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Polyhydroxylated pyrrolizidines. Part 4: Total asymmetric synthesis of unnatural hyacinthacines from a protected derivative of DGDP ☆

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Abstract—(1*R*,2*R*,3*S*,5*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-3-*epi*-hyacinthacine A_3] **1** and (1*R*,2*R*,3*S*,7a*R*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine [(+)-3-*epi*-hyacinthacine A_2] **2** have been synthesized by Wittig's methodology using aldehyde **6**, prepared from (2*R*,3*R*,4*R*,5*S*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl) pyrrolidine **3** (a partially protected DGDP), and the appropriated ylides, followed by cyclization through an internal reductive amination process of the resulting α,β-unsaturated ketone **7** and aldehyde **8**, respectively, and total deprotection.

1. Introduction

Previously[1,2] we have reported the enantiosynthesis of polyhydroxylated pyrrolizidine alkaloids related to hyacinthacines,[3] potent glycosidase inhibitors, using natural carbohydrates (hexuloses) as the source of chirality. In these reports, D-fructose was transformed into suitably protected derivatives of 2,5-dideoxy-2,5-imino-D-glucitol (DGDP) **3**[4] and into the related D-*manno* derivative DMDP,[5] both being key intermediates in those syntheses.

According to Figure 1, the pivotal character of compound **3**, should allow the possibility of synthesizing either pyrrolizidines structurally related to the natural alkaloids alexine,[6] by building-up the bicyclic skeleton from C(5′) or to australine[7] from C(2′). The former synthetic strategy was successfully achieved and 7a-*epi*-hyacinthacine A_2 (7-deoxy-alexine) and 5,7a-di*epi*-hyacinthacine A_3 were described.[2a] We report herein the results of the application of the second strategy, consisting in the C(5′) O-protection, C(2′) O-deprotection, adequately functionalized chain lengthening in this position and finally cyclization to the pyrrolizidine skeleton to afford two new unnatural hyacinthacines, namely (+)-3-*epi*-hyacinthacine A_3 **1** and (+)-3-*epi*-hyacinthacine A_2, **2**.

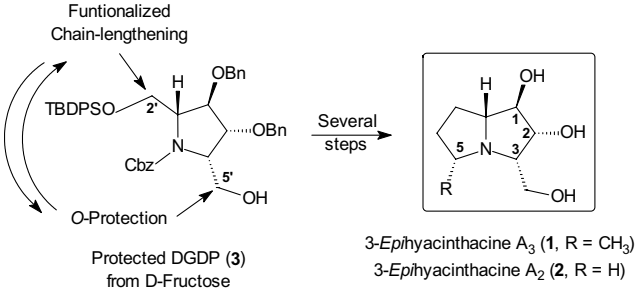

Figure 1. Synthetic strategy for the preparation of hyacinthacines **1** and **2** from protected DGDP **3**.

2. Results and discussion

Conventional benzoylation of (2*R*,3*R*,4*R*,5*S*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine **3**[4] gave the total protected derivative **4** (see Scheme 1). O-Desilylation of **4** to the corresponding partially protected pyrrolidine **5** and subsequent oxidation (TPAP/NMO) yielded the pyrrolidinic aldehyde **6** that was not investigated, but used in the next step. Thus, reaction of **6**, with either

☆ For Part 3 of the series, see Ref. 1.

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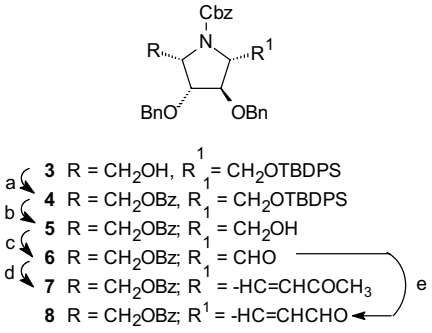
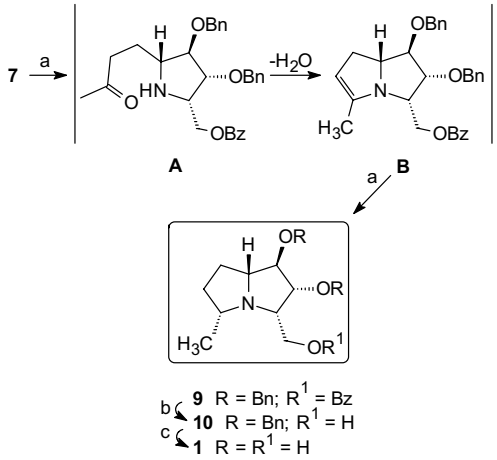
1-triphenylphosphoranilydene-2-propanone or triphenylphosphoranilydeneacetaldehyde gave the α,β-unsaturated ketone **7** and aldehyde **8**, respectively. The stereochemistry at the carbon–carbon double bond in both compounds could not be determined due to the existence of rotamers, which caused an extensive broadening of the resonance signals.



Scheme 1. Synthesis of α,β-unsaturated pyrrolidinic ketone **7** and aldehyde **8**. Reagents and conditions: (a) $BzCl/CH_2Cl_2$/TEA; (b) *n*-$Bu_4N^+F^-\cdot 3H_2O$/THF; (c) TPAP/NMO/CH_2Cl_2/4 Å MS; (d) $Ph_3PCHCOCH_3$/MePh/Δ; (e) $Ph_3PCHCHO$/MePh, 60 °C.

Catalytic hydrogenation (10% Pd–C)-cyclization of **7** afforded, in only one step, the fully protected (1*R*,2*R*,3*S*,5*R*,7a*R*)-3-benzoyloxymethyl-1,2-dibenzyloxy-5-methylpyrrolizidine **9**. According to Scheme 2, formation of **9** must take place as follows: initial hydrogenation of **7** to the intermediate *N*-deprotected saturated ketone **A**, subsequent intramolecular condensation to give the Δ^5-pyrrolizine **B**, which was not isolated and final hydrogenation to **9**.



Scheme 2. Synthesis of (+)-3-*epi*-hyacinthacine A_3 **1**. Reagents and conditions: (a) 10% Pd–C/H_2/MeOH; (b) MeONa/MeOH; (c) 10% Pd–C/H_2/HCl, then Amberlite IRA-400 (OH^- form).

The stereochemistry of the new C(5) stereogenic centre was established on the basis of extensive NOE experiments. The NOE interactions are shown in Figure 2. The definite NOE effects between C(3)H and C(5)H, and Me(5)H and C(8)H indicate the *R* configuration at C-5. In addition, the rest of the NOE interaction also confirmed the total stereochemistry of **9**.

The high stereoselectivity found in the hydrogenation of intermediate Δ^5-pyrrolizine **B**, where **9** was the only detected and isolated pyrrolizidine merits comment. Formation of **9** can be attributed, according to our previous results[2] and to Figure 2, to the peculiar shape of this kind of molecule[3] where it is appreciated that the β-face is less hindered for hydrogen attack that the α-face is, affording only compound **9**.

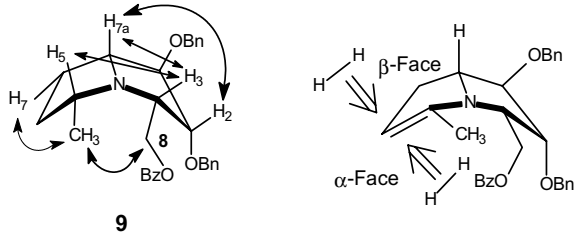
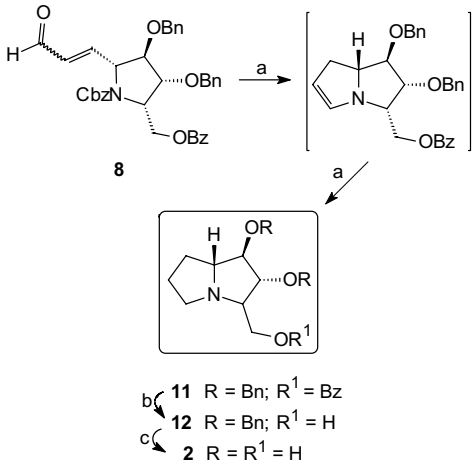


Figure 2. NOE interactions in **9** and hydrogenation pathway of intermediate Δ^5-pyrrolizine.

Finally, removal of the protecting groups in **9** gave the target molecule (+)-3-*epi*-hyacinthacine A_3 **1**, in accordance with its analytical and spectroscopic data.

Application of the above methodology (see Scheme 3) to compound **8**, allowed the synthesis of (+)-3-*epi*-hyacinthacine A_2, **2**, where structure was established on the basis of its analytical and spectroscopic data.



Scheme 3. Synthesis of (+)-3-*epi*-hyacinthacine A_2 **2**. Reagents and conditions: (a) 10% Pd–C/H_2/MeOH; (b) MeONa/MeOH; (c) 10% Pd–C/H_2/HCl, then Amberlite IRA-400 (OH^- form).

3. Conclusions

Finally, two important conclusions can be stated from the above results: that partially protected polyhydroxylated pyrrolidines, derived from common hexuloses,

together with a classical Wittig's methodology are both suitable for the enantiosynthesis of complex polyhydroxylated pyrrolizidines alkaloids and that the absolute configuration at C(5) in 5-methylpyrrolizidines is controlled by that at C(7a) in such a way that C(5)Me group and C(7a)H are always in a *trans*-disposition.

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). 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 in H_2O (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).

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

To a stirred solution of (2*R*,3*R*,4*R*,5*S*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine **3**[4] (1.28 g, 1.8 mmol) in dry dichloromethane were added triethylamine (TEA, 220 μL, 2.7 mmol), DMAP (25 mg) and benzoyl chloride (220 μL, 2 mmol) and the mixture left at room temperature for 24 h. TLC (ether/hexane 1:1) then revealed a faster-running compound. Conventional work-up of the reaction mixture and column chromatography (ether/hexane 1:3) afforded pure **4** (1.42 g, quantitative) as a colourless syrup, which had $[\alpha]_D^{28} = +7.5$, $[\alpha]_{405}^{28} = +26$ (*c* 1.2). IR (neat): 3078 (aromatic), 1724 and 1713 (COPh and $>NCO_2Bn$), 710 and 699 cm^{-1} (aromatic). NMR data (400 MHz): ^{1} H, δ 8.15–7.10 (m, 30H, 6Ph), 5.25–3.77 (m, 14H, $3CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b) and 1.07 (s, 9H, CMe_3); ^{13} C (inter alia), δ 166.33 (*C*OPh), 155.75 ($>NCO_2Bn$), 72.67 and 72.08 ($2OCH_2Ph$), 67.24 ($>NCO_2CH_2Ph$), 26.98 (CMe_3) and 19.28 (CMe_3). Mass spectrum (LSIMS): *m*/*z*: 842.3491 $[M^+ + Na]$ for $C_{51}H_{53}NO_7NaSi$ 842.3489 (deviation −0.2 ppm).

4.2. (2*S*,3*R*,4*R*,5*R*)-2′-*O*-Benzoyl-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2,5-bis(hydroxymethyl)pyrrolidine 5

To a stirred solution of **4** (3.35 g, 4.1 mmol) in THF (20 mL) was added tetrabutylammonium fluoride trihydrate (1.93 g, 6.1 mmol) and the mixture was kept at room temperature overnight. TLC (ether/hexane 1:1) then showed a new compound of lower mobility. The mixture was neutralized with acetic acid, concentrated to a residue that was dissolved in ether, washed with brine, concentrated and then submitted to column chromatography (ether/hexane 2:1) to yield pure **5** (2.38 g, quantitative) as a colourless syrup, which had $[\alpha]_D^{25} = -16.5$, $[\alpha]_{405}^{24} = -36.5$ (*c* 1.5). IR (neat): 3455 (OH), 3034 (aromatic), 1711 (COPh and $>NCO_2Bn$), 714 and 694 cm^{-1} (aromatic). NMR data (400 MHz): ^{1}H, δ 8.15–7.20 (m, 20H, 4Ph) and 5.20–3.65 (m, 14H, $3CH_2Ph$, H-2,2′a,2′b,3,4,5,5′a,5′b); ^{13}C (inter alia), δ 81.85 and 81.10 (C-3,4) 73.06 and 72.73 (2OBn) 67.75 (NCbz), 64.29 and 57.29 (C-2,5), 63.72 and 63.28 (C-2′,5′). Mass spectrum (LSIMS): *m*/*z*: 640.2308 $[M^+ + Na]$ for $C_{35}H_{35}NO_7Na$ 604.2311 (deviation +0.6 ppm).

4.3. 4-[(2′*R*,3′*R*,4′*R*,5′*S*)-5′-Benzoyloxymethyl-3′,4′-dibenzyloxy-*N*-benzyloxycarbonylpyrrolidin-2′-yl]but-3-en-2-one 7

A solution of **5** (1 g, 1.7 mmol) in dry dichloromethane (15 mL) were added activated powdered 4 Å molecular sieve (230 mg), *N*-methylmorpholine *N*-oxide (300 mg) and TPAP (30 mg) and the reaction mixture kept at room temperature for 30 min. TLC (ether/hexane 1:1) then showed a faster-running compound. The reaction was diluted with ether (20 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 aldehyde **6** (780 mg, 78%) that was used in the next step. Compound **6** (690 mg, 1.2 mmol) was dissolved in dry toluene (20 mL) and 1-triphenylphosphoranilydene-2-propanone (570 mg, 1.8 mmol) was added and the mixture was heated at 100 °C overnight. TLC (ether/hexane 2:1) then revealed the presence of a new compound of lower mobility. The solvent was eliminated and the residue supported on silica gel and submitted to column chromatography with ether/hexane (1:1) as eluent to give pure **7** (660 mg, 90%) as a pale yellow syrup, which had $[\alpha]_D^{25} = +17.5$ (*c* 1). IR (neat): 3063 (aromatic), 1722, 1706 and 1700 (CO_2Ph, $>NCO_2Bn$ and α,β-unsaturated ketone), 714 and 696 cm^{-1} (aromatic). NMR data (400 MHz): ^{1}H, δ 7.94–7.27 (m, 20H, 4Ph), 6.58 (br s, 1H, H-4), 6.16–6.04 (br m, 1H, H-3), 5.17 and 5.02 (2d, 2H, *J* 12 Hz, $>NCO_2CH_2Ph$), 4.74–4.30 (m, 8H, $2CH_2Ph$, H-3′,4′,5″a,5″b), 4.24 (br t, 1H, *J* 6 Hz) and 4.12 (br t, 1H, *J* 5.2 Hz) for H-2′,5′ and 1.92 (br s, 3H, H-1,1,1); ^{13}C (inter alia), 197.99 (C-2), 166.19 (*C*OPh), 155.22 ($>NCO_2Bn$), 145.19 (C-4), 133.10 (C-3), 84.62, 84.12, 81.86 and 81.20 (C-3′,4′ of two rotamers) 73.11 and 72.51 ($2OCH_2Ph$), 67.60 ($>NCO_2CH_2Ph$) 62.76 and 57.60 (C-2′,5′), 62.16 (C-5″) and 26.75 (C-1). Mass spectrum (LSIMS): *m*/*z*: 642.2464 $[M^+ + Na]$ for $C_{38}H_{37}NO_7Na$ 642.2468 (deviation +0.5 ppm).

4.4. 3-[(2′*R*,3′*R*,4′*R*,5′*S*)-5′-Benzoyloxymethyl-3′,4′-dibenzyloxy-*N*-benzyloxycarbonylpyrrolidin-2′-yl]prop-2-enal 8

To a solution of **6** (1.6 g, 2.8 mmol) in dry toluene (20 mL), triphenylphosphoranilydeneacetaldehyde

(1.26 g, 4.1 mmol) was added and the mixture was heated at 60 °C for 3 h. TLC (ether/hexane 1:1) then revealed the presence of a new compound of lower mobility. The solvent was eliminated and the residue supported on silica gel and submitted to column chromatography with ether/hexane (1:1) as eluent to give pure **8** (1.13 g, 67%) as a pale yellow syrup, which had $[\alpha]_D^{27} = +13$ (*c* 1). NMR data (400 MHz): ^{1}H, δ 9.20 (br s, 1H, H-1), 7.89–7.49 (m, 20H, 4Ph), 6.56 (br s, 1H, H-3), 6.17–6.06 (br m, 1H, H-2), 5.20–4.92 and 4.70–4.33 (2m, 10H, 3 CH_2Ph, H-3′,4′,5″a,5″b), 4.22 (t, 1H, *J* 6.1 Hz) and 4.08 (t, 1H, *J* 5.4 Hz) for H-2′,5′. Mass spectrum (LSIMS): *m*/*z*: 628.2313 [$M^+ + Na$] for $C_{37}H_{35}NO_7Na$ 628.2311 (deviation −0.3 ppm).

4.5. (1*R*,2*R*,3*S*,5*R*,7a*R*)-3-Benzoyloxymethyl-1,2-dibenzyloxy-5-methylpyrrolizidine 9

Compound **7** (630 mg, 1 mmol) in dry methanol (20 mL) was hydrogenated at 60 psi over 10% Pd–C (145 mg) for 7 h. TLC (ether/hexane 3:1) then showed the presence of a new compound of lower mobility. The catalyst was filtered off, washed with methanol and the filtrate and washings concentrated to a residue that was submitted to column chromatography (ether/hexane 1:1) to afford pure syrupy **9** (293 mg, 61%), which had $[\alpha]_D^{25} = +50$ (*c* 1.2). IR (neat): 3086, 3063 and 3028 (aromatic), 1721 (CO benzoate), 712 and 696 cm^{-1} (aromatic). NMR data (400 MHz): ^{1}H, 8.02 (d, 2H, $J_{o,m}$ 7.3 Hz, H-*ortho*-Bz), 7.59 (t, 1H, $J_{m,p}$ 7.2 Hz, H-*para*-Bz), 7.46 (t, 2H, H-*meta*-Bz), 7.40–7.21 (m, 10H, 2CH_2Ph), 4.73 (dd, 1H, $J_{3,8}$ 6.3, $J_{8,8'}$ 11.3 Hz, H-8), 4.68 and 4.55 (2d, 2H, *J* 12 Hz, CH_2Ph), 4.62 and 4.51 (2d, 2H, *J* 11.7 Hz, CH_2Ph), 4.52 (dd, 1H, $J_{3,8'}$ 5.6 Hz, H-8′) 4.26 (dd, 1H, $J_{1,2}$ 3.1, $J_{2,3}$ 6.6 Hz, H-2), 3.81 (dd, 1H, $J_{1,7a}$ 8 Hz, H-1), 3.03 (br q, 1H, H-3), 2.66 (ddd, 1H, $J_{7a,7\alpha}$ 10.4, $J_{7a,7\beta}$ 5.5 Hz, H-7a), 2.51 (br sex, 1H, $J_{5,6\alpha} = J_{5,6\beta} = J_{5,Me} = 6$ Hz, H-5), 2.27 (bdq, 1H, H-6β), 1.88–1.77 (m, 1H, H-7β), 1.75–1.72 (m, 1H, H-6α), 1.65 (dq, 1H, $J_{6\beta,7\alpha}$ 7.2, $J_{6\alpha,7\alpha} = J_{7\alpha,7\beta} = 10.7$ Hz, H-7α) and 1.28 (d, 3H, Me); ^{13}C (inter alia), δ 166.37 (*C*OPh), 89.02 (C-2), 85.35 (C-1), 73.98 (C-7a), 71.82 and 71.66 (2 *C*H$_2$Ph), 63.50 (C-8), 63.27 (C-3), 55.05 (C-5), 37.16 (C-6), 25.76 (C-7) and 21.14 (Me). Mass spectrum (LSIMS): *m*/*z*: 494.2301 [$M^+ + Na$] for $C_{30}H_{33}NO_4Na$ 494.2307 (deviation +1.2 ppm).

4.6. (1*R*,2*R*,3*S*,5*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine 1, [(+)-3-epi-hyacinthacine A$_3$]

To a solution of **9** (250 mg, 0.53 mmol) in anhydrous methanol (5 mL) was added 1 N sodium methoxide (1.2 mL) and the mixture was left for 30 min. TLC (ether/hexane 3:1) then revealed a slower-running compound, presumably **10**. The mixture was acidified (concd HCl) and hydrogenated (10% Pd–C, 110 mg) at 60 psi for 12 h. TLC (ether/methanol/TEA 5:1:0.1) then showed a new nonmobile compound. The catalyst was filtered off, washed with methanol and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form) and concentrated. Column chromatography (ether/methanol/TEA 5:1:0.1) of the residue gave pure **1** (64 mg, 64%), which had $[\alpha]_D^{26} = +17$, $[\alpha]_{405}^{25} = +41$ (*c* 1.3, methanol). NMR data (400 MHz, methanol-d_4): ^{1}H, δ 4.20 (dd, 1H, $J_{1,2}$ 4.4, $J_{2,3}$ 7.3 Hz, H-2), 3.83 (dd, 1H, $J_{3,8}$ 6.2, $J_{8,8'}$ 11.1 Hz, H-8), 3.74 (dd, 1H, $J_{3,8'}$ 4.2 Hz, H-8′), 3.65 (dd, 1H, $J_{1,7a}$ 8.7 Hz, H-1), 2.70 (dt, 1H, H-3), 2.50 (ddd, 1H, $J_{7a,7\beta}$ 5.7, $J_{7a,7\alpha}$ 10.5 Hz, H-7a), 2.45 (br sex, 1H, $J_{5,6\alpha} = J_{5,6\beta} = J_{5,Me} = 6.2$ Hz, H-5), 2.22 (brdq, 1H, H-6β), 1.78 (dddd, 1H, $J_{6\alpha,7\beta}$ 2.6, $J_{6\beta,7\beta}$ 8.8, $J_{7\alpha,7\beta}$ 11.6 Hz, H-7β), 1.65 (dddd, 1H, $J_{6\alpha,7\alpha}$ 10.7, $J_{6\alpha,6\beta}$ 13 Hz, H-6α), 1.47 (dq, 1H, $J_{6\beta,7\alpha}$ 7.4 Hz, H-7α), and 1.19 (d, 3H, Me); ^{13}C, δ 85.30 (C-2), 81.03 (C-1), 74.47 (C-7a), 66.65 (C-3), 61.54 (C-8), 57.41 (C-5), 37.55 (C-6), 25.05 (C-7) and 21.19 (Me). Mass spectrum (LSIMS): *m*/*z*: 210.1104 [$M^+ + Na$] for $C_9H_{17}NO_3Na$ 210.1106 (deviation +1.1 ppm).

4.7. (1*R*,2*R*,3*S*,7a*R*)-3-Benzoyloxymethyl-1,2-dibenzyloxypyrrolizidine 11

Compound **8** (1.13 g, 1.9 mmol) in dry methanol (30 mL) was hydrogenated at 60 psi over 10% Pd–C (360 mg) for 14 h. TLC (ether/TEA 1:0.1) then showed the presence of a new compound of lower mobility. Work-up of the reaction mixture as for **9**, gave a residue that was submitted to column chromatography (ether) on silica gel, previously saturated with NH_3 gas, to afford pure syrupy **11** (470 mg, 55%), which had $[\alpha]_D^{25} = +30$ (*c* 1.9). NMR data (400 MHz): ^{1}H, δ 8.04–7.20 (m, 15H, 3Ph), 4.72 (dd, 1H, $J_{3,8}$ 6.5, $J_{8,8'}$ 11.4 Hz, H-8), 4.64 (dd, 1H, $J_{3,8'}$ 7.2 Hz, H-8′), 4.58 and 4.41 (2d, 2H, *J* 12 Hz, CH_2Ph), 4.57 and 4.50 (2d, 2H, *J* 12 Hz, CH_2Ph), 4.08 (dd, 1H, $J_{1,2}$ 0.7, $J_{2,3}$ 4.4 Hz, H-2), 3.81 (br d, 1H, H-1), 3.71 (dt, 1H, H-3), 3.55 (dt, 1H, $J_{1,7a}$ 3.2, $J_{7a,7\alpha} = J_{7a,7\beta} = 7.5$ Hz, H-7a), 3.09 (dt, 1H, $J_{5,6}$ 6.4, $J_{5,5'} = J_{5,6'} = 8.9$ Hz, H-5), 2.89 (dt, 1H, $J_{5',6}$ 8.7, $J_{5',6'}$ 2.3 Hz, H-5′), 2.15 (ddt, 1H, *J* 2.5, *J* 7.5, *J* 10.2 Hz, H-7β), 1.96–1.77 (m, 2H, H-6,6′) and 1.63 (ddt, 1H, *J* 7.6, *J* 10, *J* 12 Hz, H-7); ^{13}C (inter alia), δ 166.51 (*C*OPh), 88.13 (C-1), 86.55 (C-2), 71.77 and 71.48 (2*C*H$_2$Ph), 70.80 (C-7a), 62.25 (C-3), 61.83 (C-8), 48.57 (C-5), 30.42 (C-7) and 26.91 (C-6). Mass spectrum (LSIMS): *m*/*z*: 458.2326 [$M^+ + H$] for $C_{29}H_{32}NO_4$ 458.2331 (deviation +1.2 ppm).

4.8. (1*R*,2*R*,3*S*,7a*R*)-1,2-Dibenzyloxy-3-hydroxymethylpyrrolizidine 12

Conventional debenzoylation of **11** (470 mg, 1 mmol) in 0.2 N sodium methoxide in dry methanol (7 mL) gave after work-up and column chromatography (ether/methanol 5:1) on silica gel, previously saturated with NH_3 gas, pure syrupy **12** (330 mg, 92%), which had $[\alpha]_D^{28} = +19$ (*c* 1). NMR data (300 MHz): ^{1}H, δ 7.29–7.23 (m, 10H, 2Ph), 4.61 and 4.45 (2d, 2H, *J* 12 Hz, CH_2Ph), 4.55 and 4.49 (2d, 2H, *J* 12 Hz, CH_2Ph), 4.10 (dd, 1H, $J_{1,2}$ 2.1, $J_{2,3}$ 5 Hz, H-2), 3.97 (dd, 1H, $J_{3,8}$ 6.3, $J_{8,8'}$ 11.6 Hz, H-8), 3.91 (dd, 1H, $J_{3,8'}$ 5.8 Hz, H-8′), 3.78 (dd, 1H, $J_{1,7a}$ 4.2 Hz, H-1), 3.40–3.34 (m, 2H, H-3,7a), 3.51

(br s, 1H, OH), 3.03 (dt, 1H, $J_{5\alpha,5\beta}$ 8.8, $J_{5\alpha,6\alpha} = J_{5\alpha,6\beta} =$ 6.5 Hz, H-5α), 2.78 (bdt, 1H, $J_{5\beta,6\alpha} = J_{5\beta,6\beta} = 3.2$ Hz, H-5β), 2.10 (ddt, 1H, J 2.9, J 7.5, J 10.7 Hz, H-7β), 1.96–1.72 (m, 2H, H-6α,6β) and 1.62 (m, 1H, H-7α); ^{13}C (inter alia), δ 88.73 (C-1), 87.47 (C-2), 72.04 and 71.59 (2CH$_2$Ph), 70.30 (C-7a), 65.03 (C-3), 59.75 (C-8), 48.01 (C-5), 30.25 (C-7) and 26.82 (C-6). Mass spectrum (LSIMS): m/z: 354.2068 [M$^+$ + H] for $C_{22}H_{28}NO_3$ 354.2069 (deviation +0.2 ppm).

4.9. (1*R*,2*R*,3*S*,7a*R*)-1,2-Dihydroxy-3-hydroxymethylpyrrolizidine 2, [(+)-3-*epi*-hyacinthacine A$_2$]

Compound **12** (280 mg, 0.8 mmol) in dry methanol (30 mL) was hydrogenated (10% Pd–C, 170 mg) in acid medium (concd aqueous HCl, four drops) at 50 psi for 48 h. TLC (ether/methanol 3:1) then showed a not mobile compound. The catalyst was filtered off, washed with methanol and the filtrate and washings neutralized with Amberlite IRA-400 (OH$^-$ form), then concentrated. Column chromatography (ether/methanol/TEA 5:1:0.1) of the residue gave pure **2** (110 mg, 80%), which had $[\alpha]_D^{26} = +2.5$ (c 0.8, methanol). NMR data (300 MHz, methanol-d_4): ^{1}H, δ 4.06 (dd, 1H, $J_{1,2}$ 1.5, $J_{2,3}$ 3.7 Hz, H-2), 3.97 (dd, 1H, $J_{3,8}$ 6.6, $J_{8,8'}$ 11.4 Hz, H-8), 3.91 (dd, 1H, $J_{3,8'}$ 7 Hz, H-8′), 3.89 (t, 1H, $J_{1,7a}$ 1.7 Hz, H-1), 3.34 (dt, 1H, H-3), 3.33 (m, 1H, H-7a), 3.18 (ddd, 1H, $J_{5,6}$ 5.8, $J_{5,6'}$ 9.1, $J_{5,5'}$ 10.5 Hz, H-5), 2.93–2.85 (m, 1H, H-5′), 2.19–2.08 (m, 1H, H-7), 1.98–1.89 (m, 1H, H-6) and 1.82–1.62 (m, 2H, H-6′,7′); ^{13}C, δ 80.02 (C-1), 79.92 (C-2), 72.67 (C-7a), 65.12 (C-3), 57.57 (C-8), 48.27 (C-5), 29.66 (C-7), and 26.36 (C-6). Mass spectrum (LSIMS): m/z: 173.1050 [M$^+$] for $C_8H_{15}NO_3$ 173.1052 (deviation +0.8 ppm).

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