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Enantiospecific Synthesis of (+)-Hyacinthacine A_2

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We report an efficient synthesis of (+)-hyacinthacine A_2 in six steps from (*S*)-*N*-Cbz-vinylgylcine. The key strategies were the olefin cross metathesis (CM), Sharpless asymmetric dihydroxylation, and a sequential double reductive cyclization.

Introduction

3-(Hydroxymethyl)pyrrolizidines occupy a new class of polyhydroxylated pyrrolizidines isolated from flowering and leguminous plants.[1] The first examples of this family were alexine, isolated in 1988 from *Alexa leiopetala* by Nash and co-workers,[2] and australine, isolated in the same year from the seeds of *Castanospermum australe* by Molyneux and co-workers.[3] Recently, a series of hyacinthacines were isolated from bluebells (*Hyacinthoides non-scripta*)[4] and grape hyacinths (*Muscari armeniacum*)[5] by Asano and co-workers (Figure 1).

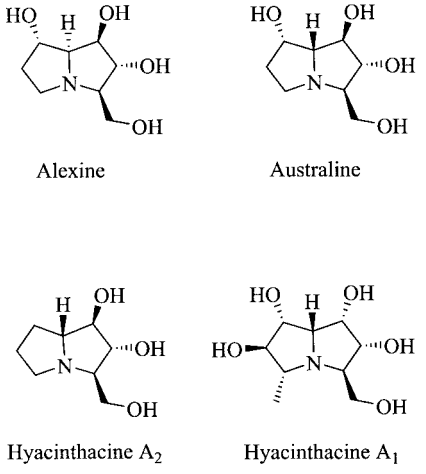

Figure 1. Various 3-(hydroxymethyl)pyrrolizidines.

As sugar mimics, many of these alkaloids possess gylcosidase inhibition activity, which makes them potent drug candidates against viral infections, cancer, and diabetes.[6] Hyacinthacine A_2, for example, was found to be a selective inhibitor of amyloglucosidase (*Aspergillus niger*) with an IC_{50} value of 8.6 μM.[5]

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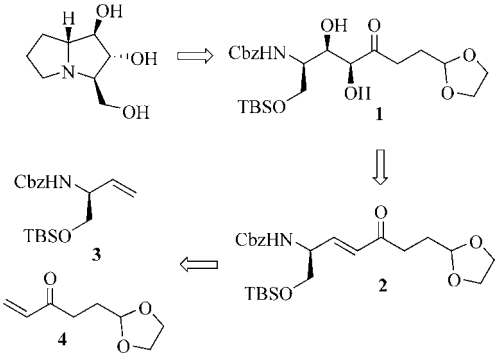
The first synthesis of hyacinthacine A_2, utilising ring-closing metathesis as the key step, was reported by Martin and co-workers in 2001.[7] This confirmed the absolute configuration of hyacinthacine A_2, proposed by Asano and co-workers, as (1*R*,2*R*,3*R*,7a*R*)-1,2-dihydroxy-3-(hydroxymethyl)pyrrolizidine. Two quite similar syntheses with 1,3-dipolar cycloaddition as the key reactions were reported by Tamura[8] and Goti.[9] Izquierdo and co-workers prepared a series of hyacinthacines by reductive cyclization of the corresponding pyrrolidines.[10]

Previous work in our group has established a methodology for the synthesis of *cis*-fused pyrrolizidines by olefin cross metathesis (CM) followed by reductive amination.[11] This strategy offers the potential to use the resulting C–C double bonds in the CM product for further functionalization. The synthetic strategy for hyacinthacine A_2 was as follows: as the synthetic precursor for the reductive cyclization we envisaged the diol **1**, which would be prepared by Sharpless asymmetric dihydroxylation of CM product **2**, in turn available from two simple building blocks, enantiopure allyamine **3** and enone **4** (Scheme 1).

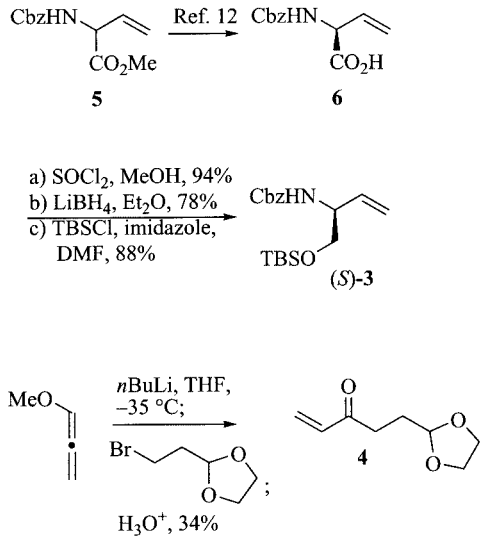


Scheme 1. Retrosynthetic analysis of hyacinthacine A_2.

Results and Discussion

An expedient synthesis of enantiopure allylamine **3** utilizing an enzymatic resolution of (±)-*N*-Cbz-vinylglycine

methyl ester (**5**) has been established within our group.[12] Successive esterification of **6**, reduction of the ester group by $LiBH_4$, and protection of the hydroxy group as a TBS ether gave allylamine (*S*)-**3**, as outlined in Scheme 2. The optical rotation of the product $\{[a]_D^{20} = -31.2$ (c = 1.2, CH_2Cl_2)} was complementary to its known (*R*) counterpart {ref.[12] $[a]_D^{22} = +31.8$ (c = 1.2, CH_2Cl_2)}.



Scheme 2. Synthesis of CM partners.

Alkylation of lithiated methoxyallene[13] with commercially available 2-(2-bromoethyl)-1,3-dioxolane yielded, after acidic workup, the enone **4**, as shown in Scheme 2.[11] According to TLC monitoring the alkylation reaction proceeded smoothly, but some allene intermediate decomposed during the acidic workup, resulting in a moderate yield of 34%.

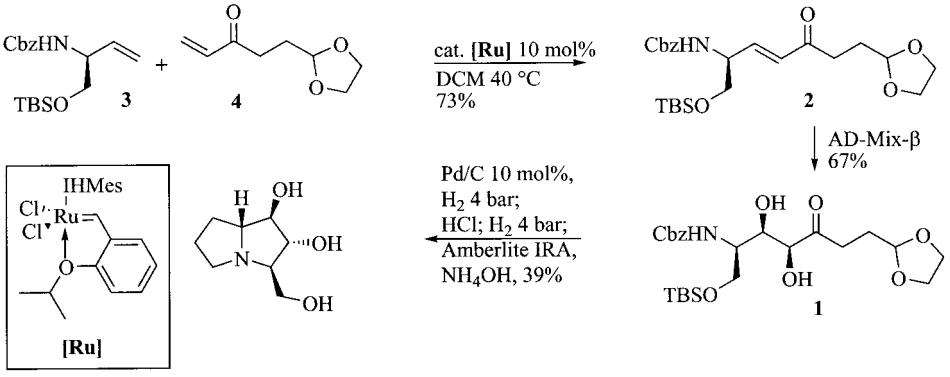
CM between allylamine **3** and enone **4** (1:2) was conducted in dichloromethane at reflux in the presence of 10 mol-% Hoveyda–Blechert ruthenium catalyst [Ru].[14] This catalyst shows higher reactivity than the second-generation Grubbs' catalyst[15] in reactions involving, for example, fluorinated substrates[16] and acrylonitrile derivatives.[17] It also shows high stability towards water and oxygen and so can be stored under ambient atmosphere at room temp. The CM gave the (*E*) enone **2** in 73% yield after 3 days (Scheme 3). The high (*E*) selectivity of the CM reaction was a great advantage for the subsequent Sharpless asymmetric dihydroxylation reaction.

The CM is slow, presumably because of the formation of a six-membered chelate between ruthenium and the carbonyl oxygen of the Cbz group, as has also been observed in CM of homoallyl esters or homoallyl amides.[18] The chelation effect slows down the metathesis activity and lowers the catalytic turnover. Since CM is an intermolecular process, chelation effects are more pronounced than in intramolecular reactions such as ring-closing metathesis.[18b] In general, performing the reaction at elevated temperature (at 80 °C in toluene, for example) may increase the yield, but in this case the decomposition of the catalyst proved to be faster than the completion of the reaction.

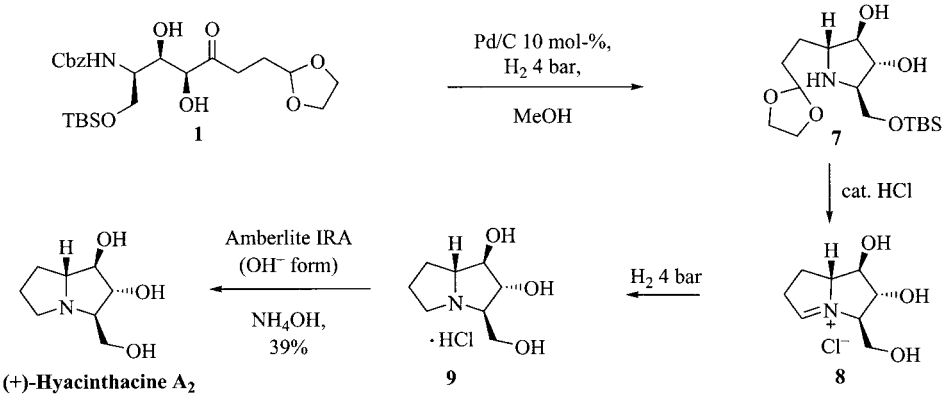
We then investigated the dihydroxylation of enone **2**. The osmylation of electron-deficient olefins, such as α,β-unsaturated carbonyl compounds, is very slow since osmium tetroxide is an electrophilic reagent. The large TBS group may play a role in controlling the diastereoselectivity (substrate control), but it may also reduce the reaction rate by the steric hindrance.

We first applied a dihydroxylation procedure under acidic conditions (pH 4–6) with the use of citric acid and 4-methylmorpholine.[19] After 6 days at room temp. the expected product and its diastereomer were isolated in a 1:2 ratio and a yield of 42%. We then applied a procedure developed for α,β-unsaturated ketones[20] under basic conditions with potassium hexaferricyanide and a buffer system (K_2CO_3/$NaHCO_3$) in the absence of the chiral ligand to study the substrate control. After 14 days, the expected diol was isolated in 44% yield and with a *de* of 33%. These results confirmed our assumption that the TBS group could indeed exert moderate substrate control, dependent on the reaction conditions, though simultaneously retarding the reaction.

We then conducted the reaction with the use of AD-Mix-β (Scheme 3). With addition of three equivalents of methanesulfonamide,[21] the expected diol was isolated in 42% yield and with a *de* of 88% after 8 days at room temp. The best results were achieved with the use of excess AD-Mix-β (2.1 g per mmol enone), methanesulfonamide (3.8 equivalents), and K_2OsO_4 (with a total of 0.015 equivalents).[22]



Scheme 3. Synthesis of hyacinthacine A_2 [IHMES = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene].



Scheme 4. Sequential double reductive cyclization.

Total conversion was achieved within one day, providing the diol **1** in 67% yield and with a *de* of 88%.

The expected diol and its diastereomer were chromatographically separable. The diastereoselectivity was determined by ^{1}H NMR and the diol configuration was determined by nOe experiments after cyclization.

To cyclize the diol **1** we first applied the one-pot tandem procedure, which had been successfully applied in the syntheses of *cis*-fused pyrrolizidines.[11] Unfortunately, these attempts resulted in low yields and the formation of side products. The first cyclization step occurred very slowly under atmospheric pressure, and so it was decided to use a higher pressure of hydrogen and neutral conditions. Once the pyrrolidine intermediate had been formed, the protecting group would be removed under acidic conditions, followed by the second cyclization, reduction of the iminium salt, and neutralization. The double reductive cyclization was thus carried out sequentially, with the optimized procedure shown in Scheme 4.

The first cyclization step was conducted at 4 bar hydrogen for 3 days at room temp. to give the pyrrolidine **8**.[23] Without isolation of the intermediate, hydrochloric acid was added to cleave both the dioxolane and the TBS protecting groups, followed by the second cyclization to yield the iminium salt **9**. Hydrogenation of the iminium salt at 4 bar for 3 days afforded the hydrochloride salt of hyacinthacine A_2 (**10**). Amberlite IRA 401 (OH^- form) was added to remove the chloride ions in the solution, followed by addition of ammonia to remove the chloride ions bonded to the product. The formation of a less polar product and the disappearance of the polar salt could be monitored by TLC. The final purification by preparative TLC gave hyacinthacine A_2 in 39% yield.

The configurations of pyrrolidine **8** and the final product were determined by nOe experiments. The pyrrolidine **8** showed enhancements between H-2 and H-4 and between H-3 and H-5, while the final product showed enhancements of H-7a with H-2, H-1 with H-3 and H-7, and H-3 with H-5, consistently with the reported structure of hyacinthacine A_2 (Figure 2). This also confirmed the diol configuration and the *cis*-fused configuration of the product, which was in accordance with our previous results for 3,5-dialkylpyrrolizidine syntheses.[11] The IR spectrum supported this, as no Bohlmann band was detected. The spectroscopic data and the optical rotation of the product {$[a]_D^{20}$ = +11.2 (c = 0.52, H_2O)} were in agreement with the reported values [ref.[7] $[a]_D^{25}$ = +12.5 (c = 0.6, H_2O); ref.[9] $[a]_D^{25}$ = +12.7 (c = 0.13, H_2O); ref.[10b] $[a]_D^{25}$ = +10.5 (c = 0.6, H_2O)].

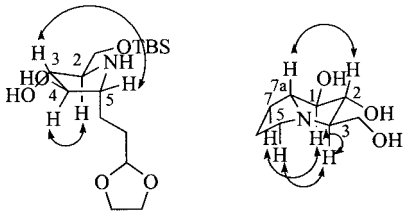


Figure 2. Correlation observed in the nOe spectra of pyrrolidine **8** and hyacinthacine A_2.

Conclusion

In summary, we have described a concise synthesis of (+)-hyacinthacine A_2 in six steps, starting from (–)-*N*-Cbz-vinylglycine, in an overall yield of 12%. The key steps of our convergent synthesis were the highly stereoselective CM reaction, diastereoselective Sharpless asymmetric dihydroxylation, and the final sequential double reductive cyclization. Further syntheses based on this strategy are currently underway and will be reported in due course.

Experimental Section

General Remarks: All moisture-sensitive reactions were conducted under nitrogen in preheated glassware. Commercial reagents were used without further purification. All solvents were purified and dried prior to use. Thin-layer chromatography analysis (TLC) was performed with silica gel 60 F_{254} precoated plates (0.2 mm thickness) with fluorescent indicator. Components were detected by UV (254 nm) and visualized with potassium permanganate reagent (2.5% $KMnO_4$ in 5% aqueous $NaHCO_3$ solution). Preparative TLC was conducted on silica-rapid plates (F_{254}, 20 × 20 cm, 60 A) from ICN Biomedicals. Column chromatography was performed on silica gel (40–63 μm). Melting points were determined on a Leica–Galen melting point microscope with a Wagner–Munz control

module and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded at room temp. with Bruker spectrometers and the chemical shifts are referenced to the internal solvent peaks ($CDCl_3$ or D_2O) in ppm. The IR spectra were obtained as ATR (Attenuated Total Reflectance) on a Perkin–Elmer 881 spectrometer. MS and HRMS spectra were measured with a Finnigan MAT 95 SQ or Varian MAT 711 by EI (electron ionization) and FAB (fast atom bombardment) methods at 70 eV. The optical rotations were recorded on a Perkin–Elmer 341 polarimeter at 20 °C, with use of the sodium D-line at 589 nm, and are given as $[\alpha]_D$ values (concentration in grams/100 mL of solvent).

Methyl (*S*)-2-(Benzyloxycarbonylamino)but-3-enoate: Thionyl chloride (0.37 mL, 5.1 mmol) was added slowly to anhydrous methanol (4 mL) at 0 °C. After the system had been stirred for 15 min, L-Cbz-vinylglycine (**6**) (1 g, 4.2 mmol) was added in small portions and the mixture was allowed to warm to room temp. overnight. Water (5 mL) was added and the mixture was extracted with MTBE (4×10 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated. Purification by column chromatography (SiO_2, hexane/ethyl acetate, 9:1) gave the methyl ester (996 mg, 94%) as a clear oil. R_F = 0.71 (SiO_2, hexane/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = –8.9 (*c* = 0.82, MeOH) {ref.[24] $[\alpha]_D^{20}$ = –8.86 (*c* = 1.84, MeOH)}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, CO_2Me), 4.86–4.98 (m, 1 H, 2-H), 5.13 (s, 2 H, CH_2Ph), 5.28 (dd, *J* = 10.5 and 1.5 Hz, 1 H, 4-H), 5.37 (dd, *J* = 17.5 and 1.5 Hz, 1 H, 4-H), 5.46 (br. d, *J* = 7.5 Hz, 1 H, NH), 5.91 (ddd, *J* = 17.5, 10.5, and 5.5 Hz, 1 H, 3-H), 7.29–7.41 (m, 5 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.4 (CO_2CH_3), 56.0 (C-2), 66.9 (CH_2Ph), 117.6 (C-4), 127.9, 128.0 (Ar), 132.1 (C-3), 136.0 (Ar), 155.4 (NCO), 170.7 (C-1) ppm.

Benzyl (*S*)-[1-(Hydroxymethyl)allyl]carbamate: Anhydrous methanol (0.13 mL) and methyl (*S*)-2-(benzyloxycarbonylamino)but-3-enoate (411 mg, 1.7 mmol) in anhydrous diethyl ether (5 mL) were added successively to a suspension of $LiBH_4$ (72 mg, 3.3 mmol) in anhydrous diethyl ether (7 mL) and the mixture was stirred at room temp. for 2 h. Water (5 mL) was added and the mixture was extracted with MTBE (3×15 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated. Purification by column chromatography (SiO_2, hexane/ethyl acetate, 3:2) gave the alcohol (285 mg, 78%) as a white solid. R_F = 0.24 (SiO_2, hexane/ethyl acetate, 3:2). M.p. 47–48 °C. $[\alpha]_D^{20}$ = –27.4 (*c* = 1.54, $CHCl_3$) {ref.[25] $[\alpha]_D^{20}$ = –32.2 (*c* = 1.46, $CHCl_3$)}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.92 (br. s, 1 H, OH), 3.65–3.78 (m, 2 H, 1-H), 4.34 (s, 1 H, 2-H), 5.13 (br. s, 3 H, CH_2Ph, NH), 5.21–5.34 (m, 2 H, 4-H), 5.91 (ddd, *J* = 17.5, 10.5, and 5.5 Hz, 1 H, 3-H), 7.30–7.41 (m, 5 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.9 (C-2), 64.5 (CH_2Ph), 66.8 (C-1), 116.4 (C-4), 127.9, 128.0, 128.4 (Ar), 135.1 (C-3), 136.2 (Ar), 156.4 (NCO) ppm. MS (EI, 70 °C): *m*/*z* (%) = 278 $[M]^+$ (2%), 91 (100).

Benzyl (*S*)-[1-(*tert*-Butyldimethylsilanyoxymethyl)allyl]carbamate (3): *tert*-Butylchlorodimethylsilane (233 mg, 1.55 mmol) was added to a solution of benzyl (*S*)-[1-(hydroxymethyl)allyl]carbamate (285 mg, 1.3 mmol) in anhydrous DMF (2 mL) and the mixture was stirred at 0 °C for 10 min. Imidazole (219 mg, 3.22 mmol) was added portionwise and the reaction mixture was further stirred at 0 °C for 3 min and at room temp. for 18 h. MTBE was added and the mixture was washed with aqueous $NaHCO_3$ solution (10%). The organic phase was dried with $MgSO_4$ and the solvents were evaporated. Purification by column chromatography (SiO_2, hexane/ethyl acetate, 9:1) gave **3** (405 mg, 88%) as a white solid. R_F = 0.15 (SiO_2, hexane/ethyl acetate, 3:2). M.p. 60–61 °C (ref.[12] 59–61 °C). $[\alpha]_D^{20}$ = –31.2 (*c* = 1.2, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, *t*Bu), 3.55–3.80 (m, 2 H, 1-H), 4.25 (br. s, 1 H, 2-H), 5.10 (s, 2 H, CH_2Ph), 5.10 (m, 1 H, 4-H), 5.23 (d, *J* = 17.5 Hz, 1 H, 4-H), 5.85 (ddd, *J* = 17.5, 10.5, and 5.5 Hz, 1 H, 3-H), 7.45 (m, 5 H, Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.6 ($SiMe_2$), 18.2 (Si–*C*), 25.7 [(CH_3)$_3$C], 54.6 (CHN), 65.1 (CH_2O), 66.6 (CH_2Ar), 115.8 (CH_2 = CH), 128.4 (Ar), 128.4 (Ar), 136.1 (CH$_2$ = CH), 136.4 (Ar), 155.8 (CO) ppm. MS (EI, 25 °C): *m*/*z* (%) = 278 $[M - C_4H_9]^+$ (62%), 243 (72), 234 (75), 200 (65), 165 (43), 149 (70), 91 (100).

5-(1,3-Dioxolan-2-yl)pent-1-en-3-one (4): Methoxyallene (643 mg, 9 mmol) was dissolved in anhydrous THF (8 mL) and the solution was cooled to –35 °C. *n*-BuLi (5.5 mL, 9 mmol, 1.6 M in hexane) was added dropwise. After the system had been stirred for 1 h at the same temperature, 2-(2-bromoethyl)-1,3-dioxolane (0.83 g, 4.6 mmol) in anhydrous THF (4 mL) was added. The mixture was warmed to 0 °C while stirring for 3 h and hydrolyzed by addition of aqueous HCl solution (1 M, 15 mL) and stirring at 0 °C for 10 min. The mixture was extracted with diethyl ether (3×20 mL). The combined organic layers were dried with $MgSO_4$ and carefully evaporated under reduced pressure (until 400 mbar). Purification by flash column chromatography (SiO_2, diethyl ether/pentane, 1:1) gave enone **4** (246 mg, 34%) as a yellow oil, which was stored as 1 M solution in anhydrous CH_2Cl_2 at –20 °C. R_F = 0.37 (SiO_2, diethyl ether/pentane, 1:1). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.01 (dt, *J* = 7.2 and 4.4 Hz, 2 H, 5-H), 2.72 (t, *J* = 7.5 Hz, 2 H, 4-H), 3.83–4.00 (m, 4 H, 7, 8-H), 4.93 (t, *J* = 4.4 Hz, 6-H), 5.83 (dd, *J* = 10.5 and 0.9 Hz, 1 H, 1-H), 6.23 (dd, *J* = 17.7 and 0.8 Hz, 1 H, 1-H), 6.36 (dd, *J* = 17.6 and 10.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.7 (C-5), 33.4 (C-4), 65.0 (C-7, 8), 103.4 (C-6), 128.1 (C-1), 136.2 (C-2), 199.9 (C-3) ppm. IR (ATR): $\tilde{\nu}$ = 1713, 1139, 1032 cm^{-1}. MS (EI, 25 °C): *m*/*z* (%) = 155 $[M - H]^+$ (3%), 73 (100). HRMS ([*M* – H], $C_8H_{11}O_3$): calcd. 155.0708, found 155.0710.

Benzyl [(*E*)-(*S*)-1-(*tert*-Butyldimethylsilanyloxymethyl)-6-(1,3-dioxolan-2-yl)-4-oxo-hex-2-enyl]carbamate (2): [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(*o*-isopropoxyphenylmethylene)ruthenium ([**Ru**], 10 mg, 16 μmol) was added to a solution of allylamine **3** (54 mg, 0.16 mmol) and enone **4** (0.16 mL, 0.16 mmol, 1 M solution in anhydrous CH_2Cl_2) in anhydrous CH_2Cl_2 (3.2 mL) under nitrogen. The mixture was then heated at reflux for 3 days. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 3:1) to give ene-dione **2** (54 mg, 73%) as a yellow oil. R_F = 0.6 (SiO_2, hexane/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = –0.53 (*c* = 0.95, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, $SiMe_2$), 0.85 (s, 9 H, *t*Bu), 1.99 (dt, *J* = 7.0 and 4.0 Hz, 2 H, 7-H), 2.65 (m, 2 H, 6-H), 3.63–3.76 (m, 2 H, 2-H), 3.77–4.00 (m, 4 H, 9, 10-H), 4.40 (m, 1 H, 2-H), 4.90 (s, 1 H, 9-H), 5.10 (s, 2 H, 12-H), 5.19 (br. s, 1 H, NH), 6.23 (d, *J* = 16.0 Hz, 1 H, 4-H), 6.75 (dd, *J* = 16.0 and 4.0 Hz, 1 H, 3-H), 7.32 (m, 5 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.4 ($SiMe_2$), 18.3 (Si–*C*), 25.9 [(CH_3)$_3$C], 27.7 (C-7), 34.4 (C-6), 53.7 (C-1), 64.7 (C-2), 65.0 (C-9, 10), 67.1 (CH_2Ph), 103.4 (C-8), 128.3, 128.6 (Ar), 130.2 (C-4), 136.3 (Ar), 143.6 (C-3), 155.8 (CO_2), 198.9 (C-5) ppm. IR (ATR): $\tilde{\nu}$ = 1723, 1701, 1678, 1636, 1253, 1111, 980 cm^{-1}. MS (EI, 120 °C): *m*/*z* (%) = 463 $[M]^+$ (2%), 91 (100), 73 (32). HRMS ($[M]^+$, $C_{24}H_{37}O_6NSi$): calcd. 463.2390, found 463.2381. CHN-analysis ($C_{24}H_{37}NO_6Si$): calcd. C 62.17, H 8.05, N 3.02; found C 62.04, H 7.95, N 3.15.

Benzyl [(1*R*,2*R*,3*S*)-1-(*tert*-Butyldimethylsilanyloxymethyl)-6-(1,3-dioxolan-2-yl)-2,3-dihydroxy-4-oxo-hexyl]carbamate (1): AD-Mix-β (768 mg), $NaHCO_3$ (97 mg), $MeSO_2NH_2$ (138 mg), and $K_2OsO_4 \cdot 2H_2O$ (1.5 mg) were dissolved in *tert*-butyl alcohol/water

(1:1, 1.8 mL) and stirred for 10 min. CM product **2** (169 mg, 0.36 mmol) in *tert*-butyl alcohol/water (1:1, 1.8 mL) was added and the mixture was stirred at room temp. for 18 h. Na_2SO_3 (700 mg) and water (1 mL) were added, and the mixture was stirred for a further 1 h and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed sequentially with aqueous NaOH solution (1 M, 2 × 10 mL), water (2 × 10 mL), and brine, and dried with $MgSO_4$, and the solvents were evaporated. Purification by column chromatography (SiO_2, hexane/ethyl acetate, 3:1 → 3:2) gave the diol **1** and its diastereomer (isolated yield 122 mg with 115 mg diol **1**, 67% yield) as a clear oil. R_F = 0.2 (SiO_2, hexane/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = –10.1 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $SiMe_2$), 0.86 (s, 9 H, *t*Bu), 1.20–1.29 (m, 1 H, OH), 1.96–2.09 (m, 2 H, 7-H), 2.55–2.82 (m, 2 H, 6-H), 3.70 (dd, *J* = 10.3 and 5.1 Hz, 1 H, 1-H), 3.74–4.00 (m, 5 H, 2, 9, 10-H), 4.05 (dd, *J* = 10.3 and 2.6 Hz, 1 H, 1-H), 4.10 (t, *J* = 9.0 Hz, 1 H, 3-H), 4.19 (dd, *J* = 19.4 and 3.6 Hz, 1 H, 4-H), 4.92 (m, 1 H, 8-H), 5.10 (br. s, 2 H, CH_2Ph), 5.54 (d, *J* = 8.5 Hz, 1 H, NH), 7.34 (m, 5 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.5 ($SiMe_2$), 18.3 (Si–*C*), 25.9 [(CH_3)$_3$C], 27.2 (C-7), 32.5 (C-6), 54.1 (C-2), 62.1 (C-1), 65.1 (C-9, 10), 67.3 (CH_2Ph), 70.7 (C-3), 76.9 (C-4), 103.2 (C-8), 128.3, 128.7, 136.1 (Ar), 157.1 (CO_2), 210.4 (C-5) ppm. IR (ATR): $\tilde{\nu}$ = 1715, 1509, 1254, 1087, 1046, 779 cm^{-1}. MS (EI, 130 °C): *m*/*z* (%) = 496 [*M* – H]$^+$ (<1%), 91 (100). HRMS ([*M* – H], $C_{24}H_{38}NO_8Si$): calcd. 496.2367, found 496.2379.

Data for the Diastereomer of Diol 1: R_F = 0.14 (SiO_2, hexane/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = –22.3 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $SiMe_2$), 0.85 (s, 9 H, *t*Bu), 1.22–1.32 (m, 1 H, OH), 1.94–2.07 (m, 2 H, 7-H), 2.55–2.82 (m, 2 H, 6-H), 3.70–4.00 (m, 7 H, 1, 2, 9, 10-H), 4.20 (br. s, 2 H, 3, 4-H), 4.90 (m, 1 H, 8-H), 5.10 (br. s, 2 H, CH_2Ph), 5.35 (d, *J* = 8.5 Hz, 1 H, NH), 7.30 (m, 5 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.5 ($SiMe_2$), 18.2 (Si–*C*), 25.9 [(CH_3)$_3$C], 27.4 (C-7), 32.3 (C-6), 54.0 (C-2), 63.9 (C-1), 65.0 (C-9, 10), 67.3 (CH_2Ph), 72.5 (C-3), 76.9 (C-4), 103.0 (C-8), 128.3, 128.6, 136.3 (Ar), 176.6 (CO_2), 209.3 (C-5) ppm.

(+)-Hyacinthacine A_2: Diol **1** (30 mg, 60 μmol) in methanol (10 mL) was hydrogenated at 4 bar over Pd/C (10%, 7 mg, 6 μmol) for 3 days. TLC analysis showed that the first cyclization had occurred [R_F = 0.47 (SiO_2, MeOH)]. Concentrated HCl (3 drops) was then added and the mixture was further stirred at room temp. overnight. The heterogeneous mixture was again hydrogenated at 4 bar for 3 days. After filtration through celite, the filtrate was neutralized with Amberlite IRA 401 (wet, OH^- form). After filtration and evaporation, the residue containing the HCl salt was dissolved in methanol (5 mL), and ammonia (6 drops) was added. The mixture was stirred for 30 min, concentrated, and purified by preparative TLC (SiO_2, methanol/ammonia 98:2) to give the hyacinthacine A_2 (4 mg, 39%) as a yellow oil. R_F = 0.14 (SiO_2, methanol). $[\alpha]_D^{20}$ = +11.2 (*c* = 0.52, H_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49–1.61 (m, 2 H, 6, 7-H), 1.62–1.69 (m, 1 H, 6-H), 1.69–1.75 (m, 1 H, 7-H), 2.46–2.49 (m, 1 H, 3-H), 2.49–2.57 and 2.64–2.42 (m, 1 H, 5-H), 2.90–2.96 (m, 1 H, 7a-H), 3.40–3.47 (dd, *J* = 11.0 and 6.8 Hz, 1 H, 8-H), 3.62 (br. t, *J* = 8.0 Hz, 1 H, 1-H), 3.54–3.61 (m, 2 H, 2, 8-H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 25.2 (C-6), 30.5 (C-7), 55.6 (C-5), 63.8 (C-8), 66.7 (C-7a), 69.9 (C-3), 78.0 (C-2), 80.9 (C-1) ppm. IR (ATR): $\tilde{\nu}$ = 3313, 2922, 2868, 1115, 1040 cm^{-1}. MS (FAB): *m*/*z* (%) = 174 [*M* + H]$^+$ (100%).

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