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First total synthesis and absolute configuration of naturally occurring (−)-hyacinthacine A_7 and its (−)-1-*epi*-isomer☆

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Abstract

A convergent synthesis of the naturally occurring alkaloid (−)-hyacinthacine A_7, a glycosidase inhibitor of the pyrrolizidine class, is described. The homochiral starting material was tri-orthogonally protected DMDP **10**, derived from D-fructose. Key steps of the synthesis were the carbon-chain lengthening at C(5′) in **10** to the α,β-unsaturated pyrrolidine ketone **12** and the one-pot construction of the bicyclic pyrrolizidine system of **13** and **14**. Another key step was the partial inversion of the configuration at C(1) in **13** which led, after total deprotection, not only to the naturally occurring target molecule **9** but also to its (−)-1-*epi*-isomer **19**.

1. Introduction

Polyhydroxylated pyrrolizidine alkaloids (PHPAs)[2] bearing a hydroxymethyl group adjacent to the ring nitrogen [C(3), Fig. 1] are relatively uncommon in nature, only 24 different compounds of this sort have been isolated so far. Several members of this class of alkaloids, including alexine (**1**) and australine (**2**), the first ones being described,[2] have been isolated from leguminosae exhibit promising biological activity[2,3] (e.g., **1** displays antiviral and anti-HIV activity).[4] In 2000, Asano et al. reported the first isolation, from an extract of the bulbs of *Muscari Armeniacum* (Hyacinthaceae), of hyacinthacines A_1–A_3 (**3**–**5**, respectively) together with those belonging to the B and C series in 1999.[5] Lately in 2002, the same author accounted on the isolation, from an extract of the bulbs of *Scilla sibirica*, of new members of this A series, named as hyacinthacines A_4–A_7 (**6**–**9**, respectively).[6] Many of these alkaloids display potent glycosidase inhibitory activity, which makes them either potential drug or therapeutic lead candidates against viral infections, cancer, and diabetes.[7]

The greater part of the synthetic routes to these azasugars starts with a carbohydrate analogue resembling, if possible, the majority of its stereocenters. However, non-carbohydrate approaches such as ring closing metathesis,[8] cyclization of

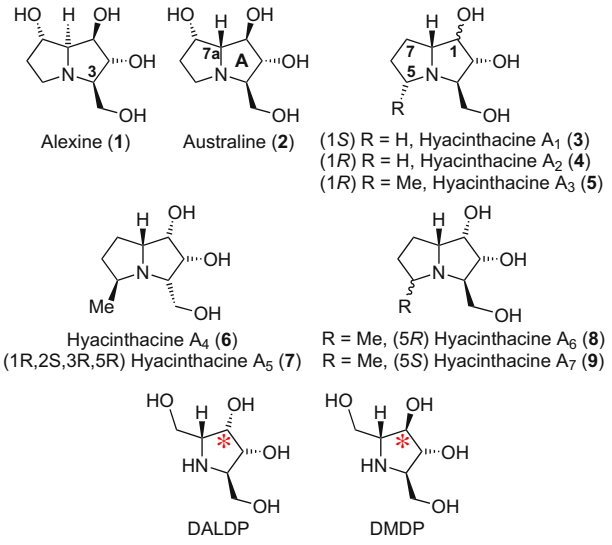

Figure 1. Naturally occurring pyrrolizidine alkaloids of the A series and polyhydroxylated pyrrolidines (imino or azasugars).

☆ Part 11 of this series. For Part 10, see Ref. 1.

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acetylenic sulfones with chloroamines,[9] tandem inter [4+2]/inter [3+2] cycloaddition process,[10] triple reductive aminations,[11] cuprate chemistry,[12] and diastereoselective *syn*-dihydroxylation[13] are becoming more popular. Defenders of non-carbohydrate synthetic strategy claim that these routes are superior because they exhibit increased stereoselectivity and are more efficient at introducing the amine moiety.[11] If possible, a flexible and stereocontrolled synthetic approach taking advantage of the carbohydrate's inherent stereochemistry and an efficient introduction of the amine function would be desired.

With the aim of proving the whole chemical space occupied by the polyhydroxylated pyrrolizidine alkaloids, syntheses of the above compounds have been and must continue to be developed. In addition, naturally occurring azasugars are scarcely present in the natural sources and are often difficult to purify from them,[14] and therefore, synthetic routes to these iminosugars and analogues, are also desirable. In this context and in the recent past years, our group have put into practice a synthetic methodology, consisting in the use of appropriately functionalized and orthogonally protected pyrrolidines[15] as key intermediate for the preparation of more complex PHPAs.[1,16] On the other hand, such polyhydroxylated pyrrolidines were prepared from the commercially available hexulose D-fructose. Even though the preparation of the PHPAs **3** and **8**, from an appropriately protected derivative of DALDP, has been recently disclosed by our group,[16i] we wander on the possibility of using the more easily available DMDP as the homochiral starting material, since the configuration at the starred carbon is the only difference in both pyrrolidines, an inversion of such configuration at any stage of the synthetic route would be sufficient. Thus, herein we describe our studies on hyacinthacine A_7 (**9**), which culminated in the first total synthesis and absolute configuration determination of this natural product.

2. Results and discussion

Our retrosynthetic pathway toward PHPA **9** is illustrated in Figure 2, in which an inversion of the configuration at C(1) in **9** leads to new pyrrolizidines with a stereochemistry at the **A**-ring exactly matching with that existing in the tri-orthogonally protected and stereochemically loaded 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, **10**),[15f] a simple cleavage of N(4)–C(5) bond in the pyrrolizidines skeleton and a Wittig-type disconnection at C(3)–C(4) of the α,β-unsaturated pyrrolidine ketone **12**, reveals key **10** as the precursor.

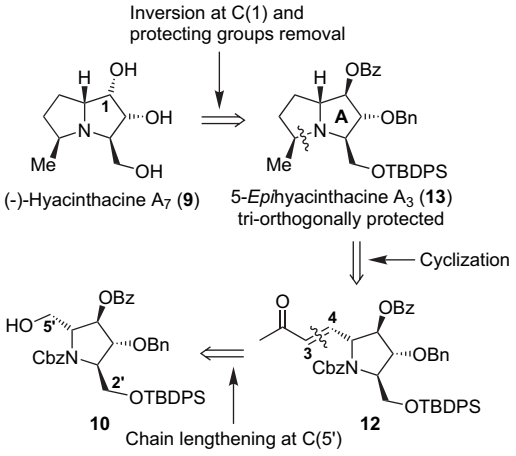
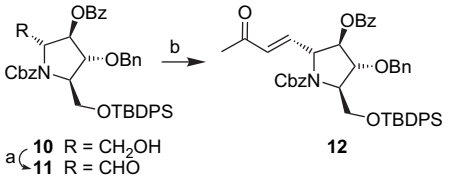


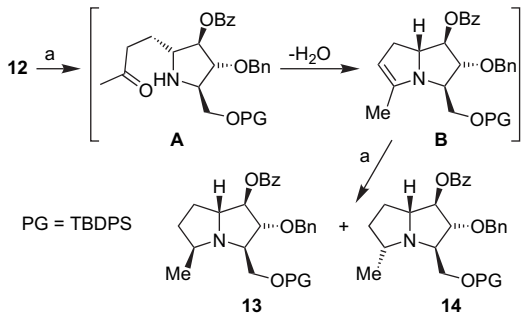
Figure 2. Retrosynthesis of (−)-hyacinthacine A_7 (**9**) from a tri-orthogonally protected derivative of DMDP (**10**).

Following the above retrosynthesis, and based on results from previous studies,[16a,b] we began the synthesis with (2*R*,3*R*,4*R*,5*R*)-4-benzoyloxy-3-benzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl) pyrrolidine (**10**, Scheme 1).[15f] Oxidation of **10** with *N*-methylmorpholine *N*-oxide (NMO) catalyzed by tetra-*n*-propylammoniumperruthenate (TPAP) yielded the aldehyde **11** according to its IR spectra (ν 1710 cm^{-1}, CHO). Subsequent treatment of **11** with 1-triphenylphosphoranylidene-2-propanone afforded (*E*)-4-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′-benzoyloxy-4′-benzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]but-3-en-2-one (**12**) in a highly stereoselective manner. The structure of **12**, which exists as a mixture of two rotamers (~1.1:1 ratio), was determined on the basis of its analytical and spectroscopic data, whereas the *E* configuration at C(3,4) was established from the $J_{3,4}$ value (16.1 Hz).



Scheme 1. Synthesis of α,β-unsaturated pyrrolidine ketone **12**. Reagents and conditions: (a) TPAP/NMO/Cl_2CH_2/4 Å MS, rt; (b) $Ph_3P{=}CHCOCH_3$/MePh, 80 °C.

Catalytic hydrogenation (10% Pd/C)–cyclization of **12** afforded, in only one step, a mixture of the fully protected (1*R*,2*R*,3*R*,5*S*,7a*R*)-(**13**) and (1*R*,2*R*,3*R*,5*R*,7a*R*)-1-benzoyloxy-2-benzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine (**14**). According to Scheme 2, formation of **13** and **14** must take place as follows: catalytic hydrogenation converted **12** into the *N*-deprotected saturated pyrrolidine ketone **A**, an intramolecular condensation reaction gave the



Scheme 2. Synthesis of totally protected derivatives of 5-*epi*-hyacinthacine A_3 (**13**) and hyacinthacine A_3 (**14**) from **12**. Reagents and conditions: (a) 10% Pd/C/H_2, 60 psi, rt.

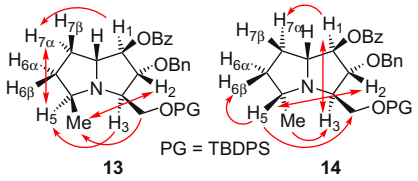


Figure 3. Main observed NOE effects in compounds **13** and **14**.

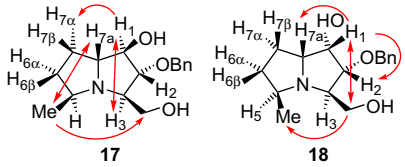
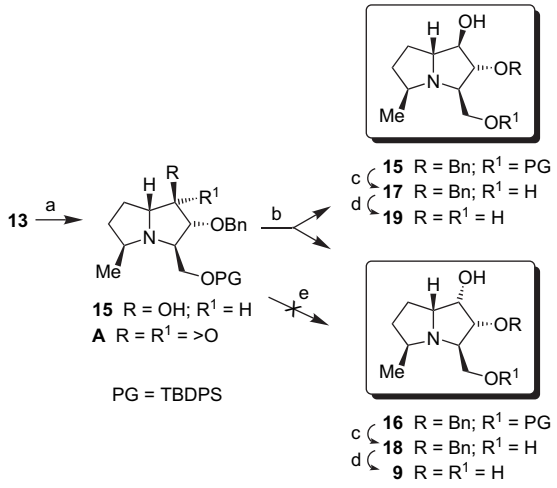


Figure 4. Main observed NOE effects in compounds **17** and **18**.

intermediate Δ^5-pyrrolizine **B**, not isolated, which is finally hydrogenated to afford a mixture of **13** and **14** in ~1:1 ratio, easy and successfully separated by chromatographic means.

The configuration of the new stereogenic center C(5) in **13** and **14**, was established on the basis of extensive NOE experiments and results are displayed in Figure 3. Thus, the definite NOE effects between C(3)H and C(5)H, C(5)H and C(7α)H, and Me(5)H with C(2)H and C(8)H in **13**, indicate the *S* configuration at C(5). Whereas, the NOE effects between C(3)H and Me(5)H, and C(5)H with C(2)H and C(8)H in **14**, indicate the *R* configuration for that stereogenic center. In addition, the rest of the NOE interactions also confirmed the total stereochemistry of **13** and **14**.

Conversion of **13** into the target molecule **9** (see Scheme 3) was achieved as follows: conventional debenzoylation of **13** afforded pyrrolizidine **15** that was Swern oxidized to the intermediate ketone **A**, not isolated, but $NaBH_4$ reduced to yield a mixture of starting **15** and the inversion product **16** that was separated by chromatography. Compounds **15** and **16** were, respectively, *O*-desylilated to afford the corresponding **17** and its C(1) inversion product **18**. Attempt to generate **16** from **15** stereospecifically by using Mitsunobu hydroxyl inversion[17] failed.



Scheme 3. Synthesis of **19** and **9** from **13**. Reagents and conditions: (a) MeONa (cat.)/MeOH, 0 °C→rt; (b) (i) Swern oxidation, (ii) $NaBH_4$/MeOH, 0 °C; (c) TBAF·$3H_2O$/THF, rt; (d) 10% Pd/C/H_2/HCl/MeOH then Amberlite IRA-400 (OH^- form); (e) (i) BzOH/DEAD/Ph_3P/THF, rt, (ii) MeONa (cat.)/MeOH.

Structural elucidations of **17** and **18** were based on their analytical and spectroscopic data. Thus, exhaustive NOE experiments on such compounds (see Fig. 4) demonstrated their whole stereochemistry, being on interest those existing effects between H(1)–H(3,7α), Me(5)–H(7a,8) indicating, respectively, their α and β-disposition in **17**, whereas the NOE effects between H(1)–H(2,7a,8), Me(5)–H(8) in **18** confirm the β-disposition for all of them.

Finally, catalytic hydrogenolysis with H_2 and 10% Pd/C convert **17** and **18** to (−)-1-*epi*-hyacinthacine A_7 (**19**) and (−)-hyacinthacine A_7 (**9**), respectively, in accordance with their analytical and spectroscopic data, confirming that 1*S*,2*R*,3*R*,5*S*,7a*R* are the actual absolute configurations of the stereogenic centers in natural product **9**. PHPA **19** is currently being evaluated for its ability to inhibit carbohydrate-processing enzymes.

3. Conclusions

In summary, the first stereoselective synthesis of naturally occurring (−)-hyacinthacine A_7 as well as that of its (−)-1-*epi*-isomer have been achieved starting from a triorthogonally protected derivative of DMDP. The inherent chirality of DMDP is in part realized in the target alkaloids, the required carbon-chain lengthening was easily completed through a Wittig olefination reaction, and the pyrrolizidine structure was installed through an one-pot intramolecular reductive amination process. This route will provide an easy access to many other PHPAs that will be useful tools for SAR studies in glycobiology.

4. Experimental

4.1. General procedures

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, ARX-400, and AMX-500 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sex, sextet; 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. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was developed on precoated silica gel 60 F_{254} aluminum 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 and HRMS.

4.2. (E)-4-[(2′R,3′R,4′R,5′R)-3′-Benzoyloxy-4′-benzyloxy-N-benzyloxycarbonyl-5′-tert-butyldiphenylsilyloxymethyl-pyrrolidin-2′-yl]but-3-en-2-one (12)

To a stirred solution of (2*R*,3*R*,4*R*,5*R*)-4-benzoyloxy-3-benzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine[15f] (**10**, 1.46 g, 2 mmol) in dry DCM (20 mL) were added activated 4 Å MS (1 g), NMO (350 mg, 3 mmol), and TPAP (100 mg) and the reaction mixture was kept at rt for 3 h. TLC (Et_2O) then indicated the absence of the starting material and the presence of 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 presumably aldehyde **11** (1.29 g, 89%); ν (neat): 3068 and 3032 (aromatic), 1738 (CHO), 1724 and 1710 (C=O, Bz and Cbz), 740 and 700 cm^{-1} (aromatic). This material was used in the next step.

To a solution of **11** (1.29 g, 1.8 mmol) in dry toluene (30 mL) was added 1-triphenylphosphoranylidene-2-propanone (1.6 g, 5 mmol) and the mixture was heated at 80 °C overnight. TLC (1:1, Et_2O/hexane) then revealed the presence of a slightly slower-running compound. The reaction mixture was filtered and supported on silica gel, then chromatographed (2:3, Et_2O/hexane) to afford **12** (1.21 mg, 78%) as a thick syrup; $[\alpha]_D^{28}$ +6, $[\alpha]_{405}^{28}$ +22 (*c* 1.3); ν (neat): 3069 and 3033 (aromatic), 1710 and 1681 (C=O Bz, C=O conjugated ketone, and Cbz), 739 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ 7.90–7.10 (3m, 25H, 5 Ph), 6.80 and 6.72 (2dd, 1H, $J_{2',4}$=7.4 and 7.8 Hz, H-4, two rotamers), 6.29 and 6.10 (2d, 1H, $J_{3,4}$=16.1 Hz, H-3, two rotamers), 5.33 (br d, 1H, J=5.1 Hz, H-3′), 5.26 and 4.87 (2d, 2H, J=12.1 Hz, CH_2Ph), 5.05 and 4.94 (2d, 2H, J=12.2 Hz, CH_2Ph), 4.79–4.34 (2br m, 5H, CH_2Ph and H-4′,5″a,5″b, two rotamers), 4.31 and 4.11 (2dd, 1H, J=4.8, 9.5 Hz, H-2′, two rotamers), 3.67 and 3.62 (2br t, 1H, J=10.2 Hz, H-5′, two rotamers), 2.20 and 2.02 (2br s, 3H, H-1,1,1, two rotamers), 1.03 and 0.97 (2s, 9H, CMe_3, two rotamers). ^{13}C NMR (100 MHz, inter alia): δ 198.01 (C-2), 165.36 (COPh), 154.41 and 154.21 (CO, Cbz, two rotamers), 82.84, 82.10, 80.66 and 79.65 (C-3′,4′, two rotamers), 71,74 and 71.60 (CH_2Ph, two rotamers), 67.40 (Cbz), 65.92 and 65.52 (C-2′,5′), 62.28 and 61.55 (C-5″, two rotamers), 27.23 (C-1), 26.92 (CMe_3), and 19.34 and 19.23 (CMe_3, two rotamers). HRMS (LSIMS): *m/z* 790.3166 [M^++Na]. For $C_{47}H_{49}NO_7SiNa$ 790.3176 (deviation +1.3 ppm).

4.3. (1R,2R,3R,5S,7aR)-(13) and (1R,2R,3R,5R,7aR)-1-Benzoyloxy-2-benzyloxy-3-tert-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine (14)

Compound **12** (1.14 g, 1.48 mmol) in dry MeOH (30 mL) was hydrogenated at 60 psi over 10% Pd/C (200 mg) for 24 h. TLC (2:1, Et_2O/hexane) then showed the presence of two new compounds. The catalyst was filtered off, washed with MeOH, and the filtrate and washings were concentrated to a residue that was submitted to column chromatography (1:2, Et_2O/hexane) to afford first pure syrupy **13** (407 mg, 44%), which had $[\alpha]_D^{27}$ −9 (*c* 1); ν (neat): 3070 and 3048 (aromatic), 1721 (C=O, Bz), 739 and 701 cm^{-1} (aromatic). ^1H NMR data (400 MHz): δ 7.98–7.29 (5m, 20H, 4Ph), 5.37 (t, 1H, $J_{1,2}$=$J_{1,7a}$=2.8 Hz, H-1), 4.84 and 4.62 (2d, 2H, J=12.1 Hz, CH_2Ph), 4.35 (t, 1H, $J_{2,3}$=2.8 Hz, H-2), 3.76 (t, 1H, $J_{3,8}$=$J_{8,8'}$=10.2 Hz, H-8), 3.72 (dd, 1H, $J_{3,8'}$=6.3 Hz, H-8′), 3.63 (dt, 1H, $J_{7,7a}$=$J_{7',7a}$=7.7 Hz, H-7a), 3.30–3.25 (m, 1H, H-3), 3.24–3.16 (m, 1H, H-5), 2.21–2.13 (m, 1H, H-7), 2.04–1.91 (m, 2H, H-6,7′), 1.46–1.38 (m, 1H, H-6′), 1.04 (s, 9H, CMe_3), and 1.03 (d, 3H, $J_{5,Me}$=6.0 Hz, Me). ^{13}C (100 MHz, inter alia): δ 166.18 (COPh), 86.60 (C-2), 83.62 (C-1), 72.05 (CH_2Ph), 71.29 (C-3), 70.44 (C-7a), 66.15 (C-8), 63.18 (C-5), 34.30 (C-6), 30.80 (C-7), 27.00 (Me and CMe_3), and 21.90 (CMe_3). HRMS (LSIMS): *m/z* 620.3190 [M^++H]. For $C_{39}H_{46}NO_4Si$ 620.3196 (deviation +1.0 ppm).

Eluted second was **14** (360 mg, 40%) as a colorless syrup, which had $[\alpha]_D^{27}$ −31 (*c* 1.2); ν (neat): 3070 and 3048 (aromatic), 1720 (C=O, Bz), 736 and 709 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 8.10–7.32 (5m, 20H, 4Ph), 5.53 (t, 1H, $J_{1,2}$=$J_{1,7a}$=1.7 Hz, H-1), 4.88 and 4.82 (2d, 2H, J=12.0 Hz, CH_2Ph), 4.42 (br s, 1H, H-2), 3.82 (dd, 1H, $J_{3,8}$=6.0 Hz, $J_{8,8'}$=10.0 Hz, H-8), 3.76 (m, 1H, H-7a), 3.74 (t, 1H, $J_{3,8'}$=10.0 Hz, H-8′), 3.45 (ddd, 1H, $J_{2,3}$=2.1 Hz, H-3), 3.29 (dq, 1H, H-5), 2.17–1.98 (m, 2H, H-7,7′), 1.98–1.82 (m, 1H, H-6), 1.68–1.55 (m, 1H, H-6′), 1.23 (d, 3H, $J_{5,Me}$=6 Hz, Me), and 1.17 (s, 9H, CMe_3). ^{13}C NMR (75 MHz, inter alia): δ 166.08 (COPh), 87.05 (C-2), 82.10 (C1), 72.03 (CH_2Ph), 70.11 (C-7a), 67.02 (C-8), 64.59 (C-3), 59.18 (C-5), 31.69 (C-6), 28.95 (C-7), 27.12 (Me and CMe_3), and 19.47 (CMe_3). HRMS (LSIMS): *m/z* 642.3018 [M^++Na]. For $C_{39}H_{45}NO_4SiNa$ 642.3016 (deviation −0.4 ppm).

4.4. (1R,2R,3R,5S,7aR)-2-Benzyloxy-3-tert-butyldiphenylsilyloxymethyl-1-hydroxy-5-methylpyrrolizidine (15)

To an ice-water cooled and stirred solution of **13** (580 mg, 0.94 mmol) in anhydrous MeOH (10 mL) was added 1 M MeONa in the same solvent (0.5 mL) and the reaction mixture was allowed to reach room temperature and left for 12 h. TLC (2:1, Et_2O/hexane) then showed a slower-running compound. The mixture was neutralized with acetic acid, concentrated to a residue that was submitted to column chromatography (2:1, Et_2O/hexane → Et_2O) to yield pure **15** (430 mg, 89%) as a colorless syrup, which had $[\alpha]_D^{28}$ 14 (*c* 1); ν (neat): 3319 (OH), 3070, 739 and 701 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 7.78–7.26 (3m, 15H, 3Ph), 4.65 and 4.59 (2d, 2H, J=11.9 Hz, CH_2Ph), 4.09 (t, 1H, $J_{1,2}$=$J_{1,7a}$=3.7 Hz, H-1), 3.97 (t, 1H, $J_{2,3}$=3.9 Hz, H-2), 3.86 (dd, 1H, $J_{3,8}$=5.6, $J_{8,8'}$=10.5 Hz, H-8), 3.80 (dd, 1H, $J_{3,8}$=5.5 Hz, H-8′), 3.68 (dt, 1H, $J_{7,7a}$=$J_{7',7a}$=7.8 Hz, H-7a), 3.23 (dquint, 1H, J=6.4, 7.0 Hz, H-5), 3.14 (br q, 1H, H-3), 2.18–2.01 (m, 2H, H-6,7), 1.87–1.74 (m, 1H, H-7′), 1.54–1.47 (m, 1H, H-6′), 1.15 (d, 3H, $J_{5,Me}$=6.3 Hz, Me), and 1.10 (s, 9H, CMe_3).

^{13}C NMR (75 MHz, inter alia): δ 89.53 (C-2), 80.89 (C-1), 72.26 (CH_2Ph), 71.98 (C-3), 71.79 (C-7a), 66.75 (C-8), 64.03 (C-5), 33.87 (C-6), 29.68 (C-7), 27.08 (CMe_3), 21.29 (Me), and 19.39 (CMe_3). HRMS (LSIMS): *m/z* 516.2933 [M^++H]. For $C_{32}H_{42}NO_3Si$ 516.2934 (deviation +0.1 ppm).

*4.5. (1R,2R,3R,5S,7aR)-(**17**) and (1S,2R,3R,5S,7aR)-2-Benzyloxy-1-hydroxy-3-hydroxymethyl-5-methylpyrrolizidine (**18**)*

To a stirred and cooled (−78 °C) solution of 2 M oxalyl chloride (462 μL, 0.92 mmol) in anhydrous DCM (10 mL) was added DMSO (126 μL, 1.77 mmol) dropwise under argon and the mixture maintained for 30 min. A solution of **15** (400 mg, 0.78 mmol) in the same solvent (5 mL) was added and the reaction mixture was left at −78 °C for 60 min. TEA (322 μL, 2.3 mmol) was added and after 2 h at −50 °C, TLC (Et_2O) then showed a faster-running compound. The reaction was allowed to reach room temperature and then water (15 mL) was added. The aqueous layer was removed and extracted with DCM. The combined organic extracts were washed with brine and concentrated to afford a residue that was subjected to flash chromatography (Et_2O) to afford the corresponding pyrrolizidin-1-one (360 mg, 90%) (ν (neat): 1755 cm^{-1} (CO)) that was subsequently treated with $NaBH_4$ (41 mg, 1.1 mmol) in anhydrous MeOH (20 mL) at 0 °C for 30 min. TLC (EtOAc) then showed two lower-running compounds. After work-up, column chromatography (1:1, Et_2O/hexane) afford syrupy **15** (100 mg, 29%) and **16** (160 mg, 46%), which were separately *O*-desilylated.

Compound **15** (100 mg, 0.19 mmol) in THF (10 mL) was treated at rt with TBAF·$3H_2O$ (68 mg, 0.21 mmol) for 12 h. TLC (EtOAc) then revealed a slower-running compound. The reaction mixture was supported on silica gel and submitted to chromatography (Et_2O → 3:1, Et_2O/MeOH) to afford pure **17** (45 mg, 85%), which had $[\alpha]_D^{26}$ 36 (*c* 1); ν (neat): 3340 (OH), 737 and 698 cm^{-1} (aromatic). ^{1}H NMR (400 MHz): δ 7.34−7.28 (m, 5H, Ph), 5.05 (br s, 2H, OH-1,8), 4.68 and 4.58 (2d, 2H, J=11.6 Hz, CH_2Ph), 4.04 (t, 1H, $J_{1,2}$=$J_{1,7a}$=3.6 Hz, H-1), 3.94 (t, 1H, $J_{2,3}$=3.6 Hz, H-2), 3.77−3.55 (m, 3H, H-7a,8,8′), 3.20−3.10 (m, 2H, H-3,5), 2.20−2.12 (m, 1H, H-7), 2.02−1.95 (m, 1H, H-6), 1.82−1.72 (m, 1H, H-7′), 1.57−1.46 (m, 1H, H-6′), and 1.19 (d, 3H, $J_{5,Me}$=6.3 Hz, Me). ^{13}C NMR (100 MHz): δ 138.14, 128.76, 128.11, and 127.84 (Ph), 89.03 (C-2), 80.54 (C-1), 72.77 (C-7a), 72.59 (CH_2Ph), 71.29 (C-3), 64.28 (C-5), 61.82 (C-8), 34.14 (C-6), 30.33 (C-7), and 20.01 (Me). HRMS (EI): *m/z* 277.1666 [M^+]. For $C_{16}H_{23}NO_3$ 277.1678 (deviation −4.3 ppm).

Compound **16** (160 mg, 0.31 mmol) in THF (10 mL) was treated at rt with TBAF·$3H_2O$ (110 mg, 0.34 mmol) overnight. Work-up and column chromatography as above afforded pure **18** (56 mg, 65%), which had $[\alpha]_D^{25}$ 57 (*c* 1); ν (neat): 3401 (OH), 737 and 698 cm^{-1} (aromatic); ^{1}H NMR (400 MHz): δ 7.38−7.30 (m, 5H, Ph), 4.60 (s, 2H, CH_2Ph), 4.05 (dd, 1H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=8.8 Hz, H-2), 3.89 (t, 1H, $J_{1,7a}$=3.2 Hz, H-1), 3.64 (dd, 1H, $J_{3,8}$=3.6 Hz, $J_{8,8'}$=10.8 Hz, H-8), 3.58−3.53 (m, 2H, H-7a,8′), 2.95−2.86 (2m, 2H, H-3,5), 2.36 (br s, 1H, OH), 2.18−2.10 (m, 1H, H-7), 2.04−1.97 (m, 1H, H-6), 1.78−1.71 (m, 1H, H-7′), 1.55−1.45 (m, 1H, H-6′), 1.06 (d, 3H, $J_{5,Me}$=6.0 Hz, Me). ^{13}C (100 MHz), δ 137.75, 128.86, 128.42, and 128.10 (Ph), 84.03 (C-2), 73.26 (CH_2Ph), 70.00 (C-1), 67.84 and 67.49 (C-3,7a), 63.14 (C-5), 60.85 (C-8), 36.19 (C-6), 23.15 (C-7), and 21.55 (Me). HRMS (EI): *m/z* 277.1667 [M^+]. For $C_{16}H_{23}NO_3$ 277.1678 (deviation −4.0 ppm).

*4.6. (1R,2R,3R,5S,7aR)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [**19**, (−)-1-epi-hyacinthacine A_7]*

A solution of **17** (35 mg, 0.126 mmol) in MeOH (10 mL) was acidified (concd HCl) and hydrogenated (10% Pd/C, 40 mg) at 70 psi for 12 h. The catalyst was filtered off, washed with MeOH and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form) and concentrated to afford pure **19** (15 mg, 63%) as a colorless thick syrup, which had $[\alpha]_D^{29}$ −162 (*c* 0.5, H_2O). ^{1}H NMR (500 MHz, MeOH-d_4): δ 3.85 (t, 1H, $J_{1,2}$=$J_{2,3}$=7.4 Hz, H-2), 3.69 (t, 1H, $J_{1,7a}$=7.4 Hz, H-1), 3.66 (dd, 1H, $J_{3,8}$=4.3 Hz, H-8), 3.59 (dd, 1H, $J_{3,8'}$=5.2 Hz, $J_{8,8'}$=11.1 Hz, H-8′), 3.30 (q, 1H, $J_{7,7a}$=$J_{7',7a}$=7.4 Hz, H-7a), 3.04 (br sex, 1H, $J_{5,6}$=$J_{5,6'}$=$J_{5,Me}$=6.3 Hz, H-5), 2.72 (dt, 1H, H-3), 2.09 (ddt, 1H, J=4.8, 7.4, 12.5 Hz, H-7), 2.01 (ddt, 1H, J=5.6, 7 Hz, H-6), 1.75 (m, 1H, H-7′), 1.48 (br dq, 1H, J=8.5, 12.4 Hz, H-6′), and 1.10 (d, 3H, Me). ^{13}C NMR (125 MHz): δ 85.74 (C-1), 83.06 (C-2), 75.00 (C-3), 72.41 (C-7a), 67.28 (C-5), 66.51 (C-8), 37.48 (C-6), 33.28 (C-7), and 23.87 (Me). HRMS (EI): *m/z* 187.1199 [M^+]. For $C_9H_{17}NO_3$ 187.1208 (deviation −4.8 ppm).

*4.7. (1S,2R,3R,5S,7aR)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [**9**, (−)-hyacinthacine A_7]*

A solution of **19** (45 mg, 0.16 mmol) in MeOH (10 mL) was debenzylated with 10% Pd/C (40 mg) as above to afford pure **9** (23 mg, 76%) as a colorless thick syrup, which had $[\alpha]_D^{29}$ 36.4 (*c* 1, MeOH), $[\alpha]_D^{28}$ −34 (*c* 1, H_2O) [lit.[6] $[\alpha]_D$ −51.8 (*c* 0.45, H_2O)]. ^{1}H NMR (500 MHz, MeOH-d_4): δ 4.10 (dd, 1H, $J_{1,2}$=3.8 Hz, $J_{2,3}$=9.3 Hz, H-2), 3.95 (t, 1H, $J_{1,7a}$=3.6 Hz, H-1), 3.92 (m, 1H, H-7a), 3.85 (dd, 1H, $J_{3,8}$=3.7 Hz, H-8), 3.73 (dd, 1H, $J_{3,8'}$=4.8 Hz, $J_{8,8'}$=11.6 Hz, H-8′), 3.32 (m, 1H, H-5), 3.13 (m, 1H, H-3), 2.29 (m, 1H, H-7α), 2.17 (m, 1H, H-6α), 1.91 (m, 1H, H-7β), 1.67 (m, 1H, H-6β), and 1.29 (d, 3H, $J_{5,Me}$=6.4 Hz, Me). ^{13}C NMR (125 MHz): δ 78.78 (C-2), 75.08 (C-1), 73.71 (C-3), 72.38 (C-7a), 69.55 (C-5), 63.88 (C-8), 38.43 (C-6), 25.94 (C-7), and 21.20 (Me). HRMS (EI): *m/z* 187.1214 [M^+]. For $C_9H_{17}NO_3$ 187.1208 (deviation +3.2 ppm).

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Supplementary data

^{1}H and ^{13}C NMR spectra for compounds **9**, **13**, **14**, **17**–**19**, homo and heteronuclear 2D-NMR spectra for compounds **9** and **19** (16 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.009.

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