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A New Synthetic Approach to (+)-Hyacinthacine A_1 and the First Total Synthesis and Absolute Configuration Assignment of Naturally Occurring (+)-Hyacinthacine A_6[‡]

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Naturally occurring (1*S*,2*R*,3*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine [(+)-hyacinthacine A_1 (**1**)] and (1*S*,2*R*,3*R*,5*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-hyacinthacine A_6 (**2**)] have been synthesized by Wittig's methodology using aldehyde **7**, prepared from (2*R*,3*S*,4*R*,5*R*)-3,4-bis(benzyloxy)-2′-*O*-(*tert*-butyldiphenylsilyl)-2,5-bis(hydroxymethyl)pyrrolidine (**3**, partially protected DALDP), as the homochiral starting material and the appropriated ylide to afford either the corresponding α,β-unsaturated ester **8** or ketone **9**, which were submitted to internal lactamization and reductive amination, respectively, to give the corresponding intermediate pyrrolizidin-5-one **11** and the totally protected pyrrolizidine **14**. Compounds **11** and **14** were easily transformed into the above hyacinthacines **1** and **2**, respectively.

Introduction

Polyhydroxylated pyrrolidine (DMDP), piperidine (DMJ), indolizidine (castanospermine), pyrrolizidine (alexine and australine) and nortropane (calystegine B_2) alkaloids (imino- or azasugars) have increasingly gained attention because of their capacity to inhibit glycosidases. This class of inhibitors was first discovered in plants in which these azasugars were found to protect the plants by inhibiting the carbohydrate-processing enzymes of predators.[1]

3-(Hydroxymethyl)pyrrolizidines form a new class of polyhydroxylated pyrrolizidines isolated from flowering and leguminous plants.[2] The first examples of this family were alexine, isolated in 1988 from *Alexa leiopetala* by Nash et al.,[3] and australine, isolated in the same year from the seeds of *Castanospermum australe* by Molyneux et al.[4] (see Figure 1). More recently, a series of hyacinthacines have been isolated from bluebells (*Hyacinthoides non-scripta*),[5] grape hyacinths (*Muscari armeniacum*)[6] and from the bulbs of *Scilla sibirica*,[7] *Scilla peruviana*[8] and *Scilla socialis*[9] by Asano and co-workers.

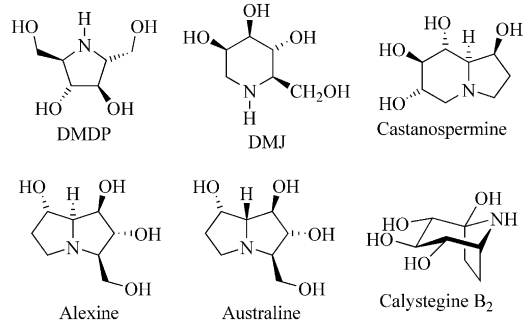

Figure 1. Naturally occurring polyhydroxylated alkaloids (imino- or azasugars).

Since the discovery of these nitrogen-containing inhibitors, many medical studies have been performed to find out if their inhibitory activity could be used in therapeutic applications. Swainsonine is one of the most widely studied polyhydroxylated alkaloids. Clinical trials have shown that it prevents tumour formation at new invasion sites, enhances antibody response to cancerous tumours and improves stem cell formation in bone marrow.[10] Other studies have shown azasugars to aid the treatment of diabetes and HIV/AIDS.[1,11,12] Consequently, these inhibitors have enormous medical potential; however, the few naturally occurring iminosugars that have been isolated so far represent only a small fraction of the possible azasugars that could be potent medical agents.

With the aim of exploring the whole chemical space occupied by the azasugars, syntheses of these compounds have

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been and must continue to be developed. In addition, naturally occurring azasugars are present in scarce quantities in natural sources and are often difficult to be purified,[13] and therefore synthetic routes to these iminosugars and analogues are also wanted. In this context in recent years our group has developed a synthetic methodology involving the use of appropriately functionalized and protected pyrrolidines[14] as key intermediates for the preparation of more complex polyhydroxylated pyrrolizidine alkaloids (PHPAs).[15] On the other hand, such polyhydroxylated pyrrolidines have been prepared from the commercially available hexulose, D-fructose. Herein, we describe our studies on (+)-hyacinthacine A_1 (**1**) and (+)-hyacinthacine A_6 (**2**) which culminated in the second reported total enantioselective synthesis of **1**[16] and the first total synthesis and absolute configuration assignment of **2**.[7]

Our retrosynthetic strategy towards PHPAs **1** and **2** is illustrated in Figure 2 in which a simple cleavage of the N(4)–C(5) bond in the pyrrolizidine skeleton and a Wittig-type disconnection at either C(2)–C(3) or C(3)–C(4) of the α,β-unsaturated pyrrolidine ester **8** and ketone **9**, respectively, reveals the key triorthogonally protected and stereochemically loaded 2,5-dideoxy-2,5-imino-D-altritol (DALDP, **3**)[14c] as the precursor.

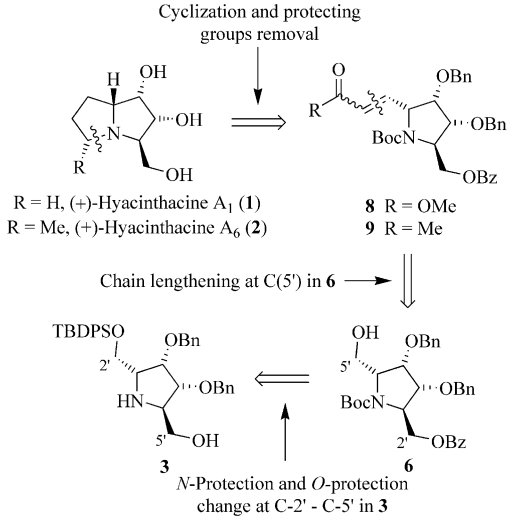
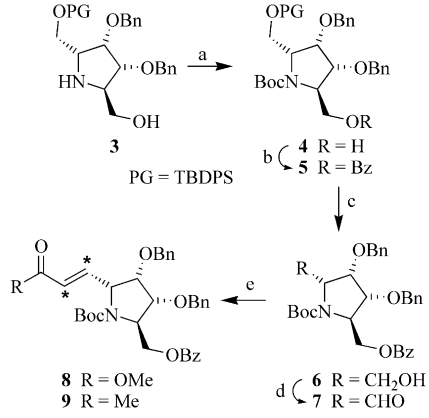


Figure 2. Retrosynthesis of hyacinthacines A_1 (**1**) and A_6 (**2**) from a triorthogonally protected derivative of DALDP (**3**).

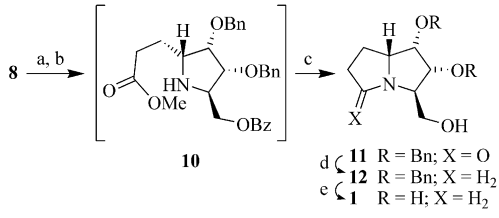
Results and Discussion

According to the above retrosynthetic analysis and based on the results from previous studies,[15] we began the synthesis (see Scheme 1) with (2*R*,3*S*,4*R*,5*R*)-3,4-bis(benzyloxy)-2′-*O*-(*tert*-butyldiphenylsilyl)-2,5-bis(hydroxymethyl)-pyrrolidine (**3**) which was chemoselectively transformed into its *N*-Boc derivative **4** by treatment with di-*tert*-butyl dicarbonate in dichloromethane (DCM)/triethylamine (TEA). Conventional benzoylation of **4** to the corresponding 5-(benzoyloxymethyl) derivative **5** followed by *O*-desilylation afforded the pyrrolidine **6**, opportunely leaving the primary alcohol free for oxidation to aldehyde **7** (IR evidence: $\tilde{\nu}$ = 1725 cm^{-1} and no hydroxy absorption band) by *N*-methylmorpholine *N*-oxide (NMO) catalyzed by tetra-*n*-propylammonium perruthenate (TPAP) in preparation for Wittig-chain lengthening. In the event, either methyl (triphenylphosphoranylidene)acetate or 1-(triphenylphosphoranylidene)-2-propanone reacted with aldehyde **7** to yield the corresponding α,β-unsaturated ester **8** or ketone **9**, respectively, as a mixture of rotamers (^{1}H NMR evidence). As expected, only the stereoisomer with the (*E*) configuration was obtained in both cases (**8**: $J_{2,3}$ = 15.6 Hz; **9**: $J_{3,4}$ = 16.0 Hz).



Scheme 1. Synthesis of α,β-unsaturated pyrrolidine ester **8** and ketone **9** from triorthogonally protected DALDP (**3**). Reagents and conditions: a) (tBuOCO)$_2$O/DCM/TEA, r.t.; b) BzCl/DCM/TEA, r.t.; c) TBAF·3H_2O/THF, r.t.; d) NMO/TPAP/DCM/MS (4 Å), r.t.; e) for **8** Ph_3P=$CHCO_2Me$, for **9** Ph_3P=CHCOMe/MePh, 80 °C. [** refer to H(2)–H(3) in ester **8** and H(3)–H(4) in ketone **9**.]

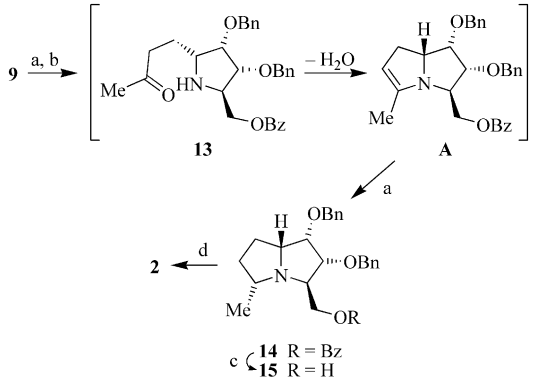
Scheme 2 displays all the chemical transformations necessary to achieve the synthesis of **1**. Thus, catalytic (10% Pd/C) hydrogenation of **8** afforded the intermediate saturated pyrrolidine ester (no signals due to vinylic protons were observed in the ^{1}H NMR spectrum of an aliquot of the reaction mixture) which was not further investigated but submitted to *N*-deprotection in an acidic medium to afford intermediate **10**. This intermediate was subsequently treated with base (MeONa/MeOH) to promote internal lactamization and concomitant *O*-debenzoylation to afford the pyrrolizidin-5-one **11** which was completely characterized on the basis of its analytical and spectroscopic data. Reduction



Scheme 2. Synthesis of (+)-hyacinthacine A_1 (**1**) from **8**. Reagents and conditions: a) 10% Pd/C, H_2, balloon, r.t.; b) i. TFA/DCM, room temp.; ii. neutralization with MeONa/MeOH; c) MeONa (cat.)/MeOH, Δ; d) H_3B·SMe_2/THF, then MeOH, Δ; e) conc. HCl/conditions of (a), then Amberlite IRA-400 (OH^- form) and chromatography on Dowex 50W×8 (200–400 mesh).

of the lactam carbonyl group with $H_3B{\cdot}SMe_2$ complex to **12** followed by its total *O*-debenzylation finally gave (+)-hyacinthacine A_1 (**1**) which had physical and spectroscopic data in accordance with those previously reported for the natural product.[6]

According to a similar protocol, but with **9**, the naturally occurring (+)-(**2**) was synthesized for the first time (see Scheme 3). Thus, catalytic hydrogenation and *N*-deprotection of **9** yielded the intermediate pyrrolidine ketone **13**, intramolecular condensation gave the intermediate Δ^5-pyrrolizine **A**, which was not isolated, and hydrogenation finally gave the fully protected pyrrolizidine **14**, slightly contaminated, which could be isolated in a pure state after Zemplen debenzoylation to **15**.



Scheme 3. Synthesis of (+)-hyacinthacine A_6 (**2**) from **9**. Reagents and conditions: a) 10% Pd/C, H_2, MeOH, room temp., b) i. conc. HCl/MeOH, r.t.; ii. neutralization with MeONa/MeOH; c) MeONa (cat.)/MeOH, r.t.; d) conc. HCl/conditions of (a), then Amberlite IRA-400 (OH^- form) and chromatography on Dowex 50W×8 (200–400 mesh).

The configuration of the new stereogenic centre C-5 in **15** was determined on the basis of extensive NOE experiments, results of which are displayed in Figure 3. Thus, the definite NOE effects observed between 5-Me and 3-H and between 5-H and 2-H/8-H in **15**, indicate the (*R*) configuration at C-5. In addition, the rest of the NOE interactions also confirmed the complete stereochemistry of **15**.

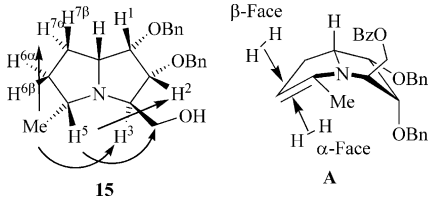


Figure 3. Main observed NOE effects in **15** and scheme for the hydrogenation of intermediate Δ^5-pyrrolizine **A**.

The high stereoselectivity found in the hydrogenation of intermediate Δ^5-pyrrolizine **A**, in which **2** was the only pyrrolizidine detected and isolated, merits comment. The formation of **2** can be attributed, according to our previous results[15b] and Figure 3, to the particular shape of this kind of molecule[6,17] in which the β-face is less hindered for hydrogen attack than the α-face, preferentially affording compound **2**.

Finally, total *O*-deprotection of **15** allowed us to achieve the first enantioselective synthesis of (+)-hyacinthacine A_6 (**2**) which had analytical, spectroscopic and optical data in accordance with those reported for the naturally occurring product. For example, the optical rotation of the synthetic material was $[\alpha]_D^{26}$ = +15.8 (*c* = 0.5, water) and that of natural (+)-hyacinthacine A_6 was $[\alpha]_D^{26}$ = +16.3 (*c* = 0.22, water).[7]

Conclusions

The highlights of this report are a new synthetic route to (+)-hyacinthacine A_1, the first total enantioselective synthesis of naturally occurring (+)-hyacinthacine A_6, its actual configuration being (1*S*,2*R*,3*R*,5*R*,7a*R*), and, finally, that partially triorthogonally protected polyhydroxylated pyrrolidines derived from common hexuloses, combined with a classical Wittig methodology, are in general amenable to the preparation of analogues and derivatives of hyacinthacines that will be useful in the evaluation of the biological and therapeutic potential of this kind of compounds.

Experimental Section

General Remarks: Solutions were dried with $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in $CDCl_3$ (internal standard Me_4Si). IR spectra were recorded with a Perkin-Elmer FT-IR Spectrum One instrument and mass spectra were recorded with a Hewlett-Packard HP-5988A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection was achieved by employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulfuric acid containing 0.8% cerium sulfate (w/v) and heating. Column chromatography was performed on silica gel (Merck 7734). All compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, MS and HRMS.

(2*R*,3*S*,4*R*,5*R*)-3,4-Bis(benzyloxy)-*N*-(*tert*-butyloxycarbonyl)-2′-*O*-(*tert*-butyldiphenylsilyl)-2,5-bis(hydroxymethyl)pyrrolidine (4): Triethylamine (TEA, 510 μL, 3.66 mmol) and di-*tert*-butyl dicarbonate (700 mg, 3.23 mmol) were added to a stirred solution of **3** in dry dichloromethane (DCM, 20 mL) cooled in ice/water (1.25 g, 2.15 mmol), and the mixture was kept at room temperature (r.t.) overnight. TLC (Et_2O/hexane, 1:1, v/v) then revealed the presence of a faster running compound. The reaction mixture was quenched with methanol (MeOH, 1 mL), then supported on silica and submitted to chromatography (Et_2O/hexane, 1:3, v/v) to give **4** as a colourless syrup. Yield: 1.45 g (quantitative). $[\alpha]_D^{28}$ = +11 (*c* = 1). IR (neat): $\tilde{\nu}$ = 3425 (OH), 3069 (aromatic), 1690 (C=O, Boc), 731 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ = 7.70–7.27 (m, 20 H, 4 Ph), 4.83 and 4.72 (2 d, *J* = 12.0 Hz, 2 H, CH_2Ph), 4.70–4.61(2 d, *J* = 12 Hz, 2 H, CH_2Ph), 4.38 (dd, *J* = 8, *J* = 9.2 Hz, 1 H), 4.15–3.55 (5 br. m, 7 H), 1.25 and 1.06 (2 s, 18 H, 2 CMe_3) ppm. ^{13}C NMR (inter alia): δ = 79.9 and 77.7 (C-3,4), 73.1 and 72.6 (2 CH_2Ph), 64.8 and 62.9 (C-2′,5′), 64.7 and 61.2 (C-2,5), 28.4 and 27.2 (2 CMe_3), 19.8 (2 CMe_3) ppm. HRMS (LSIMS): calcd.

for $C_{41}H_{51}NO_6NaSi$ $[M + Na]^+$ 704.3383; found 704.3375 (deviation +1.2 ppm).

(2*R*,3*R*,4*S*,5*R*)-2′-*O*-Benzoyl-3,4-bis(benzyloxy)-*N*-(*tert*-butyloxycarbonyl)-5′-*O*-(*tert*-butyldiphenylsilyl)-2,5-bis(hydroxymethyl)pyrrolidine (5): TEA (450 μL, 3.22 mmol), DMAP (50 mg) and BzCl (272 μL, 2.34 mmol) were added to a stirred solution of **4** (1.45 g, 2.13 mmol) in dry DCM (25 mL) and the mixture was left at room temp. overnight. TLC (Et_2O/hexane, 1:1, v/v) then revealed a faster running compound. Conventional workup of the reaction mixture and column chromatography (Et_2O/hexane, 1:3, v/v) afforded pure **5** (1.3 g, 78%) as a colourless syrup. $[\alpha]_D^{27} = +14$ ($c = 1$). IR (neat): $\tilde{\nu}$ = 3069 and 3032 (aromatic), 1724 (COPh), 1698 (>NBoc), 737 and 708 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ = 7.88–7.23 (4 m, 25 H, 5 Ph), 4.90–3.75 (5 m, 12 H, 2 CH_2Ph, 2,2′a,2′b,3,4,5,5′a,5′b-H), 1.30 and 1.08 (2 s, 18 H, 2 CMe_3) ppm. ^{13}C NMR (inter alia): δ = 166.2 (COPh), 80.5, 79.2 and 78.2 (C-3,4, 2 rotamers), 72.8 and 72.4 (2 *C*H_2Ph), 63.5 and 62.7 (C-2′,5′), 60.9 and 60.6 (C-2,5), 28.4 and 27.2 (2 C*Me*$_3$), 19.4 (*C*Me_3) ppm. HMRS (LSIMS): calcd. for $C_{48}H_{55}NO_7NaSi$ $[M + Na]^+$ 808.3646; found 808.3650 (deviation –0.5 ppm).

(2*R*,3*R*,4*S*,5*R*)-2′-*O*-Benzoyl-3,4-bis(benzyloxy)-*N*-(*tert*-butyloxycarbonyl)-2,5-bis(hydroxymethyl)pyrrolidine (6): TBAF·$3H_2O$ (500 mg, 1.59 mmol) was added to a stirred solution of **5** (1.13 g, 1.44 mmol) in THF (20 mL), and the mixture was kept at room temp. overnight. TLC (Et_2O/hexane, 1:1, v/v) then showed a new compound of lower mobility. The mixture was neutralized with acetic acid, concentrated to a residue that was dissolved in Et_2O, washed with brine, concentrated and then submitted to column chromatography (Et_2O/hexane, 1:5, v/v → Et_2O) to yield pure **6** (700 mg, 88%) as a colourless syrup. $[\alpha]_D^{29}$ –30 ($c = 1$). IR (neat): $\tilde{\nu}$ = 3459 (OH), 3088 and 3064 (aromatic), 1723 (COPh), 1696 (>NBoc), 712 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ = 7.94–7.27 (4 m, 15 H, 3 Ph), 4.78–3.85 (7 m, 13 H, 2 CH_2Ph, 2,2′a,2′b,3,4,5,5′a,5′b-H,OH), 1.50 (s, 9 H, CMe_3) ppm. ^{13}C NMR (inter alia): δ = 166.29 and 166.16 (COPh, 2 rotamers), 155.1 and 154.3 (Boc, 2 rotamers), 81.4, 80.9 and 78.6 (C-3,4, 2 rotamers), 72.76, 72.57, 72.35 and 72.23 (2 *C*H_2Ph, 2 rotamers), 63.54, 63.06, 61.3 and 59.6 (C-2′,5′, 2 rotamers), 61.23, 61.21, 60.99 and 59.36 (C-2,5, 2 rotamers), 28.65 and 28.63 (C*Me*$_3$, 2 rotamers), 19.5 (*C*Me_3) ppm. HRMS (LSIMS): calcd. for $C_{32}H_{37}NO_7Na$ $[M + Na]^+$ 570.2468; found 570.2466 (deviation +0.3 ppm).

Methyl 3-[(2*E*,2′*R*,3′*S*,4′*R*,5′*R*)-5′-(Benzoyloxymethyl)-3′,4′-bis(benzyloxy)-*N*′-(*tert*-butyloxycarbonyl)pyrrolidin-2′-yl]propenoate (8): Activated powdered molecular sieves (4 Å) (100 mg), *N*-methylmorpholine *N*-oxide (210 mg, 1.77 mmol) and TPAP (100 mg) were added to a solution of **6** (645 mg, 1.18 mmol) in dry DCM (20 mL), and the reaction mixture was kept at room temperature for 1 h. TLC (Et_2O/hexane, 1:1, v/v) then showed a faster running compound. The reaction mixture was diluted with Et_2O (30 mL), filtered through a bed of silica gel 60 (Scharlau, 230–400 mesh) and thoroughly washed with Et_2O. The combined filtrate and washings were concentrated to aldehyde **7** which was dissolved in toluene (20 mL). Methyl (triphenylphosphoranylidene)acetate (470 mg, 1.4 mmol) was added, and the reaction mixture was refluxed for 24 h. The solvent was removed and the residue submitted to column chromatography (Et_2O/hexane, 1:5 → 2:1, v/v) to afford syrupy **8** (420 mg, 59%, from **6**). $[\alpha]_D^{30} = -12$ ($c = 1$). IR (neat): $\tilde{\nu}$ = 1723, 1715, 1699 and 1662 (PhCO, α,β-unsaturated ester, >NBoc and C=C), 738, 712 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ = 7.94–7.27 (3 m, 15 H, 3 Ph), 6.81 (dd, $J_{2,3}$ = 15.6, $J_{2',3}$ = 5.6 Hz, 1 H, 3-H), 5.96 (d, 1 H, 2-H), 4.72–3.73 (br. m, 10 H, 2 CH_2Ph and 2′,3′,4′,5′,5′′a,5′′b-H), 3.68 and 3.60 (2 br. s, 3 H, OMe, 2 rotamers), 1.46 and 1.40 (2 br. s, 9 H, CMe_3, 2 rotamers) ppm. ^{13}C NMR (inter alia): δ = 166.35 and 166.29 (COPh, C-1), 147.2 (C-3), 123.8 (C-2), 72.2 (*C*H_2Ph), 62.4, 51.8 (OMe), 28.5 (C*Me*$_3$) ppm. HRMS (LSIMS): calcd. for $C_{35}H_{39}NO_8Na$ $[M + Na]^+$ 624.2573; found 624.2568 (deviation +0.9 ppm).

4-[(3*E*,2′*R*,3′*S*,4′*R*,5′R)-5′-(Benzoyloxymethyl)-3′,4′-bis(benzyloxy)-*N*′-(*tert*-butyloxycarbonyl)pyrrolidin-2′-yl]but-3-en-2-one (9): Activated molecular sieves (4 Å) (100 mg), NMO (250 mg, 2.15 mmol) and TPAP (100 mg) were added to a stirred solution of **6** (785 mg, 1.44 mmol) in dry DCM (15 mL), and the reaction mixture was kept at room temp. for 90 min. TLC (Et_2O/hexane, 3:1, v/v) then indicated the absence of the starting material and the presence of a faster running compound. The reaction mixture was diluted with Et_2O (50 mL), filtered through a bed of silica gel 60 (Scharlau, 230–400 mesh) and thoroughly washed with Et_2O. The combined filtrate and washings were concentrated to afford presumably aldehyde **7**. This material was used in the next step. 1-(Triphenylphosphoranylidene)-2-propanone (685 mg, 2.15 mmol) was added to a stirred solution of the above **7** in dry toluene (20 mL) and the mixture refluxed. After 2 h, TLC (Et_2O/hexane, 3:1, v/v) revealed the presence of a new compound of slightly lower mobility. The solvent was removed, and the residue was purified by chromatography on silica gel (Et_2O/hexane, 1:5, v/v) to give pure **9** (600 mg, 71% from **6**) as a colourless syrup. $[\alpha]_D^{26} = -30$ ($c = 1$). IR (neat): $\tilde{\nu}$ = 3063 and 3031 (aromatic), 1722 and 1699 (BzO, α,β-unsaturated ketone and >NBoc), 738 and 712 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ = 7.79 (d, $J_{o,m}$ = 7.2 Hz, 2 H, *ortho*-H, Bz), 7.49 (t, $J_{m,p}$ = 7.2 Hz, 1 H, *para*-H, Bz), 7.32 (t, 2 H, *meta*-H, Bz), 7.30–7.18 (m, 10 H, 2 Ph), 6.46 (dd, $J_{2',4}$ = 6.0, $J_{3,4}$ = 16 Hz, 1 H, 4-H), 6.08 (d, 1 H, 3-H), 4.78–3.79 (4 br. m, 10 H, 2 CH_2Ph and 2′,3′,4′,5′,5′′a,5′′b-H), 2.00–1.90 (2 br. s, 3 H, 1-H, 2 rotamers), 1.41 and 1.32 (2 br. s, 9 H, CMe_3, 2 rotamers) ppm. ^{13}C NMR (inter alia), δ = 197.7 (C-2), 166.1 (Bz), 155.1 (Boc), 145.9 and 144.2 (C-3,4), 81.0, 78.4, 76.9 and 75.7 (C-3′,4′, 2 rotamers), 71.6 (2 *C*H_2Ph), 63.1 (C-5′′), 61.8 and 60.3 (C-2′,5′), 28.0 (C*Me*$_3$), 27.2 (C-1) ppm. HRMS (LSIMS): calcd. for $C_{35}H_{39}NO_7Na$ $[M + Na]^+$ 608.2624; found 608.2621 (deviation +0.6 ppm).

(1*S*,2*R*,3*R*,7a*R*)-1,2-Bis(benzyloxy)-3-(hydroxymethyl)pyrrolizidin-5-one (11): Compound **8** (512 mg, 0.85 mmol) in dry MeOH (20 mL) was hydrogenated with H_2 from a balloon in the presence of 10% Pd/C (80 mg) for 2 h. TLC (Et_2O/hexane, 2:1, v/v) then showed the presence of a new compound of slightly lower mobility. The catalyst was filtered off, washed with MeOH, and the filtrate and washings were concentrated to a residue that was dissolved in DCM (8 mL) and cooled (ice/water). TFA (8 mL) was added to this stirred solution and the mixture left for 1.5 h. TLC (Et_2O/hexane, 2:1, v/v) then revealed a non-mobile compound. The solvent was removed and the residue co-distilled with toluene to give a new residue which was dissolved in MeOH and basified by addition of 2 N MeONa/MeOH and refluxed for 2 h. TLC (Et_2O/MeOH, 20:1, v/v) showed a slower running compound. The reaction mixture was neutralized and submitted to column chromatography (Et_2O/MeOH, 20:1 → 10:1, v/v) to afford pure **11** (270 mg, 86% from **8**) as a colourless syrup. $[\alpha]_D^{27} = -6$, $[\alpha]_{405}^{27} = -10$ ($c = 1$). IR (neat): $\tilde{\nu}$ = 3365 (OH), 3031 (aromatic), 1667 (C=O lactam), 739 and 698 cm^{-1} (aromatic). ^1H NMR (500 MHz): δ = 7.40–7.28 (m, 10 H, 2 Ph), 4.66 and 4.63 (2 d, J = 12.0 Hz, 2 H, CH_2Ph), 4.61 and 4.50 (2 d, J = 11.9 Hz, 2 H, CH_2Ph), 4.21 (br. q, 1 H, 7a-H), 3.93 (dd, $J_{3,8}$ = 2.6, $J_{8,8'}$ = 12.0 Hz, 1 H, 8-H), 3.86 (dd, $J_{1,2}$ = 5.5, $J_{2,3}$ = 3.0 Hz, 1 H, 2-H), 3.83 (m, 1 H, 3-H), 3.68 (dd, $J_{3,8'}$ = 7.9 Hz, 1 H, 8′-H), 3.51 (dd, $J_{1,7a}$ = 7.9 Hz, 1 H, 1-H), 2.68 (ddd, $J_{6,6'}$ = 16.7 Hz, 1 H, 6-H), 2.44 (dd, $J_{6',7'}$ = 8.9, $J_{6',7}$ = 0 Hz, 1 H, 6′-H),

2.28 (br. dt, $J_{6,7} = J_{7,7a} = 7.8$, $J_{7,7'} = 12.3$ Hz, 1 H, 7-H), 1.74 (tt, $J_{6,7'} = 12.3$, $J_{7',7a} = 9.2$ Hz, 1 H, 7′-H) ppm. ^{13}C NMR (inter alia): δ = 174.5 (C-5), 81.9 (C-2), 81.0 (C-1), 72.5 and 72.4 (2 *C*H$_2$Ph), 65.6 (C-7a), 64.7 (C-3), 63.0 (C-8), 35.7 (C-6), 26.9 (C-7) ppm. HRMS (LSIMS): calcd. for $C_{22}H_{25}NO_4Na$ [M + Na]$^+$ 390.1681; found 390.1675 (deviation +1.7 ppm).

(1*S*,2*R*,3*R*,7a*R*)-1,2-Bis(benzyloxy)-3-(hydroxymethyl)pyrrolizidine (12): An $H_3B{\cdot}SMe_2$ complex solution in anhydrous THF (10 M, 670 μL) was added dropwise to a stirred solution of **11** (247 mg, 0.67 mmol) in anhydrous THF (10 mL) under argon and the mixture left at room temp. for 1.5 h. TLC (Et$_2$O/MeOH, 5:1, v/v) then revealed the absence of **11** and the presence of a faster running compound, presumably the borane–amine complex. MeOH (1 mL) was cautiously added, and the reaction mixture was concentrated to a residue which was dissolved in MeOH (5 mL) and refluxed for 12 h, by which time the borane–amine complex was no longer observed by TLC. The reaction mixture was concentrated, and the residue was purified by chromatography on silica gel (Et$_2$O/MeOH, 15:1, v/v → Et$_2$O/MeOH/NH$_4$OH, 5:1:0.5, v/v) to give pure **12** (140 mg, 59%) as a colourless viscous syrup. $[\alpha]_D^{29}$ = +91 (*c* = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3330 (OH), 3031, 737 and 698 cm^{-1} (aromatic). ^{1}H NMR (500 MHz, [D$_4$]MeOH): δ = 7.37–7.22 (m, 10 H, 2 Ph), 4.58 and 4.51 (2 d, *J* = 11.5 Hz, 2 H, CH$_2$Ph), 4.57 and 4.53 (2 d, *J* = 11.8 Hz, 2 H, CH$_2$Ph), 3.86 (dd, $J_{1,2}$ = 5.1, $J_{2,3}$ = 8.4 Hz, 1 H, 2-H), 3.82 (dd, $J_{3,8}$ = 4.1, $J_{8,8'}$ = 12.1 Hz, 1 H, 8-H), 3.75 (dd, $J_{3,8'}$ = 8.0 Hz, 1 H, 8′-H), 3.74 (dd, 1 H, 1-H), 3.57 (dt, $J_{1,7a}$ = 3.1, $J_{7a,7}$ = $J_{7a,7'}$ = 8.0 Hz, 1 H, 7a-H), 3.43 (dt, 1 H, 3-H), 2.89 (ddd, *J* = 6.7, *J* = 2.4, $J_{5,5'}$ = 9.5 Hz, 1 H, 5-H), 2.79 (dt, *J* = 9.8, *J* = 5.6 Hz, 1 H, 5′-H), 2.09 (ddt, *J* = 2.4, *J* = 7.4, $J_{7,7'}$ = 12.6 Hz, 1 H, 7-H), 1.85 (m, 1 H, 6-H), 1.70 (m, 1 H, 6′-H), 1.42 (ddt, *J* = 7.7, *J* = 10.6 Hz, 1 H, 7′-H) ppm. ^{13}C NMR (inter alia): δ = 85.2 (C-1), 82.4 (C-2), 75.9 and 75.5 (2 *C*H$_2$Ph), 72.1 (C-7a), 68.7 (C-3), 63.6 (C-8), 51.6 (C-5), 33.9 (C-7), 30.3 (C-6) ppm. HRMS (LSIMS): calcd. for $C_{22}H_{28}NO_3$ [M + H]$^+$ 354.2069; found 354.2068 (deviation +0.2 ppm).

(1*S*,2*R*,3*R*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)pyrrolizidine [(+)-Hyacinthacine A$_1$ (1)]: Compound **12** (120 mg, 0.34 mmol) in MeOH (15 mL) and conc. HCl (five drops) was hydrogenated (482 kPa H$_2$) in the presence of 10% Pd/C (50 mg) for 20 h. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were treated with Amberlite IRA-400 resin (OH$^-$ form). Evaporation of the solvent afforded a residue that was retained on a column of Dowex 50W×8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH$_4$OH to afford pure **1** (55 mg, 93%) as a colourless viscous syrup. $[\alpha]_D^{27}$ = +47 (*c* = 0.65, water) {ref.[6] $[\alpha]_D$ +38.2 (*c* = 0.23, water); ref.[16b] $[\alpha]_D^{20}$ = +45 (*c* = 0.23, water)}. ^{1}H NMR (500 MHz, [D$_4$]MeOH): δ = 3.88 (dd, $J_{1,2}$ = 5.5, $J_{2,3}$ = 9.0 Hz, 1 H, 2-H), 3.84 (dd, $J_{3,8}$ = 4.1, $J_{8,8'}$ = 12.1 Hz, 1 H, 8-H), 3.81 (dd, $J_{3,8'}$ = 8.0 Hz, 1 H, 8′-H), 3.76 (dd, 1 H, 1-H), 3.39 (dt, $J_{1,7a}$ = 2.4, $J_{7a,7}$ = $J_{7a,7'}$ = 7.9 Hz, 1 H, 7a-H), 3.21 (dt, 1 H, 3-H), 2.91 (ddd, *J* = 2.1, *J* = 9.0 Hz, 1 H, 5-H), 2.79 (dt, $J_{5,5'}$ = 9.8, *J* = 5.8 Hz, 1 H, 5′-H), 2.14 (ddt, *J* = 2.5, *J* = 7.6, $J_{7,7'}$ = 12.6 Hz, 1 H, 7-H), 1.87 (m, 1 H, 6-H), 1.69 (m, 1 H, 6′-H), 1.50 (ddt, *J* = 7.6, *J* = 10.4 Hz, 1 H, 7′-H) ppm. ^{13}C NMR: δ = 76.9 (C-1), 72.5 (C-2), 72.1 (C-7a), 67.1 (C-3), 60.9 (C-8), 49.1 (C-5), 30.9 (C-7), 27.4 (C-6) ppm. HRMS (LSIMS): calcd. for $C_8H_{15}NO_3$ [M]$^+$ 173.1052; found 173.1050 (deviation +0.8 ppm).

(1*S*,2*R*,3*R*,5*R*,7a*R*)-1,2-Bis(benzyloxy)-3-(hydroxymethyl)-5-methylpyrrolizidine (15): Compound **9** (600 mg, 1.03 mmol) in MeOH (20 mL) was hydrogenated with H$_2$ from a balloon in the presence of 10% Pd/C (100 mg) for 2 h. The reaction mixture was filtered, and an aliquot was concentrated to afford the intermediate saturated ketone (IR evidence). The reaction mixture was then acidified with conc. HCl (0.2 mL) and left at room temp. for 72 h. Neutralization of the reaction mixture with 2 N MeONa/MeOH and subsequent hydrogenation in the presence of 10% Pd/C (100 mg) for 12 h gave, after removal of the catalyst and column chromatography (Et$_2$O/hexane, 1:3 → Et$_2$O), compound **14** (150 mg), slightly contaminated. Finally, Zemplen debenzoylation of **14** with 2 N MeONa/MeOH (0.5 mL) for 12 h followed by column chromatography (Et$_2$O/hexane, 1:1 → 2:1, v/v) afforded pure **15** (90 mg, 24% from **9**) as a syrup. $[\alpha]_D^{24}$ = +35 (*c* = 1). IR (neat): $\tilde{\nu}$ = 3441 (OH), 3063, 3031, 736 and 697 cm^{-1} (aromatic). ^{1}H NMR (500 MHz): δ = 7.36–7.26 (m, 10 H, 2 Ph), 4.79 and 4.57 (2d, *J* = 11.8 Hz, 2 H, CH$_2$Ph), 4.60 and 4.58 (2d, *J* = 12.5 Hz, 2 H, CH$_2$Ph), 4.20 (dd, $J_{1,2}$ = 6.0, $J_{2,3}$ = 3.7 Hz, 1 H, 2-H), 3.71 (dd, $J_{3,8}$ = 3.2, $J_{8,8'}$ = 11.0 Hz, 1 H, 8-H), 5.53 (m, 2 H, 1,8′-H), 3.16 (dt, *J* = 6, *J* = 9.8 Hz, 1 H, 7a-H), 2.78 (br. s, 1 H, 3-H), 2.56 (br. sext, $J_{5,6}$ = $J_{5,6'}$ = 6.0 Hz, 1 H, 5-H), 2.21 (m, 1 H, 6-H), 1.79 (m, 1 H, 7-H), 1.78 (m, 1 H, 6′-H), 1.44 (m, 1 H, 7′-H), 1.13 (d, $J_{Me,5}$ = 6.0 Hz, 3 H, Me) ppm. ^{13}C NMR: δ = 138.7, 128.5, 128.18 and 127.75 (CH$_2$*Ph*), 85.3 (C-2), 80.2 (C-1), 73.1 and 72.1 (2 *C*H$_2$Ph), 72.7 (C-7a), 67.7 (C-3), 61.9 (C-8), 54.9 (C-5), 37.3 (C-6), 25.3 (C-7), 21.2 (Me) ppm. HRMS (LSIMS): calcd. for $C_{23}H_{30}NO_3$ [M + H]$^+$ 368.2226; found 368.2227 (deviation –0.4 ppm).

(1*S*,2*R*,3*R*,5*R*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)-5-methylpyrrolizidine [(+)-Hyacinthacine A$_6$ (2)]: A solution of **15** (70 mg, 0.19 mmol) in MeOH (15 mL) was acidified (conc. HCl, five drops) and hydrogenated (413 kPa H$_2$) in the presence of 10% Pd/C (50 mg) for 48 h. The catalyst was filtered off, washed with MeOH, and the filtrate and washings were neutralized with Amberlite IRA-400 (OH$^-$ form) and concentrated to a residue that was retained on a column of Dowex 50W×8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH$_4$OH to afford pure **2** (34 mg, 96%) as a colourless viscous syrup. $[\alpha]_D^{26}$ = +15.8 (*c* = 0.5, water) {ref.[7] $[\alpha]_D^{26}$ = +16.3 (*c* = 0.22, water)}. ^{1}H NMR (300 MHz, D$_2$O): δ = 4.11 (t, $J_{1,2}$ = $J_{2,3}$ = 6.2 Hz, 1 H, 2-H), 3.82 (dd, $J_{3,8}$ = 5.0, $J_{8,8'}$ = 11.7 Hz, 1 H, 8-H), 3.91 (br. t, 1 H, 1-H, 3.67 (dd, $J_{3,8'}$ = 6.2 Hz, 1 H, 8′-H), 2.79 (dt, $J_{1,7a}$ = 6.5, $J_{7a,7\alpha}$ = $J_{7a,7\beta}$ = 9.4 Hz, 1 H, 7a-H), 2.59 (br. sext, $J_{5,6\alpha}$ = $J_{5,6\beta}$ = $J_{5,Me}$ = 6.7 Hz, 1 H, 5-H), 2.47 (br. q, 1 H, 3-H), 2.25 (br. dq, $J_{6\beta,7\alpha}$ = $J_{6\beta,7\beta}$ = 8.2, $J_{6\alpha,6\beta}$ = 12.0 Hz, 1 H, 6β-H), 1.81 (m, 1 H, 7β-H), 1.63 (m, 1 H, 6α-H), 1.41 (br. dq, $J_{6\alpha,7\alpha}$ = 7.6, $J_{7\alpha,7\beta}$ = 10.8 Hz, 1 H, 7α-H), 1.12 (d, 3 H, Me) ppm. ^{13}C NMR: δ = 77.0 (C-2), 74.1 (C-7a), 70.9 (C-1), 69.8 (C-3), 61.8 (C-8), 56.2 (C-5), 35.9 (C-6), 23.3 (C-7), 19.6 (Me) ppm. HRMS (LSIMS): calcd. for $C_9H_{17}NO_3Na$ [M + Na]$^+$ 210.1106; found 210.1103 (deviation +1.1 ppm).

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **11** and **12** and 2D ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra for compounds **1** and **2**.

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[1] L. E. Fellows, *Chem. Br.* **1987**, *23*, 842–844.
[2] For a recent review, see: S. G. Pyne, M. Tang, *Curr. Org. Chem.* **2005**, *9*, 1393–1418.
[3] R. J. Nash, L. E. Fellows, J. V. Dring, G. W. J. Fleet, A. E. Derome, T. A. Hamor, A. M. Scofield, D. J. Watkins, *Tetrahedron Lett.* **1988**, *29*, 2487–2490.

[4] R. J. Molyneux, M. Benson, R. Y. Wong, J. E. Tropea, A. D. Elbein, *J. Nat. Prod.* **1988**, *51*, 1198–1206.
[5] A. Kato, I. Adachi, M. Miyauchi, K. Ikeda, T. Komae, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, M. R. Wormald, G. W. J. Fleet, N. Asano, *Carbohydr. Res.* **1999**, *316*, 95–103.
[6] N. Asano, H. Kuroi, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, I. Adachi, A. A. Watson, R. J. Nash, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.
[7] T. Yamashita, K. Yasuda, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, G. W. J. Fleet, N. Asano, *J. Nat. Prod.* **2002**, *65*, 1875–1881.
[8] N. Asano, K. Ikeda, M. Kasahara, Y. Arai, H. Kizu, *J. Nat. Prod.* **2004**, *67*, 846–850.
[9] A. Kato, N. Kato, I. Adachi, J. Hollinshead, G. W. J. Fleet, C. Kuriyama, K. Ikeda, N. Asano, R. J. Nash, *J. Nat. Prod.* **2007**, *70*, 993–997.
[10] P. E. Goss, M. A. Baker, J. P. Carver, J. W. Dennis, *Clin. Cancer Res.* **1995**, *1*, 935–944.
[11] N. Asano, *Curr. Top. Med. Chem.* **2003**, *3*, 471–484.
[12] Q. Meng, M. Hesse, *Helv. Chim. Acta* **1991**, *74*, 445–450.
[13] B. Winchester, G. W. J. Fleet, *Glycobiology* **1992**, *2*, 199–210.
[14] a) I. Izquierdo, M.-T. Plaza, R. Robles, F. Franco, *Carbohydr. Res.* **2001**, *330*, 401–408; b) I. Izquierdo, M.-T. Plaza, F. Franco, *Tetrahedron: Asymmetry* **2002**, *13*, 1503–1508; c) I. Izquierdo, M.-T. Plaza, M. Rodríguez, F. Franco, A. Martos, *Tetrahedron* **2005**, *61*, 11697–11704; d) I. Izquierdo, M.-T. Plaza, M. Rodríguez, J. A. Tamayo, A. Martos, *Tetrahedron* **2006**, *62*, 2693–2697; e) I. Izquierdo, M.-T. Plaza, V. Yáñez, *Tetrahedron* **2007**, *63*, 1440–1447.
[15] a) I. Izquierdo, M.-T. Plaza, R. Robles, F. Franco, *Tetrahedron: Asymmetry* **2001**, *12*, 2481–2487; b) I. Izquierdo, M.-T. Plaza, F. Franco, *Tetrahedron: Asymmetry* **2002**, *13*, 1581–1585; c) I. Izquierdo, M.-T. Plaza, F. Franco, *Tetrahedron: Asymmetry* **2003**, *14*, 3933–3935; d) I. Izquierdo, M.-T. Plaza, F. Franco, *Tetrahedron: Asymmetry* **2004**, *15*, 1465–1469; e) I. Izquierdo, M.-T. Plaza, J. A. Tamayo, *Tetrahedron* **2005**, *61*, 6527–6533; f) I. Izquierdo, M.-T. Plaza, J. A. Tamayo, *J. Carbohydr. Chem.* **2006**, *25*, 281–295; g) I. Izquierdo, M.-T. Plaza, J. A. Tamayo, M. Rodríguez, A. Martos, *Tetrahedron* **2006**, *62*, 6006–6011.
[16] a) For an approach, see: A. Toyao, O. Tamura, H. Takagi, H. Ishibashi, *Synlett* **2003**, 35–38; b) for a total synthesis, see: L. Chabaud, Y. Landais, P. Renaud, *Org. Lett.* **2005**, *7*, 2587–2590; c) for a recent chemoenzymatic synthesis of hyacinthacine A_1 stereoisomers, see: J. Calveras, J. Casas, T. Parella, J. Joglar, P. Claplés, *Adv. Synth. Catal.* **2007**, *349*, 1661–1666.
[17] M. R. Wormald, R. J. Nash, P. Hrnciar, J. D. White, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **1998**, *9*, 2549–2558.

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