The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo400386f • Publication Date (Web): 04 Apr 2013

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Asymmetric Approach to Hyacinthacines B_1 and B_2

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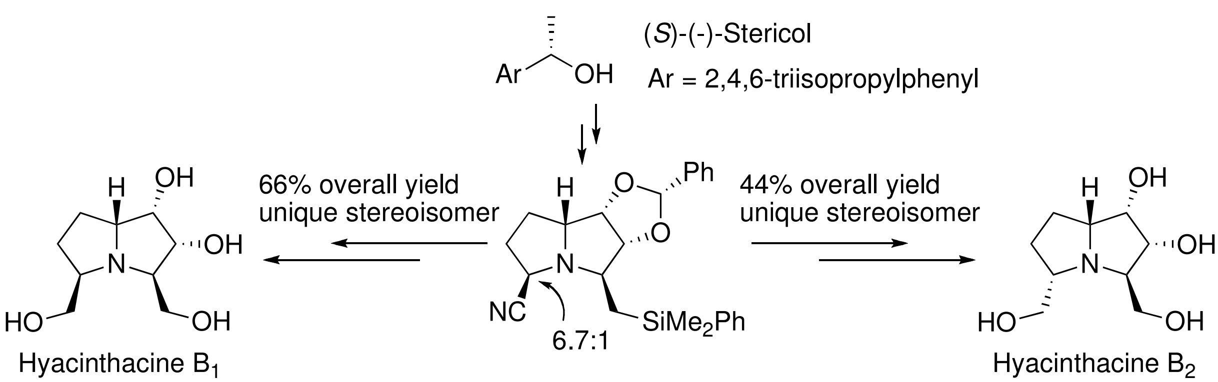


ABSTRACT: Naturally occurring hyacinthacines B_1 and B_2 have been prepared from a common, easily available, advanced intermediate. The approach features several highly stereoselective

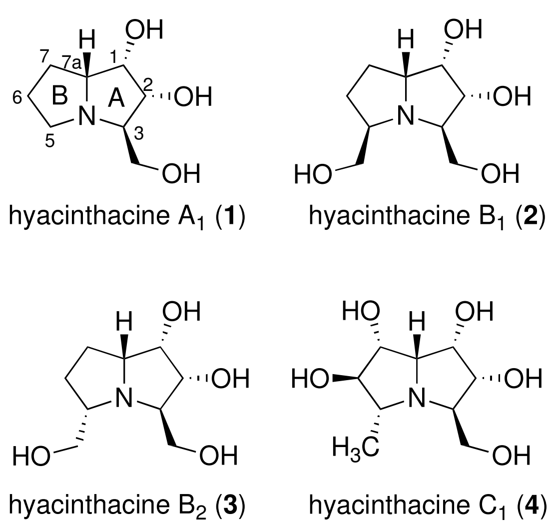
transformations: *inter alia*, a dichloroketene–enol ether [2+2] cycloaddition, a Bruylants alkylation, and an amino-nitrile alkylation–reduction.

INTRODUCTION

Glycosidase inhibition has received considerable attention over the past several years, mainly because glycosidases, which catalyze the hydrolysis of oligosaccharides and glycoconjugates, are involved in an array of diverse biological processes.[i] Inhibitors of these enzymes can thus be viewed as potential drugs against various human diseases.[ii] With relatively few compounds presently in clinical use, however, research aimed at finding new inhibitors continues unabated.[iii]

The iminosugars[iv] are currently among the most studied glycosidase inhibitors and the hyacinthacines, which are polyhydroxylated pyrrolizidines, figure prominently within this group (Figure 1).[v] Since the isolation of the first of the hyacinthacine alkaloids by Asano and coworkers in 1999,[vi] more than 20 have been identified. These iminosugars are characterized by the presence of an hydroxymethyl substituent at C-3 and are divided into 3 groups, A, B, and C, depending on the number of hydroxyl and hydroxylmethyl substituents on ring B of the pyrrolizidine system.[vii]

Figure 1. Examples of Hyacinthacines



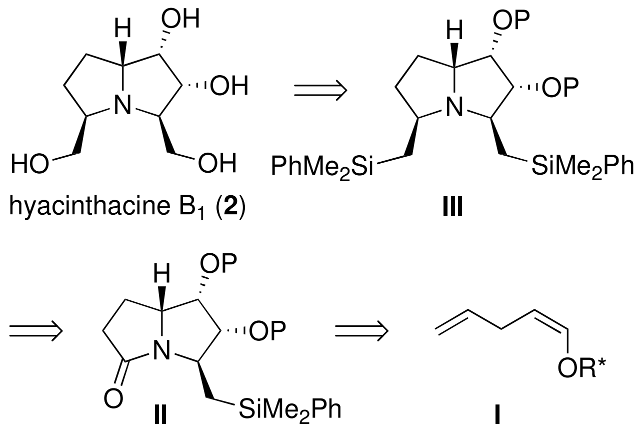
The hyacinthacines have been shown to possess strong, selective biological activities, which, coupled with their compact, highly functionalized structures, make them worthwhile synthetic targets. Not surprisingly, synthetic efforts toward the hyacinthacines have so far focused primarily on the preparation of the simpler group A members, in both racemic form and natural form (using chiral pool or enzymatic techniques).[viii,ix] A few years ago, we reported the first non-chiral pool/non-enzymatic approach to natural hyacinthacine A_1,[x] which relied on a strategy based on asymmetric dichloroketene–chiral enol ether cycloaddition,[xi] previously applied[xii,xiii,xiv] for the preparation of a variety of other alkaloids.[xv] We now describe in detail[xvi] the extension of this work to access the more structurally complexe hyacinthacines B_1 and B_2. These alkaloids, isolated in low yield (22 mg/kg and 5 mg/kg, respectively) by Asano and coworkers from bulbs of *Scilla campanulata*, have been shown to be selective inhibitors of ß-glucosidase and ß-galactosidase.[vi] Their structures are characterized by the presence of five stereocenters and two synthetically challenging hydroxymethyls at C-3 and C-5. To the best of our knowledge, only one other approach to these alkaloids, which employed L-pyroglutamic acid for chirality, has been reported.[ixa]

RESULTS AND DISCUSSION

Synthesis of Hyacinthacine B_1

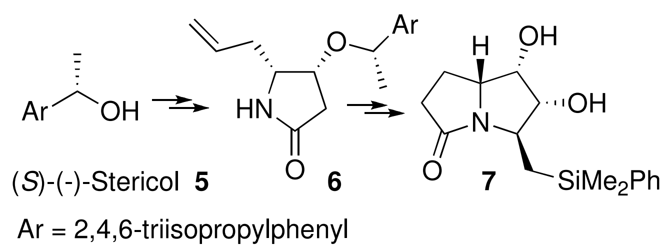
It was envisaged that hyacinthacine B_1 would be obtained from the disilyl derivative **III** through an uncommon double Tamao-Fleming oxidation to generate in a single step the requisite hydroxymethyl groups. The C-5 dimethylphenylsilylmethyl substituent might be introduced stereoselectively through a Bruylants reaction[xvii] of the amino-nitrile obtained through reductive cyanation of pyrrolizidinone **II**. Significantly, pyrrolizidinone **II** seemed to offer as well several means to access hyacinthacine B_2 (see below). The unprotected pyrrolizidinone **II** (P=H) had earlier been prepared from enol ether **I** (R*OH = Stericol®).[x]

Scheme 1. Retrosynthesis of (+)-Hyacinthacine B_1



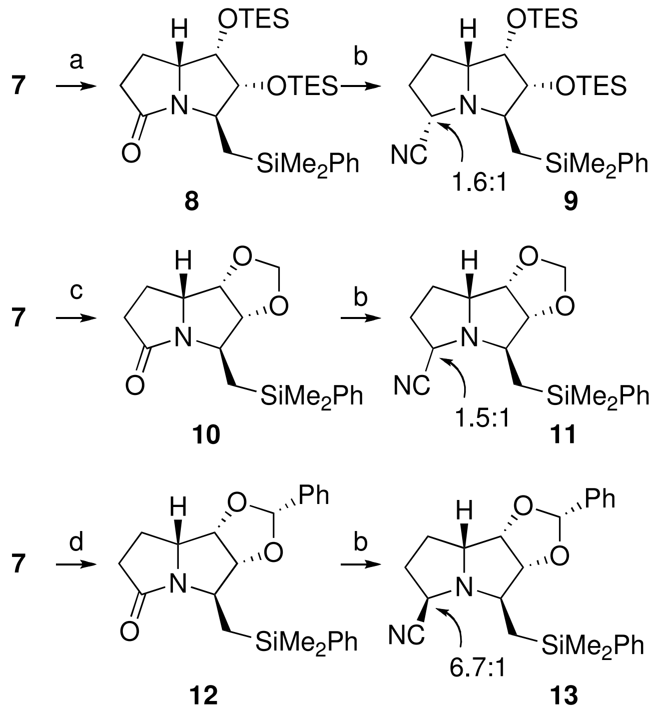
The synthesis started from the commercially available chiral auxiliary (*S*)-(–)-Stericol® **5**,[xviii] which was transformed in a highly stereoselective manner into pyrrolizidinone **7** via lactam **6**[xivb,xix] (Scheme 2).[x] The key diastereoselective steps in this preparation included: a [2+2] cycloaddition of dichloroketene to the Stericol-derived dienol ether, a Bruylants-like addition of a silylmethyl substituent, and an *endo*-selective dihydroxylation.

Scheme 2. Preparation[x] of Pyrrolizidinone **7**



The protection of the cis hydroxyls in **7** was expected to be crucially important in the approach not only because of introduction–removal considerations, but also the attendant steric hindrance that could play a significant role in the subsequent C-5 alkylation. Thus, different groups were examined. Protection with triethylsilyl groups and a methylidene group proceeded smoothly to give lactams **8** and **10** in 94% and 88% yields, respectively (Scheme 3).

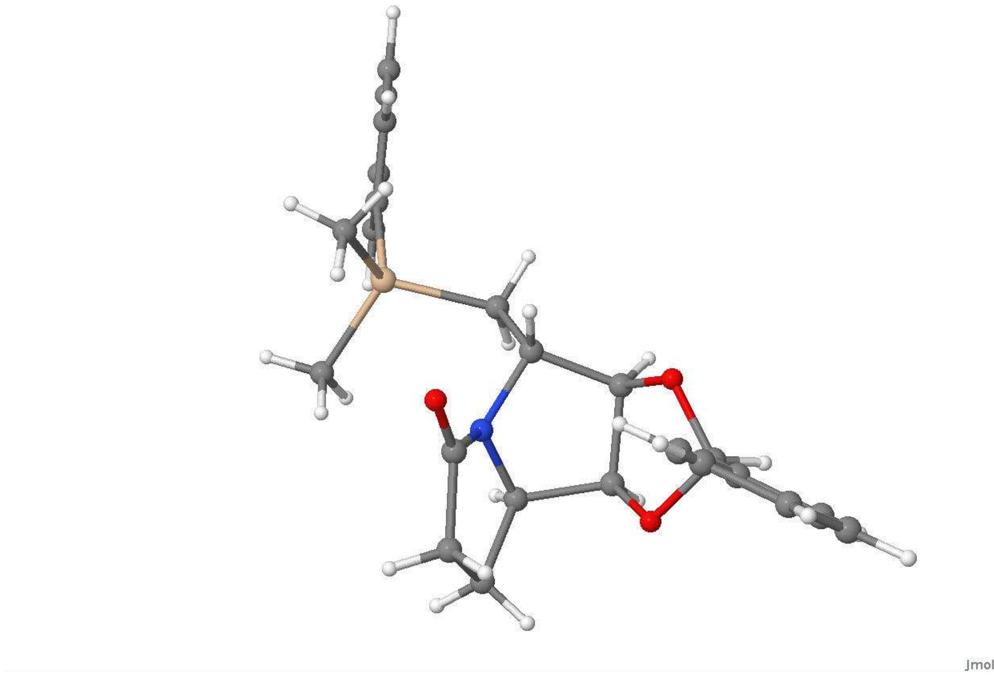
Scheme 3.[a] Diol Protection and Amino-Nitrile Formation



[a] Reagents and conditions: (a) TESCl, imidazole, CH_2Cl_2, 20 °C, 94%. (b) DIBAL-H/*n*-BuLi ate complex, THF, 20 °C, then TMSCN, 0 °C, 89% for **9** from **8**, 93% for **11** from **10**, 97% for **13** from **7** (2 steps). (c) P_2O_5, $CH_2(OMe)_2$, CH_2Cl_2, 20 °C, 88%. (d) $PhCH(OMe)_2$, *p*-TSA, CH_2Cl_2, 20 °C.

Benzylidene protection of **7** was particularly interesting in that a single, crystalline acetal was formed in excellent yield; structural determination by X-ray diffraction analysis[xx] revealed that the *phenyl group of the acetal was endo in the tricyclic structure* (Figure 2). This endo stereoselectivity, while at first surprising, is in fact often encountered with cyclic diols[xxi] and is believed to result from kinetic acetal formation, with minimization of allylic strain[xxii] ($A^{1,3}$) in the cyclization of the intermediate oxonium ion.[xxiii]

Figure 2. Solid State Structure of Benzylidene **12**

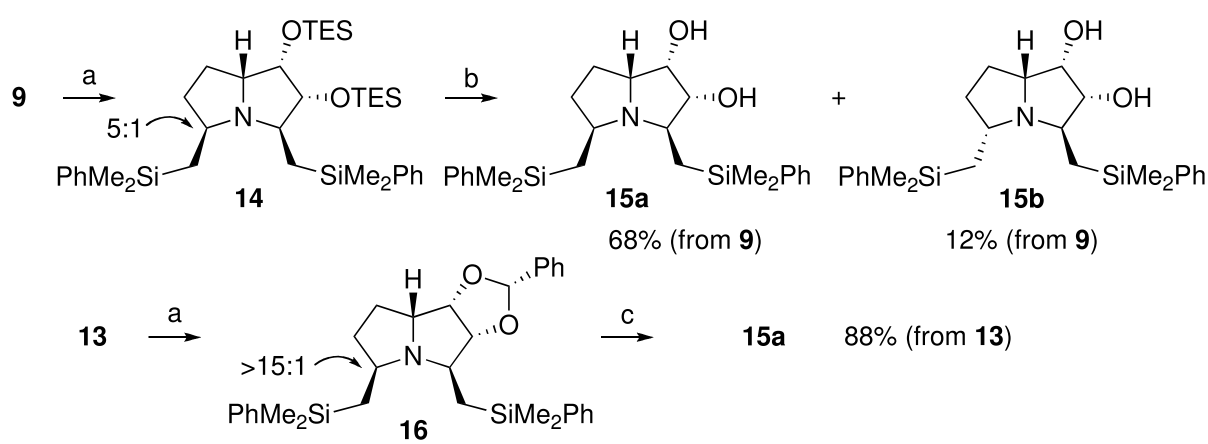


The transformation of the lactams to the corresponding amino-nitriles[xxiv] by reductive cyanation, studied initially with the bis-TES derivative **8**, turned out to be more challenging than expected: reductive cyanation with the often used DIBAL-H/KCN system[xxv] led invariably to significant amounts of over-reduced material, while the use of Schwartz's reagent with TMSCN[xxvi] led primarily to recovered starting material. Fortunately, however, the DIBAL-H/*n*-BuLi ate complex[xxvii] smoothly produced the desired hemiaminal, which, following treatment in situ with TMSCN, gave in 89% yield an inconsequential 1.6:1 mixture of the epimeric amino-nitriles **9** (Scheme 3), with the silylmethyl group governing the observed selectivity.[xxviii] This procedure applied to the methylidene-protected derivative **10** provided in 89% yield the expected amino-nitrile derivatives **11** as a 1.5:1 mixture (see below for stereochemical assignment), less pronounced than had been expected. When lactam **12** was subjected to the reductive cyanation conditions, however, the amino-nitriles **13** were obtained in 97% overall yield from **7** (2 steps) as a 6.7:1 mixture.[xxix] This facial discrimination proved to be a harbinger of the stereoselectivity of the upcoming alkylation.

With a highly efficient formation of the amino-nitriles in hand, the Bruylants reaction[xvii] was next examined. The mixture of amino-nitriles **9** reacted with dimethylphenylsilylmethylmagnesium chloride in ether–THF at room temperature to afford a 5:1 epimeric mixture of the corresponding alkylated pyrrolizidines **14** (Scheme 4). A sample of the major isomer, separated with difficulty by silica gel chromatography, provided ^{1}H NMR data in agreement with the depicted structure. Particularly diagnostic was the strong NOE (10%) between the C-3 and C-5 hydrogens. The TES groups were next removed from **14** by treatment with TBAF and the resultant mixture could now be easily separated by chromatography to give diol **15a** and its C-5 epimer **15b** in 68% and 12% overall yields, respectively, from **9**. For additional proof of the stereochemical assignments from the Bruylants reaction, the pure diol **15b** was silylated to give back the minor C-5 epimer of **14**, which displayed no NOE between the C-3 and C-5 hydrogens, but one between those at C-5 and C-7a.

Better yet, when the mixture of amino-nitriles **13** was treated similarly with the same Grignard reagent, *a unique* stereoisomer (**16**) was formed (by ^{1}H NMR: single signal for the benzylidene acetal hydrogen at 5.70 ppm). Acetal cleavage with aqueous acid then furnished diol **15a** in 88% overall yield from **13** (2 steps).

Scheme 4.[a] Bruylants Reaction and Diol Deprotection

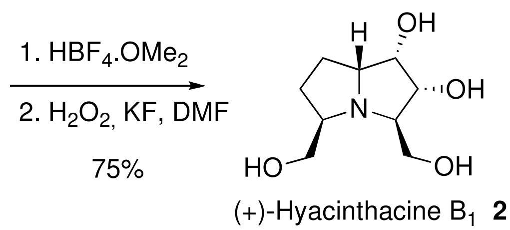


[a] Reagents and conditions: (a) $Me_2PhSiCH_2MgCl$, Et_2O–THF, 20 °C. (b) TBAF, THF, 20 °C. (c) TFA (20%), THF–H_2O, 55 °C.

Silyl oxidation can be performed through several different procedures,[xxx] but few have been successfully used with a potentially oxidizable amino group in the substrate.[xxxi] With a model substrate, the basic oxidation conditions developed by Smitrovich and Woerpel[xxxia] proved insufficiently reactive, whereas treatment with tetrafluoroboric acid, followed by basic work-up and hydrogen peroxide oxidation, produced the corresponding protodesilylated amine oxide as the major product. However, by eliminating the basic treatment following the first step so as to keep the nitrogen protonated and thus limit its oxidation, it was found that the desired alcohol was cleanly formed, without significant amounts of the *N*-oxide. To our delight, on application of these conditions, the disilyl derivative **15a** *underwent clean double oxidation to afford hyacinthacine B_1 in 75% yield, without discernible N-oxide formation* (Scheme 5). This result is noteworthy since double Tamao-Fleming oxidations are relatively few in the literature[xxxii] and, moreover, attendant nitrogen oxidation is often difficult to suppress.[xxxiii] Synthetically derived (+)-hyacinthacine B_1 ($[\alpha]_D$ +40) was spectroscopically and chromatographically indistinguishable from an authentic sample of the natural product ($[\alpha]_D$ +41.3).[vi,xxxiv]

Scheme 5. Double Tamao-Fleming Oxidation of **15a** to give (+)-Hyacinthacine B_1

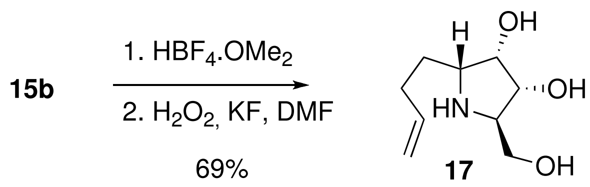
15a



Synthesis of Hyacinthacine B_2

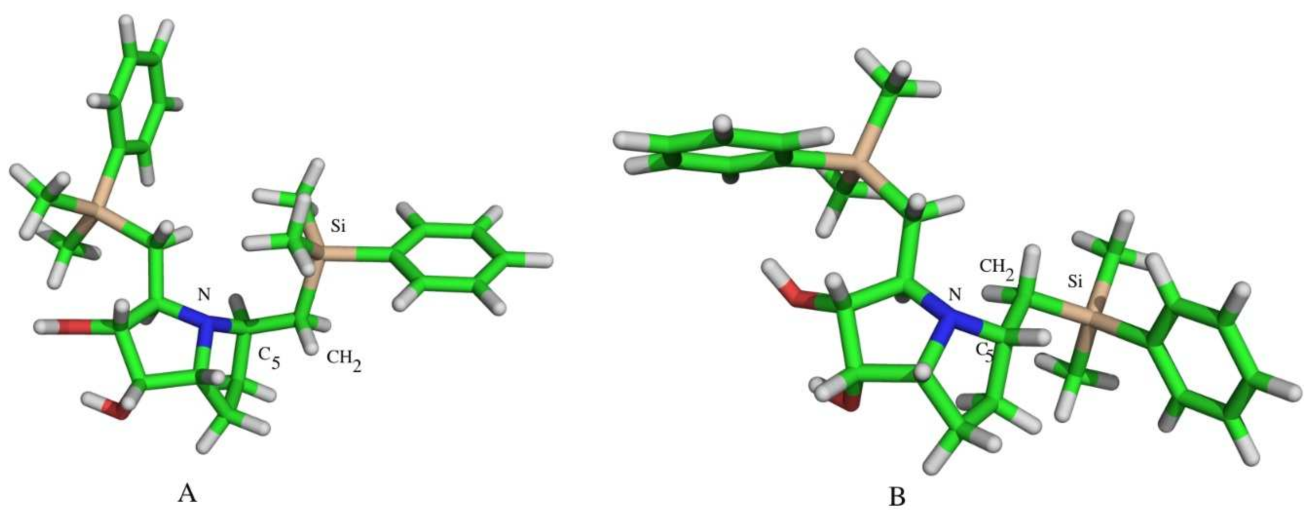
In order to evaluate the possibility of accessing hyacinthacine B_2 through a similar strategy, the minor diol **15b** was subjected to the above oxidation conditions. Surprisingly, this isomer did not undergo transformation into the expected polyhydroxylated pyrrolizidine, but suffered an oxidation-fragmentation to generate pyrrolidine **17** in 69% yield after treatment with basic Dowex (Scheme 6).

Scheme 6. Oxidation-Fragmentation of **15b**



This dichotomous behavior of the isomeric disilanes **15a** and **15b** most likely results from conformational biases. Calculations[xxxv,xxxvi] indicate that in **15a** the silane in question enjoys a degree of conformational freedom (a preferred conformation places the silane toward the nitrogen, dihedral angle of –61.4°, Figure 3A), where as in **15b** it is essentially blocked opposite the nitrogen (dihedral angle of –176.3°, Figure 3B) and favorably disposed to participate in a Grob-type fragmentation.[xxxvii] A different approach, which did not involve a double Tamao-Fleming oxidation, was obviously required for reaching hyacinthacine B_2.

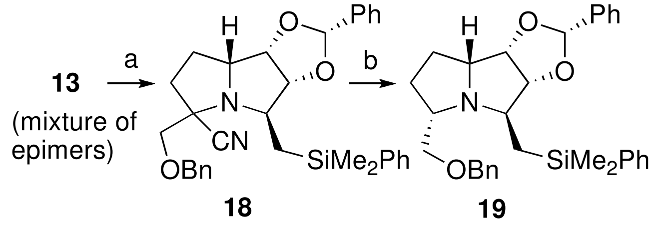
Figure 3. Calculated conformations for **15a** and **15b**



A potential alternative emerged with the observation that the mixture of amino-nitriles **11** (unassigned stereochemistry, scheme **3**), in solution at –30 °C, underwent over several days a 1.5:1 to 9:1 modification of the epimeric composition. It was subsequently found that on heating a DMF solution of the epimers, the 9:1 ratio could be attained in only 45 min.[xxxviii] While these isomers could be separated by silica gel chromatography, their stereo attribution could not be made with absolute confidence. For this reason, CN → CH_2OH transformation (methanolysis, reduction), Tamao-Fleming oxidation, and diol deprotection in the major isomer were carried out; unfortunately, hyacinthacine B_1 and not B_2 was produced. The cyano and silylmethyl group were thus, in fact, cis in the major isomer of **11** (scheme **3**) and yet another strategy for the synthesis of hyacinthacine B_2 was required.

The complete diastereselectivity induced above with the benzylidene protecting group suggested that an approach based on hydride reduction[xxxix] of an *alkylated amino-nitrile*[xl] might constitute a viable strategy for preparing hyacinthacine B_2.[xli] This approach would be particularly attractive in that both hyacinthacines would result from a common, late intermediate. After considerable experimentation, it was found that treatment of amino-nitriles **13** with LDA at low temperature, followed by addition of an excess of benzyl chloromethyl ether, gave the corresponding amino-nitrile **18** in high diastereomeric purity by NMR (Scheme 7). For a successful alkylation, it was necessary to operate with rigorous exclusion of oxygen to avoid reversion of the substrate to lactam **12**.[xlii] Although the crude product was not stable to purification, it could be smoothly reduced with sodium borohydride in methanol at 0 °C to afford after purification *uniquely* the desired stereoisomer **19** in 49% yield (55% brsm, 2 steps). Thus, once again, the benzylidene protection allowed total, and in this case opposite, stereocontrol in the introduction of a latent C-5 hydroxymethyl group.

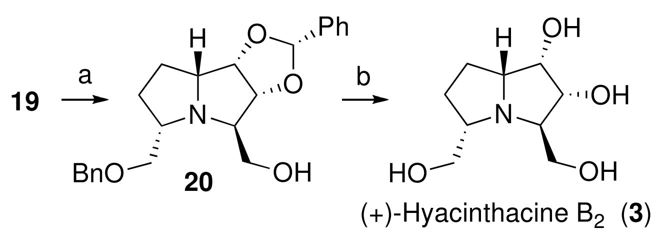
Scheme 7.[*a*] Alkylation of **13** and Reduction



[a] Reagents and conditions: (a) LDA, THF, –60 °C; benzyl chloromethyl ether, –60 °C; (b) $NaBH_4$, MeOH, 0 °C, 49% (55% brsm, 2 steps).

To our temporary dismay, attempted Tamao-Fleming oxidation of silane **19** under the conditions that had previously been used successfully for hyacinthacine B_1 led mainly to degradation. Fortunately, however, the conditions developed by Smitrovich and Woerpel[xxxia] were found to be productive and furnished the expected primary alcohol **20** in essentially quantitative yield (Scheme 8). The completion of the synthesis was realized by double deprotection through acidic hydrogenolysis, followed by deprotonation with basic Dowex resin, to provide (+)-hyacinthacine B_2 in 89% yield from silane **19** (2 steps). Synthetically derived (+)-hyacinthacine B_2 provided ^{1}H and ^{13}C NMR data in excellent accord with those described for the naturally derived material.[vi,xliii]

Scheme 8.[a] Completion of the Synthesis of (+)-Hyacinthacine B_2



[a] Reagents and conditions: (a) KH, *t*-BuOOH, TBAF, DMF, 0 °C. (b) H_2, Pd-C, 6N HCl, EtOH, 20 °C; Dowex (OH^- form), H_2O, 89% (2 steps).

Conclusion

Hyancinthacines B_1 and B_2 have been prepared efficiently from a common, advanced intermediate, which is obtained in enantiopure form through asymmetric cycloaddition methodology. These syntheses are characterized by excellent levels of stereocontrol of the 5 stereogenic centers and high overall yields from the starting chiral auxiliary (6.5% and 4.4%, respectively). Critical to the success of this work is the synthetic versatility of the amino-nitrile moiety, which provides highly selective access to these diastereomeric hyacinthacines. Synthetic studies toward other C-5 substituted hyacinthacines are currently in progress in our laboratory.

Experimental Section

General experimental details

All experiments were carried out under argon atmosphere unless otherwise stated. THF and Et_2O were distilled over Na-benzophenone. CH_2Cl_2 was distilled over CaH_2 and DMF over $CaSO_4$. All other products were directly used as received from commercial sources without purification. NMR spectra were recorded on a Bruker Avance 300, Bruker Avance 400 or Varian U+ 500 spectrometer in chloroform-*d*, unless otherwise stated. All coupling constants have been calculated, when possible, by using the method described by Hoye *et al*.[xliv] Melting points are uncorrected. IR spectra were recorded as neat samples or in CH_2Cl_2 solution on a Nicolet 397 FT-spectrometer. The mass spectra were recorded on a Nermag R10 mass spectrometer in ESI mode. High-resolution mass spectrometry data were obtained via electrospray ionization with an orbitrap detector.

(5*S*,6*R*,7*S*,7a*R*)-5-((Dimethyl(phenyl)silyl)methyl)-6,7-bis(triethylsilyloxy)-hexahydro-1*H*-pyrrolizin-3-one (8). To a stirred solution of dihydroxy lactam **7** (0.200 g, 0.655 mmol) and imidazole (0.267 g, 3.92 mmol) in anhydrous dichloromethane (10 mL) at 0 °C was added 0.329 mL

(0.295 g, 1.96 mmol) of triethylsilyl chloride. The mixture was allowed to warm to 20 °C over 30 min and then stirred for 16 h, whereupon water was added. The mixture was extracted with dichloromethane, the combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was evaporated to give the crude product. Purification of this material by flash chromatography on silica gel with ethyl acetate in pentane (1:10) afforded 0.330 g (94%) of lactam **8**: $[\langle]_D^{24}$ –23 (*c* 3.2, $CHCl_3$); IR (film) 2955, 2904, 2873, 1693, 1583, 1458, 1382, 1242, 1181, 1116, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) ™ 0.34 (s, 3 H), 0.38 (s, 3 H), 0.51-0.63 (m, 12 H), 0.87-0.97 (m, 19 H), 1.17 (dd, *J* = 14.7, 5.2 Hz, 1 H), 1.71-1.80 (m, 1 H), 2.04-2.16 (m, 1 H), 2.17-2.26 (m, 1 H), 2.30-2.41 (m, 1 H), 3.59 (ddd, *J* = 7.0, 5.0, 5.0 Hz, 1 H), 3.75 (dd, *J* = 4.5, 3.5 Hz, 1 H), 3.81-3.87 (m, 1 H), 4.00 (dd, *J* = 5.0, 3.5 Hz, 1 H), 7.32-7.36 (m, 3 H), 7.50-7.55 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ –2.8 (CH_3), 2.7 (CH_3), 4.9 (CH_2), 6.7 (CH_3), 6.8 (CH_3), 19.8 (CH_2), 20.3 (CH_2), 32.4 (CH_2), 58.4 (CH), 61.3 (CH), 73.6 (CH), 82.2 (CH), 127.6 (CH), 128.7 (CH), 133.5 (CH), 139.5 (C), 178.4 (C); MS (ESI) *m/z* 556 (MNa^+), 456 $(M\text{-}Ph)^+$; HRMS (ESI) calcd for $C_{28}H_{51}NO_3Si_3Na$: 556.3069. Found: 556.3065 (MNa^+).

(3*R*,5*S*,6*R*,7*S*,7a*R*) and (3*S*,5*S*,6*R*,7*S*,7a*R*)-5-((Dimethyl(phenyl)silyl)methyl)-6,7-bis(triethylsilyloxy)-hexahydro-1*H*-pyrrolizine-3-carbonitriles (9). A stirred solution of compound **8** (0.122 g, 0.228 mmol) in anhydrous THF (3.0 mL) was treated at 0 °C with a freshly prepared solution of DIBALH-BuLi ate complex (2.5 mL, prepared from 2.8 mL of 1.0 M DIBAL-H in hexanes and 1.1 mL of 2.5 M *n*-BuLi in hexanes in 1.2 mL of anhydrous THF). The reaction mixture was allowed to warm to 20 °C over 30 min and stirred for 16 h, whereupon it was cooled to –60 °C and treated with 0.243 mL (0.193 g, 1.94 mmol) of TMSCN. After being allowed to warm to 0 °C over 1 h, the mixture was diluted with water and then ethyl acetate and filtered through a small pad of celite. The filtrate was concentrated under reduced pressure to give the crude nitriles, which were purified by flash chromatography with ethyl acetate in pentane (1:10) to give 0.111 g (89%) of the amino-nitriles **9** as a 1.6:1 diastereomeric mixture. A comparable sample was separated for characterization purposes. Major isomer (in mixture with small amount of minor isomer): ^{1}H NMR (400 MHz, $CDCl_3$) ™ 0.31 (s, 3 H), 0.33 (s, 3 H), 0.60-0.69 (m, 12 H), 0.93-1.03 (m, 18 H), 1.08 (dd, *J* = 15.5, 5.0 Hz, 1 H), 1.25 (dd, *J* = 15.2, 5.0 Hz, 1 H), 1.57-1.65 (m, 1 H), 1.80-1.89 (m, 1 H), 1.99-2.12 (m, 2 H), 3.10-3.14 (m, 1 H), 3.27-3.32 (m, 1 H), 3.36-3.42 (m, 1 H), 3.70-3.77 (m, 2 H), 7.30-7.34 (m, 3 H), 7.51-7.55 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ –1.7 (CH_3), 5.1 (CH_2), 6.9 (CH_3), 19.6 (CH_2), 22.9 (CH_2), 33.2 (CH_2), 52.8 (CH), 60.0 (CH), 65.2 (CH), 65.3 (CH), 72.9 (CH), 82.5 (CH), 118.2 (CN), 127.6 (CH), 128.7 (CH), 133.6 (CH), 140.0 (C). Minor isomer: [〈]$_D^{24}$ +50 (*c* 0.5, $CHCl_3$); IR (film) 2960, 2910, 2876, 2234 (*w*), 1957, 1453, 1246, 1148, 1007 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) ™ 0.38 (s, 3 H), 0.42 (s, 3 H), 0.48-0.62 (m, 12 H), 0.86-0.99 (m, 20 H), 1.65-1.74 (m, 1 H), 1.88-1.98 (m, 1 H), 2.11-2.22 (m, 2 H), 2.94 (ddd, *J* = 7.0, 7.0, 3.3 Hz, 1 H), 3.53 (ddd, *J* = 8.0, 6.4, 4.5 Hz, 1 H), 3.62 (dd, *J* = 3.3, 3.3 Hz, 1 H), 3.82 (dd, *J* = 6.8, 6.8 Hz, 1 H), 4.11 (dd, *J* = 6.4, 3.3 Hz, 1 H), 7.33-7.37 (m, 3 H), 7.52-7.57 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ –2.6 (CH_3), –1.6 (CH_3), 4.8 (CH_2), 4.9 (CH_2), 6.8 (CH_3), 21.8 (CH_2), 25.6 (CH_2), 31.8 (CH_2), 56.8 (CH), 65.3 (CH), 67.4 (CH), 73.9 (CH), 80.9 (CH), 121.4 (CN), 127.8 (CH), 128.9 (CH), 133.6 (CH), 139.2 (C); MS (ESI) *m/z* 545 (MH^+); HRMS (ESI) calcd for $C_{29}H_{53}N_2O_2Si_3$: 545.3409. Found: 545.3413 (MH^+); Anal. calcd for $C_{29}H_{52}N_2O_2Si_3$: C, 63.91; H, 9.62; N, 5.14. Found: C, 63.81; H, 9.54; N, 4.78.

(3a*R*,4*S*,8a*R*,8b*S*)-4-((Dimethyl(phenyl)silyl)methyl)-hexahydro-[1,3]dioxolo[4,5-*a*]pyrrolizin-6-one (10). To a stirred solution of diol **7** (14.3 mg, 0.047 mmol) in DCM (0.22 mL) at 20 °C was added dimethoxymethane (0.22 mL) and phosphoric anhydride (31.0 mg, 0.218 mmol). After being stirred for 16 h, the reaction mixture was quenched with a cold saturated solution of sodium bicarbonate and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the resultant crude material by flash chromatography on silica gel with ether in dichloromethane (3-10%) provided 13.1 mg (88%) of protected diol **10**: $[\langle]_D^{24}$ –59 (*c* 1.0, $CHCl_3$); IR (film) 3068, 2954, 1690, 1407 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) ™ 0.36 (s, 3 H), 0.40 (s, 3 H), 0.95 (A of ABX, *J* = 14.8, 10.3 Hz, 1H), 1.02 (B of ABX, *J* = 14.8, 6.6 Hz, 1H), 1.82 (dddd, *J* = 6.2, 8.9, 9.1, 13.2 Hz, 1 H), 2.11 (dddd, *J* = 4.2, 6.7, 10.8, 13.2 Hz, 1 H), 2.26-2.39 (m, 2 H), 3.68 (ddd, *J* = 4.1, 4.1, 8.9, 1 H), 4.23 (ddd, *J* = 0.0, 6.6, 10.3 Hz, 1 H), 4.31-4.36 (m, 2 H), 4.69 (s, 1 H), 4.92 (s, 1 H), 7.33-7.37 (m, 3 H), 7.48-7.53 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) ™ -3.6 (CH_3), -2.8 (CH_3), 17.1 (CH_2), 19.2 (CH_2), 32.8 (CH_2), 56.3 (CH), 61.6 (CH), 80.0 (CH), 89.6 (CH), 96.1 (CH_2), 127.7 (CH), 129.0 (CH), 133.4 (CH), 138.7 (C), 175.6 (C); MS (ESI) *m/z* 240 (MH^+ - C_6H_6), 318 (MH^+), 340 (MNa^+), 635 ($2MH^+$); HRMS (ESI) calcd for $C_{17}H_{24}NO_3Si$: 318.1525. Found: 318.1522 (MH^+).

(3a*R*,4*S*,6*R*,8a*R*,8b*S*) and (3a*R*,4*S*,6*S*,8a*R*,8b*S*)-4-((Dimethyl(phenyl)silyl)methyl)-hexahydro-4*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine-6-carbonitriles (11). A stirred solution of compound **10** (0.037 g, 0.117 mmol) in anhydrous THF (3.0 mL) was treated at 0 °C with a freshly prepared solution of DIBALH-BuLi ate complex (0.38 mL), as described for compound **9** to give 0.045g of crude oil (1.6:1 diastereomeric mixture) which was heated in DMF at 145°C for 45 min. The 9:1 diastereomeric mixture obtained after removal of solvent was purified by flash chromatography on silica gel with ethyl acetate 5 to 15% in pentane to give 0.033 g (86%) of the major isomer of amino-nitriles **11** and 0.0026 g (7%) of the minor isomer. Major isomer: $[\langle]_D^{24}$ +14 (*c* 0.25, $CHCl_3$); IR (film) 3063, 2953, 2922, 2225, 1096 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) ™ 0.35 (s, 6 H), 0.84 (A of ABX, *J* = 14.8, 9.9 Hz, 1 H), 0.86 (B of ABX, *J* = 14.8, 6.6 Hz, 1 H), 1.85-2.08 (m, 3 H), 2.12-2.25 (m, 1 H), 3.40-3.50 (m, 2 H), 3.93 (dd, *J* = 5.8, 7.9 Hz, 1 H), 4.22 (dd, *J* = 0.0, 5.6 Hz, 1 H), 4.33 (dd, *J* = 5.6, 5.6 Hz, 1H), 4.55 (s, 1 H), 4.98 (s, 1 H), 7.25-7.31 (m, 3 H), 7.44-7.52 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ -3.0 (CH_3), -2.6 (CH_3), 21.4 (CH_2), 23.9 (CH_2), 31.9 (CH_2), 54.2 (CH), 63.7 (CH), 65.7 (CH), 82.7 (CH), 90.4 (CH), 96.1 (CH_2), 121.2 (C), 127.8 (CH), 128.9 (CH), 133.6

(CH), 139.1 (C); MS (ESI) *m/z* 251 (MH^+ - C_6H_6), 302 (MH^+ - HCN), 329 (MH^+); HRMS (ESI) calcd for $C_{18}H_{25}N_2O_2Si$: 3291685, Found: 329.1683 (MH^+). Minor isomer: [〈]$_D^{24}$ –12 (*c* 0.32, $CHCl_3$); IR (film) 3073, 2953, 2926, 2238, 1090 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) ™ 0.33 (s, 3 H), 0.34 (s, 3 H), 1.07 (d, *J* = 7.8 Hz, 2 H), 1.79-1.89 (m, 1 H), 2.00-2.12 (m, 1 H), 2,18-2,31 (m, 2 H), 3.51 (ddd, *J* = 2.4, 7.8, 7.8 Hz, 1 H), 3.57-3.67 (m, 2 H), 4.28 (dd, *J* = 5.0, 5.0 Hz, 1H), 4.44 (dd, *J* = 2.4, 5.0 Hz, 1 H), 4.83 (s, 1 H), 5.32 (s, 1 H), 7.32-7.37 (m, 3 H), 7.48-7.53 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ -2.4 (CH_3), -2.3 (CH_3), 22.3 (CH_2), 23.5 (CH_2), 33.6 (CH_2), 52.4 (CH), 61.9 (CH), 65.7 (CH), 81.6 (CH), 91.8 (CH), 96.4 (CH_2), 119.6 (C), 127.8 (CH), 128.9 (CH), 133.4 (CH), 139.1 (C); MS (ESI) *m/z* 251 (MH^+ - C_6H_6), 302 (MH^+ - HCN), 329 (MH^+), HRMS (ESI) calcd for $C_{18}H_{25}N_2O_2Si$: 329.1685, Found: 329.1682 (MH^+).

(2*S*,3a*R*,4*S*,8a*R*,8b*S*)-4-((Dimethyl(phenyl)silyl)methyl)-2-phenylhexahydro-[1,3]dioxolo[4,5-*a*]pyrrolizin-6-one (12). To a stirred solution of diol **7** (0.105 g, 0.34 mmol) in DCM (3.4 mL) at 20 °C was added $PhCH(OMe)_2$ (0.072 mL, 0.48 mmol) and *p*-TSA.H_2O (6.4 mg, 0.03 mmol). After being stirred for 16 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 136 mg of crude **12**, which was used without further purification. An analytical sample was obtained by purification of comparable crude material by flash chromatography on silica gel with ethyl acetate in pentane (1:10), which afforded **12** as a white solid: mp 134-135 °C; $[\alpha]^{\mathbf{23}}_{\mathbf{D}}$ –72 (c 2.1, $CHCl_3$); IR (film) 3076, 2946, 1688, 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (s, 3 H), 0.46 (s, 3 H) , 0.98 (B of ABX, *J* = 14.7, 10.7 Hz, 1 H) , 1.06 (A of ABX, *J* = 14.7, 6.5 Hz, 1 H) , 1.85 – 1.72 (m, 1 H) , 2.10 (dddd, *J* = 13.2, 8.0, 8.0, 3.4 Hz, 1 H) , 2.41 – 2.26 (m, 2 H) , 3.72 (ddd, *J* = 8.9, 3.4, 3.4 Hz, 1 H) , 4.47 (dd, *J* = 10.7, 6.5 Hz, 1 H) , 4.56 – 4.50 (m, 2 H) , 5.61 (s, 1 H) , 7.45 – 7.31 (m, 8 H), 7.63 – 7.49 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -3.6 (CH_3), -2.8 (CH_3), 16.7 (CH_2), 18.8 (CH_2), 32.7 (CH_2), 57.0 (CH), 61.6 (CH), 81.1 (CH), 90.1 (CH), 105.4 (CH), 127.0 (CH), 127.7 (CH), 128.5 (CH), 129.0 (CH), 129.8 (CH), 133.4 (CH), 135.4 (C), 138.8 (C),176.4 (C); MS (ESI) *m/z* 316 $(M-Ph)^+$, 416 (MNa^+), 809 $(2M+Na)^+$; HRMS (ESI) calcd for $C_{23}H_{27}NO_3NaSi$: 416.1652. Found: 416.1646 (MNa^+).

(2*S*,3a*R*,4*S*,6*R*,8a*R*,8b*S*) and (2*S*,3a*R*,4*S*,6*S*,8a*R*,8b*S*)-4-((Dimethyl(phenyl)silyl)methyl)-2-phenylhexahydro-4*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine-6-carbonitriles (13). A stirred solution of the above crude lactam **12** in anhydrous THF (3.0 mL) was treated at 0 °C with 1.6 mL of a freshly prepared solution of DIBALH-BuLi ate complex (prepared from 5.5 mL of 1.0 M DIBAL-H in hexanes and 2.0 mL of 2.5 M *n*-BuLi in hexanes in 2.5 mL of anhydrous THF at 0 °C). The reaction was allowed to warm to 20 °C and was monitored by TLC. After 1.5 h, the reaction mixture was cooled to 0 °C and TMSCN (0.236 mL, 0.187 g, 1.89 mmol) was added. After an additional 20 min, EtOAc and water were added and the resulting mixture was stirred for another 20 min. The mixture was then directly filtered through a plug of Celite and the latter was washed with EtOAc. The filtrate was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with ethyl acetate in pentane (2:8) to afford 0.135 g (97% overall from **7**) of a 6.7:1 mixture of amino-nitriles **13** as a colorless oil. Pure, analytical samples of each epimers could be secured by a second chromatography on silica gel. Major isomer: $[\alpha]^{21}_D$ +57 (c 2.2, $CHCl_3$); IR (film) 3063, 2919, 2237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.44 (s, 6 H), 0.99 (d, *J* = 8.2 Hz, 2 H), 2.08 – 1.92 (m, 2 H), 2.32 –2.13 (m, 2 H), 3.63 – 3.56 (m, 1 H), 3.65 (t, *J* = 8.2 Hz, 1 H), 4.08 (dd, *J* = 8.1, 6.3 Hz, 1 H), 4.53 (dd, *J* = 6.0, 0.8 Hz, 1 H), 4.61 (dd, *J* = 6.0, 4.9 Hz, 1 H), 7.38 – 7.34 (m, 3 H), 5.68 (s, 1 H), 7.60 – 7.54 (m, 2 H), 7.39 (s, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.9 (CH_3), -2.6 (CH_3), 21.4 (CH_2) , 23.4 (CH_2) , 31.8 (CH_2), 54.0 (CH), 63.9 (CH), 65.7 (CH), 83.7 (CH), 91.2 (CH), 104.8 (CH), 121.2 (C), 126.0 (CH), 127.7 (CH), 128.5 (CH), 128.9 (CH), 129.3 (CH), 133.6 (CH), 135.9 (C), 139.2 (C); MS (ESI) *m/z* 405 (MH^+), 378 $(M-CN)^+$, 327 $(M-Ph)^+$; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_2Si$: 405.19928.

Found: 405.20002 (MH^+). Minor isomer: $[\alpha]^{21}_D$ +15 (c 0.7, $CHCl_3$); IR (film) 2923, 2236, 1459, 1426, 1407, 1248, 1112 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8) δ 0.31 (s, 6 H), 0.90 (B of ABX, *J* = 14.7, 7.4 Hz, 1 H), 0.97 (A of ABX, *J* = 14.7, 7.8 Hz, 1 H), 1.28 (dddd, *J* = 12.8, 6.7, 6.7, 5.6 Hz, 1 H), 1.46 (dddd, *J* = 12.1, 7.9, 6.7,6.7 Hz, 1 H), 1.86 (dddd, *J* = 12.1, 6.7, 5.6, 5.6 Hz, 1 H), 2.01 (dddd, *J* = 12.8, 7.9, 6.7, 6.7 Hz , 1 H), 3.16 (ddd, *J* = 6.7, 6.7, 5.3 Hz, 1 H), 3.28 (dd, *J* = 6.7, 5.6 Hz, 1 H), 3.85 (ddd, *J* = 7.8, 7.4, 3.1 Hz, 1 H), 4.02 (dd, *J* = 5.6, 5.3 Hz, 1 H), 4.16 (dd, *J* = 5.6, 3.1 Hz, 1 H), 7.25 – 7.17 (m, 6 H), 5.60 (s, 1 H), 7.73 – 7.69 (m, 2 H), 7.46 – 7.40 (m, 2 H); ^{13}C NMR (100 MHz, toluene-d_8) δ -2.5 (CH_3), -2.2 (CH_3), 22.4 (CH_2), 24.8 (CH_2), 33.3 (CH_2), 52.2 (CH), 63.4 (CH), 65.8 (CH), 82.1 (CH), 91.2 (CH), 106.6 (CH), 118.5 (C), 127.5 (CH), 128.0 (CH), 128.4 (CH), 129.1 (CH), 129.3 (CH), 133.8 (CH), 136.8 (C), 139.7 (C); MS (ESI) *m/z* 427 (MNa^+), 405 (MH^+), 378 $(M\text{-}CN)^+$, 327 $(M\text{-}Ph)^+$.

(1*S*,2*R*,3*S*,5*R*,7a*R*)-3,5-Bis((dimethyl(phenyl)silyl)methyl)-1,2-bis(triethylsilyloxy)-hexahydro-1*H*-pyrrolizine (**14**). To the diastereomeric mixture of amino-nitriles **9** (0.201 g, 0.369 mmol) in anhydrous ether (7.0 mL) was added at 0 °C dimethylphenylsilylmethylmagnesium chloride (3.7 mL, 0.8 M in THF, 3.0 mmol). The reaction mixture was allowed to warm to 20 °C over 45 min and stirred for 48 h, after which it was cooled to 0 °C and treated with a saturated aqueous solution of NH_4Cl. The mixture was extracted with ethyl acetate and the combined organic layers were washed with water, dried over anhydrous Na_2SO_4,, and filtered. Concentration of the filtrate under reduced pressure gave the crude product **14** (5:1 diastereomeric mixture), which was used directly below. A comparable sample was subjected to silica gel chromatography for characterization purposes. Mixture of isomers: IR (film) 3068, 3048, 2953, 2876, 1426, 1249, 1112 cm^{-1}; MS (ESI) *m/z* 668 (MH^+); HRMS (ESI) calcd for $C_{37}H_{66}NO_2Si_4$: 668.4165. Found: 668.4166 (MH^+). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) ™ 0.21 (s, 6 H), 0.29 (s, 3 H), 0.34 (s, 3 H), 0.42-

0.50 (m, 6 H), 0.52-0.59 (m, 6 H), 0.73 (dd, *J* = 13.7, 12.7 Hz, 1 H), 0.83-0.89 (m, 9 H), 0.90-0.95 (m, 9 H), 0.98-1.12 (m, 3 H), 1.14-1.27 (m, 1 H), 1.41-1.50 (m, 1 H), 1.66-1.75 (m, 1 H), 2.00-2.11 (m, 1 H), 2.82-2.88 (m, 1 H), 3.15-3.25 (m, 1 H), 3.50 (ddd, *J* = 15.3, 7.2, 7.2 Hz, 1 H), 3.66 (dd, *J* = 3.3, 3.3 Hz, 1 H), 4.12 (dd, *J* = 7.2, 3.3 Hz, 1 H), 7.29-7.35 (m, 6 H), 7.42-7.47 (m, 2 H), 7.48-7.53 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ –2.2 (CH_3), –2.1 (CH_3), –1.4 (CH_3), 4.9 (CH_2), 5.0 (CH_2), 6.8 (CH_3), 6.9 (CH_3), 23.3 (CH_2), 23.6 (CH_2), 26.4 (CH_2), 34.5 (CH_2), 65.0 (CH), 65.2 (CH), 65.8 (CH), 74.5 (CH), 80.8 (CH), 127.6 (CH), 127.7 (CH), 128.6 (CH), 128.8 (CH), 133.5 (CH), 133.7 (CH), 139.5 (C), 139.8 (C); Minor isomer (from re-silylation of **15b**): ^{1}H NMR (400 MHz, $CDCl_3$) ™ 0.21 (s, 3 H), 0.23 (s, 3 H), 0.28 (s, 3 H), 0.32 (s, 3 H), 0.49-0.67 (m, 12 H), 0.77 (dd, *J* = 14.3, 11.8 Hz, 1 H), 0.88-0.99 (m, 18 H), 1.00-1.12 (m, 3 H), 1.27-1.37 (m, 2 H), 1.45-1.54 (m, 1 H), 1.89-1.98 (m, 1 H), 2.95-3.03 (m, 1 H), 3.18 (ddd, *J* = 7.5, 4.1, 4.1 Hz, 1 H), 3.35 (ddd, *J* = 8.5, 5.3, 5.3 Hz, 1 H), 3.63 (dd, *J* = 4.1, 4.1 Hz, 1 H), 3.99 (dd, *J* = 5.3, 4.1 Hz, 1 H), 7.28-7.37 (m, 6 H), 7.43-7.47 (m, 2 H), 7.48-7.53 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ –2.3 (CH_3), –2.1 (CH_3), –1.4 (CH_3), 4.9 (CH_2), 5.2 (CH_2), 6.9 (CH_3), 7.0 (CH_3), 16.7 (CH_2), 24.1 (CH_2), 24.7 (CH_2), 32.1 (CH_2), 58.6 (CH), 59.0 (CH), 66.2 (CH), 73.3 (CH), 80.3 (CH), 127.6 (CH), 128.0 (CH), 128.6 (CH), 128.7 (CH), 133.0 (CH), 133.5 (CH), 133.7 (CH), 139.5 (C), 139.9 (C).

(1*S*,2*R*,3*S*,5*R*,7a*R*) and (1*S*,2*R*,3*S*,5*S*,7a*R*)-3,5-Bis((dimethyl(phenyl)silyl)methyl)-hexahydro-1*H*-pyrrolizine-1,2-diols (15a,b). A solution of the above crude diastereomeric mixture **14** in THF at 20 °C was treated with TBAF (1.1 mL, 1.0 M in THF) and then stirred for 4 h, after which water was added and the mixture was extracted with chloroform. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude diols, which were purified by flash silica gel chromatography with methanol–aqueous NH_4OH–chloroform (0.4:0.4:10) to afford 0.111 g (68% from **9**) of the major isomer **15a** and 0.019 g (12% from **9**) of the minor isomer **15b**. Minor isomer: $[〈]_D^{24}$ –9 (*c* 1.1,

$CHCl_3$); IR (film) 3378, 3072, 3048, 2953, 2910, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) ™ 0.24 (s, 3 H), 0.26 (s, 3 H), 0.32 (s, 3 H), 0.34 (s, 3 H), 0.73 (dd, *J* = 14.0, 13.0 Hz, 1 H), 1.00-1.19 (m, 3 H), 1.32-1.52 (m, 2 H), 1.64-1.71 (m, 1 H), 1.73-1.87 (m, 1 H), 2.10-2.70 (br s, 2 H), 3.06-3.26 (m, 2 H), 3.38-3.49 (m, 1 H), 3.71 (dd, *J* = 6.6, 4.5 Hz 1 H), 3.85 (dd, *J* = 4.5, 4.5 Hz, 1 H), 7.29-7.38 (m, 6 H), 7.42-7.49 (m, 2 H), 7.50-7.57 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ –2.2 (CH_3), –1.6 (CH_3), 17.3 (CH_2), 22.2 (CH_2), 23.1 (CH_2), 32.8 (CH_2), 57.2 (CH), 57.8 (CH), 65.6 (CH), 71.3 (CH), 80.6 (CH), 127.79 (CH), 127.88 (CH), 128.9 (CH), 133.4 (CH), 133.6 (CH), 139.7 (C). Major isomer: $[〈]_D^{24}$ +24 (*c* 0.9, $CHCl_3$); IR (film) 3388, 3068, 3048, 2952, 2908, 1426, 1248, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) ™ 0.28 (s, 6 H), 0.33 (s, 3 H), 0.38 (s, 3 H), 0.89 (dd, *J* = 14.2, 11.5 Hz, 1 H), 1.14 (dd, *J* = 14.7, 11.0, Hz, 1 H), 1.20-1.40 (m, 3 H), 1.61-1.71 (m, 1 H), 1.79-1.98 (m, 2 H), 2.21 (br s, 2 H), 2.71 (ddd, *J* = 11.0, 8.1, 3.0 Hz, 1 H), 2.84-2.91 (m, 1 H), 3.55 (ddd, *J* = 7.5, 7.5, 4.2 Hz, 1 H), 3.68-3.73 (m, 1 H), 3.76 (dd, *J* = 4.2, 4.2 Hz, 1 H), 7.32-7.39 (m, 6 H), 7.47-7.52 (m, 2 H), 7.53-7.58 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) ™ –2.4 (CH_3), –2.0 (CH_3), –1.2 (CH_3), 23.1 (CH_2), 23.6 (CH_2), 24.0 (CH_2), 34.8 (CH_2), 64.6 (CH), 64.8 (CH), 65.5 (CH), 72.5 (CH), 80.9 (CH), 127.7 (CH), 128.0 (CH), 128.8 (CH), 129.0 (CH), 133.5 (CH), 139.4 (C), 139.7 (C); MS (ESI) *m/z* 440 (MH^+); HRMS (ESI) calcd for $C_{25}H_{38}NO_2Si_2$: 440.2436. Found: 440.2435 (MH^+).

(1*S*,2*R*,3*S*,5*R*,7a*R*)-3,5-Bis((dimethyl(phenyl)silyl)methyl)-hexahydro-1*H*-pyrrolizine-1,2-diol (15a from 13). To the diastereomeric mixture of amino-nitriles **13** (10.0 mg, 0.025 mmol) in anhydrous ether (0.5 mL) at 0 °C was added a solution of dimethylphenylsilylmethylmagnesium chloride (0.247 mL, 0.8 M in THF, 0.20 mmol). The reaction mixture was allowed to warm to 20 °C over 45 min and stirred for 48 h, after which it was cooled to 0 °C and treated with a saturated aqueous solution of NH_4Cl. The mixture was extracted with ethyl acetate and the combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and filtered. Concentration of the filtrate under reduced pressure gave the crude product **16**, which was used directly below. A comparable sample was subjected to silica gel chromatography for characterization purposes: IR (film): 3068, 3020, 2951, 2920, 1664, 1589, 1561, 1426, 1248, 1113, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 3 H), 0.15 (s, 3 H), 0.34 (s, 3 H), 0.36 (s, 3 H), 0.64 (dd, *J* = 11.6, 14.2 Hz, 1 H), 0.94 -1.08 (m, 3 H), 1.19 - 1.32 (m, 1 H), 1.78 - 1.89 (m, 2 H), 2.02- 2.13 (m, 1 H), 3.23 - 3.33 (m, 1 H), 3.37 (dd, *J* = 6.5, 9.0 Hz, 1 H), 3.66 (ddd, *J* = 4.1, 4.1, 8.6 Hz, 1 H), 4.49 (dd, *J* = 0.6, 6.1 Hz, 1 H), 4.59 (dd, *J* = 5.3, 11.1 Hz, 1 H), 5.67 (s, 1 H), 7.28- 7.41 (m, 13 H), 7.50-7.55 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -2.4, (CH_3), -2.3 (CH_3), -2.2 (CH_3), -2.1 (CH_3), 22.3 (CH_2), 22.5 (CH_2), 23.6 (CH_3), 34.6 (CH_2), 60.9 (CH), 61.7 (CH), 64.7 (CH), 84.8 (CH), 91.1 (CH), 105.4 (CH), 126.7 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.7 (CH), 129.1 (CH), 133.4 (CH), 133.6 (CH), 136.4 (C), 139.0 (C), 139.6 (C); MS (ESI) *m/z* 528 (MH^+); HRMS (ESI) calcd for $C_{32}H_{42}O_2NSi_2$: 528.27486. Found: 528.27407 (MH^+). The above crude mixture was dissolved in 0.600 mL of TFA/H_2O/THF (1:2:3) and heated at 60 °C for 3 h. After being allowed to cool to 20 °C, the reaction mixture was quenched by the addition of 1N NaOH and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel with methanol–aqueous NH_4OH–chloroform (0-5%) to afford 9.6 mg (88%) of pure diol **15a**.

(1*S*,2*R*,3*R*,5*R*,7a*R*)-3,5-Bis(hydroxymethyl)-hexahydro-1*H*-pyrrolizine-1,2-diol (Hyacinthacine B_1 (2)). A solution of diol **15a** (66 mg, 0.150 mmol) in dichloromethane (2.0 mL) at 20 °C was treated with 0.182 mL (0.200 g, 1.50 mmol) of tetrafluoroboric acid dimethyl ether complex and stirred for 5 h, whereupon the solution was evaporated under reduced pressure. A solution of the resulting crude material in dimethylformamide (1.5 mL) was treated with 86 mg (1.48 mmol) of potassium fluoride and, after 30 min, cooled to 0 °C and treated with 0.288 mL (0.101 g, 35% in water, 2.96 mmol) of aqueous hydrogen peroxide. The reaction mixture was allowed to warm to 20 °C over 1 h and then heated at 40 °C for 2 h. Solid $NaHSO_3$ (0.308 g) was added to the reaction mixture at 0 °C (until the starch-iodide test was negative) and the mixture was then filtered through a small pad of sand, which was washed with dimethylformamide. The filtrate was concentrated under reduced pressure at 20 °C to afford the crude product, which was purified by flash silica gel chromatography with methanol–aqueous NH_4OH–chloroform (1:1:5) and then passed throught a Dowex (OH^-) ion exchange column with water to afford 23 mg (75%) of pure hyacinthacine B_1 (**2**): [〈]$_D^{24}$ +40 (*c* 0.4, H_2O); IR (film) 3352, 2928, 2880 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) ™ 1.52-1.61 (m, 1 H), 1.73-1.82 (m, 1 H), 2.00-2.10 (m, 1 H), 2.10-2.20 (m, 1H), 2.91 (ddd, *J* = 9.0, 6.1, 3.1 Hz, 1 H), 3.03-3.10 (m, 1 H), 3.42 (dd, *J* = 11.0, 6.4 Hz, 1 H), 3.44 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.54-3.58 (m, 1 H), 3.60 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.78 (dd, *J* = 10.9, 3.1 Hz, 1 H), 3.83 (dd, *J* = 3.8, 3.8 Hz, 1 H), 3.92 (dd, *J* = 8.8, 4.1 Hz, 1 H); ^{1}H NMR (400 MHz, D_2O) ™ 1.46-1.55 (m, 1 H), 1.73-1.82 (m, 1 H), 1.91-2.08 (m, 2 H), 2.85-2.92 (m, 1 H), 2.97-3.05 (m, 1 H), 3.42 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.49-3.54 (m, 1 H), 3.55 (dd, *J* = 11.0, 6.5 Hz,1 H), 3.60 (dd, *J* = 11.5, 6.5 Hz, 1 H), 3.73 (dd, *J* = 11.5, 4.0 Hz, 1 H), 3.90-3.95 (m, 2 H); ^{13}C NMR (100.6 MHz, CD_3OD) ™ 25.0 (CH_2), 31.2 (CH_2), 65.6 (CH_2), 67.4 (CH_2), 69.3 (CH), 71.4 (CH), 72.4 (CH), 74.6 (CH), 77.6 (CH); ^{13}C NMR (100. 6 MHz, D_2O) ™ 25.3 (CH_2), 32.3 (CH_2), 66.1 (CH_2), 67.5 (CH_2), 69.4 (CH), 71.9 (CH), 72.1 (CH), 74.9 (CH), 78.2 (CH); MS (ESI) *m/z* 204 (MH^+); HRMS (ESI) calcd for $C_9H_{18}NO_4$: 204.1230. Found: 204.1230 (MH^+).

(2*R*,3*S*,4*R*,5*R*)-2-(But-3-enyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol (17). A solution of diol **15b** (16.0 mg, 0.036 mmol) in dichloromethane (1.0 mL) was stirred with 0.044 mL (48 mg, 0.36 mmol) of terafluoroboric acid dimethyl ether complex for 5 h at 20 °C. The solvent was then evaporated and the resulting crude product was dissolved in DMF (0.5 mL) was treated with 21 mg (0.36 mmol) of potassium fluoride. After being stirred for 30 min, the reaction mixture was cooled to 0 °C and 0.070 mL (24 mg, 35% in water, 0.72 mmol) of hydrogen peroxide solution was added.

After being allowed to warm to 20 °C over 1 h, the reaction mixture was heated at 40 °C for 2 h. The excess peroxide was destroyed by addition of solid $NaHSO_3$ (75 mg) at 0 °C and the resulting reaction mixture was filtered through small pad of sand, which was then washed with DMF. The solvents were evaporated under reduced pressure at 20 °C to afford the crude product, which was purified by flash chromatography on silica gel with methanol–aqueous NH_4OH–chloroform (1:1:5). This resulting salt, after passage over Dowex (OH^-) with water, gave 4.7 mg (69%) of pure **17**. ^{1}H NMR (400 MHz, D_2O) δ 1.53-1.64 (m, 1 H), 1.65-1.76 (m, 1 H), 2.14 (q, *J* = 7.6, 14.4 Hz, 2 H), 3.09-3.20 (m, 2 H), 3.63 (dd, *J* = 6.4, 12.0 Hz, 1 H), 3.73 (dd, *J* = 4.2, 11.3 Hz, 1 H), 4.01 (dd, *J* = 4.2, 4.2 Hz, 2 H), 4.04 (dd, *J* = 4.2, 6.2 Hz, 1 H), 5.07 (m, 2H), 5.92 (dddd, *J* = 6.6, 6.6, 10.1, 10.1 Hz, 1 H); ^{13}C NMR (75.5 MHz, D_2O) δ 28.1 (CH_2), 30.4 (CH_2), 58.8 (CH), 61.5 (CH), 62.9 (CH_2), 73.0 (CH), 74.5 (CH), 114.9 (CH_2), 139.1 (CH); MS (ESI) *m/z* 188 (MH^+); HRMS (ESI) calcd for $C_9H_{18}O_3N_1$: 188.1281. Found: 188.1278 (MH^+).

(2*S*,3a*R*,4*S*,6*S*,8a*R*,8b*S*)-6-(Benzyloxymethyl)-4-((dimethyl(phenyl)silyl)methyl)-2-phenylhexahydro-4*H*-[1,3]dioxolo[4,5-a]pyrrolizine (19). To a stirred solution of $^iPr_2NH$ (0.770 mL, 0.556 g, 5.49 mmol) in freshly distilled THF (2.2 mL) at –35 °C under Ar was added dropwise 2.0 mL of *n*-BuLi (2.5 M in hexanes, 5.0 mmol). The solution was allowed to warm to 0 °C over 30 min and then degassed by three freeze-thaw cycles. A 0.440-mL (0.44 mmol) portion of this LDA solution was added to a degassed solution of amino-nitriles **13** (89 mg, 0.22 mmol) in THF (1.1 mL) at –60 °C and the mixture was stirred for 15 min. Benzyl chloromethyl ether (0.093 mL, 0.105 g, 0.67 mmol) was then added at –60 °C and stirring was continued for 30 min before the addition of saturated aqueous NH_4Cl. The reaction mixture was allowed to warm to 20 °C and was extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting, unstable crude product **18** was directly used without purification: ^{1}H NMR (400 MHz, Toluene-d_8) δ 0.31 (s, 3 H, H), 0.34 (s, 3 H), 0.89 (B of ABX, J = 14.6, 9.9 Hz, 1 H), 1.12 (A of ABX, J = 14.6, 5.0 Hz, 1 H), 1.45 – 1.36 (m, 1 H), 1.75 – 1.64 (m, 1 H), 2.14 – 2.05 (m, 1 H), 2.25 – 2.17 (m, 1 H), 2.98 (B of AB, J = 9.1 Hz, 1 H), 3.20 (A of AB, J = 9.1 Hz, 1 H), 3.40 (ddd, J = 6.9, 6.9, 5.0 Hz, 1 H), 4.03 (dd, J = 5.9, 5.0 Hz , 1 H), 4.05 (ddd, J = 9.9, 5.0, 3.2 Hz, 1 H), 4.19 (dd, J = 5.9, 3.2, 1 H), 4.22 (B of AB, J = 12.2 Hz, 1 H), 4.27 (A of AB, J = 12.2 Hz, 1 H), 5.60 (s, 1 H), 7.27 – 7.16 (m, 10 H), 7.49 – 7.43 (m, 3 H),7.78 – 7.73 (m, 2 H); ^{13}C NMR (100 MHz, Toluene-d_8) δ -2.4 (CH_3), -2.2 (CH_3), 24.1 (CH_2), 24.3 (CH_2), 37.6 (CH_2), 64.1 (CH), 66.0 (C), 66.9 (CH), 73.57 (CH_2), 76.4 (CH_2), 82.2 (CH), 90.8 (CH), 106.9 (CH), 120.0 (C), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 129.2 (CH), 129.5 (CH), 134.0 (CH), 136.7 (C), 138.3 (C), 139.6 (C); MS (ESI) *m/z* 498 $[M\text{-}CN]^+$, 525 $[M+H]^+$.To a solution of the crude product in anhydrous MeOH (1.0 mL) at 0 °C was added $NaBH_4$ (42 mg, 1.11 mmol). The reaction mixture was stirred for 1 h at this temperature and then water was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with MeOH saturated with NH_3 in EtOAc (2-10%) to give 54 mg (49%, 55% brsm, 2 steps) of ether **19**, along with 9 mg of amino-nitrile **13**. Ether **19**: $[\alpha]^{25}_D$ +15 (c 1.2, $CHCl_3$); IR (film) 3373, 2918, 2845, 1665, 1455, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 3 H), 0.33 (s, 3 H), 0.87 (A of ABX, J = 14.5, 9.4 Hz, 1 H), 1.10 (B of ABX, J = 14.5, 5.9 Hz, 1 H), 1.66 – 1.53 (m, 1 H), 1.77 – 1.66 (m, 1 H), 1.98 – 1.82 (m, 1 H), 3.16 – 3.08 (m, 1 H), 3.20 (B of ABX, J = 9.1, 6.1 Hz, 1 H), 3.38 (A of ABX, J = 9.1, 6.2 Hz, 1 H), 3.46 – 3.33 (m, 1 H), 3.60 (dd, J = 9.4, 5.9 Hz, 1 H), 4.26 (B of AB, J = 12.1 Hz, 1 H), 4.31 (A of AB, J = 12.1 Hz, 1 H), 5.73 (s, 1 H), 4.50 – 4.43 (m, 2 H), 7.40 – 7.27 (m, 10 H), 7.57 – 7.47 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.4 (CH_3), -2.3 (CH_3), 17.0 (CH_2), 22.0 (CH_2), 31.3 (CH_2), 56.6 (CH), 58.1 (CH), 66.5 (CH), 73.2 (2 CH_2), 80.8 (CH), 91.8 (CH), 105.4 (CH), 126.9 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.9 (CH), 129.2 (CH), 133.7

(CH), 137.2 (C), 138.7 (C), 139.7 (C); MS (ESI) *m/z* 500.2 (MH^+); HRMS (ESI) calcd for $C_{31}H_{38}NO_3Si$: 500.2615. Found: 500.2618 (MH^+).

((2*S*,3a*R*,4*R*,6*S*,8a*R*,8b*S*)-6-(Benzyloxymethyl)-2-phenylhexahydro-4*H*-[1,3]dioxolo[4,5-a]pyrrolizin-4-yl)methanol (20). 30% KH in mineral oil (27 mg, 0.20 mmol) under Ar was washed with pentane and DMF (0.250 mL) was added. The mixture was cooled to 0 °C and carefully treated with a solution of ^{t}BuOOH (0.021 mL, 6.0 M in decane, 0.13 mmol) and, after 10 min, with a solution of **19** (10.5 mg, 0.021 mmol) in DMF (0.150 mL) and a solution of TBAF (0.042 mL, 1.0 M in THF, 0.04 mmol). After 1 h at 0 °C, the reaction mixture was allowed to warm to 20 °C and was stirred for 1 h. Saturated aqueous $Na_2S_2O_3$ was then added and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product. Chromatography on silica gel with MeOH saturated with NH_3 in dichlormethane (1:10) afforded 11 mg (> 100%) of alcohol **20**: $[\alpha]^{25}_D$ +35.7 (c 0.8, $CHCl_3$); IR (film) 3375, 2926, 2853, 1674, 1403, 1086 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 – 1.81 (m, 2 H), 1.81 – 1.92 (m, 1 H), 2.01 – 2.16 (m, 1 H), 3.31 – 3.40 (m, 2 H), 3.40 – 3.47 (m, 1 H), 3.51 – 3.62 (m, 2 H), 3.66 (ddd, *J* = 6.3, 4.6, 1.5 Hz, 1 H), 3.78 – 3.70 (m, 1 H), 4.28 (B of AB, *J* = 11.9 Hz, 1 H), 4.34 (A of AB, *J* = 11.9 Hz, 1 H), 4.64 – 4.57 (m, 2 H), 5.84 (s, 1 H), 7.45 – 7.27 (m, 8 H), 7.55 – 7.47 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 (CH_2), 30.6 (CH_2), 60.9 (CH), 62.4 (CH_2), 63.6 (CH), 67.2 (CH), 71.8 (CH_2), 73.2 (CH_2), 82.6 (CH), 86.8 (CH), 105.6 (CH), 126.5 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 129.3 (CH), 136.6 (C), 138.2 (C); MS (ESI) *m/z* (MH^+); HRMS (ESI) calcd for $C_{23}H_{28}NO_4$: 382.2013; Found**:** 382.2017 (MH^+).

(+)-Hyacinthacine B_2 (3). To a solution of alcohol **20** (8.0 mg, 0.021 mmol) in ethanol (0.300 mL) and THF (0.050 mL) was added 10% Pd/C (2.0 mg) and 6 N HCl (5 drops). The reaction mixture was stirred at 20 °C for 16 h under hydrogen. The mixture was then filtered through a plug of Celite, which was washed with MeOH. The filtrate was concentrated under reduced pressure and the residue was placed on a column of Dowex resin (H^+ form), which was washed successively with MeOH, water, and concentrated aqueous NH_4OH. The aqueous NH_4OH fractions were concentrated under reduced pressure to give 5.2 mg of protonated hyacinthacine B_2: ^1H NMR (400 MHz, D_2O) δ 1.81 (m, 2H, H_6 and H_7), 1.91 (m, 1H, H_6), 2.07 (m, 1H, H_7), 3.58 – 3.51 (m, 1H, H_3), 3.66 – 3.59 (m, 1H, H_5), 3.71 (B of ABX, *J* = 12.8, 2.4 Hz, 1H, H_8), 3.74 (s, 1H, H_{9b}), 3.76 (s, 1H, H_{9a}), 3.91 (A of ABX, *J* = 12.8, 3.1 Hz, 1H, H_8), 4.13 – 4.06 (m, 2H, H_1 and H_2), 4.15 (ddd, *J* = 8.5, 4.3, 4.1 Hz, 1H, H_{7a}); ^{13}C NMR (100 MHz, D_2O) δ 25.0 (CH_2), 29.9 (CH_2), 58.2 (CH_2), 60.2 (CH_2), 64.6 (CH), 69.3 (CH), 71.8 (CH), 72.8 (CH), 73.6 (CH). This material was placed on a column of Dowex resin (OH^- form), which was then washed with water to give 3.8 mg (89%, 2 steps) of (+)-hyacinthacine B_2 (**3**): $[\alpha]^{23}_D$ +25 (c 0.32, H_2O); IR (film) 3344, 2925, 2883, 1661, 1401, 1035 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.72 – 1.84 (m, 1 H), 1.94 – 2.09 (m, 3 H), 3.27 (ddd, *J* = 8.6, 6.4, 4.3 Hz, 1 H), 3.33 (pseudo-q, *J* = 5.1 Hz, 1 H), 3.66 (ddd, *J* = 7.0, 7.0, 3.9 Hz, 1 H), 3.73 (dd, *J* = 11.5, 6.4 Hz, 1 H), 3.81 – 3.91 (m, 3 H), 4.07 (dd, *J* = 3.9, 3.9 Hz, 1 H), 4.11 (dd, *J* = 8.6, 3.9 Hz, 1 H); ^{13}C NMR (100 MHz, D_2O) δ 79.4 (CH), 74.6 (CH), 69.3 (CH), 66.8 (CH_2), 64.5 (CH_2), 64.3 (CH), 64.2 (CH), 33.1 (CH_2), 25.0 (CH_2); MS (ESI) *m/z* 204 (MH^+); HRMS (ESI) calcd for $C_9H_{18}NO_4$: 204.1230; Found**:** 204.1229 (MH^+).

Acknowledgment. We thank the CNRS and the Université Joseph Fourier (UMR 5616, FR 2607) for financial support, the French Ministry for a doctoral fellowship (to J.S.), and Professor N. Asano for a comparison sample of natural hyacinthacine B_1.

Supporting Information Available: X-ray crystallographic analysis data for single crystal of compound **12**, ^1H, ^{13}C and COSY NMR spectra of compounds **2**, **3**, **8 – 17**, **19**, **20** and NOESY spectra of compounds **9** (minor), **14** and **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[xviii] (*R*)- and (*S*)-Stericol® are available from Sigma-Aldrich. (*S*)-Stericol® was chosen on the basis of previous work[xii-xiv] that indicated it would lead to natural hyacinthacines B_1 and B_2.

[xix] The lactam was obtained as a 93:7 (^{1}H NMR) mixture of diastereomers. The minor enantiomer filtered out over the remainder of the synthesis.

[xx] The analysis was performed on a racemic sample that was obtained by synthesis from racemic Stericol®. After basic analysis, the crystal appeared to be monoclinic with $P2_1$ space group, which was unexpected since the product was racemic and $P2_1$ is a non centrosymmetric space group. A closer look revealed, however, that the crystal was a racemic twin with two domains and BASF = 0.58501. This confirmed that the product was truly racemic and explained some meaningless residual electronic density peaks. Crystal data for $C_{23}H_{27}NO_3Si$ Monoclinic, $P2_1$, a = 12.493(3) Å, b = 6.4889(13) Å, c = 13.275(3) Å, β = 97.91(3)°, V = 1065.9(4)Å^3 , Z = 2, d_{calcd} = 1.226 mg/m^3, F(000) = 420, λ Mo Kα = 0.71073 Å, Θ_{max} range 3.4-25°, 17796 measured reflections, 3624 [R(int) = 0.0338] independent reflections, R(1) [1 > 2σ (I)] = 0.0800, wR2 [all data] = 0.0970, GOF (all data) = 1.099

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xxviii The assignment of stereochemistry was made on the basis of a strong NOE between H-3 and H-5 in the minor isomer and its absence in the case of the major isomer.

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xxxiii For example, Somfai and coworkers in their synthesis of (+)-alexine obtained a 2:1 mixture of the product of double oxidation and the *N*-oxide in 62% combined yield.[32g]

xxxiv The corresponding tetracetates were also found to be identical by chromatography (TLC) in several different solvent systems and by ^{1}H and ^{13}C NMR.

xxxv In order to study the rotation around the C5-CH_2Si bond (figure 3), a potential energy surface (PES) scan of **15a** and **15b** was performed at the semi-empirical level of theory (PM6). Geometry optimizations were done by freezing the dihedral angle N-C5-CH_2-Si at different values between -180 and 180 degrees. Two minima with a weak energy difference and a PES quite flat were found for **15a**, whereas only one minimum was identified for **15b**. To support these results, new calculations at a high level of theory (B3lyp/6-311++G**) were performed. For **15a**, using the two minima obtained at the PM6 level as a starting point, geometry optimizations converged toward structures close to their starting point. The electronic energy value of the two minima was different by only 2.6 kcal/mol. A transition state between these two minima was localized. Its electronic energy was 3.1 kcal/mol higher than the most stable minimum, allowing the rotation around the C5-CH_2Si bond for this isomer. For **15b**, the geometry optimization still converged to a minimum close to the structure obtained at the PM6 level (dihedral angle: -176.3 degrees). Others optimizations were performed with different dihedral angle values. The energy of these optimized structures increased gradually, suggesting that the rotation is not energetically favorable (for example, a 12.1 kcal/mol energy difference was obtained between the minimum and the structure with a dihedral angle of -60 degrees).

xxxvi All the calculations were carried out with Gaussian 09, revision A.1: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G.

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[xxxviii] Acid or base catalysis, however, produced significant amounts of degradation products.

[xxxix] For a review on reductive decyanation, see: Mattalia, J-M.; Marchi-Delapierre, C.; Hazimeh, H.; Chanon, M. *ARKIVOC* **2006**, *4*, 90.

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[xliii] The optical rotation of **3** ($[\alpha]_D$ +25) was different from that published[vi] for the natural product ($[\alpha]_D$ +41.3). We believe, however, that the reported value (identical for natural hyacinthacine B_1 and B_2) results from a typographical error. Unfortunately, a sample of natural B_2 could not be secured.

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