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Total synthesis of the 5-epimers of naturally occurring (−)-hyacinthacine A_5 and unnatural (+)-hyacinthacine A_4☆

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Abstract—(1*R*,2*S*,3*R*,5*S*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine **10** [(+)-5-*epi*hyacinthacine A_5] and (1*R*,2*S*,3*R*,5*S*,7a*S*)-1,2-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine **17** [*ent*-5-*epi*hyacinthacine A_4] have been synthesized by either Horner–Wadsworth–Emmons (HWE) or Wittig methodology using aldehydes **6** and **13**, prepared from (2*R*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine **5** (partially protected DALDP) and (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine **12** (partially protected DGADP), respectively, and the appropriated ylide, followed by cyclization through an internal reductive amination process of the corresponding intermediate pyrrolidinic ketones **7** and **14** and subsequent deprotection.

1. Introduction

Several important biological process, such as intestinal digestion, lysosomal catabolism and post-translational modification, which are closely related to the endoplasmic reticulum (ER) quality control and ER-associated degradation of glycoproteins are mediated by glycosidases. On the other hand, imino or azasugars can inhibit glycosidases because of a structural resemblance of their sugar moiety to natural substrates and hence have enormous potential as biochemical tools in glycolscience as well as therapeutic agents.[2] From a structural point of view, naturally occurring iminosugars are classified into five classes: polyhydroxylated pyrrolidines (DMDP), piperidines (DMJ), indolizidines (castanospermine), pyrrolizidines (alexine and australine) and *nor*-tropans (calystegine B_2).

While the presence of polyhydroxylated piperidine and pyrrolidine alkaloids is widespread in many unrelated plant families, polyhydroxylated pyrrolizidine alkaloids (PHPAs) are restricted to specific ones.[3] Thus, a particular kind of these alkaloids, known as hyacinthacines, has been isolated from bluebells (*Hyacinthoides non-scripta*), grape hyacinths (*Muscari armeniacum*) and from the bulbs of *Scilla sibirica*, *Scilla peruviana* and more recently from *Scilla socialis* by Asano et al.[4] In addition, their scarcity in the natural sources together with the drawbacks found during their isolation and purification makes necessary to implement synthetic routes to these compounds. In this context and in the recent past years, our group have put into practice a synthetic methodology for the preparation of the above PHPAs.[5]

Of the different naturally occurring PHPAs with branching at C(3,5) known so far, (−)-hyacinthacine A_5 **1**, a moderate inhibitor ($IC_{50} = 110\ \mu M$) of amyloglucosidase from *Aspergillus niger*, and (−)-hyacinthacine A_4 **2**, both isolated from an extract of the bulbs of *S. sibirica* (Liliaceae),[4c] show functionalization and stereochemistry at the A-ring (see Fig. 1) matching exactly that present in the orthogonally protected derivative of 2,5-dideoxy-2,5-imino-D-altritol **3** (DALDP) and 2,5-dideoxy-2,5-imino-D-galactitol **4** (DGADP), respectively, in such a way that both could be considered as excellent homochiral starting materials for their corresponding enantiosyntheses. To the best of our knowledge, only one synthesis of the 5-epimer of (−)-hyacinthacine A_4 from D-glucose has been reported[6] but none for either **1** or **2**. On the other hand, stereocontrolled syntheses of **3** and **4**, from the commercially available hexulose D-fructose, have been recently disclosed by our group.[7,8]

Herein we report the stereospecific synthesis of 5-*epi*hyacinthacine A_5 **10** obtained from **3** in five steps (21% yield) and

☆ Part 10 of this series. For Part 9, see Ref. 1.

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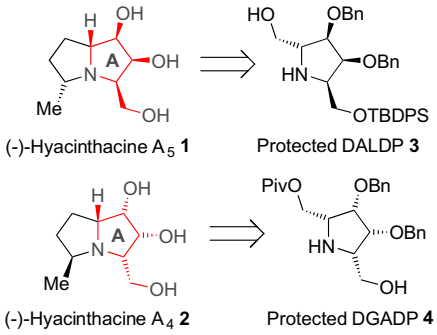


Figure 1. Retrosynthesis showing the functional and stereochemical relationship between the A-ring of hyacinthacines **1** and **2** with that of 2,5-dideoxy-2,5-iminocyclitols **3** (DALDP) and **4** (DGADP), respectively.

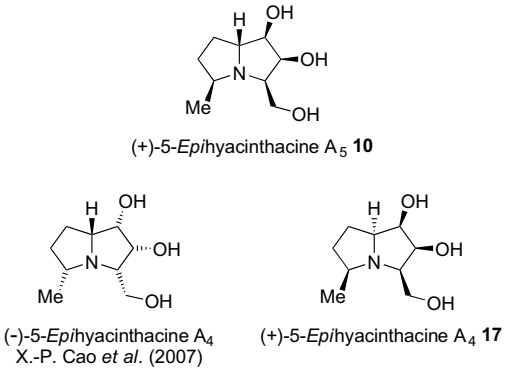
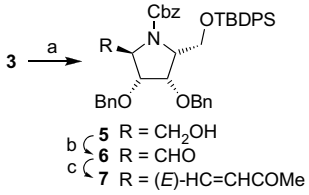


Figure 2. Some of the hyacinthacines described herein.

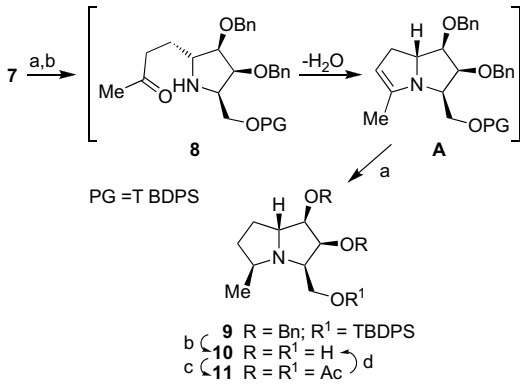
ent-5-*epi*hyacinthacine A_4 **17** from pyrrolidine **4**, in six steps (10% yield) (Fig. 2).

2. Results and discussion

In the synthesis described herein, the starting pyrrolidine **3** was previously N-protected as its Cbz derivative **5**, which was then oxidized (NMO/TPAP) to pyrrolidinic aldehyde **6** and finally allowed to react with diethyl (2-oxopropyl)phosphonate in a basic medium to afford, in a highly stereoselective manner, 4-[(3*E*,2′*R*,3′*R*,4′*S*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]but-3-en-2-one **7**, in accordance with the $J_{3,4}$ values of 16.2 and 16.1 Hz, shown by H-3 in the mixture of rotamers[9] (Scheme 1).



Scheme 1. Chemoselective N-protection and carbon-chain lengthening at C(5′) in **3**. Reagents and conditions: (a) CbzCl/Me_2CO/K_2CO_3; (b) NMO/TPAP/CH_2Cl_2/4 Å MS; (c) $(EtO)_2P(O)CH_2COCH_3$/NaH/THF, rt.



Scheme 2. Synthesis of (+)-5-*epi*hyacinthacine A_5 **10**. Reagents and conditions: (a) Raney-nickel/H_2/MeOH; (b) (i) 10% Pd–C/H_2/HCl, then Amberlite IRA-400 (OH^- form), (ii) TBAF·3H_2O/THF; (c) Ac_2O/DMAP (cat.)/Py, rt; (d) MeONa (cat.)/MeOH, rt.

9. The NOE interactions are shown in Figure 3. The definite NOE effects between C(3)H–C(5)H, C(3)H–C(1)H and Me(5)H–C(8)H were crucial in order to establish the (*S*)-configuration at C-5. In addition, the rest of the NOE interactions also confirmed the total stereochemistry of **9** and made it possible to assign the resonance signals for H-6α,6β,7α,7β.

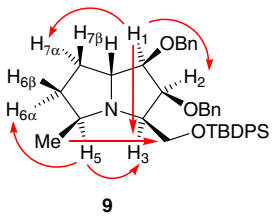


Figure 3. Main NOE interactions in **9**.

Catalytic hydrogenation (Raney-nickel) of **7** (see Scheme 2) unchained a tandem process consisting of concomitant carbon–carbon double bond hydrogenation, N-deprotection to the saturated pyrrolidinic ketone **8**, not isolated, which subsequent intramolecular condensation gave the intermediate Δ^5-pyrrolizine **A** that was finally hydrogenated to the fully protected (1*R*,2*S*,3*R*,5*S*,7a*R*)-1,2-dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine **9**.

The stereochemistry of the new C(5) stereogenic centre was established on the basis of extensive NOE experiments on

The surprising and highly stereoselective formation of **9**, contrary to previous results[5a,b,d,g] where the hydrogenation usually proceeds in such a way that the C(7a)H and C(5)Me result in a *trans*-relationship, can be attributed, according to Figure 4, to the special shape adopted by the intermediate Δ^5-pyrrolizine **A**, where it is clearly appreciated that the α-face is more favoured for hydrogen attack than the β-face.

Removal of the protecting groups in **9** gave the target molecule (+)-5-*epi*hyacinthacine A_5 **10** that was also character-

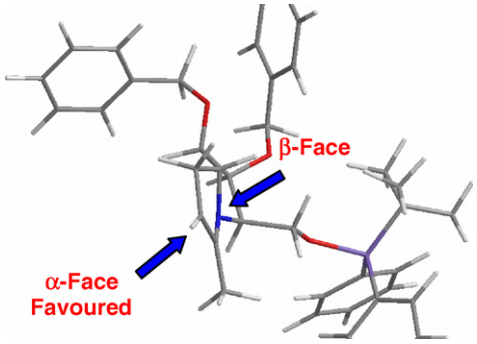
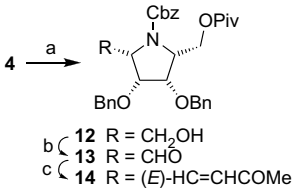


Figure 4. Minimized structure (MOPAC) for intermediate Δ^5-pyrrolizine **A**.

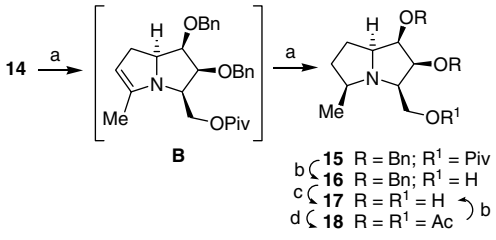
ized as its per-*O*-acetyl derivative **11**, in accordance with their analytical and spectroscopic data.

The enantiomeric pivotal character of **4** would allow the synthesis of looking-glass hyacinthacine **17**. Thus, in a similar synthetic route, pyrrolidine **4** was N-protected to derivative **12**, which subsequent oxidation (NMO/TPAP) afforded the pyrrolidinic aldehyde **13** that as before was not investigated, but used in the next step. Aldehyde **13** readily reacted with 1-triphenylphosphoranylidene-2-propanone giving 4-[(3*E*,2′*S*,3′*R*,4′*S*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-pivaloyloxymethylpyrrolidin-2′-yl]-but-3-en-2-one (**14**) (see Scheme 3).



Scheme 3. Chemoselective N-protection and carbon-chain lengthening at C(5′) in **4**. Reagents and conditions: (a) $CbzCl/Me_2CO/K_2CO_3$; (b) NMO/TPAP/CH_2Cl_2/4 Å MS; (c) $Ph_3P{=}CHCOCH_3$/MePh, 80 °C.

In Scheme 4 and as for **7**, the catalytic hydrogenation of **14** afforded a single isomeric pyrrolizidine identified as (1*R*,2*S*,3*R*,5*S*,7a*S*)-1,2-dibenzyloxy-5-methyl-3-pivaloyl oxymethylpyrrolizidine **15**.



Scheme 4. Synthesis of (+)-5-*epi*hyacinthacine A_4 **17**. Reagents and conditions: (a) 10% Pd–C/H_2/MeOH; (b) MeONa (cat.)/MeOH; (c) 10% Pd–C/H_2/HCl, then Amberlite IRA-400 (OH^- form); (d) Ac_2O/DMAP (cat.)/Py, rt.

The absolute configuration of the new stereogenic centre C(5) was established on the basis of the NOE effects found (see Fig. 5). Thus, the definite NOE effects between C(3)H–C(5)H, C(3)H–C(7a)H and Me(5)H–C(8)H were essential in order to establish the (*S*)-configuration at C-5. As before, the rest of the NOE interactions also confirmed the total stereochemistry of **15** and made it possible to assign the resonance signals for H-6α,6β,7α,7β.

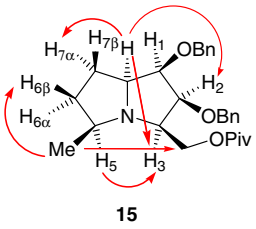


Figure 5. Main NOE interactions in **15**.

The above finding was in accordance with the already mentioned results and the hydrogenation took place by the less hindered α-face, C(7a)H and C(5)Me adopting the usual *trans*-relationship, as expected on the basis of Figure 6, where the minimized structure of intermediate Δ^5-pyrrolizine **B** is displayed.

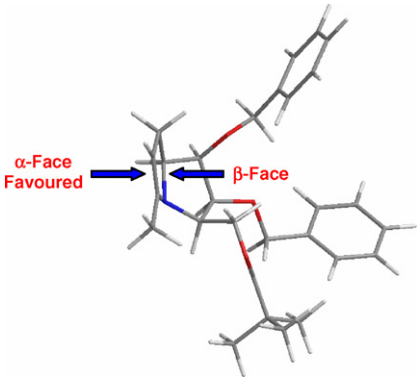


Figure 6. Minimized structure (MOPAC) for intermediate Δ^5-pyrrolizine **B**.

As for **9**, removal of the protecting groups in **15** gave the target molecule (+)-5-*epi*hyacinthacine A_4 **17**, after purification through its per-*O*-acetyl derivative **18**, in accordance with its analytical and spectroscopic data.

3. Conclusions

The first total stereospecific syntheses of two unknown hyacinthacines **10** and **17**, both related with (−)-hyacinthacine A_5 (**1**) and A_4 (**2**), were achieved, indicating that the general methodology developed by our group is of practical use in preparation of isomers of naturally occurring PHPAs that would be of value in SAR studies.

4. Experimental

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). 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. 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). The non-crystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, MS and HRMS.

4.1. (2*R*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine 5

To a well stirred solution of **3**[7] (970 mg, 1.67 mmol) in dry acetone (15 mL), anhydrous potassium carbonate (1.5 g) and benzyl chloroformate (CbzCl, 330 μL, 2.34 mmol) were added and the mixture kept at rt for 2 h. TLC (Et_2O/MeOH 20:1) then revealed the presence of a faster-running compound. The mixture was filtered and the solid thoroughly washed with acetone after which the filtrate and washings concentrated to a residue that was submitted to chromatography (Et_2O/hexane 1:4 → Et_2O/MeOH 2:1) to give **5** as colourless syrup. Yield: 800 mg (67%); $[\alpha]_D^{25} = +6$, $[\alpha]_{405}^{26} = +21$ (*c* 1, $CHCl_3$). IR (neat): 3429 (OH), 3067 (aromatic), 1699 (C=O, Cbz), 737 and 700 cm^{-1} (aromatic). NMR data (400 MHz)[9]: ^1H, δ 7.70–7.12 (m, 25H, 5 Ph), 5.10 and 4.85 (2 d, 2H, *J* 12.4 Hz, CH_2Ph), 4.78 and 4.68 (2 d, 2H, *J* 11.8 Hz, CH_2Ph), 4.68 and 4.58 (2 d, 2H, *J* 12 Hz, CH_2Ph), 4.35–3.60 (4 br m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.01 (s, 9H, CMe_3); ^{13}C (100 MHz), δ 155.63 (C=O, Cbz), 79.50 and 77.35 (C-3,4), 73.04 and 72.38 (2*C*H_2Ph), 67.18 (*C*H_2Ph, Cbz), 64.80 and 61.13 (C-2,5), 63.58 and 62.51 (C-2′,5′), 26.94 (C*Me*$_3$), and 19.26 (*C*Me_3). HRMS (LSIMS): *m*/*z* 738.3226 [M^++Na]. For $C_{44}H_{49}NO_6NaSi$ 738.3227 (deviation +0.1 ppm).

4.2. 4-[(3*E*,2′*R*,3′*R*,4′*S*,5′*R*)-3′,4′-Dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]but-3-en-2-one 7

To a stirred solution of **5** (800 mg, 1.12 mmol) in dry CH_2Cl_2 (25 mL) were added activated 4 Å molecular sieves (0.5 g), *N*-oxide-*N*-methylmorpholine (NMO, 196 mg, 1.68 mmol) and tetra-*n*-propylammonium perruthenate (TPAP, 40 mg) after which the reaction mixture was kept at rt for 60 min. TLC (Et_2O/hexane 4:1) 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 **6**. This material was used in the next step.

To a well stirred suspension of sodium hydride (60% 134 mg, 3.36 mmol) in anhydrous THF (10 mL), diethyl (2-oxopropyl)phosphonate (600 μL, 3.36 mmol) was added and the mixture left at room temperature for 1 h, after which time a solution of aldehyde **6** in THF (10 mL) was added. After 15 min TLC (Et_2O/hexane 4:1) revealed the presence of a new compound of slightly lower mobility. The solvent was eliminated and the residue was partitioned into Et_2O/water. The organic phase was separated and concentrated to a residue that was submitted to column chromatography with Et_2O/hexane (1:1) as eluent to give pure **7** (510 mg, 60% from **5**) as a colourless syrup, which had $[\alpha]_D^{26} = +18$ (*c* 1, $CHCl_3$). IR (neat): 3032 (aromatic), 1704 and 1678 (α,β-unsaturated ketone C=O and Cbz), 737 and 699 cm^{-1} (aromatic). NMR data (300 MHz): ^1H, δ 7.60–7.10 (m, 25 H, 5Ph), 6.42 and 6.33 (2 br dd, 1H, $J_{2',4}$ 6.3 Hz, H-4, two rotamers), 5.92 and 5.85 (2 br d, 1H, $J_{3,4}$ 16.2 and 16.1 Hz, H-3, two rotamers), 5.12–3.70 (4 br m, 12H, 3CH_2Ph and H-2′,3′,4′,5′,5″a,5″b), 2.10 and 1.90 (2 br s, 3H, H-1,1,1, two rotamers), 1.00 and 0.93 (2 br s, 9H, CMe_3, two rotamers). ^{13}C (75 MHz), δ 197.70 (C-2), 154.57 (Cbz), 81.02 and 77.84 (C-3′,4′), 73.00, 72.63 and 67.16 (2CH_2Ph, and Cbz), 63.10 (C-5″), 62.83, 60.66 and 60.46 (C-2′,5′, two rotamers), 27.72 (C-1), 26.98 (C*Me*$_3$) and 19.30 (*C*Me_3). HRMS (LSIMS): *m*/*z* 776.3379 [M^++Na]. For $C_{47}H_{51}NO_6NaSi$ 776.3383 (deviation +0.3 ppm).

4.3. (1*R*,2*S*,3*R*,5*S*,7a*R*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine 9

Compound **7** (510 mg, 0.71 mmol) in MeOH (15 mL) was hydrogenated at 60 psi over wet Raney-nickel (600 mg) overnight. TLC (Et_2O/hexane 4:1) then showed the presence of a new compound. The catalyst was filtered off, washed with MeOH and the filtrate and washings concentrated to a residue that was submitted to column chromatography (Et_2O/hexane 2:1) to afford pure syrupy **9** (260 mg, 60%), which had $[\alpha]_D^{25} = +31$ (*c* 1, $CHCl_3$). IR (neat): 3069, 3030, 738 and 700 cm^{-1} (aromatic). NMR data (300 MHz): ^1H, δ 7.65–7.15 (2 m, 20H, 4Ph), 4.78 and 4.69 (2 d, 2H, *J* 11.8 Hz, CH_2Ph), 4.50 and 4.36 (2 d, 2H, *J* 12.2 Hz, CH_2Ph), 4.23 (t, 1H, $J_{1,2} = J_{2,3} = 3.6$ Hz, H-2), 4.00 (t, 1H, $J_{3,8} = J_{8,8'} = 9.5$ Hz, H-8), 3.68 (dt, 1H, $J_{7a,7\beta}$ 5.7, $J_{1,7a} = J_{7a,7\alpha,} = 8.5$ Hz, H-7a), 3.58 (dd, 1H, $J_{3,8'}$ 5.1 Hz, H-8′), 3.47 (dd, 1H, H-1), 2.79 (m, 1H, H-3), 2.46 (sex, 1H, $J_{5,6\beta} = J_{5,6\alpha} = J_{5,Me} = 6.3$ Hz, H-5), 1.96 (m, 1H, H-7β), 1.71 (m, 1H, H-6α), 1.49–1.33 (m, 2H, H-6β,7α), 1.00 (s, 9H, CMe_3) and 0.73 (d, 3H, Me); ^{13}C (75 MHz), δ 85.87 (C-1), 80.12 (C-2), 73.83 and 71.87 (2CH_2Ph), 69.71 (C-3), 66.78 (C-7a), 63.33 (C-8), 62.86 (C-5), 34.84 (C-6), 29.73 (C-7), 27.05 (C*Me*$_3$), 21.66 (Me) and 19.30 (*C*Me_3). HRMS (LSIMS): *m*/*z* 606.3407 [M^++H]. For $C_{39}H_{48}NO_3Si$ 606.3403 (deviation −0.6 ppm).

4.4. (1*R*,2*S*,3*R*,5*S*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-5-*epi*hyacinthacine A_5, 10]

A solution of **9** (250 mg, 0.41 mmol) in MeOH (20 mL) was acidified (concd HCl) and hydrogenated (10% Pd–C, 80 mg) at 60 psi for 14 h. The catalyst was filtered off, washed with MeOH and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form) and concentrated. ^{1}H NMR of the residue showed the absence of benzyl group and that the TBDPS group still remain. The residue was dissolved in THF (10 mL) and treated with a solution of TBAF·3H_2O (200 mg, 0.63 mmol) in the same solvent (5 mL) at rt for 4 h. TLC (Et_2O/MeOH/NH_4OH 4:1:1) then revealed a new compound. The solvent was removed and the residue submitted to chromatography (Et_2O/MeOH 5:1) to afford pure **10** (66 mg, 86%), which had $[\alpha]_D^{28} = +12$, $[\alpha]_{405}^{28} = -30$ (*c* 1, MeOH). NMR data (300 MHz, MeOH-d_4): ^{1}H, δ 4.13 (t, 1H, $J_{1,2} = J_{2,3} = 4.2$ Hz, H-2), 3.75 (dd, 1H, $J_{3,8}$ 7.9, $J_{8,8'}$ 10.7 Hz, H-8), 3.67 (dd, 1H, $J_{1,7a}$ 7.7 Hz, H-1), 3.53 (dd, 1H, $J_{3,8'}$ 5.1 Hz, H-8′), 3.39 (dt, 1H, $J_{7a,7}$ 7.5, $J_{7a,7'}$ 5.9 Hz, H-7a), 2.81–2.74 (m, 2H, H-3,5), 1.99 (ddt, 1H, $J_{6',7}$ 7.2, $J_{7,7'}$ 12.8 Hz, H-7), 1.87 (dq, 1H, $J_{5,6} = J_{6,7} = J_{6,7'} = 5.3$, $J_{6,6'}$ 12 Hz, H-6), 1.85 (ddt, 1H, $J_{6',7'}$ 8.0 Hz, H-7′), 1.4 (br dq, 1H, $J_{5,6'}$ 8.0 Hz, H-6′) and 0.85 (d, 3H, $J_{5,Me}$ 6.3 Hz, Me); ^{13}C (75 MHz), δ 79.30 (C-1), 75.19 (C-2), 70.77 (C-3), 69.83 (C-7a), 64.48 (C-5), 62.31 (C-8), 34.95 (C-6), 29.96 (C-7) and 21.21 (Me).

Conventional acetylation of **10** afforded the corresponding tri-*O*-acetyl derivative **11** as a syrup, which had $[\alpha]_D^{27} + 10$, $[\alpha]_{405}^{27} = +32$ (*c* 1, $CHCl_3$). IR (neat): 1747 cm^{-1} (C=O, acetate). NMR data (300 MHz): ^{1}H, δ 5.45 (t, 1H, H-2), 4.89 (dd, 1H, $J_{1,2}$ 4.5, $J_{1,7a}$ 6.9 Hz, H-1), 4.12 (dd, 1H, $J_{3,8}$ 7.5. $J_{8,8'}$ 11.0 Hz, H-8), 4.06 (dd, 1H, $J_{3,8'}$ 6.9 Hz, H-8′), 3.64 (br q, $J_{2,3}$ 6.7 Hz, H-3), 3.21 (dt, 1H, *J* 5.2, *J* 7.1 Hz, H-7a), 2.80 (sex, 1H, $J_{5,6} = J_{5,6'} = J_{5,Me} = 6.2$ Hz, H-5), 2.03, 1.97 and 1.96 (3 s, 9H, 3 Ac), 2.08–1.85 (m, 2H, H-6,7), 1.62–1.42 (m, 2H, H-6′,7′) and 1.05 (d, 3H, Me); ^{13}C (75 MHz), δ 170.75, 170.30, and 170.10 (3 Me*C*O), 76.59 (C-1), 73.23 (C-2), 66.33 (C-7a), 64.24 (C-3), 63.44 (C-8), 63.02 (C-5), 34.04 (C-6), 29.11 (C-7), 21.67 (Me), 20.88, 20.80 and 20.71 (3 *Me*CO). HRMS (LSIMS): *m*/*z* 336.1422 [M^++Na]. For $C_{15}H_{23}NO_6Na$ 336.1423 (deviation +0.3 ppm).

4.5. (2*R*,3*S*,4*R*,5*S*)-3,4-Dibenzyloxy-*N*-benzyloxycarbonyl-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine 12

To a well stirred solution of **4**[8] (1.63 g, 3.82 mmol) in dry acetone (15 mL), anhydrous potassium carbonate (1 g) and benzyl chloroformate (820 μL, 5.73 mmol) were added and the mixture kept at rt for 12 h. TLC (Et_2O) then revealed the presence of a faster-running compound. The mixture was filtered and the solid thoroughly washed with acetone and the filtrate and washings concentrated to a residue that was submitted to chromatography (Et_2O/hexane, 1:2 → 1:1) to give **12** as colourless syrup. Yield: 1.45 g (68%), $[\alpha]_D^{23} = +22$ (*c* 1, $CHCl_3$). IR (neat): 3441 (OH), 3065 and 3032 (aromatic), 1724 and 1699 (C=O, Piv and Cbz), 737 and 697 cm^{-1} (aromatic). NMR data (300 MHz): ^{1}H, δ 7.30–7.27 (m, 15H, 3 Ph), 5.14 and 5.02 (2 d, 2H, *J* 12.3 Hz, CH_2Ph), 4.76 and 4.55 (2 d, 2H, *J* 11.7 Hz, CH_2Ph), 4.69 and 4.67 (2 d, 2H, *J*11.2 Hz, CH_2Ph), 4.50–3.72 (4 m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.07 (s, 9H, CMe_3); ^{13}C (75 MHz), δ 178.17 (C=O, Piv), 78.82 (C-3,4), 73.76 (2 *C*H_2Ph), 67.72 (*C*H_2Ph, Cbz), 63.39 and 62.97 (C-2,5), 60.0 and 57.96 (C-2′,5′), 29.78 (C*Me*$_3$) and 27.27 (*C*Me_3). HRMS (LSIMS): *m*/*z* 584.2621 [M^++Na]. For $C_{33}H_{39}NO_7Na$ 584.2624 (deviation +0.6 ppm).

4.6. 4-[(3*E*,2′*S*,3′*R*,4′*S*,5′*R*)-3′,4′-Dibenzyloxy-*N*-benzyloxycarbonyl-5′-pivaloyloxymethylpyrrolidin-2′-yl]but-3-en-2-one 14

To a stirred solution of **12** (1.35 g, 2.41 mmol) in dry DCM (20 mL) were added activated 4 Å MS (0.5 g), NMO (425 mg, 3.6 mmol) and TPAP (100 mg) after which the reaction mixture was kept at rt for 60 min. TLC (Et_2O/hexane 1:1) then indicated the absence of the starting material and the presence of a faster-running compound. The reaction was diluted with ether (30 mL), filtered through a bed of Silica gel 60 (Scharlau, 230–400 mesh) and thoroughly washed with ether. The combined filtrate and washings were concentrated to presumably aldehyde **13** (1.19 g, 88%); $[\alpha]_D^{25} = -9$ (*c*, 0.85). IR (neat): 3068 and 3032 (aromatic), 1735 (CHO), 1710 (C=O), 735 and 710 cm^{-1} (aromatic). This material was used in the next step.

To a solution of **13** (1.19 g, 2.12 mmol) in dry toluene (20 mL) was added 1-triphenylphosphoranylidene-2-propanone (1.07 g, 3.36 mmol) and the mixture was heated at 100 °C for 3 h. TLC (ether/hexane 2:1) then revealed the presence of a slightly slower-running compound. The reaction mixture was filtered and supported on silica gel, then chromatographed (ether/hexane 1:2) to afford **14** (730 mg, 83%) as a thick syrup; $[\alpha]_D^{26} = -1$, $[\alpha]_{405}^{26} = -116$ (*c* 1, $CHCl_3$). IR (neat): 3065 and 3032 (aromatic), 1713, 1677 and 1633 (C=O Piv, C=O conjugated ketone, Cbz and C=C conjugated), 737 and 698 cm^{-1} (aromatic). NMR data (400 MHz): ^{1}H, δ 7.45–7.20 (m, 15H, 3 Ph), 6.88 (dd, 1H, $J_{2',4}$ 7.1, $J_{3,4}$ 16.2 Hz, H-4), 6.51–5.91 (2 br m, 1H, H-3,4 two rotamers), 5.30–4.00 (4 br m, 12H, 3CH_2Ph and H-2′,3′,4′,5′,5″a,5″b, two rotamers), 2.10 (br s, 3H, H-1,1,1), 1.18 and 1.17 (2 s, 9H, CMe_3, two rotamers). ^{13}C (100 MHz), δ 198.60 (C-2), 178.13 (CO, Piv), 80.27 and 77.85 (C-3′,4′), 73.60, 73.22 and 67.57 (2*C*H_2Ph and Cbz), 52.81 (C-5″), 60.80 and 58.09 (C-2′,5′), 30.39 and 29.76 (C-1, two rotamers), 27.88 and 27.28 (C*Me*$_3$, two rotamers). HRMS (LSIMS): *m*/*z* 622.2777 [M^++Na]. For $C_{36}H_{41}NO_7Na$ 622.2781 (deviation +0.6 ppm).

4.7. (1*R*,2*S*,3*R*,5*S*,7a*S*)-1,2-Dibenzyloxy-5-methyl-3-pivaloyloxymethylpyrrolizidine 15

Compound **14** (1.1 g, 1.84 mmol) in dry MeOH (15 mL) was hydrogenated at 60 psi over 10% Pd–C (100 mg) for 24 h. TLC (ether/hexane 4:1) then showed the presence of a new compound of lower mobility. The catalyst was filtered off, washed with MeOH and the filtrate and washings concentrated to a residue that was submitted to column chromatography (ether/hexane 1:1) to afford pure syrupy **15** (435 mg, 52%), which had $[\alpha]_D^{25} = -27$ (*c* 1, $CHCl_3$). IR (neat): 3064, 3030 (aromatic), 1724 (C=O, Piv), 734

and 697 cm^{-1} (aromatic). NMR data (400 MHz): ^1H, δ 7.40–7.24 (m, 10H, 2 Ph), 4.69 and 4.65 (2 d, 2H, J 12.5 Hz, CH_2Ph), 4.61 and 4.53 (2 d, 2H, J 12.0 Hz, CH_2Ph), 4.53 (dd, 1H, $J_{3,8}$ 7.2, $J_{8,8'}$ 11.4 Hz, H-8), 4.32 (dd, 1H, $J_{3,8'}$ 4.3 Hz, H-8′), 4.20 (dd, 1H, $J_{1,2}$ 5.4, $J_{2,3}$ 7.5 Hz, H-2), 3.78 (br t, 1H, $J_{1,7a}$ 3.9 Hz, H-1), 2.70 (m, 1H, H-3), 2.51 (m, 1H, H-7a), 2.41 (sex, 1H, $J_{5,6\beta} = J_{5,6\alpha} = J_{5,Me} = 6.1$ Hz, H-5), 2.11 (m, 1H, H-6β), 1.91 (dq, 1H, J 7.3, J 10.9 Hz, H-7β), 1.68 (m, 1H, H-6α), 1.50 (m, 1H, H-7α), 1.30 (d, 3H, Me), 1.18 (s, 9H, CMe_3); ^{13}C (100 MHz), δ 178.47 (CO, Piv), 84.27 (C-2), 77.55 (C-1), 77.13 and 76.71 (2CH$_2$Ph), 71.25 (C-7a), 63.87 (C-8), 61.51 (C-3), 56.33 (C-5), 35.86 (C-6), 27.45 (CMe_3), 20.88 (C-7) and 20.54 (Me). HRMS (LSIMS): m/z 452.2808 [M^++H]. For $C_{28}H_{38}NO_4$ 452.2801 (deviation −1.6 ppm).

4.8. (1*R*,2*S*,3*R*,5*S*,7a*S*)-1,2-Dibenzyloxy-3-hydroxymethyl-5-methylpyrrolizidine 16

A solution of **15** (410 mg, 0.91 mmol) in anhydrous MeOH (10 mL), was treated with 2 M MeONa in the same solvent (1 mL) for 12 h at room temperature. TLC (ether/MeOH 10:1) then showed the presence of a compound of lower mobility. The reaction mixture was concentrated and the residue submitted to column chromatography (ether → ether/MeOH 10:1) to yield **16** as a colourless syrup (140 mg, 42%) which had $[\alpha]_D^{26} = -26$ (c 1, $CHCl_3$). IR (neat): 3395 (OH), 3062, 3030, 735 and 697 cm^{-1} (aromatic). NMR data (400 MHz): ^1H, δ 7.36–7.20 (m, 10H, 2Ph), 4.72 and 4.69 (2 d, 2H, J 12.4 Hz, CH_2Ph), 4.65 and 4.45 (2 d, 2H, J 12.1 Hz, CH_2Ph), 4.18 (dd, 1H, $J_{1,2}$ 4.6, $J_{2,3}$ 8.2 Hz, H-2), 3.85 (t, 1H, $J_{1,7a}$ 3.9 Hz, H-1), 3.82 (dd, 1H, $J_{3,8}$ 3.0, $J_{8,8'}$ 11.2 Hz, H-8), 3.75 (dd, 1H, $J_{3,8'}$ 5.2 Hz, H-8′), 3.07 (ddd, 1H, H-3), 2.85 (ddd, 1H, J 3.8, J 5.8, J 9.6 Hz, H-7a), 2.71 (br sex, 1H, $J_{5,6\beta} = J_{5,6\alpha} = J_{5,Me} = 6.3$ Hz, H-5), 2.05 (m, 1H, H-6β), 1.90 (dq, 1H, J 7.2, J 10.5 Hz, H-7β), 1.66 (m, 1H, H-6α), 1.57 (m, 1H, H-7α) and 1.26 (d, 3H, Me); ^{13}C (100 MHz), δ 83.37 (C-2), 73.66 (C-1), 73.39 and 72.58 (2CH$_2$Ph), 68.33 (C-7a), 60.51 (C-3), 60.34 (C-8), 56.49 (C-5), 35.03 (C-6), 21.42 (C-7) and 20.06 (Me). HRMS (LSIMS): m/z 390.2038 [M^++Na]. For $C_{23}H_{29}NO_3Na$ 390.2045 (deviation +1.9 ppm).

4.9. (1*R*,2*S*,3*R*,5*S*,7a*S*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-5-*epi*hyacinthacine A_4, 17]

Compound **16** (130 mg, 0.35 mmol) was dissolved in dry MeOH (15 mL) and hydrogenated (10% Pd–C, 100 mg) in an acid medium (concd HCl, four drops) at 60 psi for 24 h. TLC (ether/MeOH/NH_4OH 4:1:0.1) then showed the presence of a more polar compound. The catalyst was filtered off, washed with MeOH and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form) then concentrated to a residue that was submitted to column chromatography (ether/MeOH/TEA 5:1:0.1) to afford **17** (67 mg, quantitative), which was slightly contaminated. Conventional acetylation of **17** in pyridine (2.5 mL) with acetic anhydride (1.5 mL) and DMAP (20 mg) gave the tri-*O*-acetyl derivative **18** (80 mg, 78%) with had ^1H NMR spectrum (400 MHz) as follows: δ 5.61 (dd, 1H, $J_{1,2}$ 6.2, $J_{2,3}$ 7.3 Hz, H-2), 5.18 (dd, 1H, $J_{1,7a}$ 3.9 Hz, H-1), 4.30 (dd, 1H, $J_{3,8}$ 4.8, $J_{8,8'}$ 11.1 Hz, H-8), 4.16 (dd, 1H, $J_{3,8'}$ 8.1 Hz, H-8′), 2.82 (dt, 1H, H-3), 2.69 (ddd, 1H, J 3.9, J 6.2, J 10.1 Hz, H-7a), 2.40 (br sex, 1H, $J_{5,6} = J_{5,6'} = J_{5,Me} = 6.2$ Hz, H-5), 2.13, 2.06 and 2.02 (3 s, 9H, 3Ac), 1.72–1.63 and 1.61–1.48 (2 m, 4H, H-6,6′,7,7′) and 1.23 (d, 3H, Me).

Compound **18** was submitted to Zemplen deacetylation to give pure **17** as a colourless syrup (40 mg, 83%), which had $[\alpha]_D^{27} = +10$ (c 1, MeOH) {Lit.[6] $[\alpha]_D^{22} = -10$ (c 1, MeOH) for the enantiomer}. IR (neat): 3200 cm^{-1} (OH). NMR data (400 MHz, MeOH-d_4): ^1H, δ 4.85 (dd, 1H, $J_{1,2}$ 4.9, $J_{2,3}$ 8.4 Hz, H-2), 4.23 (br d, 1H, H-1), 3.88 (dd, 1H, $J_{3,8}$ 2.6, $J_{8,8'}$ 12.9 Hz, H-8), 3.91 (dd, 1H, $J_{3,8'}$ 3.8 Hz, H-8′), 3.79 (m, 1H, H-7a), 3.69 (m, 1H, H-3), 3.57 (br sex, 1H, $J_{5,6} = J_{5,6'} = J_{5,Me} = 6.3$ Hz, H-5), 2.63 (m, 1H, H-6), 2.19–1.93 (m, 3H, H-6′,7,7′) and 1.56 (d, 3H, Me); ^{13}C (100 MHz), δ 76.87 (C-2), 75.10 (C-7a), 66.95 (C-1), 66.39 (C-3), 61.65 (C-5), 57.83 (C-8), 34.69 (C-6), 18.88 (C-7) and 16.88 (Me). HRMS (LSIMS): m/z 188.1290 [M^++H]. For $C_9H_{18}NO_3$ 188.1287 (deviation –1.9 ppm).

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