A flexible approach for the asymmetric syntheses of hyacinthacines A_2, A_3 and structural confirmation of hyacinthacine A_3†

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A concise and flexible approach for the asymmetric syntheses of polyhydroxylated pyrrolizidine alkaloids hyacinthacines A_2 and A_3 has been developed using iterative reductive alkylation of *O*,*O*′-dibenzyltartarimide (**5**) as key steps. The ambiguity about the structure of synthetic hyacinthacine A_3 due to the differences in the NMR data of the synthetic material (**2**) and the natural product (hyacinthacine A_3) was eliminated jointly by comprehensive 1D and 2D-NMR studies, and by analysis of the ^{1}H and ^{13}C NMR spectra of a mixed synthetic product and natural hyacinthacine A_3. The latter method also allowed a confirmation of the structure of the natural hyacinthacine A_3, and may be useful for structural confirmation of other hydroxylated alkaloids.

Introduction

Iminosugars (azasugars) are monosaccharide analogues with nitrogen replacing the ring oxygen. Due to the structural resemblance, they are considered as mimics of sugars.[1] Most of them exhibit promising glycosidase or glycosyltransferase inhibitory activity. Because glycoside cleavage is a biologically widespread process, glycosidase inhibitors could have many potential applications as biochemical tools, and therapeutic agents[2] such as anti-HIV, anti-diabetic, and anticancer agents. In the polyhydroxypyrrolizidine class of iminosugars (Fig. 1), such as alexine,[3] australine,[4] casuarine,[5] uniflorine,[6] and hyacinthacines,[7–10] the latter is an expanding group of pyrrolizidine-based iminosugars. Since the first isolation of hyacinthacine C_1 from *hyacinthoides non-scripta* (Hyacinthaceae),[7] a number of hyacinthacines have been isolated.[8–10] Among them, hyacinthacines A_1, A_2 (**1**), A_3 (**2**) and B_2, were isolated from the bulbs of *Muscari armeniacum* (Hyacinthaceae), which show interesting inhibitory activities against a variety of glycosidases. For example, hyacinthacine A_2 exhibits selective inhibitory activity against amyloglucosidase *Aspergillus niger* with IC_{50} of 8.6 and 17 μM respectively.[7] The important bioactivities exhibited by these iminosugars and the potential for developing them as therapeutic agents, as well as the intriguing structural features make them attractive targets, and a number of enantioselective synthetic methods have been reported.[11–15] A common structural feature of the abovementioned iminosugars resides in the presence of a hydroxymethyl substituent at C-3. The 1,2-*trans*-diol substructure constitutes an additional feature of some of them (*e.g.* australine, alexine, casuarine, uniflorine A, and hyacinthacines A_2, A_3, B_4, *etc.*).

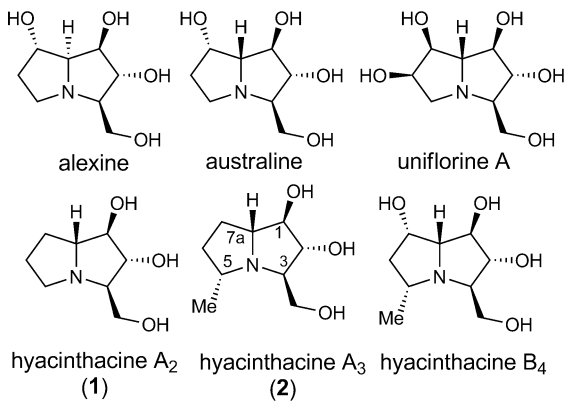

Fig. 1 Some naturally occurring polyhydroxylated pyrrolizidine alkaloids.

Several syntheses of (+)-hyacinthacine A_2 (**1**)[12] and a synthesis of (+)-hyacinthacine A_3 (**2**)[13a] have been reported, which used carbohydrates as the starting materials. While this manuscript was in preparation, Marco and co-workers reported a stereoselective synthesis of (+)-hyacinthacine A_2, and the synthesis of (+)-hyacinthacine A_3 and its 5-epimer (in *ca.* 1.2 : 1 d.r.) from Garner's (*R*)-aldehyde.[16] While the ^{1}H and ^{13}C NMR data of all the synthetic (+)-hyacinthacine A_2[12] matched well with those of the natural product,[7] significant differences existed between those of (+)-hyacinthacine A_3,[7,13a,16] which required a verification. As a continuation of our interest in the synthesis of polyhydroxylated pyrrolidines,[17] we now reported a concise and flexible approach for the syntheses of (+)-hyacinthacine A_2 (**1**) and (+)-hyacinthacine A_3 (**2**) using fully protected tartarimide **5** as the chiral building block, which is easily available from D-tartaric acid. In addition, a comprehensive structural study by means of both 1D and 2D-NMR techniques allowed the confirmation of the structures of both natural and synthetic (+)-hyacinthacine A_3.

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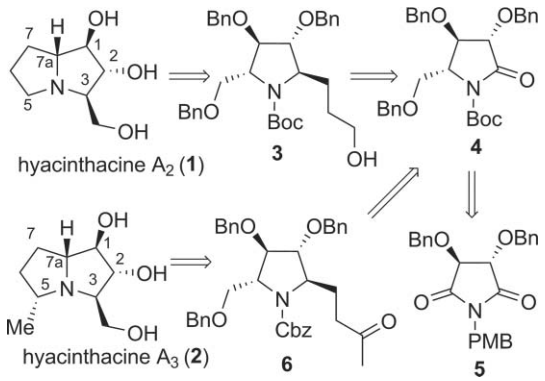
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **3a**, **10**, **1**, **13a**, **13b**, **14**, **6**, **15a**, **2**, and natural hyacinthacine A_3 provided by N. Asano. Structural verification and assignment for compound **2**. See DOI: 10.1039/b926741g

Results and discussion

In view of developing a flexible approach to some of these iminosugars, and on the basis of our previous results,[17] we designed an iterative reductive alkylation approach, which is outlined retrosynthetically in Scheme 1.

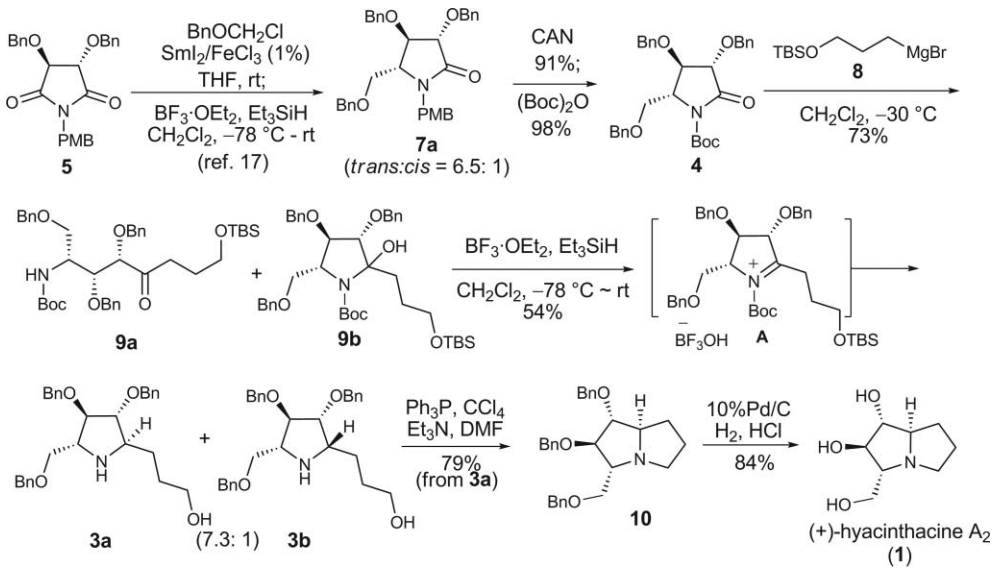


Scheme 1 Retrosynthetic analysis of hyacinthacines A_2 and A_3.

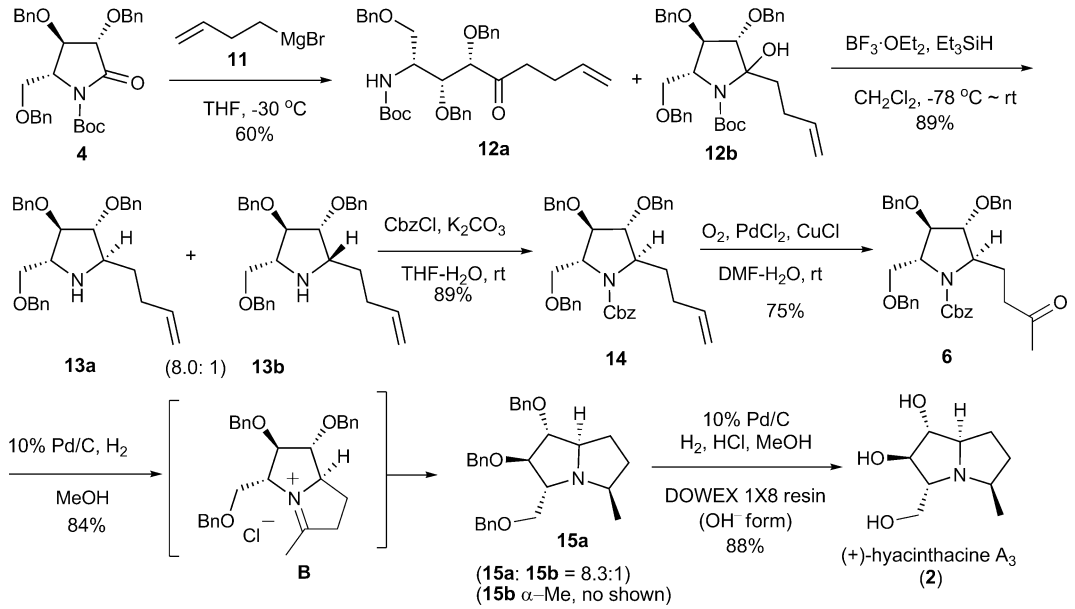
The synthesis of imide **4** from the fully protected tartarimide **5** was described in our previous report,[17] in which the stepwise reductive benzyloxymethylation (the first reductive alkylation) provided *trans*-diastereomer **7a** in high diastereoselectivity (d.r. = 6.5 : 1) (Scheme 2). The synthesis of (+)-hyacinthacine A_2 was first investigated, which started with the second reductive alkylation. Thus treatment of imide **4** with Grignard reagent[18] **8** in dichloromethane at −30 °C afforded smoothly the adduct **9a** and its tautomer **9b** in 73% combined yield with the ring-opening tautomer **9a** being predominant. A partial conversion of **9a** to **9b** was observed upon standing **9a** at rt. Taking advantage of this tautomerism, the tautomeric mixture **9a**/**9b** was subjected to boron trifluoride-mediated reductive dehydroxylation with triethylsilane,[19] which produced the aminols **3a** and **3b** in 54% combined yield with a diastereomeric ratio of 7.3 : 1 in favor of the desired diastereomer **3a**. The stereochemistry of **3a** was assigned on the basis of 2D NOESY experiments on the known intermediate **10**,[12d] and was further confirmed by ultimate synthesis of hyacinthacine A_2 (**1**). The stereochemical outcome of the reductive alkylation of **4** is consistent with our previous results.[17] It is worthy of mention that under the reaction conditions, beside the reductive dehydroxylation, both, the *N*-activating group (Boc)[20] and the *O*-protecting group (TBS)[21] were cleaved in one-pot.

Treatment of the aminol **3a** with $Ph_3P/CCl_4/NEt_3$[22] in DMF afforded efficiently the desired cyclic product **10** in 79% yield. Finally, subjection of **10** to catalytic hydrogenolytic conditions in acidic medium (H_2, 10%Pd/C, HCl, rt) provided hyacinthacine A_2 (**1**) in 84% yield. The ^1H and ^{13}C NMR spectra of the synthetic hyacinthacine A_2 (**1**) matched the reported data.[7,12] That the optical rotation of our synthetic product {$[\alpha]_D^{20}$ +12.6 (*c* 1.64, H_2O)} more closely matched those reported for the synthetic materials {$[\alpha]_D^{25}$ +12.5 (*c* 0.4, H_2O);[12a] $[\alpha]_D^{25}$ +10.5 (*c* 0.6, H_2O);[12c] $[\alpha]_D^{25}$ +12.7 (*c* 0.13, H_2O);[12b] $[\alpha]_D^{20}$ +11.2 (*c* 0.52, H_2O);[12e] $[\alpha]_D^{20}$ +12.1 (*c* 0.3, H_2O)[16]} than the natural one ($[\alpha]_D^{25}$ +20.1 (*c* 0.44, H_2O)[7]} is a phenomenon previously noted by Denmark and co-workers in their elegant synthesis of (+)-1-*epi*-australine.[15o]

Having accomplished the synthesis of hyacinthacine A_2, we then turned our attention to the synthesis of hyacinthacine A_3 (Scheme 3). For this purpose, but-3-en-1-yl group was selected as a latent 2-butanon-1-yl group, required for the formation of the pyrrolizidine ring *via* a third reductive alkylation.[23] Thus treatment of imide **4** with Grignard reagent **11** (THF, −30 °C) followed by reductive dehydroxylation ($BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, −78 °C ~ rt) of the tautomeric mixture **12a**/**12b** resulted in the formation of concomitantly *N*-Boc cleaved pyrrolidine **13a** and its diastereomer **13b** in 8 : 1 ratio. Under the Wacker oxidation conditions (O_2, $PdCl_2$, CuCl, DMF–H_2O, rt), the carbamate **14**, prepared in 89% yield by treating **13a** with CbzCl under basic conditions (K_2CO_3, THF–H_2O, rt), was converted to methyl ketone **6** in 75% yield. Subjection of **6** to catalytic hydrogenolytic conditions (H_2, 1 atm, 10%Pd/C, MeOH, rt, 12 h)[23] led, in one-pot, to the pyrrolizidine **15a** and **15b** in 8.3 : 1 ratio with a combined yield of 84%. Cleavage



Scheme 2 Asymmetric synthesis of hyacinthacine A_2.



Scheme 3 Asymmetric synthesis of hyacinthacine A_3.

of the three benzyl groups of the major diastereomer **15a** under acidic catalytic hydrogenolytic conditions (H_2, 1 atm, 10%Pd/C, HCl, MeOH, rt, 4 days) finally furnished hyacinthacine A_3 (**2**) in 88% yield. Although a one-pot transformation of the carbamate **6** to hyacinthacine A_3 (**2**) is plausible,[23] the stepwise procedure used herein allowed an easy separation of the diastereomers (**15a**/**15b**).

The ^{1}H and ^{13}C NMR data of our synthetic hyacinthacine A_3 (**2**) were in agreement with those reported by Marco and co-workers ($\Delta\delta_C \leq 0.5$),[16] although some different ^{13}C assignment (at C3, C5, C8, *cf.* Table 2 in ESI†) were noted. However, the magnitude of the optical rotations {$[\alpha]_D^{20}$ +7.5 (*c* 0.9, H_2O); lit.[7] $[\alpha]_D^{25}$ +19.2 (*c* 0.43, H_2O) for the natural product; $[\alpha]_D^{25}$ +14 (*c* 0.55, H_2O);[13a] $[\alpha]_D^{25}$ +15.1 (*c* 0.35, H_2O)[16] for synthetic products} were not consistent. In addition, some of the ^{1}H and ^{13}C NMR data were not in accordance with those reported for the natural[7] and another synthetic[13a] hyacinthacine A_3. Furthermore, the ^{1}H and ^{13}C NMR data of all the synthetic (+)-hyacinthacine A_3[13a,16] did not fully match those of the natural product.[7] It is worthy of note that similar phenomena were also observed in hyacinthacines A_1,[14j] C_3,[24] and other polyhydroxylated pyrrolizidines, such as (+)-crotanecine,[25] and (–)-rosmarinecine.[26] It was suggested that the spectral data of polyhydroxylated pyrrolizidines might be affected by pH, concentration and/or trace of elements exist in solvents, such as potassium cation.[14j,27] Thus, a comprehensive structural study was undertaken by means of both 1D and 2D-NMR techniques, and by comparison with an authentic sample.

The ^{1}H-^{1}H COSY combined with HSQC, HMBC and DEPT-135 techniques were used to determine the complete connectivity of carbon and hydrogen atoms. All the NMR data (*cf.* ESI†) indicated that our synthetic compound (**2**) has the structure proposed for hyacinthacine A_3. The 2D NOESY experiment results indicated that the stereochemistries at the newly formed chiral centers at C-5 and C-7a of compound **2** are in accordance with those proposed for hyacinthacine A_3. Finally, the structure was determined by comparison with a sample of natural hyacinthacine A_3, kindly provided by Dr N. Asano. The re-recorded ^{13}C NMR data of the natural hyacinthacine A_3 were in fully agreement with those previously reported,[7] and a minor difference exist in the two ^{1}H NMR spectra (*cf.* Table 1 and Figure 8 in ESI†). When our synthetic compound (**2**) was mixed with about same amount of the natural hyacinthacine A_3, the ^{1}H and ^{13}C NMR spectra of the mixed sample showed only one set of peaks (Fig. 2c) that matched neither with those of the natural product nor with those of the synthetic compound **2** (especially, in the circle range, Fig. 2)! Nevertheless, the presence of only one set of peaks in the ^{1}H and ^{13}C NMR spectra of the mixed synthetic and natural sample provided evidence that the two compounds are the same.

To further confirm the identity of our product, the method for the identification of polyhydroxylated pyrrolizidines recently reported jointly by Nash and Pyne was used.[28] Thus the tri-TMS derivatives of the mixture of the natural hyacinthacine A_3 and synthetic compound were prepared. GC-MS analysis showed only one peak at the retention time of 4.43 min with a *m*/*z* 300([M-CH_2OSiMe_3]$^+$) base ion and a *m*/*z* 388([M-CH_3]$^+$) characteristic fragment peak on mass spectrum.[7,10]

Thus the structure of the natural hyacinthacine A_3 was confirmed, and the structure of our synthetic compound **2** was also established as hyacinthacine A_3. In addition, our method for confirmation the structure of polyhydroxylated alkaloids was also validated.

Conclusions

In summary, (+)-hyacinthacine A_2 (**1**) and (+)-hyacinthacine A_3 (**2**) have been synthesized from imide **4**, easily available from the known *O*,*O*′-dibenzyltartarimide **5**, in four (overall yield: 26%) and six (overall yield: 27%) steps respectively. The syntheses demonstrated that the iterative reductive alkylation is a efficient strategy for flexible and highly stereoselective synthesis of polyhydroxylated pyrrolizidines. We also demonstrated that analysis of NMR spectra of a mixed synthetic product and authentic sample constitutes a valuable method for the mutual confirmation

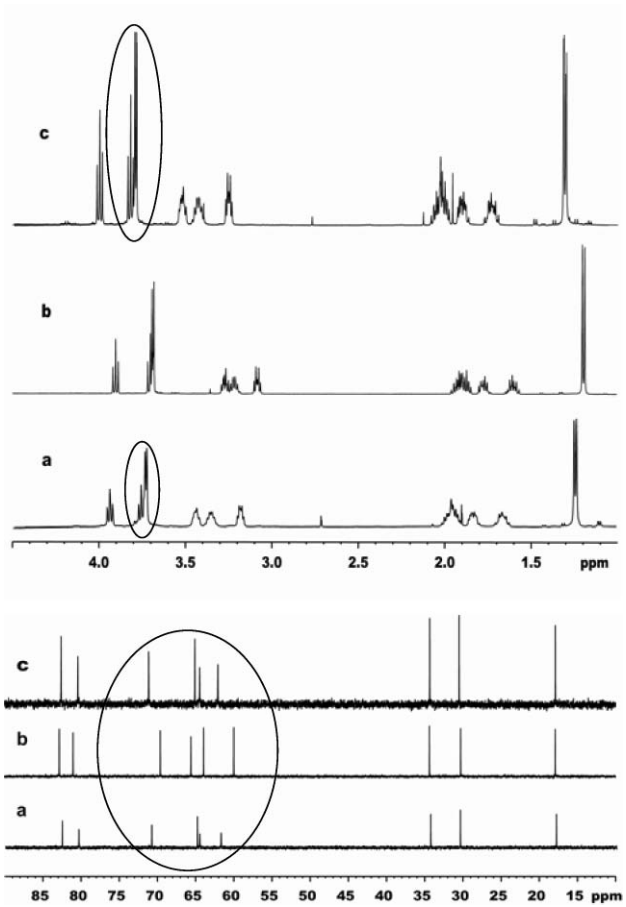


Fig. 2 ^{1}H and ^{13}C NMR spectra of: a) natural hyacinthacine A_3 provided by N. Asano; b) our synthetic hyacinthacine A_3 (**2**); c) a mixture of the natural hyacinthacine A_3 and synthetic compound.

of the structure. Because the ambiguity about the structures of synthetic compounds frequently encounters in the total synthesis of hydroxylated alkaloids, our method may be of value in tackling such kind of problems.

Experimental

3-((2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)propan-1-ol (3a)

To a cooled (–30 °C) CH_2Cl_2 solution (12 mL) of the known imide **4** (822 mg, 1.59 mmol), prepared by stepwise reductive benzyloxymethylation of tartarimide **5**,[17] was added dropwise a freshly prepared THF solution of 3-(*tert*-butyldimethylsiloxy)propyl magnesium bromide (**8**, 12 mL, 4.7 mmol), prepared from 3-(*tert*-butyldimethylsiloxy)propyl bromide (1.20 g, 4.8 mmol) and Mg (173 mg, 7.2 mmol) in THF (12 mL), under nitrogen atmosphere. After stirring at rt for 2 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1 : 9) to give two tautomers oxooctanylcarbamate **9a** and *N*,*O*-acetal **9b** (799 mg, combined yield, 73%), with the latter being an inseparable mixture of two diastereomers. This mixture was used in the next step without further separation.

To a cooled (–78 °C) solution of the tautomeric and diastereomeric mixture **9a** and **9b** (799 mg, 1.16 mmol) in anhydrous CH_2Cl_2 (10 mL) were added dropwise triethylsilane (2.2 mL, 13.9 mmol) and boron trifluoride etherate (0.23 mL, 4.6 mmol) under nitrogen atmosphere. After stirring at –78 °C for 6 h, the mixture was allowed to warm up to rt and stirred overnight. The reaction was quenched with a saturated aqueous sodium bicarbonate solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1,2-dichloroethane/methanol/aq. NH_3 = 100/2.5/1) to give two diastereomers **3a** and **3b** (208 mg, combined yield, 54%, ratio = 7.3 : 1 determined by ^{1}H NMR). Most of the two diastereomers can be separated by flash chromatography on silica gel. Major diastereomer **3a**: colorless oil: $[\alpha]_D^{20}$ 18.7 (*c* 1.4, $CHCl_3$). IR (film): 3403, 3303, 3062, 3029, 2861, 1496, 1453, 1363, 1093 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ 1.53–1.70, 1.70–1.85 (2 m, 4H), 3.11 (dt, J = 4.0, 9.8 Hz, 1H), 3.32 (dd, J = 4.9, 9.9 Hz, 1H), 3.48–3.58 (m, 3H), 3.65 (dt, J = 4.9, 9.7 Hz, 1H), 3.72 (dd, J = 3.1, 4.0 Hz, 1H), 3.95 (dd, J = 3.0, 4.8 Hz, 1H), 4.42–4.58 (m, 6H), 7.18–7.39 (m, 15H, Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 31.9, 61.7, 62.4, 62.8, 69.2, 71.6, 72.0, 73.2, 86.0, 89.7, 127.6, 127.7, 127.8, 128.4, 138.0 (2C) ppm; MS (ESI, *m*/*z*): 462 ($M+H^+$, 100). Anal. Calcd for $C_{29}H_{35}NO_4$: C, 75.46; H, 7.64; N, 3.03. Found: C, 75.29; H, 7.76; N, 3.17.

(1*R*,2*R*,3*R*,7a*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-hexahydro-1*H*-pyrrolizine (10)

To a stirring suspension of **3a** (150 mg, 0.32 mmol) and PPh_3 (171 mg, 0.65 mmol) in dry DMF (3 mL), were added dry CCl_4 (0.06 mL, 0.65 mmol) and dry Et_3N (0.09 mL, 0.65 mmol). The mixture was stirred at room temperature for 1 h and then quenched with MeOH (3 mL). After stirring for 30 min, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/PE = 1/2, 1/1) to give the known **10** as white crystals. M.p. 48–49 °C (EtOAc-P.E.) (lit.[12d] m.p. 47.5 °C). $[\alpha]_D^{20}$ –2.9 (*c* 0.7, $CHCl_3$) {lit.[12d] $[\alpha]_D^{20}$ –5 (*c* 1, $CHCl_3$)}. IR (film): 2861, 1496, 1453, 1363, 1093 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60–2.02 (m, 4H), 2.76 (td, J = 6.7, 10.6 Hz, 1H), 2.96 (td, J = 5.6, 7.3 Hz, 1H), 3.06 (td, J = 5.9, 10.5 Hz, 1H), 3.44–3.62 (m, 3H), 3.80 (dd, $J_1 = J_2$ = 5.9 Hz, 1H), 4.07 (dd, 1H), 4.50–4.75 (m, 6H), 7.20–7.36 (m, 15H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 31.7, 55.1, 67.4, 68.2, 71.9, 72.1, 72.6, 73.2, 85.7, 88.9, 127.4, 127.5, 127.6 (2C), 127.7, 128.2, 128.3 (2C), 138.3, 138.4, 138.5 ppm; MS (ESI, *m*/*z*): 444 ($M+H^+$, 100).

Hyacinthacine A_2 (1)

To a solution of pyrrolizidine **10** (120 mg, 0.28 mmol) in methanol (10 mL) was added 10% Pd/C (50 mg). After the reaction flask was purged with hydrogen, 10 drops of 6 N HCl were added and the reaction mixture was stirred for 4 days at room temperature under a hydrogen atmosphere. The catalyst was then filtered off and washed with MeOH. The filtrates were concentrated under

reduced pressure. The residue was transferred to a column of DOWEX 1 × 8 resin (OH^- form) and eluted with deionized water to give hyacinthacine A_2 (**1**, 38 mg, yield, 84%) as white crystals. M.p. 130–131 °C (H_2O); $[\alpha]_D^{20}$ +12.6 (*c* 1.64, H_2O) {$[\alpha]_D^{25}$ +12.5 (*c* 0.4, H_2O);[12a] $[\alpha]_D^{25}$ +10.5 (*c* 0.6, H_2O);[12c] $[\alpha]_D^{25}$ +12.7 (*c* 0.13, H_2O);[12b] $[\alpha]_D^{20}$ +11.2 (*c* 0.52, H_2O);[12e] $[\alpha]_D^{20}$ +12.1 (*c* 0.3, H_2O);[16] $[\alpha]_D^{25}$ +20.1 (*c* 0.44, H_2O)[7]}; IR (film): 3354, 2956, 2920, 2866, 1124 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 1.67–1.96 (m, 4H), 2.66 (ddd, J = 3.9, 6.6, 9.0 Hz, 1H), 2.70 (td, J = 5.6, 11.0 Hz, 1H), 2.86 (ddd, J = 5.9, 7.1, 10.9 Hz, 1H), 3.11 (td, J = 4.4, 7.4 Hz, 1H), 3.61 (dd, 1H, J = 6.6, 11.6 Hz, 1H), 3.66–3.77 (m, 3H) ppm; ^{13}C NMR (D_2O) δ 27.3, 32.6, 57.6, 66.0, 68.8, 72.0, 80.2, 83.1 ppm; HRESIMS calcd for $[C_8H_{15}NO_3 + H]^+$: 174.1125; found: 174.1130.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(but-3-enyl)pyrrolidine (13a)

To a stirring solution of **4** (640 mg, 1.23 mmol) in THF (12 mL) was added a solution of 4-butenyl magnesium bromide in THF at −30 °C, which was prepared from 4-bromo-1-butene (0.4 mL, 4.0 mmol) and Mg (145 mg, 6.0 mmol) in THF (8 mL) at rt. The mixture was stirred at the same temperature for 2 h before quenching with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–P.E. (1 : 11) to give a mixture of **12b** (two diastereomeric mixture) and its ring-opening tautomer **12a** (425 mg, combined yield, 60%), which was used in the next step without further separation.

To a cooled (−78 °C) solution of diastereomeric and tautomeric mixture **12a** and **12b** (425 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (8 mL) were added dropwise triethylsilane (1.8 mL, 11.1 mmol) and boron trifluoride etherate (0.5 mL, 2.96 mmol) under nitrogen atmosphere. After stirring at −78 °C for 6 h, the mixture was allowed to warm up to rt and stirred overnight. The reaction was quenched with a saturated aqueous sodium bicarbonate and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1,2-dichloroethane/$NH_3 \cdot H_2O$ = 100/1) to give two diastereomers **13a** and **13b** in 8 : 1 ratio (301 mg, combined yield, 89%). Major product **13a**: pale yellow oil. $[\alpha]_D^{20}$ 19.4 (*c* 4.0, $CHCl_3$). IR (film): 3336, 3030, 2921, 1599, 1453, 1384, 1362, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52–1.72 (m, 2H), 2.02–2.22 (m, 2H), 3.11 (td, J = 5.4, 8.1 Hz, 1H), 3.39 (m, 1H), 3.51 (m, 2H), 3.71 (dd, J = 3.1, 8.0 Hz, 1H), 3.87 (dd, J = 3.1, 4.0 Hz, 1H), 4.48–4.57 (m, 6H), 4.95 (m, 1H), 5.02 (ddd, J = 1.6, 3.4, 17.1 Hz, 1H), 5.81 (tdd, J = 6.6, 10.2, 17.1 Hz, 1H), 7.20–7.41 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 33.3, 61.4, 61.8, 70.5, 71.7, 73.2, 86.3, 89.7, 114.7, 127.6 (2C), 127.7, 127.8, 128.3, 138.2, 138.3 ppm. MS (ESI, *m*/*z*): 458 ($M+H^+$, 100). Minor product **13b**: pale yellow oil. $[\alpha]_D^{20}$ 37.0 (*c* 2.2, $CHCl_3$). IR (film): 3336, 3030, 2921, 1599, 1453, 1384, 1362, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.66–1.80 (m, 2H), 2.00–2.21 (m, 2H), 3.14 (dt, J = 3.9, 7.0 Hz, 1H), 3.27 (ddd, J = 3.8, 5.5, 5.5 Hz, 1H), 3.55 (dd, J = 5.4, 9.4 Hz, 1H), 3.59 (dd, J = 5.7, 9.4 Hz, 1H), 3.74 (d, J = 3.9 Hz, 1H), 3.82 (d, J = 3.8 Hz, 1H), 4.36 (d, J = 11.9 Hz, 1H), 4.47–4.56 (m, 5H), 4.94 (ddd, J = 1.2, 3.3, 10.2 Hz, 1H), 5.01 (ddd, J = 1.6, 3.4, 17.1 Hz, 1H), 5.82 (ddd, J = 6.6, 10.2, 17.1 Hz, 1H), 7.20–7.37 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 31.4, 61.7, 64.5, 70.8, 71.2, 71.6, 73.1, 83.9, 84.9, 114.5, 127.5, 127.6, 127.7, 128.3, 128.4, 138.2 (2C), 138.3, 138.6 ppm. MS (ESI, *m*/*z*): 458 ($M+H^+$, 100). Anal. Calcd for $C_{30}H_{35}NO_3$: C, 78.74; H, 7.71; N, 3.06. Found: C, 78.37; H, 7.52; N, 3.01.

Benzyl (2*R*,3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(but-3-enyl)pyrrolidin-1-yl carboxylate (14)

To a stirring solution of **13a** (334 mg, 0.73 mmol) and anhydrous K_2CO_3 (110 mg, 0.80 mmol) in THF (4 mL) and H_2O (4 mL) was added benzyl chloroformate (0.11 mL, 0.73 mmol). After stirring at rt for 1.5 h, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/P.E. = 1/14) to give **14** (385 mg, yield, 89%) as a colorless oil: $[\alpha]_D^{20}$ −36.9 (*c* 7.2, $CHCl_3$). IR (film): 2924, 1702, 1587, 1496, 1406, 1347, 1091 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, two rotamers, M_1: M_2 = 1 : 1) δ 1.71–2.21 (m, 8H), 3.43–3.51 (m, 2H), 3.73 (dd, J = 4.1, 8.9 Hz, 2H), 3.78–3.85 (m, 3H), 3.89 (dd, J = 2.5, 11.2 Hz, 1H), 4.05 (dd, J = 4.2, 8.7 Hz, 1H), 4.11–4.18 (m, 3H), 4.25 (dd, J = 4.0, 10.4 Hz, 1H), 4.30–4.50 (m, 9H), 4.56–4.67 (m, 3H), 4.85–5.08 (m, 6H), 5.12–5.22 (m, 2H), 5.61 (m, 1H), 5.81 (m, 1H), 7.13–7.38 (m, 40H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) mixture of two rotamers: δ 29.0, 30.4, 30.8, 62.6, 62.9, 64.0, 64.4, 66.8, 66.9, 67.8, 68.8, 70.9, 71.0, 71.2, 72.9, 73.0, 82.0, 83.1, 83.3, 84.3, 115.0, 127.5, 127.5, 127.7, 128.0, 128.1, 128.3 (2C), 128.4, 128.5, 136.6, 137.6, 137.9, 138.3, 138.5, 154.2, 154.6 ppm. MS (ESI, *m*/*z*): 592 ($M+H^+$, 100). Anal. Calcd for $C_{38}H_{41}NO_5$: C, 77.13; H, 6.98; N, 2.37. Found: C, 77.07; H, 7.26; N, 2.41.

Benzyl (2*R*,3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(3-oxobutyl)pyrrolidin-1-yl-carboxylate (6)

To a stirring solution of olefin **14** (277 mg, 0.47 mmol) in DMF (7.5 mL) and H_2O (2.5 mL) were added CuCl (50 mg, 0.52 mmol) and $PdCl_2$ (35 mg, 40 mol%), and the resulting suspension was stirred under oxygen atmosphere at 1 atm and at room temperature for 24 h. The insoluble materials were removed by filtration, and washed with CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was chromatographed on silica gel (EtOAc/P.E. = 1/8) to give **6** (214 mg, yield, 75%) as a colorless oil. $[\alpha]_D^{20}$ −38.6 (*c* 4.0, $CHCl_3$). IR (film): 3030, 2925, 1698, 1435, 1348, 1091 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, two rotamers, M: *m* = 1.24: 1) δ 1.87–2.48 (m, 14 H), 3.40 (d, J = 8.9 Hz, 1H), 3.46 (d, J = 8.9 Hz, 1H), 3.72 (dd, J = 4.1, 8.9 Hz, 1H), 3.75–3.79 (m, 3H), 3.83 (dd, J = 3.2, 9.5 Hz, 1H), 4.05 (dd, J = 4.1, 8.9 Hz, 1H), 4.12–4.18 (m, 3H), 4.26 (dd, J = 4.0, 10.4 Hz, 1H), 4.30–4.49 (m, 9H), 4.55–4.66 (m, 3H), 5.03 (d, J = 12.2 Hz, 1H), 5.04 (d, J = 12.3 Hz, 2H), 5.15 (d, J = 12.3 Hz, 2H), 5.20 (d, J = 12.2 Hz, 2H), 7.16–7.39 (m, 40H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two rotamers) δ 25.1, 26.1, 29.3, 29.5, 40.5, 40.8, 62.7, 63.1, 63.9, 64.2, 66.9, 67.0, 67.6, 68.6, 70.9, 71.0, 71.2, 72.9, 73.0, 81.6, 82.7, 83.7, 84.6, 127.5 (2C), 127.6, 127.7, 128.0, 128.1, 128.3, 128.4, 128.5, 136.4, 136.5, 137.5, 137.7, 138.2, 138.4, 154.3, 154.5, 208.0 (2C) ppm. MS (ESI, *m*/*z*): 608 ($M+H^+$, 100). Anal. Calcd for $C_{38}H_{41}NO_6$: C, 75.10; H, 6.80; N, 2.30. Found: C, 75.04; H, 6.63; N, 2.37.

(1*R*,2*R*,3*R*,5*R*,7a*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-5-methyl-hexahydro-1*H*-pyrrolizine (15a)

Compound **6** (60 mg, 0.10 mmol) in MeOH (5 mL) was hydrogenated over 10% Pd/C (30 mg) for 12 h. The catalyst was filtered off, washed with MeOH, and the filtrate and washings were concentrated to give a residue that was submitted to column chromatography (EtOAc/PE = 1/1) to afford **15a** (37 mg, yield, 84%) as a colorless oil. $[\alpha]_D^{20}$ –0.95 (*c* 2.0, $CHCl_3$). IR (film) 2963, 2857, 1601, 1451, 1360, 1259, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.8 Hz, 3H), 1.44–1.52 (m, 1H), 1.68–1.75 (m, 1H), 1.78–1.91 (m, 2H), 3.24–3.31 (m, 2H), 3.45–3.51 (m, 2H), 3.54–3.60 (m, 1H), 3.76 (t, J = 4.0 Hz, 1H), 4.06 (t, J = 4.1 Hz, 1H), 4.45–4.60 (m, 6H), 7.20–7.35 (m, 15H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 29.1, 32.5, 57.6, 61.0, 68.8, 71.5, 71.9, 73.1, 73.2, 86.9, 88.2, 127.4 (2C), 127.5, 127.6, 127.7, 128.2, 128.3 (2C), 138.4, 138.6 ppm. HRESIMS calcd for $[C_{30}H_{35}NO_3 + H]^+$: 458.2690; found: 458.2708.

(+)-Hyacinthacine A_3 (2)

To a solution of pyrrolizidine **15a** (25 mg, 0.05 mmol) in methanol (5 mL) was added 10% Pd/C (10 mg). After the reaction flask was purged with hydrogen, a few drops of HCl (6 N) were added and the reaction mixture was stirred for 4 days at room temperature under an atmosphere of hydrogen. The catalyst was then filtered off and washed with MeOH. The filtrates were concentrated under reduced pressure, transferred to a column of DOWEX 1 × 8 resin (OH^- form) and eluted with deionized water to give pyrrolizidine **2** (9.0 mg, yield, 88%) as a colorless oil. $[\alpha]_D^{20}$ +7.5 (*c* 0.9, H_2O) {lit.[7] $[\alpha]_D^{25}$ +19.2 (*c* 0.43, H_2O) for the natural product; $[\alpha]_D^{25}$ +14 (*c* 0.55, H_2O);[13a] $[\alpha]_D^{25}$ +15.1 (*c* 0.35, H_2O)[16] for a synthetic products}. IR (film) 3360, 2954, 2910, 2853, 1116 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ 1.20 (d, J = 6.8 Hz, 2H, CH_3), 1.61 (m, 1H, H-6), 1.78 (m, 1 H, H-7), 1.89 (m, 1 H, H-6′), 1.93 (m, 2 H, H-6′, H-7′), 3.09 (dt, J = 8.0, 5.3 Hz, 1H, H-3), 3.22 (m, 1H, H-5), 3.27 (m, 1H, H-7a), 3.69 (d, J = 5.0 Hz, 2H, H-8), 3.71 (t, J = 7.5 Hz, 1H, H-1), 3.91 (br t, J = 7.8 Hz, 1H, H-2) ppm. ^{13}C NMR (125 MHz, D_2O) δ 18.4, 30.7, 34.8, 60.4, 64.4, 66.1, 70.1, 81.5, 83.3 ppm. HRESIMS calcd for $[C_9H_{17}NO_3 + H]^+$: 188.1281; found: 188.1278.

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