.80 (t, 1H, J = 6 Hz), 4.06 (dd, 1H, J = 6, 7 Hz), 7.26−7.31 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 25.8, 31.7, 55.1, 67.4, 68.3, 71.9, 72.1, 72.5, 73.2, 85.7, 88.9, 127.4−128.3, 138.3, 138.4, 138.5; MS (DCI) *m/z* 444 (100) $[M + H]^+$; IR ν (cm^{-1}) 3069, 3029, 2921, 2857, 1949, 1872, 1803, 1495, 1451, 1101. Anal. Calcd for $C_{29}H_{33}O_3N$: C, 78.52; H, 7.50. Found: C, 78.43; H, 7.83.

(+)-Hyacinthacine A_2 (2). To a solution of pyrrolizidine **11** (60 mg, 0.14 mmol) in a 4:1 mixture of methanol and THF (10 mL) was added Pd/C 10% (24 mg). After the reaction flask was purged with hydrogen, 10 drops of HCl 6 N were added and the reaction mixture was stirred for 4 days at room temperature under hydrogen. The mixture was then filtered through Celite, and the filtrate was concentrated under vacuum. The residue was dissolved in a minimum of water and stirred with DOWEX 1X8 resin (OH^- form) until pH = 11.55. After filtration, the filtrate was concentrated under vacuum to give spectroscopically pure hyacinthacine A_2 (**2**) (18.5 mg, 79%): $[\alpha]^{20}_D$ +19.9 (*c* 0.97, MeOH) [lit.[10] $[\alpha]^{25}_D$ +20.1 (*c* 0.44, H_2O); lit.[11] $[\alpha]^{25}_D$ +12.5 (*c* 0.4, H_2O); lit.[12a] $[\alpha]^{25}_D$ +12.7 (*c* 0.13, H_2O); lit.[12b] $[\alpha]^{25}_D$ +10.5 (*c* 0.6, H_2O)]; ^{1}H NMR (D_2O) δ 1.70−2.00 (m, 4H), 2.66−2.77 (m, 2H), 2.85−2.93 (m, 1H), 3.10−3.17 (m, 1H), 3.61−3.81 (m, 4H); ^{13}C NMR (D_2O) δ 27.3, 32.6, 57.6, 66.0, 68.8, 72.0, 80.2, 83.1; MS (DCI) *m/z* 174 (100) $[M + H]^+$; IR ν (cm^{-1}) 3354, 2956, 2920, 2866, 1124.

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Supporting Information Available: General procedures, copies of spectra for compounds **8**−**11** and for synthetic (+)-hyacinthacine A_2 (**2**), as well as crystallographic data for compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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