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First asymmetric synthesis of pyrrolizidine alkaloids, (+)-hyacinthacine B_1 and (+)-B_2

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ABSTRACT

An enantiomerically and diastereomerically pure route has been developed for the first asymmetric synthesis of (1*S*,2*R*,3*R*,5*R*,7a*R*)- and (1*S*,2*R*,3*R*,5*S*,7a*R*)-1,2-dihydroxy-3,5-dihydroxymethylpyrrolizidine, hyacinthacine B_1 and B_2, featuring efficient and stereodefined elaboration via the asymmetric dihydroxylation (AD) of the functionalized homochiral pyrrolidine derivative prepared from (*S*)-(−)-2-pyrrolidone-5-carboxylic acid.

1. Introduction

Structurally complex alkaloidal sugar mimics with a nitrogen in the ring have been isolated from plants and microorganisms and inhibit various glycosidases in a reversible and competitive manner.[1] Since such glycosidase inhibitors have been also proved to have the potential to produce antiviral, insect antifeedant, antidiabetic, and anticancer effects as well as immune modulatory properties,[1] they have held considerable interest in the context of the synthesis of nitrogen-containing natural products. Noteworthy members among this class of compounds are polyhydroxylated pyrrolizidines such as the alexines,[2] represented by the parent alkaloid (**1**), and australine (**2**),[3] exhibiting viral and retroviral[4] including anti-HIV[5] activities as well as powerful glycosidase inhibitory property (Fig. 1). There is a significant structural resemblance to (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine, DMDP (**3**), known as a strong glycosidase inhibitor occurring in some *Derris* spp. and *Lonchocarpus* (Leguminosae).[6] Recently, a new series of hyacinthacines were isolated from bluebells (*Hyacinthoides non-scripta*)[7] and grape hyacinths (*Muscari armeniacum*)[8] by Asano et al. The presence of a hydroxymethyl function to the ring nitrogen [C(3)] distinguishes these groups from the larger class of necine bases such as dihydroxyheliotridane (**4**), which bear carbon substituents at C(1). These compounds possess five stereogenic centers, two of which are connected with adjacent two hydroxyl groups. In particular, the preparation both of unnatural epimers and other structural analogs of these compounds has created much interest since the biological activity of these molecules varies substantially with the number, position, and stereochemistry of the hydroxyl groups into the pyrrolizidine skeleton.[9] Hyacinthacine B_1 (**5a**) and B_2 (**5b**), for example, were found to be selective inhibitors of β-glucosidase and β-galactosidase and the latter was, in addition, proved to inhibit rat intestinal lactase in a competitive manner with an IC_{50} value of 3.6 μM.[8]

While many total syntheses of hyacinthacine A series (the structure without the hydroxyl group(s) in the left-side ring of the pyrrolizidine framework shown in Fig. 1) have been recently completed by several groups,[10] the synthesis of hyacinthacine B series, however, has not been achieved to date. The central feature of this report is to describe the details of the first and expeditious route for the stereoselective construction of hyacinthacine B_1 (**5a**) and B_2 (**5b**) [stereoisomer of **5a** at C(5)] via the catalytic Sharpless asymmetric dihydroxylation starting from (*S*)-(−)-2-pyrrolidone-5-carboxylic acid, thus establishing the absolute configuration of the natural products.

In formulating the synthetic plan for **5**, we recognized that the absolute configurations at C(1), C(2), and C(3) are the same as the configurations at the corresponding centers C(3), C(4), and C(5) of

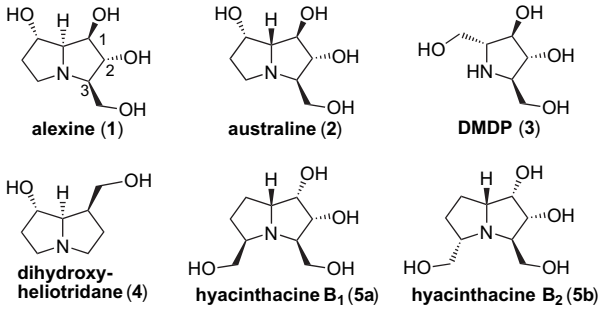

Figure 1. Structures of selected polyhydroxylated alkaloids.

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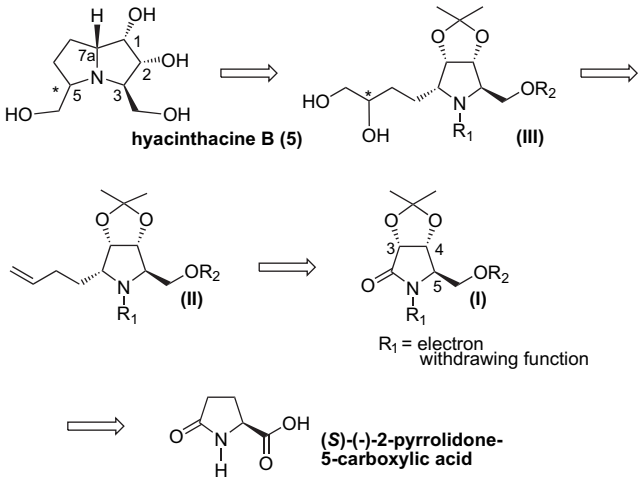


Figure 2. General retrosynthesis.

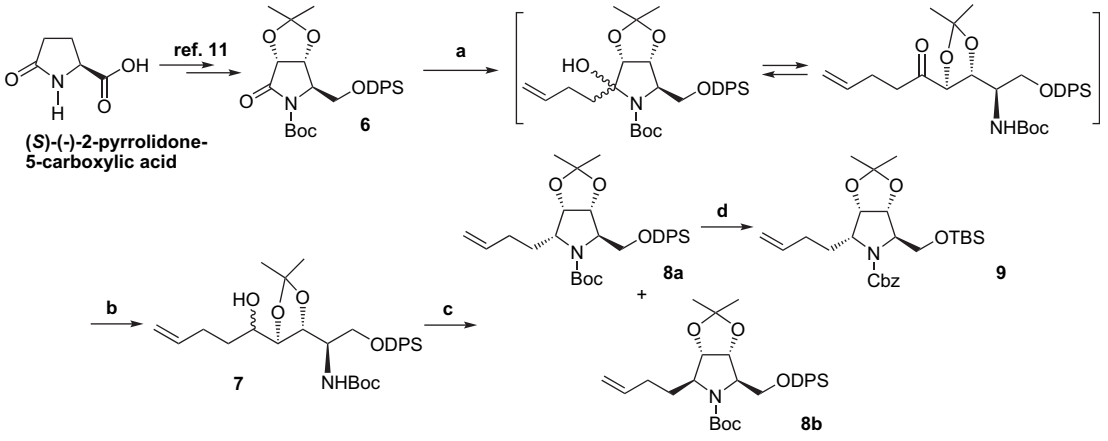
a protected lactam (**I**) derived from (*S*)-(−)-2-pyrrolidone-5-carboxylic acid (Fig. 2). Further we envisioned that the stereogenic center of C(7a) would originate from nucleophilic addition to (**I**) and successive reduction to the corresponding alcohol followed by cyclization, allowing the synthesis of the homochiral pyrrolidine intermediate (**II**). Meanwhile, the remaining stereogenic center C(5) of **5** would have to be independently set in an asymmetric dihydroxylation (AD) reaction of the pyrrolidine (**II**) to afford the corresponding diol derivative (**III**).

2. Results and discussion

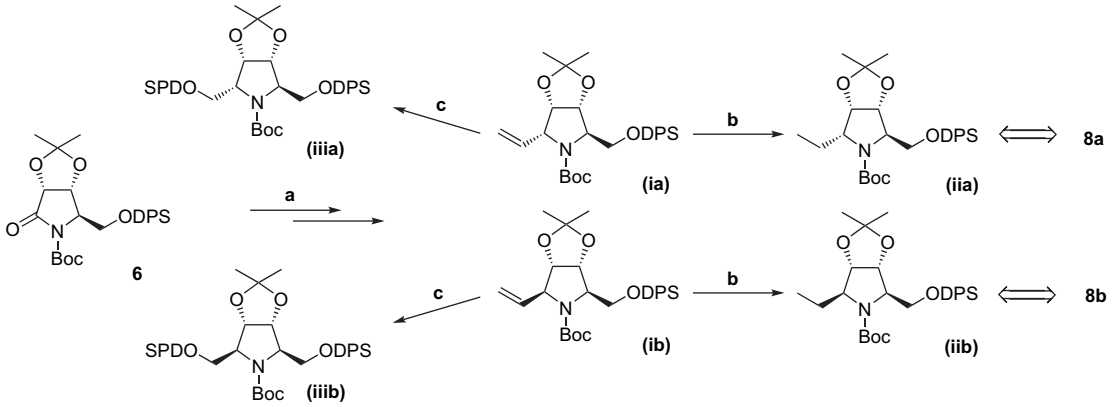
Our initial investigations were aimed at scrutinizing the feasibility of well known acetonide-protected *N*-Boc lactams (**I**) shown in Figure 2 for nucleophilic addition followed by stereoselective reduction of the corresponding hydroxyl pyrrolidine intermediates. Intrigued by previous reports regarding these reactions of the *N*-Boc lactam **6** and its derivatives prepared from (*S*)-(−)-2-pyrrolidone-5-carboxylic acid (Scheme 1),[11] where non-stereoselective results were obtained to achieve good yields of the open-chain products,[12] we investigated the reactivity of **6** in this nucleophilic addition and diastereoselective reduction sequence. Whereas the reduction of the labile hydroxyl pyrrolidine intermediate obtained from butenyl Grignard addition to **6**[13] with $NaBH_4$ only in MeOH (0.1 M solution) gave the corresponding alcohol **7** as a non-stereoselective mixture (53:47) in 45% yield,[14] remarkable enhancement in the selectivity together with the yield of these reactions was fortunately observed after detailed examination employing excess amounts of reducing agent in a dilute EtOH solution (0.005 M) to yield **7** with predominant stereoselectivity (95:5)[15] in an almost quantitative yield. After successive reactions of the diastereomer mixture **7** through mesylation and cyclization with *t*-BuOK, it was advantageously ascertained that the major product was the desired pyrrolidine derivative **8a** and able to be separated from the minor isomer **8b** (Scheme 2)[16] by column chromatography on silica gel, which proceeded in 96% two-step yield. Although an attempt toward the synthesis of the target compounds employing this *N*-Boc **8a** was initially carried out, the results from our survey have revealed formation of an intractable mixture on the construction of a pyrrolizidine ring accompanying the elimination of the Boc group. Thus, upon replacing the Boc function, the Cbz-pyrrolidine **9** was selected for further convenient transformation of the functional groups and elaborated through the promising four-step sequence (desilylation, *NaH*-assisted Boc-elimination[17] and *N*-Cbz protection, followed by TBS-silylation) from **8a**.

With the compound **9** in hand, we next focused our research on the total synthesis of hyacinthacines **5a** and **5b** as shown in Scheme 3. Thus, **9** was initially submitted to the catalytic Sharpless asymmetric dihydroxylation (AD) with AD-mix-α [$(DHQ)_2PHAL$ ligand][18] in expectation of high enantiomeric enhancement,[19] which could effect these reactions beneficially, bringing about the desired diol product **10a** with moderate stereoselectivity (**10a**/**10b**=71:29, determined by ^1H NMR), but as an inseparable mixture in 98% isolated yield. Fortunately, it has become apparent that the major diastereomer **11a** obtained after the three-step conversion of **10**, i.e., selective protection of the primary alcohol with TBSCl and mesylation followed by cyclization, was easily separated from **11b** by column chromatography on silica gel.[20] Finally, this compound was effected by deprotection with tetrabutylammonium fluoride (TBAF), which on successive treatment with trifluoroacetic acid (TFA) gave rise to the desired product **5a** in 92% isolated yield.

The spectral data of synthetic **5a**, together with the optical rotation of which matches that of the reported value {$[\alpha]_D^{26}$ +41.9 (*c* 0.4, H_2O) [lit. $[\alpha]_D$ +41.3 (*c* 1.04, H_2O)][7]}, were completely identical to those of the natural product,[7] demonstrating that the structure attributed by Asano et al. to natural hyacinthacine B_1 (**5a**) was correct and the first total synthesis of **5a** was accomplished. Thus, one of the target compounds, **5a**, was obtained in 24 steps and 21% overall yield from commercially available (*S*)-(−)-2-pyrrolidone-5-carboxylic acid.

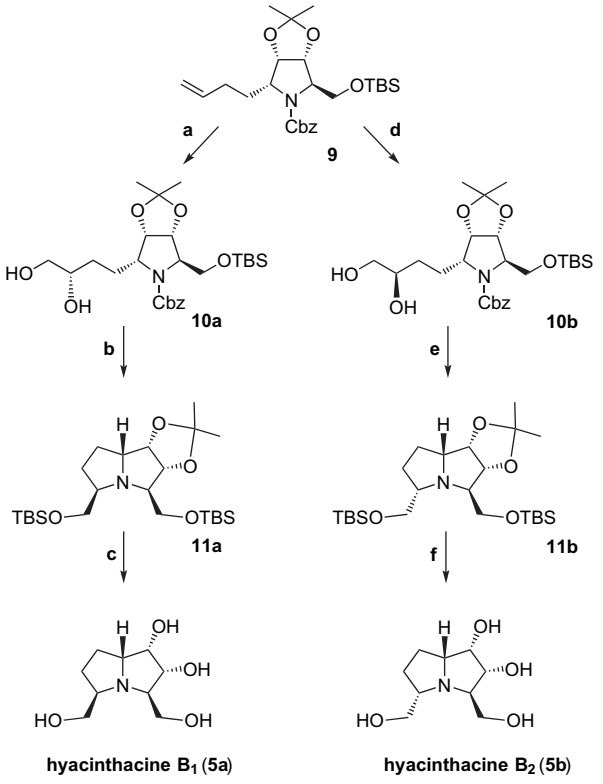


Scheme 1. Reagents and conditions: (a) $CH_2{=}CH(CH_2)_2MgBr$, THF, rt, 5 min; (b) $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 4 h, quant. (two steps); (c) (i) MsCl, Et_3N, CH_2Cl_2; (ii) *t*-BuOK, THF; 91% (**8a**) (two steps); 5% (**8b**) (two steps); (d) (i) Bu_4NF, THF, quant.; (ii) NaH, THF, rt, 2 h, quant.; (iii) CbzCl, $NaHCO_3$, MeOH; 97%; (iv) TBSCl, imidazole, DMF; 97%.



Scheme 2. Reagents and conditions: (a) (i) CH_2=CHMgCl, THF, −78 °C, 20 min; (ii) $NaBH_4$, $CeCl_3$, MeOH; 75%; (iii) MsCl, Et_3N, CH_2Cl_2; 71%; (iv) Bu_4NF, THF (separation of the two diastereomers); (v) DPSCl, imidazole, DMF; 49% (**ia**) (two steps); 41% (**ib**) (two steps); (b) H_2, Pd/C, EtOH; quant. (**iia**) and (**iib**), respectively; (c) (i) OsO_4, NMO, acetone/H_2O (1:1); (ii) $NaIO_4$, THF/H_2O (1:2); (iii) $NaBH_4$, MeOH; (iv) DPSCl, imidazole, DMF; 88% (**iiia**) (four steps); 86% (**iiib**) (four steps).

Having obtained and characterized the synthetic hyacinthacine B_1 (**5a**), we attempted the asymmetric dihydroxylation (AD) of **9** again with AD-mix-β [$(DHQD)_2PHAL$ ligand], to provide the compound **11b** (**11a**/**11b**=19:81, isolated ratio), as expected, in a reverse stereoselective manner after the three-step treatment as mentioned above. This was then subjected to deprotection reactions in the same way, resulting in the first asymmetric preparation of hyacinthacine B_2 (**5b**) {$[\alpha]_D^{27}$ +42.3 (*c* 0.25, H_2O) [lit. $[\alpha]_D$ +41.3 (*c* 0.36, H_2O)][7]} in quite high overall yield (24%) from (*S*)-(−)-2-pyrrolidone-5-carboxylic acid. The spectral data as well as the optical rotation of synthetic **5b** were also identical[21] to those of the natural product.[7]



Scheme 3. Reagents and conditions: (a) AD-mix-α [$(DHQ)_2PHAL$ ligand], *t*-BuOH/H_2O (1:1), 0 °C, 48 h; 98%; (b) (i) TBSCl, Et_3N, CH_2Cl_2; 97%; (ii) MsCl, Et_3N, CH_2Cl_2; 92%; (iii) H_2, Pd/C, EtOH; (**11a**); 69% (**11b**); 28%; (c) (i) Bu_4NF, THF; 97%; (ii) TFA, H_2O; 92%; (d) AD-mix-β [$(DHQD)_2PHAL$ ligand], *t*-BuOH/H_2O (1:1), 0 °C, 24 h; 98%; (e) (i) TBSCl, Et_3N, CH_2Cl_2; 97%; (ii) MsCl, Et_3N, CH_2Cl_2; 92%; (iii) H_2, Pd/C, EtOH; (**11a**); 19% (**11b**); 80%; (f) (i) Bu_4NF, THF; 97%; (ii) TFA, H_2O; 94%.

3. Conclusions

In summary, this work constitutes the first asymmetric synthesis of the natural pyrrolizidine alkaloids, hyacinthacines B_1 and B_2 [stereoisomer of B_1 at C(5)] in 24 steps via the asymmetric dihydroxylation (AD) of the functionalized homochiral pyrrolidine intermediate prepared from (*S*)-(−)-2-pyrrolidone-5-carboxylic acid in an overall yield of 21% and 24%, respectively, and verifies the structure proposed in the literature for these natural products. In addition, the concise synthetic strategy described herein represents an easily accessible pathway to widespread pyrrolidine, pyrrolizidine, and indolizidine types of natural products. Further synthetic studies based on this strategy are currently underway and will be reported in due course

4. Experimental section

4.1. General

All solvents and reagents were of reagent grade quality from Aldrich Chemical Company, Fluka, Acros or Wako Pure Chemicals and used without any further purification. Melting points were measured on an automated melting point system (MPA 100, Stanford Research Systems). Fourier transform infrared (FTIR) spectra were recorded on a Shimadzu FTIR-8200A spectrometer. The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were measured with a JEOL JNM-AL300 spectrometer in chloroform-*d* ($CDCl_3$) unless otherwise stated. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standard (δ=0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ=77.0) for ^{13}C NMR. The coupling constants are reported in hertz (Hz). Optical rotations were measured in 1 dm path length cell of 2 mL capacity using a JASCO Model DIP-1000 polarimeter at a wavelength of 589 nm. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Merck silica gel 60-F_{254} precoated silica gel plates by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in methanol followed by heating. Column chromatography was performed on Kanto Chemical silica gel 60N eluting with the indicated solvent system. The non-crystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, IR, high resolution mass spectra (HRMS), and microanalysis. High-performance liquid chromatography (HPLC) was carried out using a Shimadzu Model LC-10AD or 10AT intelligent pump and SPD-10A UV detector. HRMS were recorded on a JEOL JMS-T100CS spectrometer. Microanalyses were performed with a JSL Model JM 10.

4.2. Experimental procedures

*4.2.1. tert-Butyl (R)-2-(tert-butyldiphenylsilyloxy)-1-((4R,5R)-5-(1-hydroxypent-4-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-ethylcarbamate (**7**)*

To a solution of **6** (0.049 g, 0.0933 mmol) in THF (1.0 mL) was added butenylmagnesium bromide (0.2 M solution in THF, 2.8 mL, 0.559 mmol) dropwise under nitrogen at 0 °C and stirred 5 min. It was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude hydroxyl pyrrolidine as a pale yellow oil, which was used without further purification. To a solution of the above compound and powdered $CeCl_3$ (0.037 g, 0.150 mmol) (heated to 135–140 °C for 1 h with evacuation (ca. 1.0 Torr) before use) in EtOH (15.6 mL) was added $NaBH_4$ (0.876 g, 23.33 mmol) at 0 °C and stirred for 1 h. It was quenched by the addition of water (2 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=5:1) to give the diastereomer mixture (95:5, determined by ^{1}H NMR) of **7** (0.031 g, 57%, R_f=0.55, hexane/EtOAc=3:1) as a colorless oil. IR (NaCl) 3441 (O–H), 2858 (C–H), 1703 (C=O), 1641 (C=C), 1250 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (major isomer) 7.71–7.64 (m, 4H, Ar*H*), 7.43–7.26 (m, 6H, Ar*H*), 5.86 (ddt, *J*=17.0, 10.1, 6.8 Hz, 1H, CH_2=C*H*), 5.08–5.01 (m, 2H, CH_2=CH), 4.95 (dd, *J*=10.1, 1.1 Hz, 1H, C*H*), 4.25 (dd, *J*=10.1, 4.9 Hz, 1H, C*H*), 4.01–3.85 (m, 2H, CH_2), 3.77 (m, 1H, C*H*), 3.73 (dd, *J*=10.1, 2.4 Hz, 1H, C*H*), 3.00 (br, 1H, O*H*), 2.30 (m, 1H, CH_2), 2.15 (dt, *J*=14.8, 7.0 Hz, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.60 (m, 1H, CH_2), 1.46 (s, 9H, 3CH_3), 1.34 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.06 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$) δ (major isomer) 156.0, 138.8, 135.6, 135.5, 133.2, 133.1, 129.8, 129.7, 127.7, 127.6, 114.6, 108.0, 80.8, 80.5, 75.9, 68.2, 63.9, 51.1, 33.0, 29.4, 28.3, 27.8, 26.8, 25.6, 19.3; ^{13}C NMR ($CDCl_3$) δ (minor isomer) 155.5, 138.4, 135.6, 135.4, 133.2, 129.7, 129.6, 127.7, 127.6, 114.7, 108.0, 79.8, 79.4, 74.9, 68.3, 64.0, 51.0, 34.3, 30.1, 28.3, 27.8, 26.8, 24.8, 19.4; HRMS (ESI$^+$) *m*/*z* calcd for $C_{33}H_{49}NO_6Si$+Na: 606.3227, found 606.3210.

*4.2.2. (3aS,4R,6R,6aR)-tert-Butyl 4-(but-3-enyl)-6-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyldihydro-3aH-[1,3]dioxolo[4,5-c]pyrrole-5(4H)-carboxylate (**8a**)*

To a solution of **7** (0.060 g, 0.103 mmol) and Et_3N (0.084 g, 0.824 mmol) in CH_2Cl_2 (1.0 mL) was added methanesulfonyl chloride (0.035 g, 0.309 mmol) at 0 °C and stirred for 30 min. The mixture was quenched by the addition of 3% aq HCl (3 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude mesylate, which was used without further purification. To a solution of this mesylate in THF (2.0 mL) was added *t*-BuOK (0.023 g, 0.206 mmol) at 0 °C and stirred for 2 h. The mixture was quenched by the addition of water (1 mL) and stirred for additional 2 h. It was diluted with water (5 mL) and extracted with CH_2Cl_2 (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude products of two diastereomers were separated by column chromatography (silica gel, hexane/EtOAc/toluene=10:1:2) to give **8a** (0.053 g, 91.0%, R_f=0.36, hexane/EtOAc/toluene=10:1:2) and **8b** (0.003 g, 5.1%, R_f=0.30, hexane/EtOAc/toluene=10:1:2) as a viscous oil, respectively. Compound **8a**: $[\alpha]_D^{17}$ −64.2 (*c* 1.0, $CHCl_3$); IR (NaCl) 2858 (C–H), 1699 (C=O), 1641 (C=C), 1248 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64–7.58 (m, 4H, Ar*H*), 7.43–7.38 (m, 6H, Ar*H*), 5.87 (m, 1H, CH_2=C*H*), 5.05 (dd, *J*=17.0, 1.1 Hz, 1H, CH_2=CH), 4.93 (br d, *J*=9.2 Hz, 1H, CH_2=CH), 4.79 (t, *J*=6.4 Hz, 1H, C*H*), 4.69 (m, 1H, C*H*), 4.27–3.83 (m, 3H, CH_2 and C*H*), 3.65 (m, 1H, C*H*), 2.20 (m, 1H, CH_2), 2.09 (m, 1H, CH_2), 1.88–1.66 (br, 2H, CH_2), 1.50 (s, 9H, 3CH_3), 1.35 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.05 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$) δ 154.5, 138.8, 135.5, 132.8, 129.9, 129.8, 129.0, 128.2, 127.8, 125.2, 114.3, 110.9, 81.6, 80.3, 79.9, 79.4, 64.5, 62.9, 62.4, 61.8, 30.6, 28.4, 27.5, 26.8, 26.0, 24.9, 21.4, 19.1. Anal. Calcd for $C_{33}H_{47}NO_5Si$: C, 70.05; H, 8.37; N, 2.48. Found: C, 69.83; H, 8.41; N, 2.42. Compound **8b**: $[\alpha]_D^{17}$ −21.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 2858 (C-H), 1697 (C=O), 1641 (C=C), 1244 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66–7.62 (m, 4H, Ar*H*), 7.40–7.36 (m, 6H, Ar*H*), 5.73 (dt, *J*=17.0, 7.0 Hz, 1H, CH_2=C*H*), 4.97 (dd, *J*=17.0, 1.5 Hz, 1H, CH_2=CH), 4.91 (d, *J*=10.3 Hz, 1H, CH_2=CH), 4.75 (br, 1H, C*H*), 4.40 (m, 1H, C*H*), 4.10 (m, 1H, C*H*), 3.88 (m, 1H, CH_2), 3.73 (dd, *J*=10.3, 3.2 Hz, 1H, CH_2), 3.59 (m, 1H, C*H*), 2.16–2.02 (m, 2H, CH_2), 1.87–1.67 (m, 2H, CH_2), 1.46 (s, 9H, 3CH_3), 1.37 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.07 (s, 9H, 3CH_3); ^{13}C NMR ($CDCl_3$) δ 154.3, 137.5, 135.6, 135.5, 133.1, 132.9, 129.8, 129.7, 129.5, 127.8, 127.7, 127.6, 114.9, 111.5, 84.5, 83.9, 82.1, 81.3, 79.7, 65.6, 64.5, 63.9, 63.6, 33.3, 32.8, 30.3, 28.4, 27.3, 27.0, 26.5, 25.5, 19.2. Anal. Calcd for $C_{33}H_{47}NO_5Si$: C, 70.05; H, 8.37; N, 2.48. Found: C, 69.96; H, 8.35; N, 2.33.

*4.2.3. (3aS,4R,6R,6aR)-Benzyl 4-(but-3-enyl)-6-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyldihydro-3aH-[1,3]dioxolo[4,5-c]pyrrole-5(4H)-carboxylate (**9**)*

4.2.3.1. Deprotection of DPS group. A solution of **8a** (0.172 g, 0.304 mmol) and tetrabutylammonium fluoride (1.0 M solution in THF, 0.45 mL, 0.45 mmol) in THF (3 mL) was stirred for 2 h. The mixture was quenched by the addition of saturated aq $NaHCO_3$ (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude alcohol, which was purified by column chromatography (silica gel, hexane/EtOAc=1:1) to give the alcohol (0.100 g, quant., R_f=0.46, hexane/EtOAc=1:1) as a colorless oil. $[\alpha]_D^{25}$ −42.2 (*c* 1.0, $CHCl_3$); IR (NaCl) 3441 (O–H), 2858 (C-H), 1687 (C=O), 1643 (C=C), 1248 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.84 (ddt, *J*=17.0, 10.3, 6.6 Hz, 1H, CH_2=C*H*), 5.04 (dd, *J*=17.0, 1.4 Hz, 1H, CH_2=CH), 4.96 (d, *J*=10.1 Hz, 1H, CH_2=CH), 4.67 (t, *J*=6.2 Hz, 1H, C*H*), 4.38 (br, 1H, C*H*), 3.90–3.79 (m, 2H, CH_2), 3.74–3.67 (m, 2H, CH_2), 2.20 (dt, *J*=14.6, 7.4 Hz, 1H, CH_2), 2.05 (dt, *J*=14.6, 7.4 Hz, 1H, CH_2) 1.93–1.72 (m, 2H, O*H* and CH_2), 1.56–1.48 (m, 4H, CH_3 and CH_2), 1.46 (s, 9H, 3CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 154.8, 138.5, 114.5, 112.3, 81.1, 80.5, 78.4, 64.8, 62.8, 60.6, 30.5, 28.4, 26.5, 25.2. Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.56; H, 8.89; N, 4.61.

4.2.3.2. Deprotection of Boc group. To a solution of the above alcohol (0.018 g, 0.0550 mmol) in THF (0.6 mL) was added a suspension of NaH (65 wt %, 0.004 g) in THF (0.5 mL) and stirred for 2 h. It was quenched by the slow addition of water (2 mL) and extracted with CH_2Cl_2 (5×3 mL). The combined organic extracts were dried over anhydrous K_2CO_3 and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, chloroform/MeOH=20:1) to give the amino alcohol (0.013 g, quant., R_f=0.27, $CHCl_3$/MeOH=10:1) as a white solid; mp 104.2–104.8 °C. $[\alpha]_D^{24}$ −3.7 (*c* 1.0, $CHCl_3$); IR (KBr) 3441 (O–H), 2862 (C–H), 1641 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.83 (ddt, *J*=17.1, 10.3, 6.6 Hz, 1H, CH_2=C*H*), 5.05 (ddd, *J*=17.1, 3.5, 1.7 Hz, 1H, CH_2=CH), 4.98 (m, 1H, CH_2=CH), 4.52 (dd, *J*=5.3, 3.8 Hz, 1H, C*H*), 4.37 (d, *J*=5.3 Hz, 1H, C*H*), 3.48 (dd, *J*=8.7, 3.8 Hz, 2H, C*H*), 3.31–3.19 (m, 2H, CH_2), 2.92 (dt, *J*=7.0, 3.8 Hz, 1H, C*H*), 2.76–2.45 (br, 2H, O*H* and N*H*), 2.24–2.17 (ddd, *J*=14.0, 7.0, 1.1 Hz, 2H, CH_2) 1.80–1.60 (m, 2H, CH_2), 1.46 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.2, 114.9, 110.9, 83.6, 82.2, 65.4, 59.8, 59.6, 31.2, 27.8, 26.1, 24.0. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.22; H, 9.69; N, 6.16.

4.2.3.3. Protection with CbzCl. Carbobenzoxy chloride (CbzCl) (0.012 g, 0.0686 mmol) was added to a suspension of the above amino alcohol (0.013 g, 0.0572 mmol) and $NaHCO_3$ (0.010 g, 0.119 mmol) in MeOH (0.6 mL) at 0 °C. After the mixture was stirred for 3 h, it was quenched by the addition of water (5 mL) and extracted with ethyl acetate (5×3 mL). The combined organic extracts were washed with brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/EtOAc=1:1) to give the Cbz-alcohol (0.020 g, 97%, R_f=0.46, hexane/EtOAc=1:1) as a colorless oil. $[\alpha]_D^{24}$ −43.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 3441 (O–H), 1684 (C=O), 1641 (C=C), 1246 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.31 (m, 5H, Ar*H*), 5.75 (br, 1H, CH_2=C*H*), 5.17 (d, *J*=12.3 Hz, 1H, CH_2=CH), 5.07 (d, *J*=12.3 Hz, 1H, CH_2=CH), 4.92 (d, *J*=10.3 Hz, 2H, PhCH_2), 4.68 (br, 1H, C*H*), 4.43 (br, 1H, C*H*), 3.96–3.84 (m, 3H, CH_2 and C*H*), 3.72 (br, 1H, C*H*), 2.53 (br, 1H, O*H*), 2.17 (m, 1H, CH_2), 2.03 (m, 1H, CH_2), 1.84–1.71 (m, 2H, CH_2), 1.49 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.1, 138.2, 136.1, 128.5, 128.2, 128.1, 114.5, 112.3, 81.0, 78.5, 67.1, 65.0, 62.5, 60.7, 30.4, 28.2, 26.4, 25.1. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.42; H, 7.81; N, 4.19.

4.2.3.4. Protection with TBSCl. A mixture of the *Z*-alcohol obtained as noted above (0.019 g, 0.0498 mmol), imidazole (0.007 g, 0.0996 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (0.012 g, 0.0996 mmol) in DMF (0.5 mL) was stirred for 8 h. It was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=10:1) to give the TBS-ether **9** (0.023 g, 97%, R_f=0.33, hexane/EtOAc=10:1) as a colorless oil. $[\alpha]_D^{24}$ −78.4 (*c* 1.0, $CHCl_3$); IR (NaCl) 2858 (C–H), 1697 (C=O), 1639 (C=C), 1251 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.26 (m, 5H, Ar*H*), 5.78 (m, 1H, CH_2=C*H*), 5.21–4.91 (m, 4H, CH_2=CH and 2C*H*), 4.71–4.64 (m, 2H, PhCH_2), 4.10 (m, 1H, C*H*), 3.84–3.72 (m, 2H, CH_2), 3.59 (br d, *J*=9.9 Hz, 1H, C*H*), 2.16–2.02 (m, 3H, CH_2), 1.73 (m, 1H, CH_2), 1.48 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.84 (s, 9H, 3CH_3), −0.06 (s, 3H, CH_3), −0.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.0, 138.7, 136.6, 128.5, 128.2, 128.0, 114.4, 110.9, 81.7, 79.8, 66.9, 66.5, 64.7, 63.7, 63.0, 62.0, 30.5, 28.9, 27.2, 26.0, 25.8, 24.9, 18.0, −5.7, −5.8. Anal. Calcd for $C_{26}H_{41}NO_5Si$: C, 65.65; H, 8.69; N, 2.94. Found: C, 65.80; H, 8.36; N, 3.15.

*4.2.4. (3aR,4R,6R,6aS)-Benzyl 4-((tert-butyldimethylsilyloxy)-methyl)-6-((S)-3,4-dihydroxybutyl)-2,2-dimethyldihydro-3aH-[1,3]dioxolo[4,5-c]pyrrole-5(4H)-carboxylate (**10**)*

To a stirred solution of AD-mix-α (0.059 g) and $(DHQ)_2PHAL$ (0.0032 g, 0.00416 mmol) in *t*-BuOH (0.23 mL) and water (0.23 mL) was added **9** (0.020 g, 0.042 mmol) at 0 °C and stirred for 48 h at the same temperature. Powdered $NaHSO_3$ (0.052 g, 0.500 mmol) was added and the mixture was extracted with CH_2Cl_2 (5×3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc=1:1) to give the diastereomer mixture of the diol **10** (0.021 g, 98%, R_f=0.44, hexane/EtOAc=1:2) as a colorless oil. IR (NaCl) 3441 (O–H), 2858 (C–H), 1690 (C=O), 1250 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.30 (m, 5H, Ar*H*), 5.19 (dd, *J*=12.1, 1.7 Hz, 1H, C*H*), 5.03 (d, *J*=12.1 Hz, 1H, C*H*), 4.73–4.64 (m, 2H, PhCH_2), 4.11 (m, 1H, C*H*), 3.81–3.47 (m, 6H, 2CH_2 and 2C*H*), 3.09 (br, 1H, O*H*), 2.84 (br, 1H, O*H*), 2.50–2.09 (m, 2H, CH_2), 1.80–1.66 (m, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 0.84 (s, 9H, 3CH_3), −0.06 (s, 3H, CH_3), −0.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (major isomer) 155.2, 136.3, 128.5, 128.4, 128.2, 111.2, 82.0, 79.6, 71.4, 66.6, 66.3, 64.4, 63.7, 63.6, 62.7, 61.8, 29.4, 25.8, 24.7, 23.5, 18.0, −5.7, −5.8; ^{13}C NMR ($CDCl_3$) δ (minor isomer) 155.2, 136.3, 128.5, 128.3, 128.1, 111.2, 81.8, 80.0, 72.0, 66.8, 66.3, 64.5, 63.7, 63.6, 62.7, 61.7, 29.8, 25.8, 24.7, 23.5, 18.0, −5.7, −5.8. Anal. Calcd for $C_{26}H_{43}NO_7Si$: C, 61.27; H, 8.50; N, 2.75. Found: C, 61.22; H, 8.37; N, 2.94.

*4.2.5. (3aR,4R,6S,8aR,8bS)-4,6-Bis((tert-butyldimethylsilyloxy)-methyl)-2,2-dimethylhexahydro-3aH-[1,3]dioxolo-[4,5-a]pyrrolizine (**11a**)*

4.2.5.1. Regioselective protection. A mixture of the above diol **10** (0.016 g, 0.0314 mmol), Et_3N (0.016 g, 0.157 mmol), and TBSCl (0.019 g, 0.126 mmol) in CH_2Cl_2 (1.6 mL) was stirred for 48 h. It was quenched by the addition of water (5 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed (silica gel, hexane/EtOAc=10:1) to give the diastereomer mixture of the mono-TBS-ether (0.019 g, 97%, R_f=0.31, hexane/EtOAc=5:1) as a colorless oil. IR (NaCl) 3441 (O–H), 2856 (C–H), 1692 (C=O), 1252 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.30 (m, 5H, Ar*H*), 5.21–4.99 (m, 2H, 2C*H*), 4.71–4.62 (m, 2H, PhCH_2), 4.05 (m, 1H, C*H*), 3.79–3.33 (m, 6H, 2CH_2 and 2C*H*), 2.64–2.07 (br, 3H, O*H* and CH_2), 1.84–1.65 (m, 2H, CH_2), 1.49 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.89 (s, 9H, 3CH_3), 0.83 (s, 9H, 3CH_3), 0.06 (s, 6H, 2CH_3), −0.06 (s, 3H, CH_3), −0.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ (major isomer) 155.1, 136.5, 128.5, 128.3, 128.0, 111.0, 81.6, 80.0, 71.9, 67.2, 67.0, 66.6, 64.7, 63.6, 63.4, 29.5, 25.9, 25.8, 24.8, 24.1, 18.3, 18.0, −5.3, −5.4, −5.7, −5.8; ^{13}C NMR ($CDCl_3$) δ (minor isomer) 155.1, 136.5, 128.5, 128.3, 128.0, 111.0, 81.6, 80.3, 72.1, 67.2, 67.0, 66.6, 64.8, 63.7, 63.6, 63.4, 29.6, 25.9, 25.8, 24.8, 24.3, 18.3, 18.0, −5.4, −5.7, −5.8. Anal. Calcd for $C_{32}H_{57}NO_7Si_2$: C, 61.60; H, 9.21; N, 2.24. Found: C, 61.34; H, 8.85; N, 2.48.

4.2.5.2. Mesylation and cyclization. To a solution of this TBS-protected diastereomer mixture (0.025 g, 0.0401 mmol) and Et_3N (0.008 g, 0.0802 mmol) in CH_2Cl_2 (0.4 mL) was added methanesulfonyl chloride (0.007 g, 0.0602 mmol) at 0 °C and stirred for 15 min. The mixture was quenched by the addition of 3% aq HCl (3 mL) and extracted with ethyl acetate (10×3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed (silica gel, toluene/EtOAc=10:1) to give the diastereomer mixture of the mesylate (0.026 g, 92%) as a colorless oil. A solution of this mesylate (0.026 g, 0.037 mmol) and 5% Pd on carbon in EtOH (4 mL) was stirred at 0 °C for 0.5 h under hydrogen. After filtration through a pad of Celite with EtOH and concentration, the crude products of two diastereomers were separated by column chromatography (silica gel, hexane/EtOAc=5:1) to give **11a** (0.0121 g, 69%, R_f=0.53, hexane/EtOAc=5:1) and **11b** (0.005 g, 28%, R_f=0.36, hexane/EtOAc=5:1) as a colorless oil, respectively. Compound **11a**: $[\alpha]_D^{24}$ +6.1 (*c* 1.0, $CHCl_3$); IR (NaCl) 2856 (C–H), 1256 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.72 (d, *J*=5.3 Hz, 1H, C*H*), 4.50 (t, *J*=5.3 Hz, 1H, C*H*), 3.65–3.60 (m, 2H, CH_2), 3.51–3.27 (m, 5H, CH_2 and 3C*H*), 2.15–2.02 (m, 2H, CH_2), 1.89 (m, 1H, CH_2), 1.58–1.44 (m, 4H, CH_3 and CH_2), 1.31 (s, 3H, CH_3), 0.89 (s, 18H, 6CH_3), 0.05 (s, 6H, 2CH_3), 0.04 (s, 6H, 2CH_3); ^{13}C NMR ($CDCl_3$) δ,111.5, 86.1, 83.4, 70.2, 68.9, 68.5, 66.9, 65.7, 29.7, 26.7, 26.0, 25.9, 25.8, 23.8, 23.6, 18.3, −5.2, −5.3, −5.4. Anal. Calcd for $C_{24}H_{49}NO_4Si_2$: C, 61.09; H, 10.47; N, 2.97. Found: C, 60.98; H, 10.42; N, 3.11. Compound **11b**: $[\alpha]_D^{25}$ −3.6 (*c* 0.7, $CHCl_3$); IR (NaCl) 2856 (C–H), 1256 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.70 (d, *J*=6.2 Hz, 1H, C*H*), 4.47 (t, *J*=6.2 Hz, 1H, C*H*), 3.75 (dd, *J*=10.1, 6.2 Hz, 1H, CH_2), 3.67–3.56 (m, 2H, CH_2 and C*H*), 3.52–3.43 (m, 3H, CH_2 and C*H*), 3.26 (ddd, *J*=12.5, 6.2, 6.2 Hz, 1H, C*H*), 1.95–1.78 (m, 2H, CH_2), 1.78–1.61 (m, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.32

(s, 3H, CH_3), 0.89 (s, 18H, 6CH_3), 0.06 (s, 6H, 2CH_3), 0.05 (s, 6H, 2CH_3); ^{13}C NMR ($CDCl_3$) δ 111.5, 86.7, 81.4, 68.0, 65.1, 64.8, 63.3, 61.3, 30.7, 26.0, 25.9, 24.2, 23.1, 18.2, −5.2, −5.3, −5.4. Anal. Calcd for $C_{24}H_{49}NO_4Si_2$: C, 61.09; H, 10.47; N, 2.97. Found: C, 61.20; H, 10.18; N, 2.65.

*4.2.6. (1S,2R,3R,5R,7aR)-3,5-Bis(hydroxymethyl)hexahydro-1H-pyrrolizine-1,2-diol (hyacinthacine B_1) (**5a**)*

4.2.6.1. Deprotection of bis-TBS group. A solution of **11a** (0.038 g, 0.0805 mmol) and tetrabutylammonium fluoride (1.0 M solution in THF, 0.18 mL, 0.18 mmol) in THF (0.8 mL) was stirred at 0 °C for 6 h. The mixture was concentrated to give the crude product, which was purified by column chromatography (silica gel, chloroform/MeOH=10:1) to afford the diol (0.019 g, 97%, R_f=0.22, $CHCl_3$/MeOH=10:1) as a colorless oil. $[\alpha]_D^{25}$ +4.1 (*c* 0.6, $CHCl_3$); IR (NaCl) 3485 (O–H), 2874 (C–H) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.56 (dd, *J*=10.4, 5.7 Hz, 1H, C*H*), 4.50 (dd, *J*=5.7, 1.5 Hz, 1H, C*H*), 3.74 (m, 1H, C*H*), 3.68 (dd, *J*=15.3, 9.2 Hz, 1H, CH_2), 3.58 (dd, *J*=10.2, 3.5 Hz, 1H, CH_2), 3.48–3.35 (m, 3H, CH_2 and 2C*H*), 3.44 (dd, *J*=15.3, 6.5 Hz, 1H, CH_2), 2.93–2.56 (br, 2H, 2O*H*), 2.21–2.09 (m, 2H, CH_2), 1.96 (m, 1H, CH_2), 1.65 (m, 1H, CH_2), 1.50 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 112.1, 85.2, 82.7, 70.8, 67.2, 66.6, 65.8, 62.8, 28.7, 26.8, 24.3, 24.0. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.16; H, 9.07; N, 5.53.

4.2.6.2. Deprotection of acetal. To a solution of the above diol (0.013 g, 0.0534 mmol) in H_2O (0.5 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C and stirred for 24 h. The mixture was concentrated to give the crude product. Finally, the water solution of the crude product was passed through Dowex 50WX-8 (H^+ form), which was first eluted with water (20 mL), and then with 0.7 M NH_4OH followed by 1.4 M NH_4OH. Fractions were concentrated in vacuo to give **5a** (0.011 g, 92%, R_f=0.45, MeOH/H_2O/NH_4OH=20:2:1) as a colorless oil. The spectral data of synthetic hyacinthacine B_1 (**5a**) thus obtained were identical in all respects with those of the reported natural product.[7] $[\alpha]_D^{26}$ +41.9 (*c* 0.4, H_2O) {lit. $[\alpha]_D$ +41.3 (*c* 1.04, H_2O)[7]}; IR (NaCl) 3335 (O–H), 2874 (C–H) cm^{-1}; ^{1}H NMR (D_2O) δ 3.94–3.90 (m, 2H, 2C*H*), 3.72 (dd, *J*=11.2, 3.8 Hz, 1H, CH_2), 3.59 (dd, *J*=11.2, 6.2 Hz, 1H, CH_2), 3.55 (m, 1H, C*H*), 3.53 (dd, *J*=11.2, 6.6 Hz, 1H, CH_2), 3.42 (dd, *J*=11.2, 5.9 Hz, 1H, CH_2), 3.03 (m, 1H, C*H*), 2.90 (m, 1H, C*H*), 2.07–1.90 (m, 2H, CH_2), 1.77 (m, 1H, CH_2), 1.51 (m, 1H, CH_2); ^{13}C NMR (D_2O) δ 78.1, 74.9, 72.2, 72.0, 69.5, 67.3, 65.9, 32.2, 25.3; HRMS (ESI$^+$) *m*/*z* calcd for $C_9H_{17}NO_4$+H: 204.1236, found 204.1223.

The same procedure gave the pyrrolizidine **11b** and hyacinthacine B_2 (**5b**) from the corresponding Cbz-pyrrolidine **9** via the AD reaction employing AD-mix-β (yields are given in Scheme 2). The spectral data of synthetic hyacinthacine B_2 (**5b**) thus obtained were identical in all respects[21] with those of the natural product.[7]

*TBS-deprotected diol of **11b*** (pale yellow oil, R_f=0.35, $CHCl_3$/MeOH=1:1): $[\alpha]_D^{25}$ +10.7 (*c* 0.2, $CHCl_3$); IR (NaCl) 3416 (O–H), 2853 (C–H) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.59–4.55 (m, 2H, C*H*), 3.83 (dd, *J*=12.3, 3.3 Hz, 1H, CH_2), 3.76 (m, 1H, C*H*), 3.68 (dd, *J*=12.3, 5.3 Hz, 1H, CH_2), 3.65–3.62 (m, 2H, CH_2), 3.45 (ddd, *J*=12.3, 7.1, 3.3 Hz, 1H, C*H*), 3.32 (dd, *J*=12.3, 8.8 Hz, 1H, C*H*), 2.81–2.22 (br, 2H, 2O*H*), 2.08 (m, 1H, CH_2), 1.93–1.76 (m, 3H, CH_2), 1.55 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 112.2, 85.6, 81.4, 66.5, 63.4, 62.7, 62.3, 62.0, 29.8, 25.5. 23.9, 23.8. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.04; H, 8.80; N, 5.70.

*Hyacinthacine B_2 (**5b**)* (colorless oil, R_f=0.41, MeOH/H_2O/NH_4OH=6:2:1): $[\alpha]_D^{27}$ +42.3 (*c* 0.25, H_2O) {lit. $[\alpha]_D$ +41.3 (*c* 0.36, H_2O)[7]}; IR (NaCl) 3354 (O–H), 2887 (C–H) cm^{-1}; ^{1}H NMR (D_2O) δ 4.11 (dd, *J*=8.3, 4.2 Hz, 1H, C*H*), 4.09 (dd, *J*=6.0, 4.2 Hz, 1H, C*H*), 3.89 (dd, *J*=11.9, 3.8 Hz, 1H, CH_2), 3.85–3.78 (m, 3H, CH_2 and C*H*), 3.73 (dd, *J*=11.9, 5.1 Hz, 1H, CH_2), 3.43 (m, 1H, C*H*), 3.37 (ddd, *J*=8.4, 5.1, 3.9 Hz, 1H, C*H*), 2.09–1.90 (m, 3H, CH_2), 1.81 (m, 1H, CH_2); ^{13}C NMR (D_2O) δ 79.9, 75.8, 72.0, 67.4, 66.7, 66.2, 65.4, 34.2, 26.9; HRMS (ESI$^+$) *m*/*z* calcd for $C_9H_{17}NO_4$+H: 204.1236, found 204.1227.

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References and notes

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13. The reaction of **6** with Grignard reagent was undesirably accompanied with the formation of the corresponding N–H lactam derived from Boc-elimination, see: Ginovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem* **1989**, *54*, 228.
14. The diastereomeric ratio of **7** was easily estimated by ^{1}H NMR analysis as shown in the text.

15. The absolute configuration of the newly generated stereogenic center of the major product could not be determined at the present stage, however, it was easily predictable to be *S* with the aid of the thermodynamically more stable Cram's non-chelation model including the coordination of $CeCl_3$ to the carbonyl oxygen in a dilute EtOH solution.
16. As shown in Scheme 2, the absolute configurations of the newly generated stereogenic centers in **8a** and **8b** were unambiguously characterized to be *R* and *S*, respectively, by detailed comparison of their ^1H and ^{13}C NMR spectral data to those of **iia** and **iib** derived from the vinyl substituted pyrrolidines **ia** and **ib** via hydrogenation. In turn, these two compounds **ia** and **ib** were also obtained from the *N*-Boc lactam **6** based on the same synthetic procedure as that of **8a** and **8b** described in the text.[12a] On the other hand, in order to determine the absolute configurations of **ia** and **ib**, those were independently converted to **iiia** and **iiib** and estimated to have the depicted stereochemistries, respectively, based on its symmetrically spectral data of **iiib**.
17. Intrigued by hitherto known procedures such as in acidic media regarding the Boc-elimination, where an inseparable mixture was obtained due to the presence of the acid-labile acetonide group, we investigated an alternative method and were surprised to find that *NaH* could effect prominently to eliminate the Boc function smoothly after desilylation of **8a**, finally leading to the desired Cbz-containing substrate **9**. It is of great importance to note that the Boc-elimination with *NaH* in this case requires the presence of the neighboring hydroxyl group. The reason for such an unusual elimination reaction has not been yet clarified.
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19. (a) Behr, J.-B.; Erard, A.; Guillerm, G. *Eur. J. Org. Chem.* **2002**, 1256; (b) Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2801 Simple OsO_4-catalyzed dihydroxylation reactions carried out on **9** gave the non-stereoselective results.
20. The absolute stereochemistry of the newly created asymmetric carbon of **11a** derived from the AD reaction of **9** was unambiguously determined after completion of the total synthesis of **5a** based on its spectral data together with the mechanistic proof of the AD reaction pathway reported to date.[18]
21. The obtained chemical shifts and coupling constants of ^1H NMR of synthetic (**5b**) were completely in accord with the reported values of the natural product,[7] while the slight difference (0.5–2 ppm) of the chemical shifts of ^{13}C NMR spectra was observed. It is, however, generally known that variation in solvent (ionic strength, hydrogen bonding, metal ion chelation) can exert discrepancies in NMR spectra of polyhydroxylated alkaloids, see: Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549.