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Total synthesis of natural (+)-hyacinthacine A_6 and non-natural (+)-7a-*epi*-hyacinthacine A_1 and (+)-5,7a-di*epi*-hyacinthacine A_6

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Dedicated to Professor Pelayo Camps on the occasion of his 65th anniversary

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ABSTRACT

Naturally occurring (1*S*,2*R*,3*R*,5*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-hyacinthacine A_6, **2**] together with unnatural (1*S*,2*R*,3*R*,7a*S*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine [(+)-7a-*epi*-hyacinthacine A_1, **3**] and (1*S*,2*R*,3*R*,5*S*,7a*S*)-1,2-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-5,7a-di*epi*-hyacinthacine A_6, **4**] have been synthesized from a DALDP derivative [**5**, (2*R*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)-pyrrolidine], as the homochiral starting material. The synthetic process employed took advantages of Wittig methodology followed by internal lactamization, in the case of (+)-7a-*epi*-hyacinthacine A_1 (**3**), and reductive amination for (+)-hyacinthacine A_6 (**2**) and (+)-5,7a-di*epi*-hyacinthacine A_6 (**4**).

1. Introduction

Polyhydroxylated pyrrolidine (e.g., DMDP), piperidine (e.g., DMJ), indolizidine (e.g., castanospermine), pyrrolizidine (e.g., alexine and australine), and nortropane (e.g., calystegine B_2) alkaloids (imino or azasugars) have increasingly gained attention due to their capacity to inhibit glycosidases. This class of inhibitors was first discovered in plants in which these azasugars were found to inhibit the carbohydrate-processing enzymes of plant's 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 Fig. 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 et al.

Since the discovery of these nitrogen-containing inhibitors, many biological and medical studies have been performed to test if their inhibitory activity could have an application in therapeutics. 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

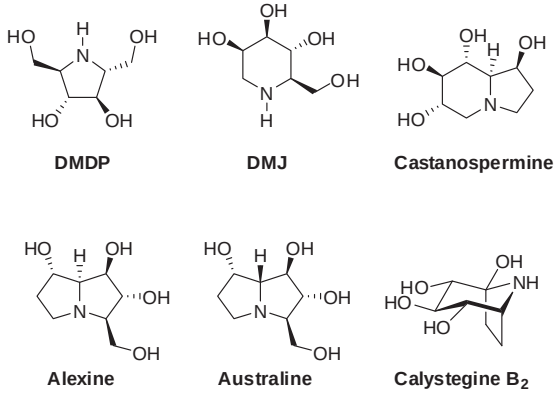

Figure 1. Naturally occurring polyhydroxylated alkaloids (imino or azasugars).

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enormous medical potential; however, the great number of naturally occurring iminosugars that have been isolated so far represent only a small fraction of the possible azasugars that could be potential therapeutical agents.

Since naturally occurring azasugars are present in scarce quantities in natural sources and are often difficult to be purified,[13] efficient syntheses of these iminosugars and analogues are wanted. In this context, our group has developed in recent years a synthetic methodology involving the use of appropriately functionalized pyrrolidines[14] as key intermediates for the preparation of more complex polyhydroxylated pyrrolizidine alkaloids (PHPAs).[15] On the other hand, such pyrrolidines have been prepared from the commercially available hexulose, D-fructose. In this article, we want to describe our studies on the synthesis of (+)-hyacinthacine A_1[16] (**1**) and (+)-hyacinthacine A_6 (**2**),[16b,17] which culminated in the total enantioespecific synthesis of natural (+)-hyacinthacine A_6 (**2**) and the non-naturally occurring (+)-7a-*epi*-hyacinthacine A_1 (**3**) and (+)-5,7a-di*epi*-hyacinthacine A_6 (**4**), previously described by us as (−)-3-*epi*-hyacinthacine A_5.[15g]

Our retrosynthetic strategy towards PHPAs **1** and **2** is shown in Figure 2. As illustrated, a simple cleavage of 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 **10** and ketone **11**, respectively, reveals the key tri-orthogonally protected 2,5-dideoxy-2,5-imino-D-altritol (DALDP, **5**)[14c] as the initial precursor.

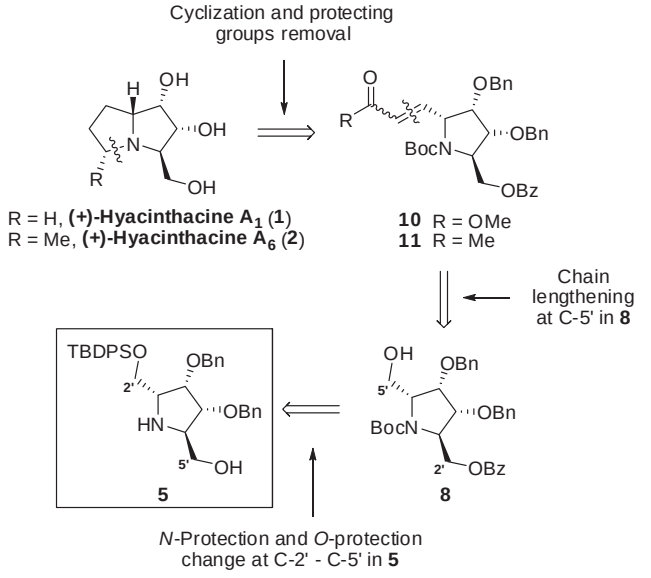
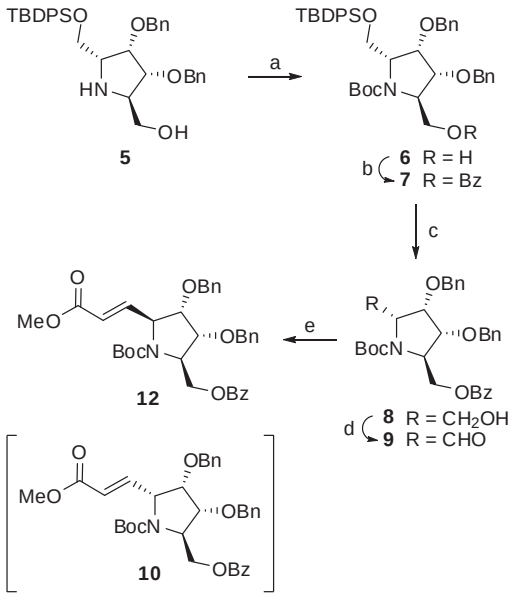


Figure 2. Retrosynthesis of hyacinthacines A_1 (**1**) and A_6 (**2**) from a tri-orthogonally protected derivative of DALDP (**5**).

2. Results and discussion

According to the above retrosynthetic analysis and based on the results from our 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 (**5**),[14c] which was chemoselectively transformed into its *N*-Boc derivative **6** by treatment with di-*tert*-butyldicarbonate in dichloromethane (DCM)/triethylamine (TEA). Conventional benzoylation of **6** to the corresponding 5-(benzoyloxymethyl) derivative **7** followed by O-desilylation afforded pyrrolidine **8**, opportunely leaving the primary alcohol free for oxidation to aldehyde **9** (IR evidence: ν=1725 cm^{-1} and no hydroxy absorption band) catalyzed by tetra-*n*-propylammonium perruthenate (TPAP) in preparation for Wittig-chain lengthening.

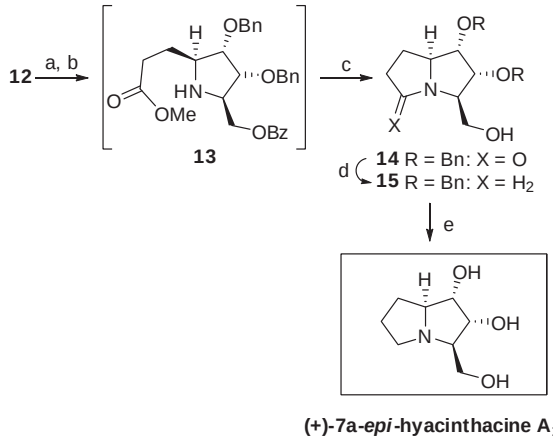
In the approach to the synthesis of (+)-hyacinthacine A_1 (**1**), methyl (triphenylphosphoranylidene)acetate was reacted with aldehyde **9** in toluene at reflux. Unexpectedly, (*E*)-α,β-unsaturated ester **12** was obtained as a single product ($J_{2,3}$=15.6 Hz). The configuration at C-2′ could not be resolved at this point, but later in the synthesis since the ^{1}H NMR appeared as an irresoluble mixture of rotamers. It appears that, under the above mentioned conditions, epimerization at C-2′ occurred,[18] producing an inversion in the configuration and consequently yielding derivative **12**. Unfortunately, further attempts to obtain ester **10** under mild conditions and with different solvents probed unsuccessful, yielding either **12** or an inseparable mixture of compounds.



Scheme 1. Synthesis of α,β-unsaturated pirrolidine ester **12** from tri-orthogonally protected DALDP (**5**). Regents and conditions: (a) (*tert*-BuOCO)$_2$O/DCM/TEA, rt, (quantitative); (b) BzCl/DCM/TEA, rt (78%); (c) TBAF·3H$_2$O/THF, rt (88%); (d) NMO/TPAP/DCM/MS (4 Å), rt; (e) $Ph_3P{=}CHCO_2Me$, PhMe, reflux, 8 h, (two steps, 59%).

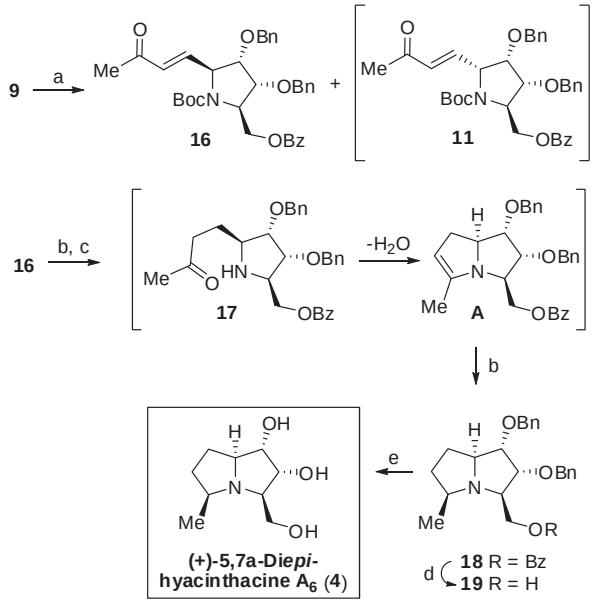
Subsequent catalytic hydrogenation of methyl ester **12** with 10% Pd/C, afforded the intermediate saturated pyrrolidine ester (no signals, due to vinylic protons, were observed in the ^{1}H NMR spectrum of an aliquot of the reaction mixture), which was not further investigated, but submitted to N-deprotection in an acidic medium to afford intermediate **13** (not isolated). This intermediate was treated with base (MeONa/MeOH) to promote internal lactamization and concomitant O-debenzoylation to afford pyrrolizidin-5-one **14**, which was characterized on the basis of its analytical and spectroscopic data. Reduction of the lactam with $H_3B{\cdot}SMe_2$ complex to intermediate **15** followed by its total O-debenzylation, finally gave (+)-7a-*epi*-hyacinthacine A_1 (**3**) whose physical and spectroscopic data were in accordance with those previously reported in the literature[19] (Scheme 2).

With pyrrolizidine **3** in our hands, and with the aim to synthesise (+)-hyacinthacine A_6 (**2**), aldehyde **9** was reacted with 1-(triphenylphosphoranylidene)-2-propanone under similar reaction conditions as described earlier (see Scheme 3). Two new products were obtained this time, but only the major one (TLC evidence) could be isolated, corresponding to α,β-unsaturated ketone **16**, the C-2′ epimer of the desired **11**. Its absolute configuration could not be resolved at this point, since the ^{1}H NMR appeared as an irresoluble mixture of rotamers. With ketone **16** as chemical precursor,



Scheme 2. Synthesis of (+)-7a-*epi*-hyacinthacine A_1 (**3**) from **12**. Reagents and conditions: (a) 10% Pd/C, H_2, balloon, rt; (b) (i). TFA/DCM, rt, (ii). neutralization with MeONa/MeOH; (c) MeONa (cat.)/MeOH, Δ, (from **12**, 86%); (d) $H_3B{\cdot}SMe_2$/THF, then MeOH, △, (59%); (e) concd HCl, 10% Pd/C, H_2, 60 psi, then Amberlite IRA-400 (OH^- form) and chromatography on Dowex 50Wx8 (200–400 mesh), (93%).

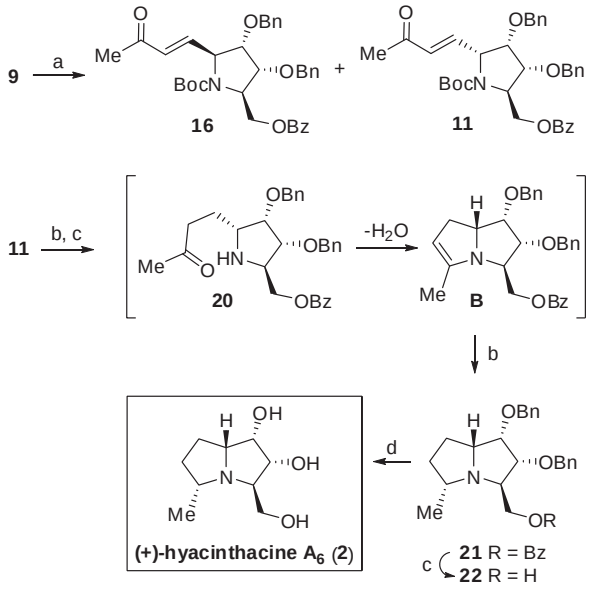
5,7a-di*epi*-hyacinthacine A_6 (**4**), previously described as (−)-3-*epi*-hyacinthacine A_5,[15g] would be obtained instead of the desired (+)-hyacinthacine A_6. Hence, catalytic hydrogenation and N-deprotection of **16** yielded the intermediate pyrrolidine ketone **17**, that after intramolecular condensation gave the Δ^5-pyrrolizine **A**, both compounds not isolated. Subsequent hydrogenation of **A** gave the fully protected pyrrolizidine **18**, slightly contaminated. Zemplen debenzoylation of **18** afforded pure **19**.



Scheme 3. Synthesis of (+)-5,7a-di*epi*-hyacinthacine A_6 (**4**) from **9**. Reagents and conditions: (a) $Ph_3P{=}CHCOMe$/PhMe, reflux, 2 h (71% for **16**); (b) 10% Pd/C, H_2, balloon, rt; (c) (i). concd HCl/MeOH rt, (ii). neutralization with MeONa/MeOH; (d) MeONa (cat.)/MeOH, rt, (from **16**, 24%); (e) concd HCl, 10% Pd/C, H_2, 60 psi, then Amberlite IRA-400 (OH^- form) and chromatography on Dowex 50Wx8 (200–400 mesh), (96%).

The configuration of the new stereogenic centre C-5 in **19** was determined on the basis of extensive NOE experiments. Positive NOE couplings were observed between H(8)–Me, H(5)–H(7a), H(5)–H(3) and H(7a)–H(3). Based on these experiments we confirmed the (*S*) configuration at C-5 and C-7a in **19** and hence established the absolute configuration of **16**. Final debenzylation of compound **19** allowed the synthesis of 5,7a-di*epi*-hyacinthacine A_6 (**4**) as a single isomer and whose analytical and spectroscopic data correspond to those previously reported by us.[15g]

To conclude, we approached the synthesis of (+)-hyacinthacine A_6 (**2**). In an attempt to obtain the necessary α,β-unsaturated ketone **11**, the reaction conditions of the Wittig olefination were modified. When aldehyde **9** and 1-(triphenylphosphoranylidene)-2-propanone were reacted at 85 °C for 24 h, compounds **16** and **11** were isolated in 24% and 40% yield, respectively (Scheme 4), with ketone **11** appearing as a mixture of two rotamers of (*E*) configuration ($J_{3,4}$=16.0 Hz).



Scheme 4. Synthesis of (+)-hyacinthacine A_6 (**2**) from **9**. Reagents and conditions: (a) $Ph_3P{=}CHCOMe$/PhMe, 80 °C, 24 h (24% for **16** and 40% for **11**); (b) 10% Pd/C, H_2, rt; (c) (i). concd ClH/MeOH rt, (ii). neutralization with MeONa/MeOH, (from **11**, 23%); (d) MeONa (cat.)/MeOH, rt, (56%); (d) concd HCl, 10% Pd/C, H_2, 60 psi, then Amberlite IRA-400 (OH^- form) and chromatography on Dowex 50Wx8 (200–400 mesh), (87%).

Catalytic hydrogenation of derivative **11** followed by chemoselective N-deprotection and hydrogenation of the resulting derivative **20**, afforded pirrolizidine **21** by means of Δ^5-pyrrolizine intermediate **B**, both compounds, **20** and **B**, were not isolated. Final protecting groups removal as described for **4**, yielded the desired (+)-hyacinthacine A_6 (**2**) whose spectroscopic and analytical data were in accordance with those previously reported.[7,16b]

The high stereoselectivity found in the hydrogenation of intermediate Δ^5-pyrrolizines **A** and **B**, merits comments. Formation of **2** and **4** can be attributed, according to our previous results[15b] and Figure 3, to the particular shape of this type of molecules.[6,20] The α- and β-face for intermediates **A** and **B**, respectively, are less hindered for hydrogen attack, therefore affording preferentially derivatives **18** and **21**, precursors of final compounds **4** and **2**.

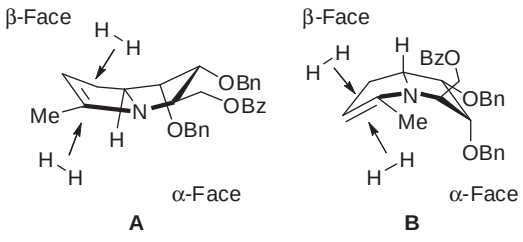


Figure 3. Proposed scheme for the hydrogenation of intermediate Δ^5-pyrrolizine **A** and **B**.

3. Conclusions

In conclusion, we report here the total enantioselective synthesis of naturally occurring (+)-hyacinthacine A_6 (**2**), and the unnatural 5,7a-di*epi*-hyacinthacine A_6 (**4**) and (+)-7a-*epi*-hyacinthacine A_1 (**3**). The synthetic approach takes advantages of quiral tri-orthogonally protected polyhydroxylated pyrrolidines derived from common hexuloses, and uses as key reaction the classical Wittig's methodology, followed by internal lactonization or reductive amination depending on the desired pyrrolizidine. This methodology demonstrates the versatility of orthogonally protected polyhydroxylated pyrrolidines in the enantioselective synthesis of natural and non-natural PHPA.

4. Experimental section

4.1. General remarks

Solutions were dried over $MgSO_4$ 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 Me_4Si). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. IR spectra were recorded with a Perkin–Elmer FT-IR Spectrum One instrument and mass spectra were recorded with a Hewlett-Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers or a NALDI ionization-time of flight (NALDI-TOF) mass spectrometer and EI mass spectrometer. Optical rotations were measured for solutions 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 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.

4.2. Synthesis and characterization

*4.2.1. (2R,3S,4R,5R)-3,4-Bis(benzyloxy)-N-(tert-butyloxycarbonyl)-2′-O-(tert-butyldiphenylsilyl)-2,5-bis(hydroxymethyl)pyrrolidine (**6**).* Triethylamine (TEA, 510 μL, 3.66 mmol) and di-*tert*-butyldicarbonate (700 mg, 3.23 mmol) were added to a stirred solution of **5** in dry dichloromethane (DCM, 20 mL) cooled in ice/water (1.25 g, 2.15 mmol) and the mixture was kept at room temperature (rt) 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 **6** as a colourless syrup. Yield: 1.45 g (quantitative); $[\alpha]_D^{28}$ +11 (*c* 1, $CHCl_3$); IR (neat): *ν* 3425 (OH), 3069 (aromatic), 1690 (C=O, Boc), 731 and 700 cm^{-1} (aromatic); ^1H NMR (400 MHz): *δ* 7.70–7.27 (m, 20H, 4Ph), 4.83 and 4.72 (2d, *J*=12.0 Hz, 2H, CH_2Ph), 4.70–4.61 (2d, *J*=12 Hz, 2H, CH_2Ph), 4.38 (dd, *J*=8, 9.2 Hz, 1H), 4.15–3.55 (5br m, 7H), 1.25 and 1.06 (2s, 18H, $2CMe_3$) ppm; ^{13}C NMR (inter alia): *δ* 79.9 and 77.7 (C-3,4), 73.1 and 72.6 ($2CH_2Ph$), 64.8 and 62.9 (C-2′,5′), 64.7 and 61.2 (C-2,5), 28.4 and 27.2 ($2CMe_3$), 19.8 ($2CMe_3$) ppm; HRMS (LSIMS): calcd for $C_{41}H_{51}NO_6NaSi$ $[M+Na]^+$ 704.3383; found 704.3375 (deviation −1.2 ppm).

*4.2.2. (2R,3R,4S,5R)-2′-O-Benzoyl-3,4-bis(benzyloxy)-N-(tert-butyloxycarbonyl)-5′-O-(tert-butyldiphenylsilyl)-2,5-bis(hydroxylmethyl)pyrrolidine (**7**).* To a stirred solution of **6** (1.45 g, 2.13 mmol) in dry DCM (250 mL) were added TEA (450 μL, 3.22 mmol), DMAP (50 mg) and BzCl (272 μL, 2.34 mmol) and the mixture left at rt overnight. TLC (Et_2O/hexane, 1:1, v/v) then revealed a faster-running compound. Conventional work-up of the reaction mixture and column chromatography (Et_2O/hexane, 1:3, v/v) afforded pure **7** (1.3 g, 78%) as a colourless syrup, which had $[\alpha]_D^{27}$ +14 (*c* 1, $CHCl_3$); IR (neat): *ν* 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, 25H, 5Ph), 4.90–3.75 (5 m, 12H, $2CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.30 and 1.08 (2s, 18H, $2CMe_3$); ^{13}C NMR (inter alia): *δ* 166.2 (COPh), 80.5, 79.2 and 78.2 (C-3,4, two rotamers), 72.8 and 72.4 ($2CH_2Ph$), 63.5 and 62.7 (C-2′,5′), 60.9 and 60.6 (C-2,5), 28.4 and 27.2 ($2CMe_3$) and 19.4 (CMe_3); HMRS (LSIMS): calcd for $C_{48}H_{55}NO_7NaSi$ $[M+Na]^+$ 808.3650; found 808.3646 (deviation −0.5 ppm).

*4.2.3. (2R,3R,4S,5R)-2′-O-Benzoyl-3,4-bis(benzyloxy)-N-(tert-butyloxycarbonyl)-2,5-bis(hydroxymethyl)pyrrolidine (**8**).* To a stirred solution of **7** (1.13 g, 1.44 mmol) in THF (20 mL) was added $TBAF\cdot 3H_2O$ (500 mg, 1.59 mmol) and the mixture was kept at rt 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 **8** (700 mg, 88%) as a colourless syrup, which had $[\alpha]_D^{29}$ −30 (*c* 1, $CHCl_3$); IR (neat): *ν* 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, 15H, 3Ph), 4.78–3.85 (7 m, 13H, $2CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b,OH) and 1.50 (s, 9H, CMe_3) ppm; ^{13}C (inter alia): *δ* 166.29 and 166.16 (COPh, two rotamers), 155.1 and 154.3 (Boc, two rotamers), 81.4, 80.9 and 78.6 (C-3,4, two rotamers), 72.76, 72.57, 72.35 and 72.23 ($2CH_2Ph$, two rotamers), 63.54, 63.06, 61.3 and 59.6 (C-2′,5′, two rotamers), 61.23, 61.21, 60.99 and 59.36 (C-2,5, two rotamers), 28.65 and 28.63 (CMe_3, two rotamers) and 19.5 (CMe_3) ppm; HRMS (LSIMS): calcd for $C_{32}H_{37}NO_7Na$ $[M+Na]^+$ 570.2466; found 570.2468 (deviation +0.3 ppm).

*4.2.4. Methyl 3-[(2E,2′S,3′S,4′R,5′R)-5′-(benzoyloxymethyl)-3′,4′-bis(benzyloxy)-N′-(tert-butyloxycarbonyl)pyrrolidin-2′-yl]propenoate (**12**).* A solution of **8** (645 mg, 1.18 mmol) in dry DCM (20 mL) were added activated powdered 4 Å molecular sieve (100 mg), *N*-methylmorpholine *N*-oxide (210 mg, 1.77 mmol) and TPAP (100 mg) and the reaction mixture kept at rt for 1 h. TLC (Et_2O/hexane 1:1, v/v) then showed a faster-running compound. The reaction 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 **9** that was dissolved in toluene (20 mL) and methyl (triphenylphosphoranylidene)acetate (470 mg, 1.4 mmol) was added and the reaction mixture refluxed for 8 h. The solvent was eliminated and the residue submitted to column chromatography (Et_2O/hexane, 1:5→2:1, v/v) to afford syrup **12** (420 mg, 59%, from **8**), which had $[\alpha]_D^{30}$ −12 (*c* 1, $CHCl_3$); IR (neat): *ν* 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, 15H, 3Ph), 6.81 (dd, 1H, $J_{2,3}$=15.6, $J_{2',3}$=5.6 Hz, H-3), 5.96 (d, 1H, H-2), 4.72–3.73 (br m, 10H, $2CH_2Ph$ and H-2′,3′,4′,5′,5″a,5″b), 3.68 and 3.60 (2br s, 3H, OMe, two rotamers), 1.46 and 1.40 (2br s, 9H, CMe_3, two rotamers); ^{13}C NMR (inter alia): *δ* 166.35 and 166.29 (COPh, C-1), 147.2 (C-3), 123.8 (C-2), 72.2 (CH_2Ph), 62.4, 51.8 (OMe) and 28.5 (CMe_3); HRMS (LSIMS): calcd for $C_{35}H_{39}NO_8Na$ $[M+Na]^+$ 624.2568; found 624.2573 (deviation +0.9 ppm).

*4.2.5. (1S,2R,3R,7aS)-1,2-Bis(benzyloxy)-3-(hydroxymethyl)pyrrolizidin-5-one (**14**).* Compound **12** (512 mg, 0.85 mmol) in dry MeOH (20 mL) was hydrogenated with 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). To this stirred solution, TFA (8 mL) was added 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 eliminated and the residue co-distilled with toluene to 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 **14** (270 mg, 86% from **12**) as a colourless syrup, which had $[\alpha]_D^{27}$ −6, $[\alpha]_{405}^{27}$ −10 (*c* 1, $CHCl_3$); IR (neat): *ν* 3365 (OH), 3031 (aromatic), 1667 (C=O lactam), 739 and 698 cm^{-1} (aromatic); ^1H NMR (500 MHz): *δ* 7.40–7.28 (m, 10H, 2Ph), 4.66 and 4.63 (2d, 2H, *J*=12.0 Hz, CH_2Ph), 4.61 and 4.50 (2d, 2H, *J*=11.9 Hz, CH_2Ph), 4.21 (m, 1H, H-7a), 3.93 (dd, 1H, $J_{3,8}$=2.6, $J_{8,8'}$=12.0 Hz, H-8), 3.86 (dd, 1H, $J_{1,2}$=5.5, $J_{2,3}$=3.0 Hz, H-2), 3.83 (m, 1H, H-3), 3.68 (dd, 1H, $J_{3,8'}$=7.9 Hz, H-8′), 3.51 (dd, 1H, $J_{1,7a}$=7.9 Hz, H-1), 2.68 (ddd, 1H, $J_{6,6'}$=16.7 Hz, H-6), 2.44 (dd, 1H, $J_{6',7'}$=8.9 Hz, H-6′), 2.28 (br dt, 1H, $J_{6,7}$=$J_{7,7a}$=7.8, $J_{7,7'}$=12.3 Hz, H-7), 1.74 (tt, 1H, $J_{6,7'}$=12.3, $J_{7',7a}$=9.2 Hz, H-7′) 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_2Ph), 65.6 (C-7a), 64.7 (C-3), 63.0 (C-8), 35.7 (C-6) and 26.9 (C-7) ppm; HRMS (LSIMS): calcd for $C_{22}H_{25}NO_4Na$ $[M+Na]^+$ 390.1675; found 390.1681 (deviation +1.7 ppm).

*4.2.6. (1S,2R,3R,7aS)-1,2-Bis(benzyloxy)-3-(hydroxymethyl)pyrrolizidine (**15**).* An $H_3B{\cdot}SMe_2$ complex solution in anhydrous THF (10 M, 670 μL) was added dropwise to a stirred solution of **14** (247 mg, 0.67 mmol) in anhydrous THF (10 mL) under argon and the mixture left at rt for 1.5 h. TLC (Et_2O/MeOH, 5:1, v/v) then revealed the absence of **14** 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_2O/MeOH, 15:1, v/v→Et_2O/MeOH/NH_4OH, 5:1:0.5, v/v) to give pure **15** (140 mg, 59%) as a colourless viscous syrup. $[\alpha]_D^{29}$ +91 (*c* 1, MeOH); IR (neat): *ν* 3330 (OH), 3031, 737 and 698 cm^{-1} (aromatic); ^1H NMR (500 MHz, MeOH-d_4): *δ* 7.37–7.22 (m, 10H, 2Ph), 4.58 and 4.51 (2d, *J*=11.5 Hz, 2H, CH_2Ph), 4.57 and 4.53 (2d, *J*=11.8 Hz, 2H, CH_2Ph), 3.86 (dd, $J_{1,2}$=5.1, $J_{2,3}$=8.4 Hz, 1H, 2-H), 3.82 (dd, $J_{3,8}$=4.1, $J_{8,8'}$=12.1 Hz, 1H, 8-H), 3.75 (dd, $J_{3,8'}$=8.0 Hz, 1H, 8′-H), 3.74 (dd, 1H, 1-H), 3.57 (dt, $J_{1,7a}$=3.1, $J_{7a,7}$=$J_{7a,7'}$=8.0 Hz, 1H, 7a-H), 3.43 (dt, 1H, 3-H), 2.89 (ddd, *J*=6.7, *J*=2.4, $J_{5,5'}$=9.5 Hz, 1H, 5-H), 2.79 (dt, *J*=9.8, *J*=5.6 Hz, 1H, 5′-H), 2.09 (ddt, *J*=2.4, 7.4, $J_{7,7'}$=12.6 Hz, 1H, 7-H), 1.85 (m, 1H, 6-H), 1.70 (m, 1H, 6′-H), 1.42 (ddt, *J*=7.7, 10.6 Hz, 1H, 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_2Ph), 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).

*4.2.7. (1S,2R,3R,7aS)-1,2-Dihydroxy-3-hydroxymethylpyrrolizidine [(+)-7a-epi-hyacinthacine A_1 (**3**)].* Compound **15** (120 mg, 0.34 mmol) in MeOH (15 mL) and concd 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 treated with Amberlite IRA-400 resin (OH^- form). Evaporation of the solvent afforded a residue that was retained on to a column of Dowex 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH_4OH to afford pure **3** (55 mg, 93%) as a colourless thick syrup. $[\alpha]_D^{27}$ +47 (*c* 0.65, water); ^1H NMR (500 MHz, MeOH-d_4): *δ* 3.88 (dd, 1H, $J_{1,2}$=5.5, $J_{2,3}$=9.0 Hz, H-2), 3.84 (dd, 1H, $J_{3,8}$=4.1, $J_{8,8'}$=12.1 Hz, H-8), 3.81 (dd, 1H, $J_{3,8'}$=8.0 Hz, H-8′), 3.76 (dd, 1H, H-1), 3.39 (dt, 1H, $J_{1,7a}$=2.4, $J_{7a,7}$=$J_{7a,7'}$=7.9 Hz, H-7a), 3.21 (dt, 1H, H-3), 2.91 (ddd, 1H, *J*=2.1, 9.0 Hz, H-5), 2.79 (dt, 1H, $J_{5,5'}$=9.8, *J*=5.8 Hz, H-5′), 2.14 (ddt, 1H, *J*=2.5, 7.6, $J_{7,7'}$=12.6 Hz, H-7), 1.87 (m, 1H, H-6), 1.69 (m, 1H, H-6′) and 1.50 (ddt, 1H, *J*=7.6, *J*=10.4 Hz, H-7′) 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) and 27.4 (C-6) ppm; HRMS (LSIMS): calcd for $C_8H_{15}NO_3$ $[M^+]$ 173.1050; found 173.1052 (deviation +0.8 ppm).

*4.2.8. 4-[(3E,2′S,3′S,4′R,5′R)-5′-(Benzoyloxymethyl)-3′,4′-bis(dibenzyloxy)-N′-(tert-butyloxycarbonyl)pyrrolidin-2′-yl]but-3-en-2-one (**16**).* To a stirred solution of **8** (785 mg, 1.44 mmol) in dry DCM (15 mL) were added activated 4 Å molecular sieves (100 mg), NMO (250 mg, 2.15 mmol) and TPAP (100 mg) and the reaction mixture was kept at rt for 90 min. TLC (Et_2, 3:1, v/v) then indicated the absence of the starting material and the presence of a faster-running compound. The reaction 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 **9**. This material was used in the next step.

To a stirred solution of the above **9** in dry toluene (20 mL) 1-(triphenylphosphoranyliene)-2-propanone (685 mg, 2.15 mmol) was added and the mixture refluxed. After 8 h, TLC (Et_2O/hexane, 3:1, v/v) revealed the presence of a new compound of slightly lower mobility. The solvent was eliminated and the residue was supported on silica gel and chromatographed (Et_2O/hexane, 1:5, v/v) to give pure **16** (600 mg, 71% from **8**) as a colourless syrup, which had $[\alpha]_D^{26}$ −30 (*c* 1, $CHCl_3$); IR (neat): *ν* 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, 2H, $J_{o,m}$=7.2 Hz, *ortho*-H, Bz), 7.49 (t, 1H, $J_{m,p}$=7.2 Hz, *para*-H, Bz), 7.32 (t, 2H, *meta*-H, Bz), 7.30–7.18 (m, 10H, 2Ph), 6.46 (dd, 1H, $J_{2',4}$=6.0, $J_{3,4}$=16 Hz, H-4), 6.08 (d, 1H, H-3), 4.78–3.79 (4br m, 10H, 2CH_2Ph and H-2′,3′,4′,5′,5″a,5″b), 2.00–1.90 (2br s, 3H, H-1,1,1, two rotamers), 1.41 and 1.32 (2br s, 9H, CMe_3, two 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′, two rotamers), 71.6 (2CH_2Ph), 63.1 (C-5″), 61.8 and 60.3 (C-2′,5′), 28.0 (C*Me*$_3$) and 27.2 (C-1) ppm; HRMS (LSIMS): calcd for $C_{35}H_{39}NO_7Na$ $[M+Na]^+$ 608.2621; found 608.2624 (deviation +0.6 ppm).

*4.2.9. (1S,2R,3R,5S,7aS)-1,2-Bis(benzyloxy)-3-(hydroxymethyl)-5-methylpyrrolizidine (**19**).* Compound **16** (600 mg, 1.03 mmol) in MeOH (20 mL) was hydrogenated with H_2 from a balloon over 10% Pd/C (100 mg) for 2 h. The reaction mixture was filtered and an aliquot was concentrated to afford intermediate saturated ketone (IR evidence). The reaction mixture was then acidified with concd HCl (0.2 mL) and left at rt 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_2O/hexane 1:3→Et_2O) compound **18** (150 mg) slightly contaminated. Finally, Zemplen debenzoylation of **18** with 2 N MeONa/MeOH (0.5 mL) for 12 h followed by column chromatography (Et_2O/hexane, 1:1→2:1, v/v) then afforded pure **19** (90 mg, 24% from **16**) as a syrup. $[\alpha]_D^{24}$ +35 (*c* 1, $CHCl_3$); IR (neat): *ν* 3441 (OH), 3063, 3031, 736 and 697 cm^{-1} (aromatic); ^1H NMR (500 MHz): *δ* 7.36–7.26 (m, 10H, 2Ph), 4.79 and 4.57 (2d, 2H, *J*=11.8 Hz, CH_2Ph), 4.60 and 4.58 (2d, 2H, *J*=12.5 Hz, CH_2Ph), 4.20 (dd, 1H, $J_{1,2}$=6.0, $J_{2,3}$=3.7 Hz, H-2), 3.71 (dd, 1H, $J_{3,8}$=3.2, $J_{8,8'}$=11.0 Hz, H-8), 5.53 (m, 2H, H-1,8′), 3.16 (m, H-7a), 2.78 (br s, 1H, H-3), 2.56 (br sex, 1H, $J_{5,6}$=$J_{5,6'}$=6.0 Hz, H-5), 2.21 (m, 1H, H-6), 1.79 (m, 1H, H-7), 1.78 (m, 1H, H-6′), 1.44 (m, 1H, H-7′) and 1.13 (d, 3H, $J_{Me,5}$=6.0 Hz, 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_2Ph), 72.7

(C-7a), 67.7 (C-3), 61.9 (C-8), 54.9 (C-5), 37.3 (C-6), 25.3 (C-7) and 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).

*4.2.10. (1S,2R,3R,5S,7aS)-1,2-Dihydroxy-3-(hydroxymethyl)-5-methylpyrrolizidine [(+)-5,7a-diepi-hyacinthacine A_6 (**4**)].* A solution of **19** (70 mg, 0.19 mmol) in MeOH (15 mL) was acidified (concd 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 neutralized with Amberlite IRA-400 (OH^- form) and concentrated to a residue that was retained on a column of Dowex 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH_4OH to afford pure **4** (34 mg, 96%) as a colourless thick syrup. $[\alpha]_D^{26}$ +15.8 (*c* 0.5, water); ^{1}H NMR (300 MHz, D_2O): δ 4.11 (t, 1H, $J_{1,2}$=$J_{2,3}$=6.2 Hz, H-2), 3.82 (dd, 1H, $J_{3,8}$=5.0, $J_{8,8'}$=11.7 Hz, H-8), 3.71 (br t, 1H, H-1), 3.67 (dd, 1H, $J_{3,8'}$=6.2 Hz, H-8′), 2.79 (dt, 1H, $J_{1,7a}$=6.5, $J_{7a,7\alpha}$=$J_{7a,7\beta}$=9.4 Hz, H-7a), 2.59 (br sex, 1H, $J_{5,6\alpha}$=$J_{5,6\beta}$=$J_{5,Me}$=6.7 Hz, H-5), 2.47 (m, 1H, H-3), 2.25 (br dq, 1H, $J_{6\beta,7\alpha}$=$J_{6\beta,7\beta}$=8.2, $J_{6\alpha,6\beta}$=12.0 Hz, H-6β), 1.81 (m, 1H, H-7β), 1.63 (m, 1H, H-6α), 1.41 (m, 1H, H-7α) and 1.12 (d, 3H, 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) and 19.6 (Me) ppm; HRMS (LSIMS): calcd for $C_9H_{17}NO_3Na$ $[M+Na]^+$ 210.1103; found 210.1106 (deviation +1.1 ppm).

*4.2.11. 4-[(3E,2′R,3′S,4′R,5′R)-5′-(Benzoyloxymethyl)-3′,4′-bis(dibenzyloxy)-N′-(tert-butyloxycarbonyl)pyrrolidin-2′-yl]but-3-en-2-one (**11**).* To a stirred solution of **8** (450 mg, 0.82 mmol) in dry DCM (8.5 mL) were added activated 4 Å molecular sieves (100 mg), NMO (145 mg, 1.23 mmol) and TPAP (72 mg) and the reaction mixture was kept at rt for 90 min. TLC (Et_2, 2:1, v/v) then indicated the absence of the starting material and the presence of a faster-running compound. The reaction was diluted with Et_2O (5 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 **9**. This material was used in the next step.

To a stirred solution of the above **9** in dry toluene (15 mL) 1-(triphenylphosphoranyliene)-2-propanone (520 mg, 1.64 mmol) was added and the mixture heated at 80 °C. After 24 h, TLC (Et_2O/hexane, 3:1, v/v) showed the absence of starting material. The solvent was eliminated and the residue was supported on silica gel and chromatographed (Et_2O/hexane, 1:1, v/v) to give pure **16** (117 mg, 24% from **8**) and the non-inversion product **11** (188 mg, 40% from **8**), which had $[\alpha]_D^{28}$ 23 (*c* 1, $CHCl_3$); IR (neat): ν 3059 and 3032 (aromatic), 1722, 1698 and 1676 (BzO, α,β-unsaturated ketone and >NBoc), 737 and 711 cm^{-1} (aromatic); ^{1}H NMR (400 MHz): δ 7.91–7.26 (m, 15H, 3Ph), 6.95 (dd, 1H, $J_{2',4}$=8.6, $J_{3,4}$=16.0 Hz, H-4), 6.17 and 6.08 (2d, 1H, H-3 two rotamers), 4.92–4.11 (m, 10H, 2CH_2Ph and H-2′,3′,4′,5′,5″a,5″b), 2.22–2.20 (2br s, 3H, H-1,1,1, two rotamers), 1.47 and 1.39 (2br s, 9H, CMe_3, two rotamers) ppm; ^{13}C NMR (inter alia): δ 198.8 (C-2), 166.0 (Bz), 153.9 (Boc), 145.1 and 144.2 (C-3,4), 80.9, 79.6, 78.8 and 78.4 (C-3′,4′, two rotamers), 72.2 and 72.0 (2CH_2Ph), 63.2, 62.7, 61.1, 60.8, 60.7 and 59.9 (C-2′,5′,5″), 28.3 (CMe_3) and 26.1 (C-1) ppm; HRMS (NALDI-TOF) calcd for $C_{35}H_{39}NO_7Na$ $[M+Na]^+$ 608.2642; found 608.2617 (deviation −4.1 ppm).

*4.2.12. (1S,2R,3R,5R,7aR)-3-(Benzoyloxymethyl)-1,2-bis(benzyloxy)-5-methylpyrrolizidine (**21**).* Compound **11** (94 mg, 0.16 mmol) in MeOH (3 mL) was hydrogenated with a balloon over 10% Pd/C (30 mg) for 3 h. The reaction mixture was filtered and concentrated to a residue used in the next step. To a cooled (ice-water) solution the residue in DCM (1.2 mL) was added TFA (0.3 mL) 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 eliminated and the residue co-distilled with toluene to a new residue that was dissolved in dry methanol (3 mL), neutralized with 2 N MeONa/MeOH and hydrogenated with 10% Pd/C (30 mg) at 55 psi for 15 h. The catalyst was filtered off, washed with MeOH and the residue supported on silica gel and chromatographed (Et_2O/MeOH, 25:1, v/v) to give pure **21** (16 mg, 23% from **11**); $[\alpha]_D^{27}$ 52 (*c* 1, $CHCl_3$); IR (neat): ν 3063 and 3026 (aromatic), 1719 (BzO); ^{1}H NMR (400 MHz): δ 7.91–7.85 (2 m, 15H, 3Ph), 4.67 and 4.55 (2d, 2H, *J*=11.7 Hz, CH_2Ph), 4.53 and 4.45 (2d, 2H, *J*=11.6 Hz, CH_2Ph), 4.47 (dd, 1H, $J_{3,8}$=4.3, $J_{8,8'}$=10.8 Hz, H-8), 4.31 (dd, 1H, $J_{3,8'}$=7.1 Hz, H-8′), 3.99 (dd, 1H, $J_{1,2}$=3.7, $J_{2,3}$=7.9 Hz, H-2), 3.90 (t, 1H, $J_{7,7a}$=4.1, H-1), 3.84 (m, 1H, H-7a), 3.61 (dt, 1H, H-3), 3.51 (m, 1H, H-5), 2.06–1.95 (m, 2H, H-6,7), 1.66–1.58 (m, 2H, H-6′,7′), 1.14 (d, 3H, $J_{Me,5}$=6.7 Hz, Me); ^{13}C NMR: δ 166.4 (CO), 138.3, 137.6, 134.9, 130.8, 128.0, 127.8, 127.7, 127.6, 127.4, 127.2 and 127.1 (CH_2*Ph*), 83.6 (C-2), 75.5 (C-1), 73.3 and 72.7 (2CH_2Ph), 66.48 and 66.51 (C-7a y C-8), 67.7 (C-3), 57.9 (C-3), 56.4 (C-5), 34.2 (C-6), 22.5 (C-7) and 16.1 (Me); HRMS (NALDI-TOF) calcd for $C_{30}H_{34}NO_4$ $[M+H]^+$ 472.2488; found 472.2476 (deviation −2.3 ppm).

*4.2.13. (1S,2R,3R,5R,7aR)-1,2-Bis(benzyloxy)-3-(hydroxymethyl)-5-methylpyrrolizidine (**22**).* To a solution of **21** (23 mg, 0.05 mmol) in dry MeOH (1.5 mL) was added MeONa (2 N, 75 μL), and the mixture was stirred at rt for 2 h. The reaction was neutralized with AcOH. Evaporation of the solvent afforded a residue that was retained on to a column of Dowex 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH_4OH to afford pure **22** (10 mg, 56%). $[\alpha]_D^{25}$ −37 (*c* 1, $CHCl_3$); IR (neat): ν 3412 (OH); ^{1}H NMR (500 MHz): δ=7.37–7.27 (2 m, 10H, 2Ph), 4.72 and 4.60 (2d, 2H, *J*=11.5 Hz, CH_2Ph), 4.65 and 4.59 (2d, 2H, *J*=11.5 Hz, CH_2Ph), 4.47 (dd, 1H, $J_{3,8}$=4.3, $J_{8,8'}$=10.8 Hz, H-8), 4.31 (dd, 1H, $J_{3,8'}$=7.1 Hz, H-8′), 3.99 (dd, 1H, $J_{1,2}$=3.9, $J_{2,3}$=7.9 Hz, H-2), 3.90 (t, 1H, $J_{1,7a}$=4.1, H-1), 3.84 (m, 1H, H-7a), 3.61 (dt, 1H, H-3), 3.51 (m, 1H, H-5), 2.06–1.95 (m, 2H, H-6,7), 1.66–1.58 (m, 2H, H-6′,7′), 1.14 (d, 3H, $J_{Me,5}$=6.7 Hz, Me); ^{13}C NMR: δ 138.1, 137.8, 128.1, 128.03, 127.98, 127.63, 127.60, 127.55, 127.50 and 127.41 (CH_2*Ph*), 81.0 (C-2), 75.7 (C-1), 73.2 and 72.3 (2CH_2Ph), 67.9 (C-7a), 65.5 (C-8), 61.6 (C-3), 59.1 (C-5), 33.0 (C-6), 22.7 (C-7) and 14.0 (Me); HRMS (NALDI-TOF) calcd for $C_{23}H_{30}NO_{30}$ $[M+H]^+$ 368.2226; found 368.2229 (deviation +0.8 ppm).

*4.2.14. (1S,2R,3R,5R,7aR)-1,2-Dihydroxy-3-(hydroxymethyl)-5-methylpyrrolizidine [(+)-hyacinthacine A_6 (**2**)].* A solution of **22** (9 mg, 0.024 mmol) in MeOH (2.5 mL) was acidified (concd HCl, three drops) and hydrogenated (10% Pd/C, 10 mg) at 70 psi for 24 h. The catalyst was filtered off, washed with MeOH and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form) and concentrated to a residue that was retained on a column of Dowex 50WX8 (200–400 mesh). The column was thoroughly washed with MeOH (25 mL), water (20 mL) and 10% Et_3N in MeOH (40 mL) to afford pure **2** (4 mg, 87%). $[\alpha]_D^{25}$ +15.1 (*c* 0.17, water), [lit.[7] $[\alpha]_D^{26}$ +16.3 (*c* 0.22, water)]: ^{1}H NMR (400 MHz, D_2O): δ 4.19 (m, 2H, H-1,2), 3.87 (m, 2H, H-7a,8), 3.80 (dd, 1H, $J_{3,8'}$=4.8, $J_{8,8'}$=12.0 Hz, H-8′), 3.57 (m, 1H, H-5), 3.36 (br dt, 1H, $J_{2,3}$=8.2, $J_{3,8}$=4.6 Hz, H-3), 2.09 (m, 2H, H-6,7), 1.83 (m, 2H, H-6′,7′) and 1.30 (d, 3H, *J*=6.8 Hz, Me); ^{13}C NMR: δ 74.4 (C-2), 72.9 (C-1), 72.0 (C-7a), 64.3 (C-8), 63.2 (C-3), 59.0 (C-5), 35.5 (C-6), 25.2 (C-7) and 16.3 (Me); HRMS (NALDI-TOF) calcd for $C_9H_{17}NO_3Na$ $[M+Na]^+$ 210.1106; found 210.1095 (deviation −5.2 ppm).

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Supplementary data

^{1}H, ^{13}C NMR spectra for compounds **2**,**3**,**4** and 2D ^{1}H–^{1}H, and ^{1}H–^{13}C COSY spectra for compounds **3**,**4**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.049.

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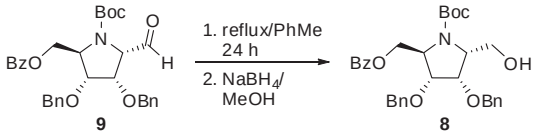

9 **8**

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