Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2481–2487

TETRAHEDRON: *ASYMMETRY*

Polyhydroxylated pyrrolizidines. Part I: Short and highly stereocontrolled syntheses of hyacinthacines

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Received 19 September 2001; accepted 8 October 2001

Abstract—Two short and highly stereocontrolled syntheses for 7a-*epi*-hyacinthacine A_2 (7-deoxyalexine) **3** and 5,7a-di*epi*-hyacinthacine A_3 **4** are, respectively, reported herein. An appropriately protected polyhydroxypyrrolidine, (2*R*,3*R*,4*R*,5*S*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine **5**, readily available from D-fructose, was chosen as the chiral starting material. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The polyhydroxylated pyrrolizidine skeleton [1-azabicyclo[3.3.0]octane] is the basic framework of a diverse group of alkaloid sugar mimics isolated from natural sources and can be classified into three main groups: those with an one carbon branch at C(1) (necines), those with the same substituent but at C(3) (alexines)[1] and finally those recently isolated with such a carbon branch both at C(3) and C(5) (hyacinthacines).[2] Most of these molecules show inhibitory activity against different kinds of glycoprotein-processing glycosidases and hence have potential as chemotherapeutic agents.[3] As a consequence of this bioactivity, great efforts have been made during the past two decades in order to achieve either the isolation of new pyrrolizidine alkaloids from nature or the design of stereocontrolled synthetic routes[3,4] to these compounds, or to their unnatural isomers, which might be of interest for SAR studies.

To the best of our knowledge, the first synthesis for a hyacinthacine was that has been recently reported by Yoda's group[5] for 7a-*epi*-hyacinthacine A_2 (7-deoxyalexine, **3**), by using a methodology previously applied to the synthesis of (+)-alexine.[4d] However, this synthesis is impractical, having serious drawbacks in that it is lengthy and poorly stereoselective. Thus, a synthesis of 26 steps and separation of mixtures of diastereomeric intermediates were necessary in order to obtain **3**. Herein, we report a new synthetic procedure that produces **3** much more directly and with high stereocontrol. In addition, the scope of this methodology was explored by also synthesizing 5,7a-di*epi*-hyacinthacine A_3 **4**, another unnatural hyacinthacine isomer.

According to the following retrosynthetic analysis for the hyacinthacine A_2 and A_3 type compounds (Scheme 1), the protected 2,5-dideoxy-2,5-imino-D-glucitol (DGDP)[6] **5** prepared from D-fructose, can be considered an excellent chiral starting material for the synthesis of such target molecules. Thus, carbon-chain lengthening either at C(2′) or C(5′) (the original C(1) and C(6) of D-fructose) by a suitably functionalized two carbon fragment, followed by further cyclization, could lead to pyrrolizidines with stereochemistry at C(7a) belonging either to that of the alexine **1** or australine **2** series, depending on whether the above mentioned carbon-chain lengthening is completed at C(5′) or C(2′), respectively, indicating that **5** has an interesting pivotal synthetic character.

2. Results and discussion

Oxidation of (2*R*,3*R*,4*R*,5*S*)-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine **5**[6] catalysed by tetra-*n*-propylammonium perruthenate[7] yielded the aldehyde **6** (see Section 3) which was directly treated with (methoxycarbonylmethylene)triphenyl phosphorane to afford methyl (*E*)-3-[(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]propenoate **7** in a highly

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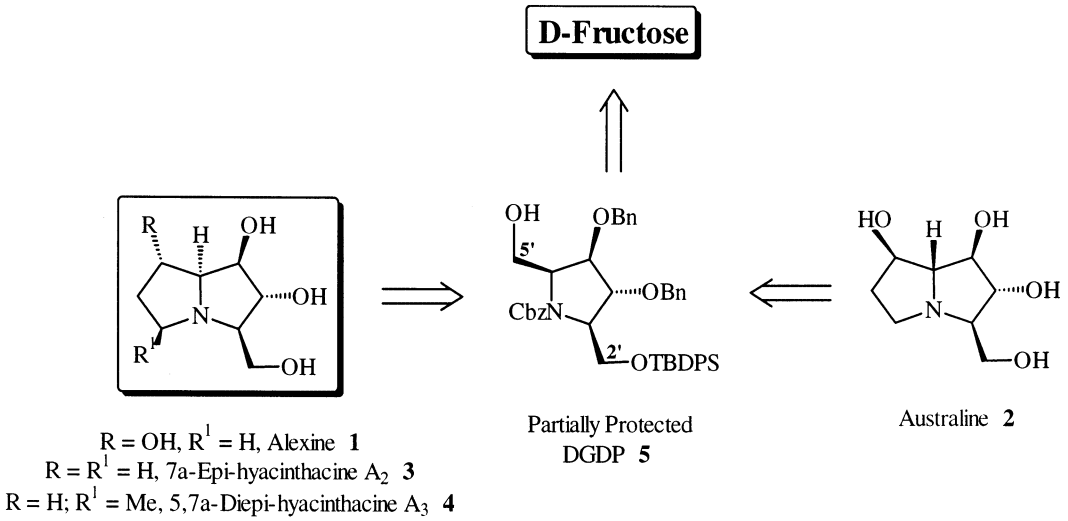
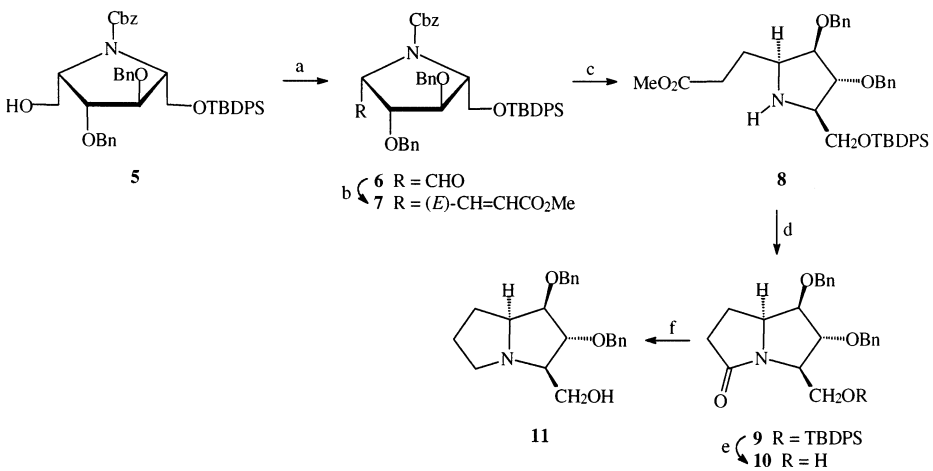
PII: S0957-4166(01)00440-2



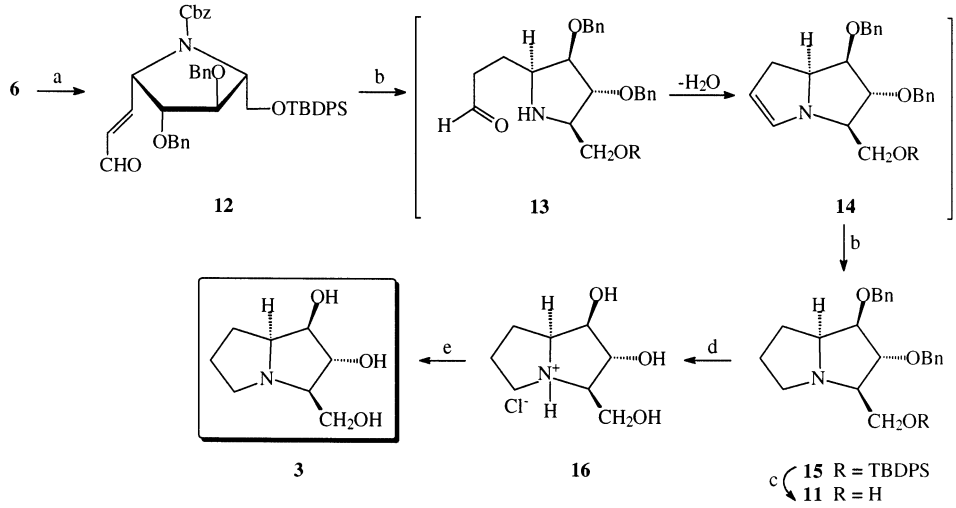
Scheme 1.

stereoselective manner. The structure of **7** was determined on the basis of its spectroscopic data and the (*E*)-configuration established from the $J_{2,3}$ value (15.8 Hz). Catalytic hydrogenation (10% Pd–C) of **7** afforded the saturated and *N*-deprotected ester **8**, which, in order to promote the required cyclization to the indolizidine skeleton, was heated with methanolic sodium methoxide[8] to effect internal *N*-acylation of the pyrrolidine moiety by the ester group, giving the fully protected γ-lactam identified as (1*R*,2*R*,3*R*,7a*S*)-1,2-dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethylpyrrolizidin-5-one **9** as the main product, together with a small amount of the *O*-desilylated derivative **10**, which was also obtained after treatment of **9** with tetra-*n*-butylammonium fluoride dihydrate in THF. The γ-lactam **10** was reduced with borane–dimethyl sulfide complex in THF producing the partially protected 7a-*epi*-hyacinthacine A_2 **11** in moderate yield (Scheme 2).

In order to shorten the synthesis and to improve the total yield of **11** from **6**, an alternative route was explored. Thus, compound **6** was treated with (triphenylphosphoranylidene)acetaldehyde giving the related (*E*)-α,β-unsaturated aldehyde **12**, which, after catalytic hydrogenation as above, afforded in only one step the fully protected (1*R*,2*R*,3*R*,7a*S*)-1,2-dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethylpyrrolizidine **15**. Formation of **15** must take place according to Scheme 3, through an initial hydrogenation of **12** to the saturated aldehyde **13**, subsequent internal condensation to the bicyclic enamine **14**, both not isolated, and final hydrogenation to **15**. Partial deprotection of **15** to **11** and hydrogenolysis of the benzyl protecting groups in acid medium (HCl) yielded the corresponding 7a-*epi*-hyacinthacine A_2 hydrochloride **16**, which was converted, after treatment with Amberlite IRA-400 (OH^-), into the required free base **3**. The ^1H and ^{13}C NMR spectra of **3**, whose signals were assigned on the basis of COSY and HETCOR experiments, were consistent with data previously reported for analogous compounds.[2b,9,10]



Scheme 2. (a) TPAP/NMO/Cl_2CH_2/4 Å MS; (b) $Ph_3P{=}CHCO_2Me/Cl_2CH_2$; (c) H_2/10% Pd–C; (d) MeONa/MeOH; (e) n-Bu_4N^+F; (f) $H_3B{:}SMe_2$/THF.

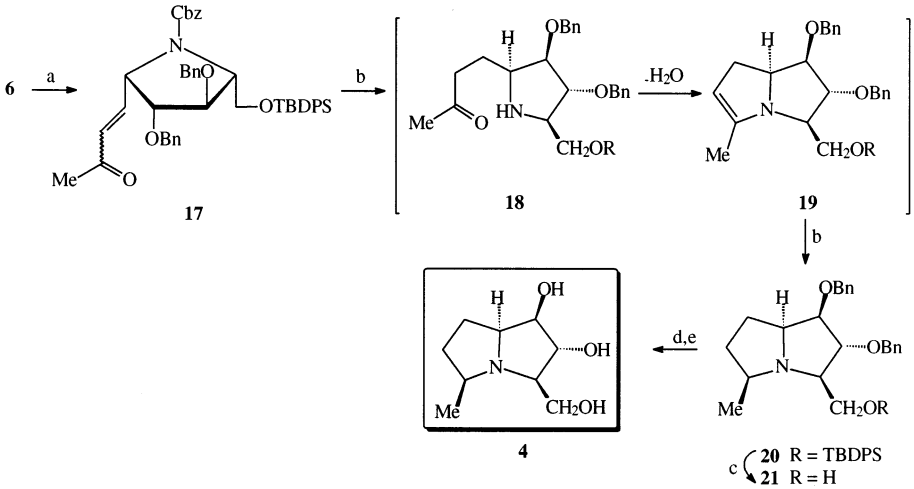


Scheme 3. (a) $Ph_3P{=}CHCHO/Cl_2CH_2$; (b) H_2/10% Pd–C; (c) n-Bu_4N^+F; (d) H_2/10% Pd–C/MeOH, HCl; (e) Amberlite IRA-400 (HO^- form).

Reaction of [(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl - 5′ - *tert* - butyldiphenyl silyloxymethylpyrrolidin-2′-yl]carbaldehyde **6** with 1-triphenylphosphoranylidene-2-propanone gave the corresponding 4-[(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]-but-3-en-2-one **17**. The structure of **17** was determined on the basis of its spectroscopic data. Nevertheless, the configuration at the C(3)–C(4) double bond (which was irrelevant to our purposes) could not be established due to the broadening showed by the C(3)H and C(4)H signals, which made measurement of the coupling constants impossible.

Catalytic hydrogenation (10% Pd–C) of **17** afforded, in only one step, the fully protected (1*R*,2*R*,3*R*,5*S*,7a*S*)-1,2-dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine **20**. Formation of **20** must take place as previously (Scheme 4): initial hydrogenation of **17** to the *N*-deprotected saturated methylketone **18**, as could be demonstrated by the isolation of a minute amount of **18** from the reaction mixture, subsequent intramolecular condensation to give the bicyclic enamine **19**, which was not isolated and final hydrogenation to **20**.

The stereochemistry of the new C(5) stereogenic centre was established on the basis of extensive NOE experiments. The NOE interactions are shown in Fig. 1. The definite NOE effects between C(5)H and C(3)H, between C(5)H and C(1)H and between C(5)H and C(7a)H indicate that C(1)H, C(3)H, C(5)H and C(7a)H are on the same side of the molecule. Thus, the configuration at C(5) is *S*. Noteworthy was the high stereoselectivity found in the hydrogenation of **19**, that can be attributed, according to Fig. 1, to its peculiar shape, where it is appreciated that the α-face is less hindered for hydrogen attack than the β-face is, preferentially affording compound **20**.



Scheme 4. (a) $Ph_3P{=}CHCOCH_3/Cl_2CH_2/\Delta$; (b) H_2/10% Pd–C; (c) n-Bu_4N^+F; (d) H_2/10% Pd–C/MeOH, HCl; (e) Amberlite IRA-400 (HO^- form).

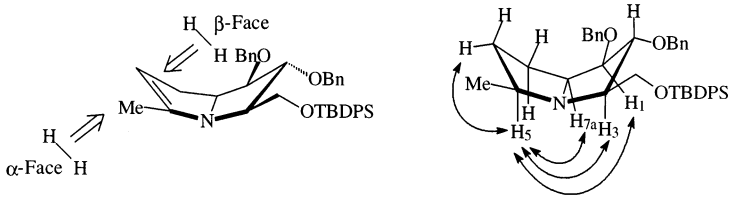


Figure 1. Hydrogenation of intermediate enamine **19** and NOE interactions for **20**.

Finally, removal of the protecting groups in **20** gave the target molecule 5,7a-di*epi*-hyacinthacine A_3 **4**, in accordance with its analytical data and ^1H, ^{13}C, and 2D ^{13}C–^1H heteronuclear shift correlation spectra.

3. Experimental

3.1. General

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). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with a Micromass Mod. Platform II and 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 charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734).

3.2. Methyl (*E*)-3-[(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]propenoate 7

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[6] (**5**, 2.64 g, 3.7 mmol) in dry dichloromethane (25 mL), was added activated 4 Å molecular sieves (2 g), *N*-methylmorpholine *N*-oxide (674 mg, 5.5 mmol) and tetra-*n*-propylammonium perruthenate (TPAP, 64 mg) and the reaction mixture was kept at room temperature for 4 h. TLC (ether/hexane, 2:1) then indicated the absence of the starting material and the presence of a faster-running compound. The reaction was filtered through a bed of silica gel 60 (Merck) and thoroughly washed with dichloromethane. The combined filtrate and washings were concentrated to a residue, presumably [(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]carbaldehyde **6** (2.5 g, 95%): ν_{max}^{film} 1739 (C=O, aldehyde) and 1706 cm^{-1} (C=O, Cbz).

To a solution of **6** (2.1 g, 2.9 mmol) in dry dichloromethane (15 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (1.34 g, 4 mmol) and the mixture was left at room temperature overnight. TLC (ether/hexane, 2:1) then revealed the absence of **6** and the presence of a new compound with slightly lower mobility. The reaction mixture was concentrated to a residue that was supported on silica gel and chromatographed (ether/hexane, 1:2) to afford **7** (2 g, 89%) as a thick syrup: $[\alpha]_D^{24}$ −8, $[\alpha]_{405}^{24}$ −21 (*c* 1); ν_{max}^{film} 3070 and 3035 (aromatic), 1734 and 1706 (C=O, conjugated ester, and C=O Cbz), 1663 (C=C, conjugated), 702 and 699 cm^{-1} (aromatic). NMR data: ^1H NMR, 7.61–7.19 (m, 25H, 5Ph), 6.96 (dd, 1H, $J_{2,3}$= 15.8, $J_{2',3}$=7.8 Hz, H-3), 6.02–5.85 (bd, 1H, H-2), 5.05–3.81 (4m, 10H, 2PhCH_2 and H-2′,3′,4′,5′,5″a,5″b). 4.62 (s, 2H, Cbz), 3.69 (s, 3H, OMe), and 1.06 (s, 9H, CMe_3); ^{13}C NMR (inter alia), 166.35 (C-1), 155.46 (Cbz), 144.44 (C-3), 123.07 (C-2), 83.17 and 81.11 (C-3′,4′), 72.40 and 71.97 (2Ph*C*H_2 and Cbz), 67.27 (C-5″), 64.24 and 61.38 (C-2′,5′), 51.49 (OCH_3), 26.98 (C*Me*$_3$), and 19.32 (*C*Me_3). Mass spectrum (LSIMS): *m*/*z*: 792.3336 [M^++Na] for $C_{47}H_{51}NO_7NaSi$ 792.3333 (deviation −0.5 ppm).

3.3. Methyl 3-[(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]-propanoate 8

Compound **7** (1.15 g, 1.5 mmol) in methanol (30 mL) was hydrogenated at 4 atm over 10% Pd–C (0.4 g) for 8 h. TLC (ether/hexane, 3:1) then showed a slower-running compound. The catalyst was filtered off, washed with methanol and the filtrate and washings were concentrated to a residue that was subjected to column chromatography (ether/hexane, 1:1) to yield pure syrupy **8** (630 mg, 66%): $[\alpha]_D^{25}$ +29, $[\alpha]_{405}^{24}$ +78 (*c* 1.1); ν_{max}^{film} 3072 and 3033 (aromatic), 1740 (C=O, ester), 740 and 701 cm^{-1} (aromatic). NMR data: ^1H NMR, 7.71–7.28 (m, 20H, 4Ph), 4.58 and 4.38 (2d, 2H, J=12 Hz, PhCH_2), 4.51 and 4.46 (2d, 2H, J=12.5 Hz, PhCH_2), 3.96 and 3.79 (2d, 2H, J=4 Hz, H-3′,4′), 3.84 (m, 2H, H-5″a,5″b), 3.67 (s, 3H, OMe), 3.21 (m, 2H, H-2′,5′), 2.47–2.29 (m, 2H, H-2a,2b), 2.04–1.94 (m, 2H, H-3a,3b), and 1.04 (s, 9H, CMe_3); ^{13}C NMR (inter alia), 174.05 (C-1), 84.48 and 84.03 (C-3′,4′), 71.84 and 70.99 (2Ph*C*H_2), 66.37 and 61.55 (C-2′,5′), 64.05 (C-5″), 51.65 (OCH_3), 31.77 (C-2), 29.95 (C*Me*$_3$), 24.21 (C-3), and 19.37 (*C*Me_3). Mass spectrum (LSIMS): *m*/*z*: 638.3300 [M^++1] for $C_{39}H_{48}NO_5Si$ 638.3302 (deviation 0.2 ppm).

3.4. (1*R*,2*R*,3*R*,7a*S*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethylpyrrolizidin-5-one 9

A stirred solution of **8** (630 mg, 1 mmol) in a 0.1 M sodium methoxide solution in anhydrous methanol (20 mL) was heated under reflux for 10 h. TLC (ether) then

showed mainly a slower-running product. The mixture was concentrated to a residue that was dissolved in ether (15 mL) and washed with water (2×10 mL), then concentrated. Column chromatography (ether/hexane, 3:2) of the residue gave syrupy **9** (430 mg, 71%): $[\alpha]_D^{25}$ +8, $[\alpha]_{405}^{26}$ +23 (*c* 1.1); ν_{max}^{film} 3074, 3050, and 3032 (aromatic), 1693 (C=O, lactam), 737 and 700 cm^{-1} (aromatic). NMR data: ^1H NMR, 7.66–7.58 and 7.40–7.14 (t and m, 20H, 4Ph), 4.80 (dd, 1H, $J_{3,8a}=4.4$, $J_{8a,8b}=9.7$ Hz, H-8a), 4.67 and 4.50 (2d, 2H, $J=11.9$ Hz, $PhCH_2$), 4.45 (s, 1H, H-2), 4.42 and 4.24 (2d, 2H, $J=12.1$ Hz, $PhCH_2$), 4.26 (m, 1H, H-7a), 3.83 (dd, 1H, $J_{3,8b}=10.4$ Hz, H-3), 3.65 (d, 1H, $J_{1,7a}=3.7$ Hz, H-1), 3.58 (t, 1H, H-8b), 2.63 (ddd, 1H, $J_{6,7}=11.8$, $J_{6,7'}=8.4$, $J_{6,6'}=16.4$ Hz, H-6), 2.42 (dd, 1H, $J_{6',7'}=9$ Hz, H-6′), 2.18 (tt, 1H, H-7), 1.85 (dt, 1H, $J_{7,7'}=11.8$ Hz, H-7′) and 1.11 (s, 9H, CMe_3); ^{13}C NMR (inter alia), 172.54 (C-5), 86.18 (C-2), 78.21 (C-1), 71.34 and 71.19 ($2PhCH_2$), 65.47 (C-7a), 61.20 (C-3), 60.29 (C-8), 36.61 (C-6), 27.10 (CMe_3), 19.77 (C-7), and 19.42 (CMe_3). Mass spectrum (LSIMS): *m*/*z*: 628.2861 [M^++Na] for $C_{38}H_{43}NO_4NaSi$ 628.2859 (deviation −0.3 ppm).

Eluted second was a small amount (18 mg) of desilylated **9** [(1*R*,2*R*,3*R*,7a*S*)-1,2-dibenzyloxy-3-hydroxymethylpyrrolizidin-5-one, **10**] as a clear thick syrup: $[\alpha]_D^{24}$ +53 (*c* 1.2); ν_{max}^{film} 3310 (OH), 3090, 3062, and 3033 (aromatic), 1669 (C=O, lactam), 737 and 697 cm^{-1} (aromatic). NMR data: ^1H NMR, 7.40–7.25 (m, 10H, 2Ph), 4.52 and 4.45 (2d, 2H, $J=12$ Hz, $PhCH_2$), 4.51 and 4.47 (2d, 2H, $J=13$ Hz, $PhCH_2$), 4.28 (dt, 1H, $J_{7,7a}=J_{7',7a}=8$, $J_{1,7a}=3.8$ Hz, H-7a), 4.20 (bs, 1H, OH), 3.86 (dd, 1H, $J_{3,8a}=9.6$, $J_{8a,8b}=12$ Hz, H-8a), 3.74 (dd, 1H, $J_{3,8b}=2.3$ Hz, H-8b), 3.78–3.69 (m, 2H, H-2,3), 3.65 (d, 1H, H-1), 2.72 (m, 1H, H-6), 2.57 (ddd, 1H, $J_{6',7}=2.1$, $J_{6',7'}=9.6$, $J_{6,6'}=16.6$ Hz, H-6′), 2.29 and 1.97 (2 m, 2H, H-7,7′); ^{13}C NMR, 174.61 (C-5), 137.26, 137.12, 128.69, 128.67, 128.21, 128.18, and 127.72 (Ph), 86.56 (C-2), 78.33 (C-1), 71.76 and 71.65 ($2PhCH_2$), 65.92 and 65.28 (C-3,7a), 63.81 (C-8), 35.88 (C-6), and 19.09 (C-7). Mass spectrum (LSIMS): *m*/*z*: 390.1681 [M^++Na] for $C_{22}H_{25}NO_4Na$ 390.1681 (deviation 0.0 ppm).

3.5. *O*-Desilylation of 9

Compound **9** (460 mg, 0.76 mmol) in THF (3 mL) was treated with a solution of tetra-*n*-butylammonium fluoride dihydrate (480 mg, 1.5 mmol) in the same solvent (3 mL) for 6 h. TLC (ether/hexane, 2:1) then showed the presence of **10**. The reaction mixture was concentrated and the residue partitioned in ether/water. The organic phase was separated and concentrated. Column chromatography (ether) of the residue yielded pure **10** (235 mg, 81%).

3.6. (1*R*,2*R*,3*R*,7a*S*)-1,2-Dibenzyloxy-3-hydroxymethylpyrrolizidine 11

To a stirred and cooled (ice-water) solution of **10** (220 mg, 0.5 mmol) in anhydrous THF (4 mL) was added a borane–dimethyl sulfide complex solution in the same solvent (10 M, 250 mL) under argon. After 30 min, the mixture was allowed to reach room temperature and maintained for an additional 6 h. Methanol (1 mL) was added and the reaction mixture was stirred under reflux for 2 h, then concentrated and repeatedly co-distilled with methanol. Column chromatography (ether/methanol/triethylamine, 5:1:0.5) of the residue afforded pure **11** (55 mg, 26%) as a clear syrup: $[\alpha]_D^{26}$ +9, $[\alpha]_{405}^{26}$ +26.5 (*c* 0.8). NMR data: ^1H NMR, 7.40–7.30 (m, 10H, Ph), 4.58 and 4.52 (2d, 2H, $J=11.8$ Hz, $PhCH_2$), 4.49 (s, 2H, $PhCH_2$), 3.98 (dd, 1H, $J_{1,2}=3$, $J_{1,7a}=6.7$ Hz, H-1), 3.87 (dd, 1H, $J_{2,3}=5.8$ Hz, H-2), 3.83 (dd, 1H, $J_{3,8a}=4.4$, $J_{8a,8b}=11.4$ Hz, H-8a), 3.76 (dd, 1H, $J_{3,8b}=6.2$ Hz, H-8b), 3.45 (q, 1H, H-7a), 3.38 (bs, 1H, HO), 3.02 (dt, 1H, H-3), 2.81 and 2.26 (2 m, 2H, H-5,5′), 2.03–1.72 (2 m, 4H, H-6,6′,7,7′); ^{13}C NMR, 138.07, 137.97, 128.47, 128.44, 127.81, 127.77 and 127.70 (Ph), 86.87 (C-1), 83.05 (C-2), 72.07 and 72.02 ($2PhCH_2$), 67.26 and 65.97 (C-3,7a), 61.42 (C-8), 47.45 (C-5), 26.81 (C-6), and 22.83 (C-7). Mass spectrum (LSIMS): *m*/*z*: 354.2071 [M^++1] for $C_{22}H_{28}NO_3$ 354.2069 (deviation −0.4 ppm).

3.7. (*E*)-3-[(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-Dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]propenal 12

To a solution of **6** (310 mg, 0.43 mmol) in dry dichloromethane (4 mL) was added (triphenylphosphoranylidene) acetaldehyde (180 mg, 0.59 mmol) and the mixture left at room temperature for 36 h. TLC (ether/hexane, 2:1) then revealed the presence of a slower-running compound. The reaction mixture was supported on silica gel and chromatographed (ether/hexane, 1:1) to afford **12** (140 mg, 44%) as a thick syrup: $[\alpha]_D^{26}$ +1, $[\alpha]_{405}^{25}$ +12 (*c* 1); ν_{max}^{film} 3071 and 3030 (aromatic), 1708, 1690 and 1647 (C=O, conjugated aldehyde, Cbz, and C=C conjugated), 739 and 697 cm^{-1} (aromatic). NMR data: ^1H NMR, 9.25 (bs, 1H, H-1), 7.65–7.15 (m, 25H, 5Ph), 6.75 and 6.20 (2bs, 2H, H-2,3), 5.05–3.90 (4m, 12H, $3PhCH_2$ and H-2′,3′,4′,5′,5″a,5″b), and 1.09 (s, 9H, CMe_3); ^{13}C NMR (inter alia), 193.46 (C-1), 133.68 (C-3), 129.92 (C-2), 83.00 and 80.05 (C-3′,4′), 72.41 and 72.02 ($2PhCH_2$ and Cbz), 67.41 (C-5″), 64.13 and 61.00 (C-2′,5′), 27.03 (CMe_3), and 19.40 (CMe_3). Mass spectrum (LSIMS): *m*/*z*: 762.3225 [M^++Na] for $C_{46}H_{49}NO_6NaSi$ 762.3227 (deviation 0.3 ppm).

3.8. (1*R*,2*R*,3*R*,5*S*,7a*S*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethylpyrrolizidine 15

Compound **12** (300 mg, 0.4 mmol) in methanol (50 mL) was hydrogenated at 4 atm over 10% Pd–C (0.2 g) for 7 h. TLC (ether/methanol/triethylamine, 20:1:0.2) then showed a slower-running compound. The catalyst was filtered off, washed with methanol and the filtrate and washings concentrated to a residue that was subjected to column chromatography (ether/methanol/triethylamine, 20:1:0.2) to yield pure syrupy **15** (106 mg, 45%): $[\alpha]_D^{26}$ −8 (*c* 1.2). NMR data: ^1H NMR, 7.73–7.15 (m, 20H, 4Ph), 4.58 and 4.44 (2d, 2H, $J=11.8$ Hz, $PhCH_2$), 4.48 (s, 2H, $PhCH_2$), 3.97 (dd, 1H, $J_{1,2}=2.8$, $J_{1,7a}=6.4$ Hz, H-1), 3.93–3.88 (m, 2H, H-8a,8b), 3.85 (dd, 1H, $J_{2,3}=5.5$ Hz, H-2), 4.46 (m, 1H, H-7a), 3.12–3.00 (m,

2H, H-3,5), 2.70 (m, 1H, H-5′), 2.01–1.74 (m, 4H, H-6,6′,7,7′), and 1.06 (s, 9H, CMe_3); ^{13}C NMR, 138.30, 135.73, 135.71, 133.43, 129.74, 128.56, 128.37, 127.77, 127.73 and 127.55 (Ph), 86.68 (C-2), 83.11 (C-1), 72.01 and 71.84 (2PhCH_2), 67.75 (C-3), 66.40 (C-7a), 63.51 (C-8), 48.62 (C-5), 27.15 (C-6), 26.93 (CMe_3), 22.76 (C-7) and 19.28 (CMe_3). Mass spectrum (LSIMS): m/z: 592.3248 [M^++1] for $C_{38}H_{46}NO_3Si$ 592.3247 (deviation −0.2 ppm).

3.9. *O*-Desilylation of 15

Compound **15** (57 mg, 0.1 mmol) was *O*-desilylated with tetra-*n*-butylammonium fluoride dihydrate (56 mg, 0.17 mmol) as above to give, after work-up and column chromatography, pure **11** (20 mg, 59%).

3.10. (1*R*,2*R*,3*R*,7a*S*)-1,2-Dihydroxy-3-hydroxymethylpyrrolizidine hydrochloride 16 and the free base 7a-*epi*-hyacinthacine A_2 3

To a solution of **11** (70 mg, 0.2 mmol) in methanol (15 mL) were added 10% Pd–C (50 mg) and conc. HCl (one drop). The mixture was hydrogenated at 4 atm overnight. TLC (methanol/triethylamine, 4:0.1) then showed (phosphomolybdic acid) a slower-running product. Work-up of the reaction mixture as above gave a residue that was percolated (methanol/triethylamine, 4:0.1) to yield **16** (38 mg, 93%) as a foam: $[\alpha]_{577}^{27}$ +17 (*c* 1.5, methanol). NMR (D_2O) data: ^1H NMR, 4.37 (q, 1H, $J_{7\alpha,7a}=J_{7\beta,7a}=8$ Hz, H-7a), 4.28 (dd, 1H, $J_{1,2}=6.5$, $J_{1,7a}=8$ Hz, H-1), 4.06 (dd, 1H, $J_{2,3}=9.2$ Hz, H-2), 4.01 (dd, 1H, $J_{3,8a}=4.4$, $J_{8a,8b}=13.3$ Hz, H-8a), 3.92 (dd, 1H, $J_{3,8b}=9.2$ Hz, H-8b), 3.64 (dt, 1H, H-3), 3.56 (ddd, 1H, $J_{5\alpha,6\beta}=2.4$, $J_{5\alpha,6\alpha}=6.7$, $J_{5\alpha,5\beta}=11.2$ Hz, H-5α), 3.28 (dt, 1H, $J_{5\beta,6\beta}=6$, $J_{5\beta,6\alpha}=11.3$ Hz, H-5β), and 2.22–1.80 (2 m, 4H, H-6α,6β,7α,7β); ^{13}C NMR, 74.19 and 73.78 (C-1,2), 67.32 and 65.39 (C-3,7a), 57.32 (C-8), 50.00 (C-5), 25.53 and 24.16 (C-6,7). Mass spectrum (LSIMS): m/z: 174.1126 [M^++1] for $C_8H_{16}NO_3$ 174.1130 (deviation −2.6 ppm).

Compound **16** (35 mg, 0.17 mmol) in methanol (3 mL) was deionized using Amberlite IRA-400 resin (OH^- form). Evaporation of the solvent gave pure **3** (22 mg, 76%) as a thick syrup: $[\alpha]_D^{26}$ +10 (*c* 1, methanol). NMR (D_2O) data: ^1H NMR, 4.11 (t, 1H, $J_{1,2}=J_{1,7a}=6.6$ Hz, H-1), 3.89 (dd, 1H, $J_{2,3}=9.1$ Hz, H-2), 3.85 (m, 2H, H-8a,8b), 3.81 (q, 1H, $J_{7\alpha,7a}=J_{7\beta,7a}=7$ Hz, H-7a), 3.18 (ddd, 1H, $J_{3,8a}=5.5$, $J_{3,8b}=8$ Hz, H-3), 3.09 (ddd, 1H, $J_{5\alpha,6\beta}=2.2$, $J_{5\alpha,6\alpha}=6.6$, $J_{5\alpha,5\beta}=9.4$ Hz, H-5α), 2.89 (dt, 1H, $J_{5\beta,6\beta}=6$, $J_{5\beta,6\alpha}=10$ Hz, H-5β), 2.00–1.93 and 1.78–1.67 (2 m, 2H, H-6α,6β), and 1.89–1.84 (m, 2H, H-7α,7β); ^{13}C, 76.35 (C-1), 76.04 (C-2), 65.38 (C-7a), 65.01 (C-3), 59.01 (C-8), 48.67 (C-5), 25.80 (C-7), and 24.32 (C-6). Mass spectrum (LSIMS): m/z: 174.1126 [M^++1] for $C_8H_{16}NO_3$ 174.1130 (deviation 2.3 ppm).

3.11. 4-[(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-Dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]but-3-en-2-one 17

To a solution of **6** (from **5**, 1 g, 1.39 mmol as above) in dry dichloromethane (8 mL) was added 1-triphenylphosphoranylidene-2-propanone (820 mg, 2.58 mmol) and the mixture stirred under reflux for 36 h. TLC (ether/hexane, 2:1) then revealed the presence of a slightly more polar compound. The reaction mixture was filtered and supported on silica gel, then chromatographed (ether/hexane, 2:3) to afford **17** as a thick syrup (770 mg, 81%): $[\alpha]_{435}^{27}$ −2.5 (*c* 1.8); ν_{max}^{film} 3065 and 3038 (aromatic), 1708, 1679 and 1633 (C=O, conjugated ketone, Cbz, and C=C conjugated), 740 and 698 cm^{-1} (aromatic). NMR data: ^1H NMR, 7.65–7.22 (m, 25H, 5Ph), 6.70 and 6.12 (2bs, 2H, H-4,3), 5.09–3.96 (6m, 12H, 3PhCH_2 and H-2′,3′,4′,5′,5″a,5″b), 2.05 (bs, 3H, H-1,1,1), and 1.08 (s, 9H, CMe_3); ^{13}C NMR (inter alia), 198.26 (C-2), 155.50 (Cbz), 83.50 and 80.82 (C-3′,4′), 72.37 and 71.91 (2PhCH_2 and Cbz), 67.33 (C-5″), 64.47 and 61.88 (C-2′,5′), 27.02 (CMe_3), 26.77 (C-1), and 19.41 (CMe_3). Mass spectrum (LSIMS): m/z: 776.3389 [M^++Na] for $C_{47}H_{51}NO_6NaSi$ 776.3383 (deviation 0.7 ppm).

3.12. (1*R*,2*R*,3*R*,5*S*,7a*S*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine 20

Compound **17** (460 mg, 0.62 mmol) in dry methanol (30 mL) was hydrogenated at 4 atm over 10% Pd–C (170 mg) for 24 h. TLC (ether/hexane, 1:2) then showed a less polar compound. The catalyst was filtered off, washed with methanol and the filtrate and washings were concentrated to a residue that was submitted to column chromatography (ether/hexane, 1:3) to yield pure syrupy **20** (230 mg, 60%): $[\alpha]_D^{28}$ +15 (*c* 1); ν_{max}^{film} 3069 and 3033 (aromatic), 737 and 698 cm^{-1} (aromatic). NMR data: ^1H NMR, 7.77–7.73, 7.48–7.29, and 7.21–7.19 (3m, 20H, 4Ph), 4.59 and 4.56 (2d, 2H, $J=13.1$ Hz, $PhCH_2$), 4.47 and 4.37 (2d, 2H, $J=11.7$ Hz, $PhCH_2$), 3.99 (d, 1H, $J_{1,2}=0$, $J_{2,3}=3.1$ Hz, H-2), 3.98 (dd, 1H, $J_{3,8}=5.7$ Hz, H-8), 3.79 (dd, 1H, $J_{3,8'}=6.7$, $J_{8,8'}=10.3$ Hz, H-8′), 3.62 (d, 1H, $J_{1,7a}=3.8$ Hz, H-1), 2.91 (bdt, 1H, $J_{7,7a}=5$, $J_{7',7a}=10$ Hz, H-7a), 2.60 (bq, 1H, H-3), 2.45 (bsex, 1H, $J_{5,6}=J_{5,6'}=6.4$ Hz, H-5), 2.20 (m, 1H, H-6), 1.86 (m, 1H, H-7), 1.72 (m, 1H, H-6′), 1.54 (m, 1H, H-7′), 1.15 (d, 3H, $J_{5,Me}=6$ Hz, Me-5), and 1.13 (s, 9H, CMe_3); ^{13}C, 138.71, 135.76, 135.71, 133.81, 133.72, 129.67, 128.42, 128.32, 128.00, 127.73, 127.61, and 127.51 (Ph), 93.17 (C-2), 78.38 (C-1), 72.89 (C-7a), 71.61 and 71.58 (2PhCH_2), 68.63 (C-3), 66.35 (C-8), 56.05 (C-5), 36.86 (C-6), 27.02 (CMe_3), 21.01 (Me-5), 20.03 (C-7), and 19.36 (CMe_3). Mass spectrum (LSIMS): m/z: 606.3405 [M^++1] for $C_{39}H_{47}NO_3Si$ 606.3403 (deviation −0.2 ppm).

3.13. *O*-Desilylation of 20

Compound **20** (290 mg, 0.47 mmol) was *O*-desilylated with tetra-*n*-butylammonium fluoride dihydrate (240 mg, 0.75 mmol) for 6 h as above to give, after work-up and column chromatography (ether/hexane, 1:1) pure (1*R*,2*R*,3*R*,5*S*,7a*S*)-1,2-dibenzyloxy-3-hydroxymethyl-5-methylpyrrolizidine **21** as a colourless syrup (145 mg,

85%): $[\alpha]_D^{29}$ +59 (*c* 1.7). NMR data: ^{1}H NMR, 7.36–7.28 (m, 10H, 2Ph), 4.58 and 4.52 (2d, 2H, $J=12.3$ Hz, $PhCH_2$), 4.46 and 4.43 (2d, 2H, $J=11.8$ Hz, $PhCH_2$), 4.22 (d, 1H, $J_{2,3}=5.5$ Hz, H-2), 3.82 (dd, 1H, $J_{3,8}=3.2$ Hz, $J_{8,8'}=11$ Hz, H-8), 3.66 (bt, 1H, H-8′), 3.60 (bd, 1H, $J_{1,7a}=3.9$ Hz, H-1), 3.04 (bs, 1H, H-7a), 2.91 (bs, 1H, H-3), 2.58 (bs, 2H, H-5, HO-8), 2.22 (m, 1H, H-6), 1.87 (m, 1H, H-7), 1.71 (m, 1H, H-6′), 1.55 (m, 1H, H-7′), and 1.20 (d, 3H, $J_{5,Me}=6.1$ Hz, Me-5); ^{13}C NMR, 138.30, 137.94, 128.53, 128.47, 128.04, 127.88, 127.84, 127.77, and 127.68 (Ph), 91.82 (C-2), 77.78 (C-1), 72.85 (C-7a), 71.96 and 71.44 ($2PhCH_2$), 67.31 (C-3), 61.15 (C-8), 55.65 (C-5), 36.85 (C-6), 20.35 (Me-5), and 19.78 (C-7). Mass spectrum (LSIMS): *m*/*z*: 368.2221 [M$^+$+1] for $C_{23}H_{30}NO_3$ 368.2226 (deviation 1.1 ppm). Anal. calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.89; H, 8.16; N, 4.28%.

3.14. (1*R*,2*R*,3*R*,5*S*,7a*S*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine (5,7a-di*epi*-hyacinthacine A_3, 4)

To a solution of **21** (113 mg, 0.31 mmol) in methanol (25 mL) were added 10% Pd–C (80 mg) and conc. HCl (two drops). The mixture was hydrogenated at 4 atm overnight. TLC (ether/methanol/triethylamine, 5:1:0.2) then showed (phosphomolybdic acid) the presence of a new compound. The catalyst was filtered off, thoroughly washed with methanol and the combined filtrate and washings were deionized with Amberlite IRA-400 resin (OH^- form, 2 mL of wet resine). Evaporation of the solvent and column chromatography (ether/methanol/triethylamine, 5:1:0.2) gave pure **4** (50 mg, 83%) that crystallized on standing, mp 83–85°C: $[\alpha]_D^{28}$ +38 (*c* 0.9, methanol). NMR (MeOH-d_4) data: ^{1}H NMR, 4.09 (d, 1H, $J_{2.3}=4.7$ Hz, H-2), 3.76 (dd, 1H, $J_{3,8}=4.1$, $J_{8,8'}=11.2$ Hz, H-8), 3.71 (dd, 1H, $J_{3,8'}=3.6$ Hz, H-8′), 3.58 (d, 1H, $J_{1,7a}=3.8$ Hz, H-1), 2.87 (ddd, 1H, $J_{7,7a}=6.4$, $J_{7',7a}=10.2$ Hz, H-7a), 2.45 (bsex, 1H, H-5), 2.29–2.19 (m, 1H, H-6), 2.21 (q, 1H, H-3), 1.71–1.61 (m, 2H, H-6′,7), 1.51–1.43 (m, 1H, H-7′), and 1.19 (d, 3H, $J_{5,Me}=6.1$ Hz, Me-5); ^{13}C NMR, 88.16 (C-2), 75.38 (C-1), 74.60 (C-7a), 71.39 (C-3), 62.74 (C-8), 57.24 (C-5), 38.02 (C-6), 20.97 (Me-5), and 20.14 (C-7). Anal. calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 58.06; H, 8.88; N, 7.78%.

Acknowledgements

The authors are deeply grateful to Ministerio de Educación y Cultura (Spain) for financial support (Project PB98-1357) and for a grant (F.F.).

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